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# DEMENDE COVID-19 Workshop

Report and Recommendations

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# Contents

**Abbreviations**

ASPIRE – Action to Support Practices Implementing Research Evidence
ARDS – acute respiratory distress syndrome
CDC – Centers for Disease Control and Prevention (US)
CMC – chemistry, manufacturing and controls
COPD – chronic obstructive pulmonary disease
DHSC – Department of Health and Social Care
EUA – emergency use authorisation
HCID – high consequence infectious disease
IHD – ischemic heart disease
JAK (inhibitor) – Janus kinase inhibitor
LFT – lateral flow test
MABs – monoclonal antibodies
MS – multiple sclerosis
MTA – multiple technology appraisal
NIHR – National Institute for Health and Care Research (UK)
NIH – National Institutes of Health (US)
NICE – National Institute for Health and Care Excellence (UK)
NHS – National Health Service (UK)
RECOVERY – Randomised Evaluation of COVID-19 Therapy
PANORAMIC – Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 in the Community
PCR – polymerase chain reaction
R&D – research and development
RSV – respiratory syncytial virus
RT-PCR – reverse transcriptase polymerase chain reaction
UKHSA – UK Health Security Agency

# 1 Executive Summary

## 1.1 Rationale for the project

Given the importance of diagnostics, vaccines, and medicines in preventing and treating the effects of infectious disease, many pharmaceutical physicians have been deeply involved in rapidly delivering new medicines and vaccines to attenuate the impact of COVID-19. Other pharmaceutical physicians have worked hard to ensure continuity of ongoing research in other disease areas and ensuring supply of existing medicines.

The Faculty of Pharmaceutical Medicine (FPM), as the membership and standard-setting body for pharmaceutical physicians, and a driver for collaborations and innovations across the life sciences ecosystem, has been in a key position to provide thought leadership during the pandemic. In order to harness the expertise of our members, along with other stakeholder groups, FPM has developed the COVID-19 'DEfining MEdical Needs and eviDEnce' (DEMENDE) multidisciplinary workshops. The outputs from the workshops have suggested approaches to encourage, incentivise and innovate in R&D and optimise the use of medical interventions in COVID-19 healthcare.

COVID-19 is a burden on health care due to pandemic and endemic disease. During COVID-19 waves we have witnessed up to 10-15% of acute hospital admissions being due to the disease itself and, directly and indirectly, a significant proportion of subsequent respiratory, cardiovascular and diabetic complications and admissions. Readmissions also occur due to delayed cardiovascular complications and strokes[1234].

The burden of long COVID is significant too, especially in general practice. The increased disease burden amongst the population and a lag in elective surgery, resulting from delays during lockdowns, confound the issue. Immunity from vaccines declines over time and the appearance of new variants results in further admissions to general practice, as well as hospitals. Staff absences due to infection control, fatigue or mental ill health also have a huge impact on the capacity of the system.

To mitigate some of these effects, the innovation of devices, vaccines, prophylactics, and treatments is therefore essential to allow us to live with COVID. We also need to find better ways to cope with future pandemics, understanding which innovations and adaptations should be deployed again in the future and which proved unnecessary or counterproductive.

In preparation for and framing of the DEMENDE workshops, FPM sought clarity on whether to and how to expand the use of existing antivirals, as well as encouraging the development of new products. For some subpopulations, not included in current labelling, use could be extended with appropriate research to markedly reduce risk of viral infection and associated morbidities. This could reduce not only respiratory risk, morbidity and mortality, but also reduce the collateral consequences to healthcare engendered by e.g., isolation, postponement of chemotherapy and other vital healthcare services.

The cycle of innovation of new products involves input at every stage from many stakeholders to drive investment, effective development, and deployment. The DEMENDE project aims to identify where the investment in R&D is most needed to address further indications such as prophylactic indications, as well as addressing how future generations of antivirals might be used and accepted. For major indications, such as reducing hospitalization and mortality for high-risk patients, this has been achieved already. However, it has not been achieved for some other indications like pre- and post- exposure prophylaxis.

The DEMENDE workshops were funded by Innovate UK. The aims of the overall project, as agreed with Innovate UK, were to:

1. Document and define global populations and sub populations for prophylaxis and treatment, as has been defined for SARS-CoV-2 and possible new indications. Consider challenges in deployment (availability of drugs / vaccines etc) and those patients with highest medical needs.
2. For each target patient population define:
    - Current medications and how their use has met the SARS-CoV-2 medical need
    - Ideal product characteristics for sub indications of viral prophylaxis and treatment
    - Approaches for antiviral clinical research, development and benefit risk assessment including such things as:
        - Defining endpoints for clinical trials and examining approaches to early development or pre-clinical development studies
        - Clinical development planning
        - Pre- and Post-marketing regulatory commitments, availability, and emergency use
3. Document considerations for the optimisation of balance between private & government funding for investment in antivirals R&D, and advantages and encouragement of funding innovative R&D and deployment in the UK
4. Discuss routes to provide cost effective educational scientific and prescribing support for health care professionals, optimizing the use of pharmaceutical medicine and other specialties
5. Conclusions and recommendations for next steps

FPM is aware that since the original proposal to Innovate UK the pandemic has gone into a different phase. We cannot live in “lockdown” forever, as the consequences are severe, and policymakers are keen to understand how to learn from the COVID experience to adapt to the continuing uncertainty posed by SARS-CoV2 and inform the response to future viral pandemics.

