Scientists for Labour

Treatment Development for COVID-19

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Scientists for Labour

Scientists for Labour is a socialist society affiliated to the Labour Party. Our aims are to both promote good science in politics, and promote Labour values in science. More information about Scientists for Labour, including how to join, can be found at https://www.scientistsforlabour.org.uk. You can follow us on Twitter @scientists4lab.

Throughout the COVID-19 crisis, Scientists for Labour are preparing briefings and summaries of the latest research into coronavirus for Labour Party representatives and their staff. If you would like to receive these briefings or have any other queries, please contact Benjamin Fernando: chair@sfl.org.uk.

Aims and Scope

This report details the current state of knowledge on emerging treatments and treatment development for COVID-19. Whilst every effort has been made to validate the statements made in this report we cannot claim that it is comprehensive, nor that it is free of error or omission. Care should be taken when extrapolating from the questions posed here to actual policy, and it should be noted that the situation is changing very rapidly.

Executive Summary

COVID-19 is a respiratory disease associated with infection of humans by the SARS-CoV-2 virus, which is a member of the coronavirus family. In the absence of a vaccine the development of therapeutics to treat COVID-19 will play an important part in limiting the death toll.

There are more than 1,000 treatments being evaluated in clinical trials as potential therapeutics for COVID-19. Two key avenues of exploration are antivirals - therapeutics which interfere with the replication of the virus; and immune modulation - those which aim to prevent a dangerous overactivation of the immune system in response to the virus. At the time of writing, no drugs have been specifically approved for the treatment of COVID-19. The United States Food and Drug Administration (FDA) has, however, granted emergency use authorization to two types of drugs which allows them to be used to treat the severely ill outside of a clinical trial. Taking something is not necessarily better than taking nothing and there is definite potential for harm in advocating use of a drug before it has been evaluated through a robust clinical trial program. There is a danger that political pressure to fast track approval in a crisis situation could result in the approval of unsafe or ineffective treatments.

For a novel drug to be determined as safe and effective it usually requires a lengthy evaluation process which includes discovery, preclinical evaluation and clinical trials. This usually takes a decade to complete. A huge amount of effort is being undertaken to fast track this process. Two of the main ways to speed up the drug development process are to repurpose already existing drugs and to fast track the clinical trials process, in particular by developing master protocols for trial design. One example is the WHO's SOLIDARITY trial, which ensures trials across countries are coordinated, robustly designed, and comparable. This is incredibly important given the preponderance of smaller clinical trials which are not necessarily well put together and hence may not contribute meaningfully to the overall level of data.

When a drug candidate is identified there are several factors to consider. Firstly a drug must be shown to be safe in suitable preclinical species at an exposure greater than would be anticipated when the drug would be used to treat humans. These studies include toxicology, usually in two species (a rodent and a non-rodent). Candidate drugs should also be examined for potential genotoxicity to identify potential liabilities in causing cancer. The clinical effect of a drug should be studied in well controlled studies in patients, with a meaningful end-point, based upon how patients feel, function, or survive. Trials must be representative of the entire population, especially given the disproportionate effect of COVID-19 on people of BAME backgrounds. When an effective drug is found there must be manufacturing capacity to produce sufficient quantities of acceptable quality and efforts must be made to ensure that the results from this global scientific endeavour are fairly priced and equally accessible to all.

Contents

1. Emerging treatments – a brief introduction

COVID-19 is a respiratory illness caused by the SARS-CoV-2 virus. It can cause a simple upper respiratory tract infection, but can also infect the lower respiratory tract, including the lungs. A lung infection (pneumonia) will induce an immune response with associated inflammation, swelling and leaky lung membranes. This can cause breathing difficulties, and therefore reduce the distribution of oxygen to the rest of the body.

Treatments for COVID-19 can target any one path of this infectious process to slow it down, or stop it entirely. There are currently over 1,400 treatments being trialled around the world.

No treatments have yet been specifically approved for COVID-19 or shown to be safe and effective for COVID-19. The US has granted an emergency use authorisation (allowing use in severely ill patients) for both hydroxychloroquine sulfate and chloroquine phosphate products (on 28 March), and for remdesivir (on 1 May). Japan also granted emergency use authorisation for remdesivir[1]. The European Medicines Agency (EMA) has not granted any emergency use authorisations, but is reviewing remdesivir data on a rolling basis[2].

COVID-19 patients could access unapproved treatments through off-label use (use of a licensed medication for an condition/patient subset that has not been approved by a national drug regulatory authority), on a compassionate-use basis (use of unlicensed medication which is still in development for patients with a life-threatening disease with no alternative authorised treatment), or as part of a randomised controlled clinical trial[3].

While some of these potential treatments are newly discovered**, the overwhelming majority of explored treatments currently already exist** to treat other conditions and are being repurposed. These may be used to treat other conditions which share some similarities to COVID-19.

The presiding concern with such early use of medication which is unapproved for COVID-19 is the **risk of dangerous side-effects or multi-drug interactions that may harm the patient**. Clinical trials ensure that the likelihood of such dangerous interactions, and a patient's risk based on their pre-existing conditions and background (e.g. ethnicity, genetic risk) are well documented. The use of medications in the absence of such trials does not contribute to building safety and efficacy data on a drug.

The following is a non-exhaustive classification of the types of treatments being explored. As of the writing of this report, the following are under clinical trials (i.e. not approved for routine medical use as their benefits/risks are unclear).

1. Antiviral medication

Mode of Action: These drugs interfere with the replication and proliferation of the virus within the human body. They reduce the total quantity of virus (known as the ***viral load***). A reduction in viral load can lead to a direct reduction in the severity of the disease. It can also reduce the effort that the immune system expends in combating it, enabling quicker recovery. Some of the attributes of SARS-CoV-2 are similar to those of other viruses, and these similarities can enable repurposing of existing antivirals. Antivirals have potential to be used in pre-, peri- or post-exposure prophylaxis, i.e. before, during, or after infection[4].