A multidisciplinary workshop was held on the 25th of March 2022. It involved chief medical officers, R&D and medical affairs staff from the UK and US from pharmaceutical companies with COVID-19 products on the market in UK, specialists from FPM with antiviral R&D or medical affairs experience, academics, clinical healthcare professionals, patient care representatives and policymakers. The workshop contributors are listed in Annex 2.

This report summarises the discussions and findings of the workshop, provides some additional context and evidence base and gives guidance to a variety of stakeholders on the potential next steps and actions.

## 1.2 Workshop Recommendations

### 1.2.1 Planning together – what do we need to do in research and development to deliver treatments across the lifecycle of a pandemic for different populations

1. A working group should be convened to bring together all the stakeholders i.e., regulators, developers, academics, care deliverers globally to discuss the most suitable pre-registration

trial designs, endpoints and programmes for future antiviral R&D and how best to deliver these trials, reviewing current guidance.

2. Existing and potential future post-licensing trial programmes – review and discussion to identify for which additional indications specific treatments might be appropriate. For example, safety and efficacy of line extensions for pre- and post-exposure prophylaxis may be helpful for subgroups of patients, such as those that need protection who are on chemotherapy or other kinds of immunosuppressives or before elective surgery.
3. Additional guidance on how to go from conditional approval to full approval from regulatory authorities is sought.
4. Further research needs to be undertaken on combination therapies. Some of this data could come from existing trial data such as RECOVERY, from health care organisations as real-world data, from registries or from specially designed clinical trials.
5. Funding must be maintained for valuable vaccine studies into resulting neutralising antibody levels and cellular immunity data.
6. Mapping of global resistance data for direct acting antivirals needs to be performed and assimilated into accessible databases, as is the case with antibiotics. New variant resistance to monoclonals is collated by CDC and NIH in the US and global agreement as to the robustness of this data should be achieved.
7. Large-scale publicly funded trials should include health economists in the design, such that they can inform reimbursement processes.
8. A mapping exercise should be undertaken to analyse which datasets of COVID patient data have not yet been analysed and which are available for further analysis. The data may provide safety data and also interaction data with other drugs.

### 1.2.2 Working together – delivering therapeutics to patients

9. With regard to diagnostics, evaluation of use of symptomatology should be explored further, and point of care diagnostics still need further products, not only for COVID, but for other respiratory viruses as well. Better delineation of patients who may need treatment in the community should be defined (with regard to longer term risk, as well as short term risk). What treatments each group might need and how or where this might be delivered i.e., in general practice, hospital care or even with some treatments, possibly pre-prescribed, as with steroids and asthma, also needs analysis.
10. A meeting should be held, in a neutral environment, for discussions on procurement of, deployment of, and access to medicines in future pandemic situations, drawing on the current example of centralisation of access for COVID-19 therapeutics. Considering whether: clinical trials in UK patients are essential, rather than broader controlled access and collecting data through registries.
11. FPM and others should raise the challenges of using conventional cost effectiveness assessments for a pandemic during the NICE MTA.
12. Ensure planning for future development of existing COVID-19 therapeutics is undertaken collaboratively and consider inclusion of medicine developers, clinicians, care organisations and policymakers in order to exploit their full potential.

13. Horizon-scanning of potential therapeutics for COVID and other infectious disease should be formalised within UKSHA and NICE.
14. Convene a group to explore maximising efficiency of maintaining elective surgery during a pandemic utilising newly available treatments or prophylactics.
15. There should be multidisciplinary stakeholder input into national guidance, such as the 'Living with COVID' UK Government strategy.

### 1.2.3 Learning together – sharing information and education

16. Encourage mapping of patient-friendly current best practice and information resource hubs for specific patient subgroups (oncology, rheumatology etc), in order to support patient organisations and other such groups with their activities. This may involve developing resource hubs by appropriately knowledgeable groups (including medicine developers and academics who map global best practice, regulators, communicators) to provide consistent public information or for collating and signposting trusted sources for specific information.
17. Information about the complementary roles of vaccines and therapeutics for different patient sub-groups should also be developed, building on resources already available.
18. How to maximise understanding, through education, of the potential impacts of the use of antiviral treatments to support the NHS should be considered by DHSC and UKSHA, associated with more formalised education of clinicians through NIHR and NHS.
19. Medicines developers, royal colleges and academic societies should be utilised more to provide input into education programmes.

### 1.2.4 Reflecting together – improving for the future

20. Robust COVID-19 infection modelling is required to evaluate the cost of the burden of COVID-19 and the effects of the past two years on chronic diseases, such as diabetes and IHD. Also, whether the management of elective treatment could be managed better. Evaluating what approaches worked well and what did not.
21. A group needs to consider what went well, what could be done better regarding the clinical trial research activities during COVID-19. This might involve ASPIRE (NIHR group of academics and clinical staff) and other stakeholders to reflect on experiences.