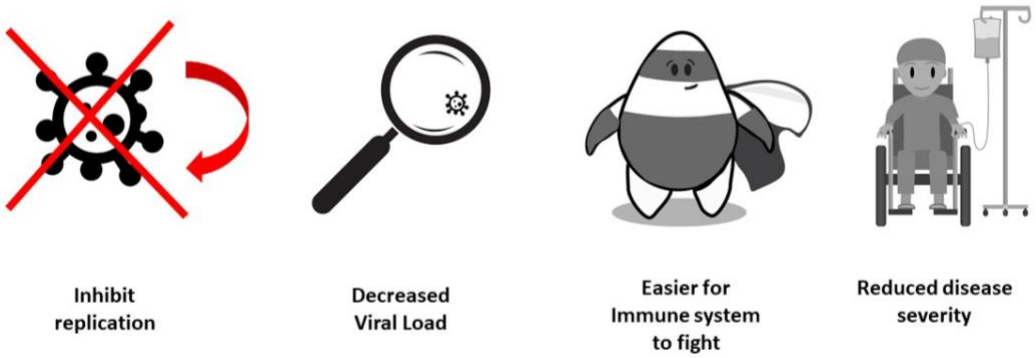

Figure 1: Schematic of antiviral mode of action. *Credit: pngdb.com, cellcartoons.net, "Cancer patient on wheelchair with sad, happy face" by KRASS e.V. Kulturelle Bildung für Kinder & Jugend is licensed under CC BY-NC-SA 2.0*

Examples:

- **Specific antiviral drugs:** These specifically interfere with viral components of the SARS-CoV-2 virus. They may target a specific structure which is similar between different viruses – as an example, viruses often code for a polymerase (an enzyme used to replicate the viral genome) which is similar across the same virus family.
  Example: Remdesivir
- **Non-specific drugs:** These could target, for example, a host factor (part of the host's cells which viruses hijack to complete their replication cycle).
  Example: Chloroquine[5]
- **Convalescent Plasma:** Blood plasma is a liquid that makes up half the volume of blood. It contains specific antibodies that the body develops to fight the SARS-CoV-2 virus. Convalescent plasma is the antibody-rich plasma of someone who has recovered, which could be used to boost the immune response of the recipient. Previous examples are the use of human antibodies transfused into new patients to treat respiratory syncytial virus and cytomegalovirus[6].
- **Dialyzable leukocyte extracts (DLE):** Mixtures of specific proteins from healthy immune cells, shown to improve immune responses[7].

Antiviral resistance: Once a virus infects a cell it undergoes rapid replication. This replication is directed by viral encoded polymerases (a type of enzyme) which are often prone to making copying errors, leading to rapid mutation of the newly-replicated virus' genetic material.

In many cases these mutations will lead to defective viruses. However, when the virus-infected cell is treated with an antiviral drug, resistant viruses can be selected for. These resistant viruses then spread throughout the infected individual, or indeed through a population. This is similar to the evolution of antibiotic resistant bacteria which have become common in hospitals in recent years.

Examples of this behaviour in viruses include HIV, which can rapidly mutate to become resistant to therapy. One method used to prevent antiviral resistance is to use a combination of antiviral drugs, commonly called a drug 'cocktail', to enable stronger antiviral action. This can ensure that resistance to one drug is mitigated by another drug[8]. Such an approach will need to ensure the combined effect of the drugs is not toxic to the patient themselves. In the long-term, it would be beneficial to have multiple antiviral drugs rather than a single treatment to ensure that resistance is less of a risk. Such an approach is taken with HIV[9].

More detail on remdesivir and (hydroxy-)chloroquine (granted an emergency use authorisation in the US) is available in the Appendix

2. Immune and inflammatory response modulators

Mode of Action: These drugs are used to suppress the immune response of the body to the infection. They limit the inflammation within the lungs and the rest of the body. This enables the body to function more normally - for example, less fluid leakage in the lungs, allowing for easier breathing. It is likely that a combination of antivirals and immunomodulating drugs will be necessary for optimum treat COVID-19[10].

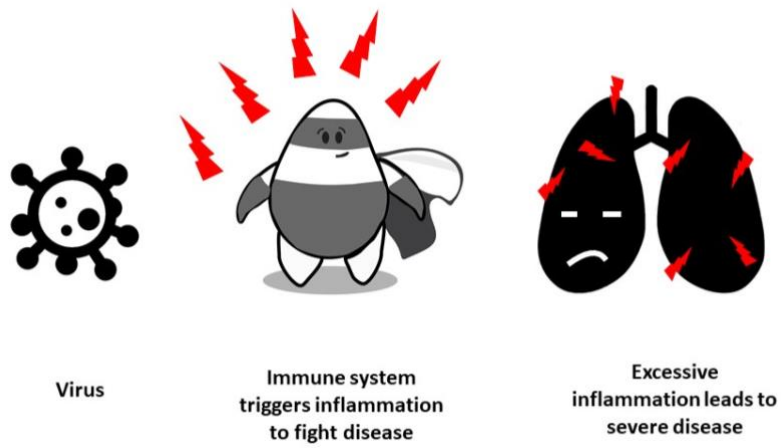

Figure 2: Schematic of overactive immune response. *Credit: pngdb.com, cellcartoons.net*

Subtypes:

- **Steroids:** Wide-action drugs which have a powerful role in blocking the inflammatory response, but can have significant side effects
- **Immunomodulators** (a class of biologics): Unlike steroids, biologics tend to bind to very specific structures in the body. This can enhance intended effects, and minimise side effects. These medications are called biologics because they are manufactured from biological sources, usually specifically developed cells.
- **Cytokine Targeting**[11]: Cytokines are signalling molecules secreted by cells of the immune system which may have a pro-inflammatory effect. There is evidence cytokines may be overproduced in response to SARS-CoV-2[12]. Removal of these pro-inflammatory components in the blood by adsorption (filtering) or by drugs could reduce inflammation in the lungs and rest of the body.

3. Targeted immune enhancing medication

Mode of Action: Given knowledge of the pathology (cause and effect of a disease) of COVID-19 is still evolving, promoting pathways which the body typically uses to defend against viral infection is an area of active research.

Subtypes:

- **Immune System Enhancing Drugs:** These drugs target, and promote, highly specific pathways in the immune system that fight the SARS-CoV-2 virus. There is some evidence T cells (a specific cell of the immune system) may be depleted in severely ill COVID-19 patients and hence promoting T cell activity is potentially beneficial[72].
  Example: InterLeukin-7 (CYT107)[73], FT516
- **Non-drug products:** Certain products (such as *Mycobacterium* extracts[13]) have been shown to enhance immune responses and improve recovery from viral infections.
- **Cell Therapy:** Patients who have weak immune systems (such as HIV patients, those with leukaemia, etc) may not have the immune cells needed to fight infection. In these patients, providing cells that directly fight the infection or indirectly support the immune response will hasten recovery[14].

4. Breathing and Oxygen Support

There are several different ways to administer oxygen. Some types (such as nasal cannulation and masks) are commonplace. Some types such as hyperbaric oxygen therapy[15], oxyhydrogen nebulisers[16], and inhaled NO, are not in common use *(for more information, see the SfL pathology and treatment report at www.scientistsforlabour.org.uk).*

5. Indirect Treatments

Patients with existing illnesses such as heart disease or diabetes are more likely to have life-threatening complications from COVID-19. The exact pathways of such interactions are not yet clear, but these treatments may help minimise such risk.

Mode-of-action: Highly variant, depends on the medical conditions that they are meant to treat.

Examples:

- Dapagliflozin (SGLT2i) to treat Diabetes Type II
- Zilucoplan to promote lung repair and improved oxygenation[17]
- Therapy for anxiety and depression exacerbated by COVID-19[18]
- Enoxaparin[19] to prevent blood clots and strokes
- Neuromuscular electrical stimulation[20] to improve physical function after prolonged illness

6. Preventative Treatment

The ideal solution to the COVID-19 pandemic is to prevent patients from being exposed to the virus, or if exposed, minimising the likelihood of an infection occurring.

Reducing exposure is performed through social distancing and the use of personal protective equipment (PPE), although it should be noted that social distancing is more effective than PPE, especially if PPE is ill-fitting and/or not used in the right way.

If exposed nonetheless, the following may help reduce the risk of getting an infection from said exposure.

- **Broad-spectrum antivirals:** for many viral infections, post-exposure antivirals can reduce the risk of getting an infection after exposure (e.g. Nitazoxanide)
- **Vaccination:** This involves exposing patients to low levels of weakened versions of an infectant/antigenic components (e.g. the SARS-CoV-2 virus) to enable the body to build an immunity. This greatly reduces the risk of future exposure to the virus causing an infection.
    - Existing Vaccines: The existing BCG vaccine is being investigated to potentially reduce the severity of COVID-19 infections[77].
    - New Vaccines: Currently being developed against SARS-CoV-2.

Please see the Scientists for Labour Report on Vaccines for further information.

2. Assessment of treatments

For a newly discovered treatment to be approved as both safe and effective, and to be made widely available, it must be evaluated in a multi-stage process which will include clinical trials (figure 3). This process, from discovery to market, takes an average of 12 years, and has a high failure rate; more than 90% of drugs reaching the first stage of a clinical trial will fail to reach the market[22, 23]. A key strategy in finding treatments for COVID-19 is fast tracking this process without losing a proper evaluation of the safety and efficacy of new medical interventions.

Some regulatory authorities will allow fast tracking of approval, or the 'compassionate use' of a product that has not been fully tested, but a justification for use must still be made. An example of this is the emergency use authorisation of hydroxychloroquine sulfate, chloroquine phosphate products and remdesivir in the United States[1]. **There is a danger that political pressure to fast track approval in a crisis situation could result in the approval of unsafe or ineffective treatments.** Taking something is not necessarily better than taking nothing and there is definite harm to advocating a drug before it has been evaluated through a robust clinical trial program.

An example in the COVID-19 pandemic is the **advocating of hydroxychloroquine and chloroquine before the results of robust clinical trials are known**. These drugs are not risk free: hydroxychloroquine is already known to have potential cardiac toxicity and negative effects on the eye[24]. There is also the potential to derail the evaluation of other treatments, due to the reluctance of patients to give up chloroquine/hydroxychloroquine treatment. This treatment many not be usable in conjunction with other drugs, or could skew the patient samples of other drug trials to those who can't take chloroquine due to, for example due to pre-existing heart problems.

Furthermore, this may create global shortages, harming patients who need the drug to treat the conditions for which it has been shown to be effective. Hospitals in Iran, New York, Spain and China began using hydroxychloroquine and chloroquine as a standard therapy for patients with COVID-19, despite guidance from the World Health Organization and several medical associations that the drugs should not be used to treat COVID-19 except in clinical trials[25].

Addendum, 26 May: the WHO has suspended its trials of hydroxychloroquine over safety fears.

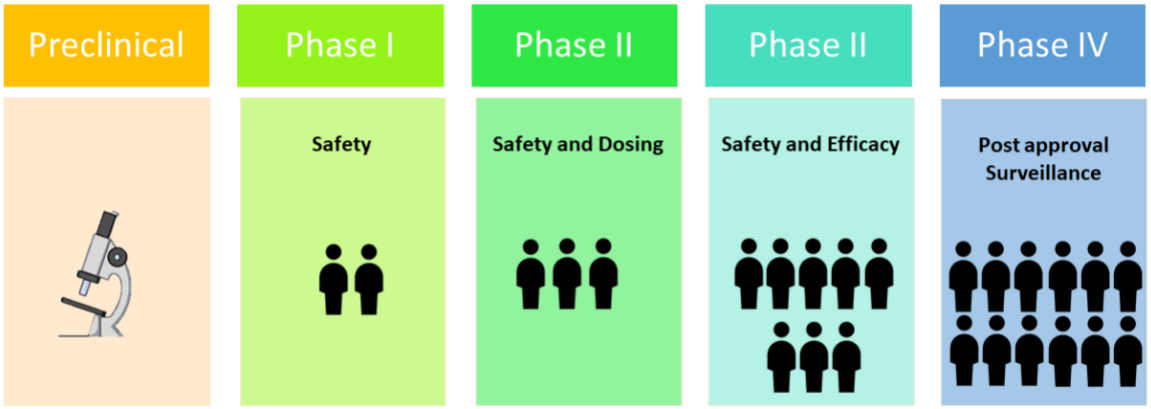

Figure 3: Stages of Treatment Evaluation (adapted from: ILDCollaborative)