# 2 Background

## 2.1 The impact of COVID-19 on public health and hospital pressures

The impact of COVID-19 on disease burden and hospital pressures extends beyond acute disease and vaccine prevention of infection. The public health implications of lack of effective treatments for more vulnerable infected patients are an increase in the burden of hospitalisations. A lack of treatment for key NHS staff, who could potentially return to work sooner, also has significant implications for the healthcare burden. Ever improving diagnostics have been used to isolate spread and treat early, whilst vaccines and treatments have prevented disease or attenuated the disease itself. The impact of medical interventions of vaccines and treatments to date are shown in Table 1.

In COVID-19 to date, current approaches to reduce morbidity and mortality are aimed at preventing hospitalisation (using vaccines and pre-exposure prophylaxis and treatment of high-risk patients) and better standards of care for hospitalised patients. These measures have had a massive impact on both morbidity and mortality of new disease but legacy pressure from past COVID-19 illness, predominantly cardiovascular conditions and diabetes, remains in the community.

Concerns are raised about vaccines due to, the longevity of the utility of current vaccines, high reinfection rates, and the challenge of rapidly developing new vaccines for new variants. We cannot assume that long term effective vaccines will be available in the future. It is imperative that other approaches must therefore be maximised to contain the impact and pressures.

In January 2022 it was estimated that 10% of NHS hospital staff were absent due to positive COVID-19 tests and with BA.2. Reduction in the length of time staff are infected would allow them to get back to work sooner. However, there would have to be restrictions. Widespread use of the three licensed direct acting antivirals may lead to development of resistance. Limited availability may be an issue. This use is not currently the primary indication on the label.

Broader use of antivirals (outside NHS constraints, but within the MHRA label) could reduce health burden (Table 1). Broader use of direct acting antivirals could reduce hospital admissions. The usage is currently limited to those with ultra-high risk, but efficacy has been demonstrated in clinical trials of patients over 60 or with risk factors. Whilst COVID-19 related admissions are only approximately 12% of total hospital admissions (in the last two waves of BA.1 and BA.2) and some may be considered other underlying conditions such as stroke, strokes may be COVID related. Broader use of monoclonal neutralising antibodies, when available, may reduce infections in these patients and consequently the need for antiviral treatment of patients unable to mount an immune response to vaccines and allow them to continue treatment such as chemotherapy.

Future planning may also need to consider protection by post exposure prophylaxis of care homes for specific outbreaks as they are for influenza using oral antivirals to prevent development of disease.

### Table 1: Impact of licensed medical interventions

| COVID 19 events challenging delivery of hospital care | Impact | Attenuation | Available medications |
|---|---|---|---|
| **REDUCTION - in hospital stay and downstream morbidity** | Hospital stay and 28-day mortality has shortened since 2020, fewer patients have thrombotic effects, better recognition of secondary bacterial pneumonia | Improvements in 28-day mortality and hospital have been shown with; antivirals (also reduction in hospital stay); steroids (in severe COVID 19); IL-6 and JAK inhibitors; and anticoagulants. Apart from antivirals, all repurposed. | Vaccines<br>Antivirals<br>Anti-inflammatories,<br>Anticoagulants,<br>Broad spectrum antibiotics |
| **REDUCTION – in number of high-risk patients being admitted for acute care and subsequent morbidity which may lead to further hospital admissions.**<br><br>COVID 19 Hospitalised patients are at risk of long-term serious morbidity and mortality | Patients hospitalised for COVID 19 in 2020 had a 29.4% risk of readmission and 12.3% died after discharge. The majority had diabetic and/or cardiovascular events (Bannerjee 21[5]). Even after vaccination incidence of cardiovascular events remains a higher risk if you are a COVID 19 patient admitted to hospital (Connolly. 22)[6]. | Vaccines prevent infection and thus hospitalisations but are challenged by new strains and long lead times for development. Neutralising antibody treatments reduce hospitalisations but are challenged by strains with shorter lead times Oral antivirals are broad spectrum and reduction in hospital events varies according to which treatment is used and novel oral antivirals have a long development time. | Vaccines are available to most of the population, and effective but need regular boosters.<br><br>Neutralising antibodies available but narrower spectrum than vaccines.<br><br>Oral antivirals available but distribution is severely restricted in the UK |
| **REDUCTION in risk of admissions and elective cancellations due to COVID 19 in individuals who cannot mount an immune response to vaccine** | Many patients are at risk of COVID-19 due to not generating immune response to vaccines, this has led to elective procedures disruption | Monoclonal Neutralising antibodies can protect these patients if the prevailing variant is sensitive | One neutralising antibody is currently available for this treatment. |

## 2.2 COVID-19 current epidemiology and prophylactics / treatments on the horizon

The DEMENDE project was started by FPM in Jan 2022, when COVID-19 appeared to be declining and becoming milder, with the aim of focusing on long-term approaches to future waves of SARS-CoV-2 infections. However, during the project, SARS-CoV-2 has continued to be problematic with the emergence, and now dominance of variant BA2 (a subset of Omicron) and the recent classification of BA.4 and BA. 5 as variants of concern. Hence, we have sought to make the recommendations applicable in the short, medium and long-term.

On the day of the main workshop on the 25th of March Worldometer[7] reported a UK 7-day average of 78,678 cases and 125 deaths in the UK. Whilst the death rate remains low, at the time of writing

over 12,000 hospital admissions per week are being attributed to COVID-19 – almost the same as the December / January peak. Over 6% of the population on any day in the last two weeks of March had +ve tests including 5.5% of people over 70 and, of those, approximately 2% will be hospitalised[8]. Almost all patients hospitalised and at risk of death are over 65 (Figure 1).