2.1 Early Drug Discovery and Preclinical Evaluation

A major part of speeding up approval of a new drug-based medical intervention is to fast track the discovery and preclinical evaluation stages. Preclinical evaluation takes place before a drug is ever evaluated in humans (clinical trials) and aims to deliver preliminary data on toxicity, pharmacokinetics (what the body does to the drug) and pharmacodynamics (what the drug does to the body) through in vitro (non-living systems e.g. cells in a test tube) and in vivo (animal) testing. Preclinical testing determines whether the drug is safe and potentially effective enough to take forward into human testing and gives an initial estimate of the potential dosage needed[26].

2.1.1 Repurposed and Novel Drugs

Repurposing existing drugs, which have already been evaluated for safety in humans and approved for use, is the fastest way to find new treatments for COVID-19 as it skips drug discovery and preclinical evaluation.

Repurposing existing drugs may also allow some stages (phase I and II) of clinical trials to be skipped. In addition to safety, ease of production can be improved as pharmaceutical supply chains for formulation and distribution already exist[27]. Repurposed drugs are also more likely to be in existing hospital circulation, allowing for immediate prescription and use, and are more likely to be off-patent, enabling considerable cost savings.

Another option is to consider experimental drugs which have performed well in preclinical animal studies for the similar coronaviruses, SARS and MERS. Crucially, whichever compound is chosen for further evaluation must be in plentiful supply or easy enough to manufacture to treat a large number of patients if successful[28].

2.1.2 Drug Discovery

There is considerable research effort going into identifying drugs that are likely to treat COVID-19. This process of discovery applies to both novel and repurposed drugs.

This is often first done using computational methods, where the chemical structures of the virus and related infection/inflammatory molecules are studied; and possible target molecules are created or identified. Basic knowledge of the virus is needed for this process. Global efforts have been underway to ensure such information (such as genetic sequences and virus ultrastructure) are made available rapidly. This is often followed by testing of the drugs against virus-infected cells in the laboratory setting, to assess their efficacy. This article gives an overview of the pace and global effort of research for further detail.

2.2 Clinical Trials

The process of drug discovery helps to identify drugs that are potentially effective against a disease. However, their actual effects on the human body are unknown. The drug may have unwanted interactions with other parts of the body, interact with other medication or may not effectively reach the sites of infection at all. For a treatment to be approved as both safe and effective, it must go through clinical trials. A randomised clinical trial with a placebo control group (a group which is treated with the current standard treatment, if it exists, or a dummy intervention) is the gold standard. and compares two or more treatments of human patients with a particular condition to determine which is the more effective. Other trial types, such as observational studies, may provide supporting evidence. The treatment being investigated could be a medicinal product, a procedure, a device or another type of therapeutic intervention.

2.2.1 Phases of a Clinical Trial

Phase I: generally dose escalation trials and the first instance of the drug being evaluated in humans. These are conducted in a small number of healthy and/or diseased volunteers to explore pharmacology (the study of a drug's mechanism of action) and tolerability.

Phase II: generally therapeutic exploratory trials. They are larger than Phase I and conducted in patients. These are designed to test safety, pharmacodynamics, pharmacokinetics and potentially answer questions for the planning of Phase III trials such as dose frequency, optimal doses and endpoints (what outcome you would like to measure in the trial). They may offer preliminary evidence of efficacy, but safety concerns and the small number of participants generally prevent any true assessments of efficacy.

Phase III: these assess the efficacy of the drug in larger and more diverse group of patients with the disease of interest. They also check for any adverse effects of the drug. They must be extremely carefully planned in order to ensure that they will give meaningful information and reliable outcomes. Generally, these compare the intervention of interest with either a standard therapy or a placebo (a dummy intervention that has no impact on the disease but may mitigate the patient's and their doctors perception of their condition with treatment or

natural recovery) and patients are randomly assigned to control (standard treatment/placebo) or treatment groups. These are often double blind trials, where neither the patient nor their doctors know which subject is receiving placebo and which active drug. Usually, for approval of a drug for marketing and distribution, regulatory authorities require two phase III studies which are well controlled and measure a meaningful clinical end point. A meaningful endpoint is one which measures how a patient feels, functions and survives. The two pivotal phase III studies should cover an acceptable number of subjects to ensure an adequate safety database and statistical significance. The number can vary according to the disease from hundreds to thousands of subjects

Phase IV: these may occur after a drug has been approved to monitor efficacy and are observational studies to 1) identify less common adverse reactions, and 2) evaluate cost and/or drug effectiveness in diseases, populations, or doses similar to or markedly different from the original study population[26].

2.2.2 Clinical Trials and COVID-19

This section gives a brief overview - further details on individual trials can be found in the Appendix.

Experimental intervention carries inherent risks. Animal studies can never exactly predict the human response to a drug and there is always the potential for serious adverse effects to occur. The robust design of a clinical trial, ensuring it is both ethical and best facilitates the planned statistical analyses, is hence crucial in determining whether an intervention is an effective treatment[29]. For COVID-19, the ultimate aim is to rapidly find treatments which slow disease progression or improve survival. This is part of the lessons learned from the Ebola crisis, where delays in setting up clinical trials hampered treatment[30].

As mentioned above there are more than 1,000 potential interventions being explored for the treatment of COVID-19.

Global Clinical Trials

A key issue highlighted with clinical trials in a pandemic is the prevalence of many smaller and not necessarily well-designed trials. These may be poor due to weak standards on control groups, poor randomization, insufficiently robust measures of clinical outcomes, and too small a sample size to give a statistically significant result. This is especially true for COVID-19 as in the absence of treatment, patients are more likely than not to improve anyhow[9,31]. An example highlighting this is the conflicting reports from smaller clinical trials on the efficacy of remdesivir over the last few weeks[29], *as reported on in the SfL Daily Briefings*.