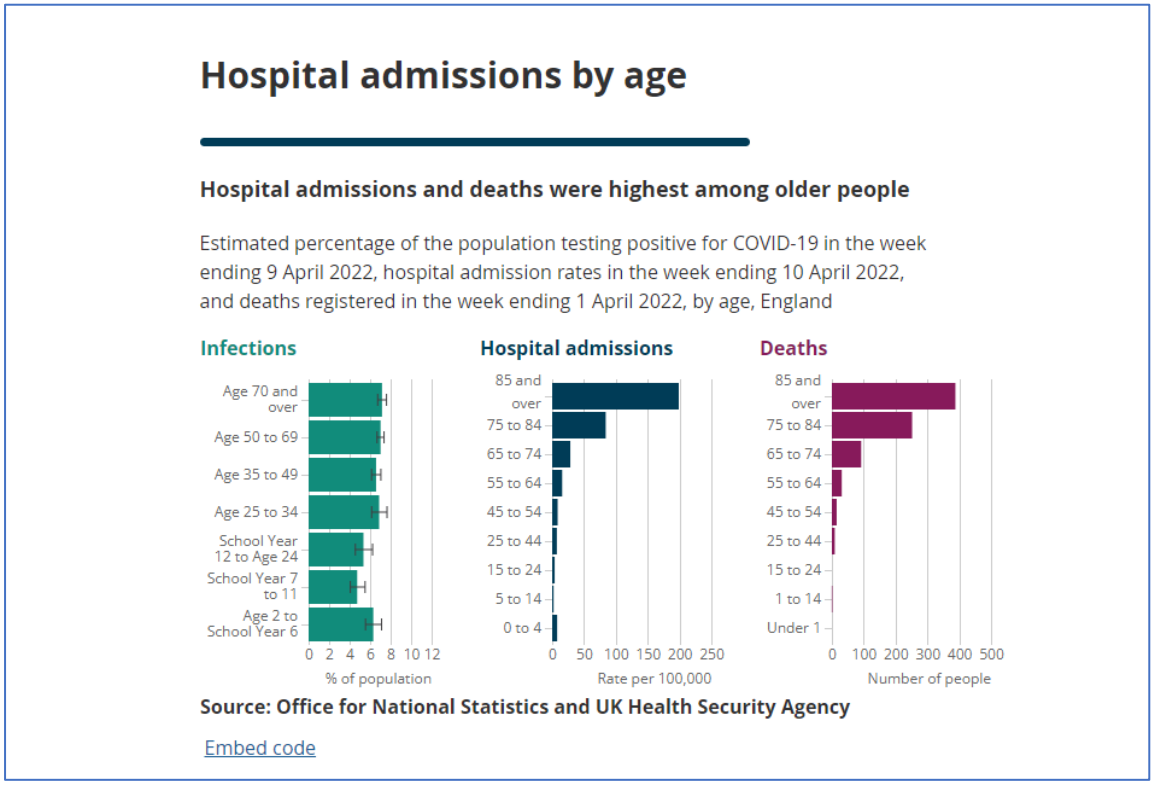


**Figure 1: Infections rates, hospital admissions and deaths ONS[9] accessed 19 04 2022**

The ideal scenario would be to have a vaccine that is effective over time and against all variants, but there is now a large amount of data showing that mRNA vaccines produce short lived immunity (approximately 3 months) for preventing infection, but longer for attenuating disease[10]. The 3rd and 4th boosters do seem to provide protection. That is less than the protection anticipated with Evusheld, the product with the longest half-life amongst currently available monoclonal neutralising antibodies. As yet, vaccines with high efficacy against Omicron are not forthcoming despite an intention to develop new vaccines within 100 days since the start of the wave. Worse still "lack of sustainable herd immunity" from SARS-CoV-2 infection itself is demonstrating a higher reinfection rate for Omicron than for Beta and Delta[11].

There are a handful of innovative new therapeutic products in phase 2 and phase 3 and realistically probably only one or possibly two are likely to become available in the next year. Some clinical trial endpoints designed during the pandemic, such as 28-day mortality, are no longer so relevant due to the low number of deaths. This has led to closure of at least one of the US NIH platform studies. To incentivise the development of second-generation cost-effective interventions for prevention and treatment and early evaluation new endpoints need to be considered. The FPM DEMENDE project is intended to identify and drive work streams gathering global data and helping to lead new approaches from the UK.

The outputs of this project, and this report, will feed into the various UK government initiatives and consultations. These include the G7 100 days report (12), the review of the UK Approaches to Biological Security (13), Future Pandemic Preparedness, the Clinical Research Vision and also provide

feedback to other UK national committees evaluating the successes and failures of the last two years. This work will also inform identification of underserved populations and ensuring equality of access to therapeutics.