Given the urgency to find new drugs, initial exploration of potential treatments for those who are seriously ill has a place. Ultimately, however, the evaluation of a potential drug will need the power of scale and the learning that comes from collaboration, alongside transparency of data and a valid control group[29].

Attempts have been made to coordinate such global clinical trials. Notable examples include:

WHO SOLIDARITY trial:

To aid treatment evaluation the WHO is aiming to fast track clinical trials by up to 80% through launching a master clinical trial and protocol to coordinate international efforts. This aims to include many thousands of patients in more than 100 countries[32]. Named SOLIDARITY and launched in late March, it has been designed to establish consistent end points. It also aims to standardise control groups and inclusion–exclusion criteria, and to be as simple as possible so that even hospitals overwhelmed by an onslaught of COVID-19 patients can still participate[33].

Once enrolled, a patient's doctor states which drugs are available at their hospital and a computer randomises the patient to one of the four treatments or the local standard of care[32,33].

Four potential treatments are being evaluated:

1. Remdesivir
2. Chloroquine or Hydroxychloroquine
3. Lopinavir with Ritonavir
4. Lopinavir with Ritonavir plus Interferon beta-1a[32].

The trial design is adaptive. This means that it is designed such that certain modifications, e.g. changing dosage and selection criteria as the trial progresses, and switching patients off ineffective treatment arms earlier, can be made. Countries have the option of adding other treatment arms to their trial as desired or as is necessary[34]. *More detail is available in the Appendix*

EUROPEAN DISCOVERY TRIAL:

The French biomedical research agency, INSERM, is coordinating an add-on trial to SOLIDARITY in Europe, named **Discovery**. This will follow the WHO's example and will include 3,200 patients from at least eight countries (Belgium, France, Germany, Luxembourg, the Netherlands, Spain, Sweden, and the United Kingdom). The European part is supported by at least the COMBACTE, PREPARE and RECOVER trials. This trial will test the same drugs as SOLIDARITY, including hydroxychloroquine but not chloroquine[35].

Clinical Trials in the UK

The National Institute for Health Research (NIHR) has established a national prioritisation process for COVID-19 research that involves the healthcare system. This aims to prevent duplication of effort and ensure that resources and capacity are not exceeded. A list of prioritised studies are available on its website[36,37].

1. **ACCORD:**

The Department of Health and Social Care (DHSC) and UK Research and Innovation (UKRI), are funding the ACCORD (Accelerating COVID-19 Research & Development platform) programme, a Phase II clinical platform to rapidly test potential drugs through early stages of clinical trials and feed them into larger clinical trials such as RECOVERY[38].

Through the Therapeutic Taskforce, the life science sector can suggest potential drugs or molecules that could be tested through the ACCORD platform. Six potential drugs are currently being tested under ACCORD[39]. It aims to get an early indication of a drug treatments' effectiveness in treating COVID-19 and, if positive results are seen, advance these drugs rapidly into the large-scale trials across the country by reducing the time taken to set up clinical studies from months to weeks[40]. *More detail is available in the Appendix*

There are **3 key national Phase III trials** and the Chief Medical Officers for the United Kingdom issued a letter advising: "Any treatment given for coronavirus other than general supportive care, treatment for underlying conditions, and antibiotics for secondary bacterial complications, should currently be as part of a trial, where that is possible"[41].

Both RECOVERY and PRINCIPLE have received funding from the UKRI and Department of Health and Social Care's £24.6 million rapid research response fund.

More detail on the first round of projects funded is available here and the projects funded in the second round can be found here.

2. **RECOVERY:**

For hospitalised patients. This is the largest trial for COVID-19 treatments globally[30]. As well as normal hospital treatment, patients with COVID-19 infection will either receive no additional experimental treatment, or will receive one of the following treatments:

1. a combination of Lopinavir-Ritonavir
2. low-dose corticosteroids, dexamethasone
3. hydroxychloroquine
4. azithromycin[24, 42, 43]

The study allows a second randomisation to enable patients with progressive COVID-19 (evidence of hyper-inflammatory state) to receive:

5. No additional treatment
6. Tocilizumab [42, 43]

The trial was approved on 11 March and aims to have data available within 3 months[44]. *More detail is available in the Appendix*

3. **REMAP-CAP:**

For critically ill patients with severe community-acquired pneumonia. This is an adaptive, randomised clinical trial that has been underway for a few years but has always had the capacity to pivot to include patients during a pandemic. It was designed by clinicians after the 2009 H1N1 pandemic[45,46].

Currently the trial is evaluating:

1. different anti-viral drugs (Lopinavir-Ritonavir and hydroxychloroquine),
2. steroids to reduce inflammation
3. treatments which act on the immune system, often used to treat other conditions such as rheumatoid arthritis, (interferon-beta 1a, anakinra, tocilizumab and sarilumab).

The aim is to enrol thousands of patients in more than 100 ICUs in the UK[45, 46]. Results will be expected around July[46]. *More detail is available in the Appendix*

4. PRINCIPLE:

Aims to find treatments for COVID-19 in older people, aged over 65 or aged 50-64 and with underlying health condition. The aim is to help those with COVID-19 symptoms get recover quickly and reduce the likelihood of a need to go to hospital[47]. Patients will be tested for COVID-19 where possible, and will receive either the usual care provided plus hydroxychloroquine 200mg twice a day for 7 days, or azithromycin for 3-5 days, or usual supportive care without any experimental treatment[37]. *More detail is available in the Appendix*

3. Considerations for treatment evaluation and development

1. Ensure manufacturing capability

Some therapies are novel and hard to produce. The US Company Gilead, which produces remdesivir, has warned that its production relies on a complex chemical synthesis — with individual steps that can take weeks to perform. Likewise antibody therapy production would need to be vastly scaled up if it is to be widely rolled out.

These and other drugs may suffer from supply chain weaknesses, (for example of raw materials), as manufacturers try to scale up to keep pace with demand. A common model of pharmaceutical companies is to reduce stockpiles of drugs and raw material stocks - the so-called **'just in time'** supply strategy. This may work well in normal times but is risky in a crisis Countries which generally supply low cost raw materials, such as China and India, may clamp down on exports to ensure availability for their own citizens.

Regulators must also inspect the quality and safety standards of a manufacturing site to assure drug quality. Relatively few sites are currently approved by regulators and the availability of inspectors is limited[48].

2. Ensure fair and equitable prices and access to drugs and intellectual property

With demand outstripping supply decisions must be made about who has first access to a successful treatment. This was evidenced in the race to stockpile Tamiflu in the 2009 H1N1 pandemic and the recent intervention of the French government when Sanofi declared that the USA would get priority for vaccine supplies because of its greater investment in development[49].

Gilead, the US based remdesivir manufacturer, has donated its current stocks. About 40%, enough to treat 78,000 people, went to the United States. Gilead has also entered into agreements with five makers of generic drugs who may produce remdesivir for distribution in 127 countries that have limited access to healthcare, without paying royalties to Gilead. The agreement will remain until the global health emergency ends, or another treatment or vaccine is found for COVID-19[48].

The WHO has committed, alongside an initial group of global health actors and private sector partners and other stakeholders including European leaders, to a global and time-limited collaboration. The "Access to Covid-19 Tools (ACT) Accelerator", aims to accelerate the development, production, and equitable global access to new COVID-19 essential health technologies[50]. This scheme aims to raise £6.6bn[51].

On the 29 May the WHO and Costa Rica are aim to launch (and ask for support for) a platform to pool data, knowledge and intellectual property for existing or new COVID-19 health products. The hope is to deliver 'global public goods' for all people and all countries. This plan is to allow numerous companies to access the information they need to produce the

technologies, thereby scaling up availability worldwide, lowering costs and increasing access[52].

Medecins Sans Frontieres have also coordinated an open letter to the UK government asking that the UK guarantee that any COVID-19 medicines or technologies created with public funds are available to all, patent-free[53]. The development and evaluation of treatments and research into the SARS-CoV-2 virus and pathology and epidemiology of COVID-19 has been a global effort and hence such calls are pertinent[54]. Concerns have been raised that both the US or UK governments still appear to prefer a more conventional model whereby intellectual property for a vaccine is held by those that developed it, and then licensed to anyone wanting to manufacture it[54].

3. Ensure fair access for other diseases and clinical trials of COVID-19 and other diseases

With many proposed drugs being repurposed, it is vital to ensure that patients with the conditions they were originally designed for still have access to their medication. Many of the drugs included in the SOLIDARITY trial are widely used in poorer nations in Africa; chloroquine (malaria), lopinavir and ritonavir (HIV)[55]. These shortages of drugs have also meant that there is not always enough to evaluate in key clinical trials, such as the absence of remdesivir in the RECOVERY trial[56]. Likewise, with many clinical trial experts focusing on COVID-19 and worries about the risk of exposure in hospitals, clinical trials for other diseases have stalled[57].

4. Ensure drug evaluation represents population diversity

COVID-19 appears to disproportionately affect people of BAME backgrounds *(please see upcoming report on BAME and COVID-19).* Clinical trials must actively work to enrol a diverse patient sample to ensure drug responses and efficacy are representative of the entire population[58].

In addition, although COVID-19 does not seem to as severely affect children, drugs should also be put into trials in infants and children if they will later be used to treat these demographics. This is critical as studies in children are very different to those in adults and it is not possible to simply scale based on weight due to metabolic differences. Similarly, studies will be needed to establish the safety of drugs for use in pregnant women, where the risk to both the mother and fetus must be appropriately assessed.

5. Policies for scientific openness during a pandemic

There is currently no legal obligation for countries to share physical pathogen samples or associated genetic sequence data which is needed to conduct scientific research on a new virus.

China shared the pathogen samples and genetic sequence data with the WHO less than two weeks after the first cluster was reported. However, in 2006, Indonesia refused to share H5N1 influenza virus samples with the WHO, claiming sovereign authority over these samples.

Invoking “The United Nations Convention on Biological Diversity (1992)” (which recognizes Parties' sovereignty over genetic resources within their borders), Indonesia argued for fairer distribution of vaccines and antivirals during influenza pandemics[59]. Some scientists are arguing that now is the time to review the policies for pandemics to ensure that the same does not occur again[59].

6. Preparing for the next pandemic

Deforestation and the expansion into animal habitats brings more people into contact and conflict with animals, from which 70% of emerging human diseases originate. Combined with increased urbanisation and air travel means it is unlikely SARS-CoV-2 will be the last pandemic[60].

Before the COVID-19 pandemic, funding for research related to coronaviruses constituted just 0.5% of global spending on infectious-disease studies, despite the previous coronavirus epidemics, SARS and MERS[61].

At the end of the biggest Ebola outbreak in 2016, more than $100 million was put into initiatives to strengthen health and disease-surveillance systems in the three countries worst hit but many of these initiatives are ending and healthcare is showing signs of erosion[62]. There are only so many drugs which can be repurposed and repurposing may not always identify the best drugs for a specific disease.

At the end of this pandemic, steps will need to be taken to ensure there is adequate long term funding for research into infectious diseases, and to improve national and global health systems[63].

4. Key Questions

Fair access:

1. How will the government ensure that UK residents have access to medication if a successful drug is found, given the likelihood of strong global demand?
2. What steps will the government take to ensure that intellectual property concerns do not prevent widespread use in the developing world of any drug developed in the UK?
3. In the event of limited supplies, how will the government prioritise distribution and take steps to ensure that not only the wealthy are able to access treatment?
4. What lessons has the government learnt from the 2009 H1N1 crisis?
5. Given the UK's commitment to the 'Access to Covid-19 Tools' (ACT) Accelerator, to ensure the acceleration of equitable global access to safe, quality, effective, and affordable COVID-19 diagnostics, therapeutics and vaccines, will the UK support the WHO and medical charities call to pool data, knowledge and intellectual property?
6. How will the government ensure there remains access to drugs for patients with the disease they were originally designed to treat (such as HIV drugs both domestically and internationally)?