# 3 Workstreams discussed and issues raised

## 3.1 Research & Development and Benefit/Risk Evidence

### 3.1.1 Current Medical Need and Clinical Development challenges

#### *3.1.1.1 To outline medical needs potentially managed with COVID-19 pharmaceutical interventions of prevention and treatment and identify where there may be gaps in existing indications of interventions such as pre- or post- exposure prophylaxis.*

From a general practice perspective, the biggest 'gaping hole' is the lack of focus or treatment of patients at high risk of developing serious disease. The current challenge is that those patients at 'ultra-high risk' should be immediately identified when they develop COVID and fast-tracked into a separate process to receive antiviral therapy. This represents a very small proportion of patients at risk, and many are not eligible when they attend the clinic.

All other high-risk patients are targeted to enter the PANORAMIC trial, with a 50% chance of receiving active molnupiravir antiviral therapy. More recently, an additional antiviral treatment arm (Paxlovid) has been added to the PANORAMIC trial, increasing the chance of receiving antiviral therapy to 66% (33% molnupiravir, 33% Paxlovid). Moreover, there are tens of thousands of at-risk patients testing positive daily, with very few hundreds being recruited into the trial, so a very large number of at-risk patients (tens of thousands daily) are left without any treatment options.

From the hospital specialist perspective, there is a need for a long acting, broad coverage (multivalent) vaccine. With regard to treatments, 'precision' approaches are lacking; there is no evaluation of which treatments are best for which patients, which results in widespread standard of care treatments being used for potentially the wrong patients. The detrimental impact on health through broad (sometimes inappropriate) use of dexamethasone in hospitalised patients is emerging, with a reported increase in onset of Type 2 diabetes being triggered.

Other unmet medical needs include treatments for Long COVID. The original clinical trials were focussed on mortality from COVID. However, as the disease is being better managed such that most patients only suffer from moderate disease, the impact of Long COVID as a chronic and debilitating illness affecting large numbers of people is significant[14].

Another important medical need is the study of children with COVID and their impact. To date the focus has been almost entirely on adults but the identification of unmet medical needs from COVID for children must be investigated.

Other gaps highlighted include the study of outbreak control, post exposure prophylaxis in care home settings or prisons, and nosocomial transmission in children. Clinical trials should also be undertaken to include individuals with specific co-morbidities, such as diabetes, a chronic pulmonary disease such as COPD or at least these subgroups analysed in more detail.

The group concluded that there were a lot of unmet medical needs, and these should be mapped out to the type of treatments suitable with a risk /benefit assessment undertaken for different patient populations including pregnant women. Suggestions for study included: learning about long COVID from lung injuries, maximising the utility of mRNA, cognitive function deficits can be assessed in patients already on trials i.e., endpoints added, post exposure prophylaxis in care home settings.

*Actions:*

Actions are listed under actions for current guidance

#### *3.1.1.2 Pre-licensing: To review current guidance for risk / benefit and health economic pre-licensing development programmes.*

Due to changing disease profiles and understandings from completed trials, guidance needs to be reviewed for the following:

- Overall programme and study designs including translational, late phase and platform designs, master protocols
- Specific trial considerations, including entry criteria (including special populations), primary and secondary endpoints), analyses and statistical approaches
- Consider using challenge studies as surrogates
- Review the trial designs and approaches for severe COVID-19 where impact is strongly confounded by sepsis, ARDS and other medical conditions
- Consider specific patient populations within the long COVID disease spectrum and consider what endpoints may be incorporated into clinical trials

It was suggested that we need new ways of doing drug development for COVID-19, which may include new endpoints and potentially categorising phases of trials in different ways.

Early in the Pandemic, COVID-19 clinical trials were predominantly in the secondary care setting, and later they moved into the primary care setting and became more decentralised. A review of the robustness of all designs needs to be undertaken and used to optimise future trials in the light of different COVID-19 outcomes.

The collaboration between medicine developers and the large platform trials needs to be evaluated. Early phase trials require placebo controls, viral load and much clinical data for safety that cannot be collected in large platform trials. Repurposed drugs do not necessarily need that level of data, as preclinical, CMC and much clinical pharmacology and some safety data already exist, and platform trials may have more utility here. The different needs, according to the place in the lifecycle of the medicine, need to be understood to get the best synergies to upscale capabilities – i.e., learn /improve our trial designs /programme designs suitable for re-purposing drugs, post approval trials etc. The group made a recommendation to bring together experts to create the optimal trial designs /programmes based on the learnings over the past 2 years.

The group also recommended that the appropriate balance between conducting smaller trials and larger trials (such as run through the NIHR) in the overall development programme is reviewed. Additionally, the classical development programmes of phase 1, followed by phases 2 and 3 consecutively has changed and the phases are merging, with an exploratory and confirmatory phase type approach; this is like the approach seen in oncology programmes and this new approach should also be evaluated.

It was also suggested that cost utility information could be collected in some trials in the future, as this information would be very useful for understanding the value of antivirals going forward.

In the UK, drug and vaccine development during the past two years of the COVID-19 pandemic has occurred at a remarkable speed, which has been a great positive. As a result, pharmaceutical companies, biotechnology companies, and academic institutions have started to collaborate in a way that did not previously exist. This momentum should be maintained as there are unknowns

regarding the pathogenesis of SARS-CoV-2 and the new variants that could circulate, even during 2022.

*Action:*

The group recommended that one or more working groups should be convened to bring together different voices and perspectives and all the learnings i.e., regulators with developers etc. We need to learn from past experiences and open discussions on the most suitable trial designs and endpoints and how best to deliver these trials.

#### *3.1.1.3 Post licensing: To review current guidance for risk / benefit and health economics for post licensing development programmes or for conversion of Conditional Approval to full license, to add additional indications or generate data in specific patient populations*

Post-licensing clinical trial guidance for the extension of the prescribing label to new uses for antiviral drug (indications) might include:

- Pre- and post-exposure prophylaxis studies
- design and length of additional trials post-licensing for safety studies
- use of registry data

There was agreement that the usual line extensions for pre- and post-exposure have not been undertaken, except with Ronapreve, and they would fulfil a further medical need. However, some post-exposure clinical trials are under way (e.g. Paxlovid), but these are large, and it is too soon for these to report.

As we move into living with COVID, treatments reducing length of disease, as well as hospitalisation events, may have value. For example, molnupiravir could reduce length of disease and virus shedding.

Participants in previous clinical trials have undergone follow-up, the trials have included both treated and non-treated participants and are a potential source of data which has been required by regulatory authorities for transition of EUA to full approval. Other data may include studies using population data and registry data have previously provided support for clinical trial data. The development of COVID-19 patient registries should be possible in the UK, due to the information collected by GPs and the NHS.

*Actions:*

Post licensing trial programmes need to be analysed to support whether guidance for line extensions might be required or encouraged. For example, line extensions for pre- and post-exposure prophylaxis may be helpful for subgroups of patients, such as those that need protection before elective surgery or bone marrow transplants.

Additional guidance on how to go from conditional approval to full approval is sought from regulatory authorities.

## 3.2 Issues faced by prescribers and thoughts for additional research

### 3.2.1 To manage prescribing when there are differential diagnoses of respiratory diseases including COVID, RSV and influenza, as patients no longer routinely use lateral flow tests and PCR tests are not performed.

The group discussed the model, used for severely at-risk sepsis patients, of using combinations and step-down therapy, and considered whether this model could be applied in certain instances with COVID.

The COVID-19 pandemic has accelerated the development of diagnostics, including lateral flow tests for SARS-CoV-2 and for antibodies to the S protein, but also for more rapid and accurate RT-PCR testing. There was agreement that routine SARS-CoV-2 testing, and PCR analysis, would have explained the early rises in infections when the diagnostics first became available.

Reduced LFT and subsequent PCR testing may miss emerging variants and sub-variants of SARS-CoV-2 and thus miss emergence of a new wave. A concern was expressed regarding preparedness for new influenza strains and vaccine-resistant SARS-CoV-2 variants, which may spread at the same time in the UK.

The issue of combined twin peaks of COVID and influenza was raised, and how to differentiate between the two. A suggestion was made that the co-morbidities could be captured and analysed, making use of artificial intelligence and modelling to help differentiate. It was noted that exploration of ongoing work on coinfection, and pre-infection with influenza and common cold viruses competing with/attenuating the impact of COVID might be useful.

*Actions:*

Evaluation of use of symptomatology should be explored further and point of care diagnostics still needs further products, not only for COVID, but for other respiratory viruses as well.

### 3.2.2 To be able to recognise and understand additional management of patients who may have a more severe reaction to COVID-19 infection due to little or no effect from by vaccines.

This should include consideration of how to prioritise high-risk patients for treatment when the general risk reduces. Some patients may need immediate and/or lasting protection, such as those having chemotherapy or bone marrow transplants. They may include people for whom access to vaccines may have been delayed, children, those who are vaccine intolerant, those for whom the vaccines are ineffective e.g., patients who immunosuppressed, and those who are not willing to have a vaccination.

It is likely that, as for patients with HIV/AIDS, COVID-19 will require a combined approach to treatment, and this requires a 'personalised' treatment approach.

However, without evidence from clinical studies and trials, it is unclear which treatment combinations may be used for each patient.

*Actions:*

Better delineation of patients who may need treatment in the community should be defined and what treatments they might need and how/where this might be delivered e.g., general practice, specialised units, hospital care or even with some treatments, possibly pre-prescribed, as with steroids and asthma, should be defined.

### 3.2.3 To understand possible combinations of treatments, including how treatments of different classes interact and how clinicians can and cannot combine treatment, especially in high-risk patients

Lack of uptake of vaccination is still a concern in the UK, in some communities and by those who fear vaccine side effects. Widespread misinformation and its resulting vaccine hesitancy is also an international concern as raised by the Independent Allocation of Vaccines Group of COVAX[15]. The availability of more conventional, adjuvated protein-based vaccines may improve vaccine uptake rates. This workstream should also look at how to enable research into combinations, including multi-company collaborations.

*Action:*

Further research needs to be completed on combination vaccines and therapies. This data could come from existing trial or real-world data and from specially designed clinical trials. Multicompany discussions should be encouraged.

## 3.3 Global issues relating to stewardship and possible direct acting antiviral combinations

### 3.3.1 Management of collection and distribution of resistance data

The UK is a leader in studies on vaccine efficacy, because of the early rollout of the vaccination programme, and UKHSA studies and databases map effectiveness, in terms of neutralising antibodies and cellular defence. However, funding of generation of this data and sequencing must be maintained. Concern regarding collating global resistance data on direct acting antivirals was raised as it was thought that there the different data bases are collated.