Development:

1. How will the government enable logistical and manufacturing solutions for the rapid production of a successful drug?
2. How is the UK Medicines and Healthcare Regulatory Agency (MHRA) working with the European Medicines Agency (EMA) or similar bodies to review regulating potential drugs, now that it is no longer a member of the EMA?
3. Should therapeutics be developed or manufactured in a country with different quality controls and standards to our own, given the urgent demand for these medications, will any divergence from UK regulatory standards be accepted?
4. How will the government continue to coordinate funding of therapeutics development and clinical trials with other bodies to whatever degree is required?
5. How will the government ensure that access to laboratory facilities is not disrupted in the event of further outbreaks of COVID-19?
7. With many clinical trials for other conditions already stalled due to COVID-19, how will the government ensure that clinical trials for other diseases do not face undue delays?
8. Given the preponderance of smaller, not necessarily well designed, clinical trials how is the government working with other bodies, such the WHO, to facilitate larger global robust clinical trials to obtain meaningful data?

Future preparedness:

1. How is the government committing to fund and develop the infrastructure, research and incentives for drug markets to ensure we are in a better position to face the next pandemic?
2. What levels does the government intend to stockpile successful antivirals to, in preparedness for secondary outbreaks of COVID-19?

5. Appendix

5.1 Promising Treatments

Remdesivir:

Remdesivir is an antiviral which targets a viral enzyme that the SARS-CoV-2 virus uses to replicate its genetic material whilst making more copies of itself. Studies using mouse coronavirus and SARS-CoV (the virus responsible for the 2002-3 SARS outbreak) have suggested that remdesivir may have a high genetic barrier (be less prone to) the development of resistance as well as reporting decreased fitness and pathogenicity in remdesivir-resistant mutants[64].

Remdesivir was initially developed to treat Ebola and is currently manufactured by the US Company, Gilead24. On 1 May, the US Food and Drug Administration (FDA) granted an 'emergency use authorization', for clinicians to use remdesivir, administered intravenously, in hospitals for people with severe COVID-191. Emergency use authorisation is not FDA approval but allows US physicians to use remdesivir in severely ill patients (adults and children with suspected or laboratory confirmed COVID-19 and severe disease defined as oxygen saturation of the blood less than 94% at room temperature; requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO))1.

This decision is based on the US National Institute of Allergy and Infectious Diseases (NIAID)'s clinical trial (ACTT) of ,1000 patients, which showed that those taking remdesivir recovered in 11 days on average, compared with 15 days for those on a placebo. This result was significant enough to stop the trial early to switch those on placebo onto the drug.

There was also a trend towards fewer deaths in trial participants receiving remdesivir but this was not statistically significant[9]. The Japanese Ministry of Health, Labour and Welfare has similarly granted emergency approval[65]. The European Medicines Agency has started a rolling review of remdesivir in order to speed up the assessment of this investigational drug for COVID-19 and has expanded its compassionate-use recommendations to include patients not on mechanical ventilation[3].

The Centre of Evidence Based Medicine (CEBM) at the University of Oxford, published a critical analysis of the FDA's decision on the 12 May. Key concerns raised included:

- The trial itself remains unpublished, so we have no information on the methods, other outcomes (like the need for ventilation or adverse effects), full results, or how the data were analysed. As of the 22 May this point has now been rectified and a peer reviewed preliminary analysis has been published[74].
- A reduction in mortality was not significantly significant which continuation of the trial might have answered.
- The trial's primary outcome was switched 13 days before the press release from an evaluation of remdesivir using a 7-point scale (including how many patients receiving remdesivir or placebo died, and how many required mechanical ventilation) to "time to

recovery". Outcome switching is not uncommon and happens in approximately a third of clinical trials. The reason given was "NIAID statisticians performed modelling of what happens if the right day is not picked for assessment, which revealed that meaningful treatment effects could be missed with that primary endpoint. Time to recovery avoids this issue". The CEBM raises concerns that "the new primary outcome was chosen because it was likely to yield a positive result, rather than because it is an important outcome for patients with COVID-19; and it contains no explanation of why this result was carried forward before any other trial information or results were released for critical peer review."

- The new endpoint, time to recovery, is far less useful than other outcomes, particularly death, but also the need for mechanical ventilation and adverse effects of the drug[66].

These points stand having received the peer reviewed report, in particular the reduction in mortality, which would have been a better measured outcome. Commentary by the principal investigators on the trial has highlighted that it is promising that sicker patients fare as well on remdesivir and that patients of white, black, and hispanic ethnicity; both males and females, and every age group, all derived equal benefit from the drug.

Likewise, that the results were the same whether they had received the drug before or after 10 days of symptoms (Figure 3 of the preliminary report)[74, 75]. On 8 May, NIAID began a clinical trial (ACTT 2) evaluating remdesivir in combination with the anti-inflammatory drug baricitinib compared with remdesivir alone[76]. Despite the emergency use authorisation, additional well-designed studies will be necessary to bolster the evidence for using remdesivir in patients with COVID-19.

There are 11 unique planned, current, or completed/suspended studies mentioning remdesivir as a treatment as of 12 May. However, CEBM warns that trials lacking a control, such as one of the two Gilead sponsored trials, are unlikely to add substantially to evidence for the efficacy of remdesivir in this context[67].

Chloroquine and Hydroxychloroquine:

Chloroquine and hydroxychloroquine are used for the prophylaxis and treatment of malaria, and the treatment of certain autoimmune conditions[3]. They have promising in vitro (test tube) activity but clinical trials so far have been inconclusive.

The President of the United States said publicly that he is taking hydroxychloroquine prophylactically and the FDA has granted emergency use approval on 28 March. Please see Section 2 for an analysis of the potential consequences of advocating a drug before robust clinical trial results are known. In the UK chloroquine is available without prescription[68].