*Actions:*

The UK is a leader in studies on vaccine impact on neutralising antibodies and cellular defence, because of the early rollout of the vaccination programme. However, funding should be maintained.

Mapping of global resistance data for direct acting antivirals needs to be performed. Companies would normally receive the reports and many state agencies also collect this data.

## 3.4 National Engagement

### 3.4.1 Optimisation of Access and Reimbursement Processes

The group sought to establish what an optimal reimbursement process would require, in light of the ongoing uncertainty relating to effectiveness and disease course – which is driven by new variants over time.

Prioritised access for COVID therapeutics has presented challenges of access and speed of deployment. The importance of timely decision-making and access to medicines is particularly significant in a rapidly evolving infectious disease, where the impact of decisions will affect large groups of patients.

Practical and ethical concerns were raised regarding the use of clinical trials for access to treatments. As an example, the Panoramic trial can recruit only 450 patients per day, of which a proportion will

receive no active treatment, when many more patients a day are at substantial risk of hospitalisation and arguably need active treatment.

Evaluation of cost-effectiveness using traditional techniques and current processes was deemed to be inadequate. This was due to:

- the ongoing rapid evolution of the SARS-CoV-2 virus, which changes the risk-benefit profile of medicines by variant
- the wide-ranging nature of the medical impact of the virus on individuals, noting that whilst some risk-factors for severe disease have been elucidated, there is still significant uncertainty regarding how any individual will be affected in the acute or chronic phase
- the difference between the outcomes measured in registration randomised controlled trials and real-world data being collected at scale, and the lack of availability of this real-world data for analysis
- the need for a robust but agile process that can be responsive in the face of new variants and emerging scientific understanding
- the limited expertise in infectious disease pharmaceutical medicine within companies brought to the process, thereby potentially hampering effective decision-making

It was noted that public money had been assigned to the gathering of clinical trial data and real-world evidence to analyse how the drugs have worked and who has benefitted from them in the UK.

However, possible analyses of this evidence were not being undertaken due to lack of funding. Planning for such analyses in future platform studies should be built into the trial planning. For example, 18,000 patients received REMDESIVIR in RECOVERY within the standard of care study arm but have not been analysed. This information could be helpful for policymakers. NB this is standard practice in all pharmaceutical-led clinical development programmes to include health economics experts in clinical trial design and evaluation of the benefits and an important measurement that has been omitted in the early stage of planning of these Covid programmes

*Actions:*

A meeting should be held for discussions on procurement of, deployment of, and access to medicines in future pandemic situations. The meeting should consider whether: lengthy clinical trials to generate more information than was required for conditional approval are appropriate, thus restricting access, rather than normal healthcare distribution channels and collecting data through registries.

FPM and others should raise the challenges of using conventional cost effectiveness assessments for a pandemic at the upcoming NICE MTA. This will help ensure that the value of treatment can be appropriately evaluated.

Large-scale publicly funded trials should include health economists in the design such that they can inform reimbursement processes.

Explore the possibility of FPM or other independent body to support processes for company funding in addition to public funding and expertise for academic trials, in order to avoid research wastage.

A mapping exercise should be undertaken to analyse what datasets are still out there that have not yet been fully utilised.

### 3.4.2 To understand the value of potential clinical indications of the existing products, such as pre and post exposure prophylaxis, and understand how they can best be used, especially in the future in light of disease prevalence and profile and uncertainty.

The discussion raised the following points, similar to work streams 6 and 7:

- There are still gaps in knowledge of who is at high-risk of infection and of severe COVID-19.
- There are still gaps in knowledge of how effective current vaccines are in terms of the degree and length of immunity.
- Without evidence from clinical studies and trials, it is unclear which treatment combinations may be used for each patient.

There is a lack of understanding by NHS prescribers of the clinical value of pre- and post-exposure prophylaxis.

*Actions:*

Ensure planning for future development of existing COVID 19 therapeutics is considered for such things as pre-and post- exposure prophylaxis and include medicine developers, clinicians, care organisations and policymakers to exploit the full potential of the therapeutics.

### 3.4.3 Engagement and Education

#### *3.4.3.1 How can we best engage patients and public with information relating to COVID vaccines and treatments?*

The group felt patients could be communicated with better, to encourage them to be vaccinated or come forward for treatment. Patients, such as those with leukaemia, have their own groups for communication (Blood Cancer UK) and they not only support patients but collate vaccine research and educate patients with cancer about being vaccinated or being treated. It is harder for other, smaller patient subgroups and organisations to undertake these activities.

It would be good to support modelling of best practice and best ways to engage with patient or healthy people subgroups (such as specific ethnic groups or pregnant women) to empower them more and encourage registries and research. A useful exercise would be to map what has already been done in the field – perhaps using a few specific at-risk groups – e.g., rheumatological, immune-suppressed, oncology patients – to find out who's doing what, where the best practice is and how this could be rolled-out / translated / modified for all organisations.

*Action:*

Encourage research in mapping patient-friendly current best practice for specific patient subgroups (e.g. oncology, rheumatology) to support patient groups and other such groups with their activities. This may involve developing resource hubs by appropriately knowledgeable groups (including medicine developers and regulators, as well as academics) to provide consistent public information or collating and signposting trusted sources.

Information about the complementary roles of vaccines and therapeutics for different patients' subgroups should also be developed, building on resources already available.

#### 3.4.3.2 *How can we increase the understanding and education of non-specialist clinicians and increase number of treatment knowledgeable infectious disease, microbiology, and respiratory physicians, for the purposes of both patient care and conducting and engaging in research and policy making?*

*Discussion*

It was discussed that there should be an ambition to maximise potential impacts of the use of antiviral treatments on public health and healthcare resource to support the NHS, which should be examined by DHSC and UKSHA, associated with more formalised education of clinicians on possible utilities of antivirals through NIHR and NHS.

Primary and secondary care non-academic physicians have been increasingly involved in clinical trials, so some information and education could be channelled through investigator meetings, and one of the roles of the NIHR is to encourage all physicians to take part in some research.

The UK 'Living with COVID' strategy may be a model for communication between groups (UK Gov 21/2/22). The document already contains valuable pointers to how vaccines and treatments might strategically be used.

*Action:*

Maximising the potential impacts of the use of antiviral treatments through understanding and education should be considered by DHSC and UKSHA, associated with more formalised education of clinicians through NIHR and the NHS.

Medicines developers, royal colleges and academic societies should be utilised to provide input into education programmes.

#### 3.4.3.3 *How can we collaborate better on **education and engagement of policymakers** and support evidence-based policy?*

The UK National Risk Register 2020[16] includes Pandemics and High Consequence Infectious Diseases (HCIDs). Given the COVID experience, and the ongoing risks that pandemics pose, it was felt that ongoing education of policymakers was essential.

A more diverse group of stakeholders should input into future iterations of the 'Living with COVID' strategy[17].

*Action:*

There should be multidisciplinary stakeholders inputting into national policy documents such as 'Living with COVID' strategy.

### 3.4.4 Reduction of indirect health impacts of SARS-CoV2

#### *3.4.4.1 Work is recommended to understand the potential role of COVID therapeutics and pharmaceutical medicine in reducing indirect health impacts of SARS-Cov2, such as effects on research and treatment for non-COVID conditions*

There was a discussion on actions to improve the agility and resilience of clinical research to the impact of pandemics and how can it be ensured that there is resilience in continuity of non-COVID research programmes in future waves or future pandemics, after the UK Clinical Research Recovery Resilience and Growth Program has finished.

There is a need to develop a plan for a balanced approach to research capabilities and capacity that is both responsive and efficient to acute needs, whilst progressing longer-term research and development needs.

Robust COVID-19 infection modelling is required to evaluate the cost of the burden of COVID-19 and the effects of the past two years on chronic diseases, such as diabetes and IHD. This also will include the cost of the side effects of the treatment given, for example diabetes after steroid treatment.

It was raised that despite a need for protection of trials in other indications it was suggested that it was important to focus on how to maintain focus and momentum in COVID studies while the immediate high public health threat may have passed. For example, recruitment in PANORAMIC (and other COVID trials) will go down once public testing stops. The group also raised the importance of post-marketing surveillance studies, as there is still a lot to learn. Other trials are needed for biomarkers predicting susceptibility to infection or progression to severe COVID-19. There are still gaps in the science regarding the pathogenesis of SARS-CoV-2 and the mechanism of action of vaccines and therapeutics. Therefore, COVID-19 scientific studies should continue in parallel with clinical trials. Pandemic preparedness was discussed, with the concern that new influenza strains may arise at the same time as new variants of SARS-CoV-2.

There is a danger that the clinical trial capacity and learnings might reduce/be lost as the clinical research community is being asked to focus more on non-COVID work. The group recommended to have more dedicated centres and investment into experienced staff, which could help address the issue of supporting NHS staff to do trials, despite possible staff absences and diversion of research staff into clinical care.

*Action:*

Robust COVID-19 infection modelling is required to evaluate the cost of the burden of COVID-19 and the effects of the past two years on chronic diseases, such as diabetes and IHD. Also explore the management of elective treatments and what approaches worked and what did not and whether new pharmaceutical or diagnostic interventions could have improved the heath care burden legacy of COVID-19.

A group needs to consider what went well, what could be done better regarding the clinical trial research activities during COVID-19. This might involve ASPIRE (NIHR group of academics and clinical staff) and other stakeholders to reflect on experiences.

#### *3.4.4.2 Explore how COVID therapeutics can help recovery of non-COVID health services in a COVID-endemic world.*

How can we improve management of elective procedures to minimise exposure and isolation of staff (potentially using antivirals to reduce viral shedding or MABs to protect hospitalised patients) and avoid backlog both during a pandemic and post pandemic?

There is also a need to explore the role of COVID therapeutics for enabling patients within non-COVID conditions to have elective treatment, such as the use of monoclonals before elective surgery.

*Action:*

Convene a group to explore maximising efficiency of maintaining elective surgery during a pandemic utilising newly available treatments or prophylactics.

## 4 Next steps

FPM is very grateful to our members and expert guests for giving their time and expertise to form the above recommendations. Given the multidisciplinary nature of medicines development and deployment, collaboration and coordination of the next steps is critical.

FPM will share this report and recommendations with key stakeholders to identify the most appropriate place for the recommendations to be taken forward, to build on existing work programmes and begin new ones where needed.

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