5.2 Promising Trials

Global Trials

GLOBAL SOLIDARITY TRIAL: The United Nations Foundation, the Swiss Philanthropy Foundation, and the World Health Organization (WHO) have created the SOLIDARITY Response Fund in order to raise money to support studies on COVID-19[69]. As of 13 May this has raised $212,454,534 from over 373,000 donors[70]. To aid treatment evaluation the WHO is aiming to fast track clinical trials by up to 80% by launching a master clinical trial and protocol to coordinate international efforts and to include many thousands of patients in more than 100 countries[32]. Named SOLIDARITY and launched in late March, SOLIDARITY has been designed to establish consistent end points, control arms and inclusion–exclusion criteria and to be as simple as possible so that even hospitals overwhelmed by an onslaught of COVID-19 patients can participate[33].

If a COVID-19 patient is eligible to enrol, their data alongside informed consent is entered into the WHO website. This includes any of the underlying health conditions: diabetes, heart disease, chronic lung disease, chronic liver disease and asthma, extending to HIV and tuberculosis in the African region. The severity of illness at entry is determined by recording: shortness of breath, being given oxygen, already on a ventilator, and, if lungs are imaged, major bilateral abnormality. Their doctor states which drugs are available at their hospital and a computer randomises the patient to one of the four treatments or the local standard of care[32,33].

This umbrella trial, SOLIDARITY, is being conducted by the WHO to test four potential treatments:

6. Remdesivir
    a. Antiviral previously tested as an Ebola treatment. It has promising results in animal studies for similar coronaviruses: Middle East Respiratory Syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS).
7. Chloroquine or Hydroxychloroquine
    a. Used to treat malaria and rheumatology conditions respectively. In China and France, small studies provided some indications of possible benefit of chloroquine phosphate against pneumonia caused by COVID-19 but need confirmation through randomized trials.
8. Lopinavir with Ritonavir
    a. Licensed treatment for HIV. While there are indications from laboratory experiments that this combination may be effective against COVID-19, studies done so far in COVID-19 patients have been inconclusive.
9. Lopinavir with Ritonavir plus Interferon beta-1a.
    a. Inteferon beta-1a belongs to a class of molecules among the first to be produced by the body against viruses[32].

Critical anonymized information for the trial will only be collected at the randomization stage and when the patient is discharged or dies: which study drugs were given (and for how many days); whether ventilation or intensive care was received (and, if so, when it began), date of

discharge, or date and cause of death while still in hospital. Endpoints which are assessed are the day the patient left the hospital or died, the duration of the hospital stay, and whether the patient required oxygen or ventilation[32, 33].

Clinical Trials in the UK

ACCORD: The Department of Health and Social Care (DHSC) and the UK Research and Innovation (UKRI), are funding the ACCORD (Accelerating COVID-19 Research & Development platform) programme, a Phase II clinical platform[38]. ACCORD is a partnership between the Government Scientific Office, the NIHR's Biomedical Research Centres and Clinical Research Facilities, and expert centres in Northern Ireland, Scotland ,and Wales, clinical research company IQVIA and biopharmaceutical company AstraZeneca to rapidly test potential drugs through early stages of clinical trials and feed them into larger clinical trials such as RECOVERY.

Six potential drugs are being entered into ACCORD. So far only BerGenBio's investigational drug bemcentinib, which inhibits a protein on cells to prevent viral entry, is announced on the government website and is entering phase 2 trials as part of ACCORD. This is estimated to speed up development by months to years. Two others of the six are expected to be drugs being developed by Astrazeneca[39].

There are 3 key national trials and the Chief Medical Officers for the United Kingdom issued a letter advising: "Any treatment given for coronavirus other than general supportive care, treatment for underlying conditions, and antibiotics for secondary bacterial complications, should currently be as part of a trial, where that is possible"[41].

RECOVERY: For hospitalised patients. This is the largest trial for COVID-19 treatments globally[30]. As of 16 May there were 10,150 participants across 176 active sites[43]. The randomised clinical trial is set up to initially evaluate 5 treatments in hospitalised patients with COVID-19 but is an adaptive design so that new treatments can be added as they become available[30]. The trial includes drugs which they have a reason to believe might work, have a known safety profile, and have enough of a supply for a large trial[3]. It has been reported that remdesivir was not included due to difficulties to secure supplies[56].

As well as normal hospital treatment patients with COVID-19 infection will either receive no additional experimental treatment, or will receive one of the following treatments:
- a combination of Lopinavir-Ritonavir (antiviral drugs commonly used to treat HIV)
- low-dose corticosteroids, dexamethasone (used to reduce inflammation)
- hydroxychloroquine (similar to a drug used to treat malaria).
- azithromycin (a commonly used antibiotic which blocks a pathway the uses to enter cells[24,42,43])

The study allows a second randomisation for patients with progressive COVID-19 (evidence of hyper-inflammatory state):

- No additional treatment
- Tocilizumab (an anti-inflammatory treatment given by injection).[42, 43]

The main outcomes will be death, discharge, need for ventilation and need for

renal replacement therapy[42]. The trial was approved on the 11th March and aims to have data available within three months[44].

This trial is supported by a grant to the University of Oxford from UK Research and Innovation/National Institute for Health Research (NIHR), of £2.1 million from the £24.6 million rapid research response[37,71]. Core funding is also provided by NIHR Oxford Biomedical Research Centre, Wellcome, the Bill and Melinda Gates Foundation, the Department for International Development, Health Data Research UK, the Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding[43].

REMAP-CAP: For critically ill patients with severe community-acquired pneumonia. This is an adaptive, randomised clinical trial that has been going for a couple of years but has always had the capacity to pivot to include patients during a pandemic having been designed by clinicians after the 2009 H1N1 pandemic[45,46]. The type of trial design, response adaptive randomisation, allows more patients to be allocated to a treatment which is appearing to give effective results[46].

Currently the trial is evaluating

- different anti-viral drugs (Lopinavir-Ritonavir and hydroxychloroquine),
- steroids to reduce inflammation
- treatments which act on the immune system, often used to treat other conditions such as rheumatoid arthritis, (interferon-ß1a, anakinra, tocilizumab and sarilumab).

The trial will look at how these drugs work in combination. Additional treatments will be added over time. As of 16/05/2020, 463 patients with suspected or proven COVID-19 have been randomised, with the trial taking place across 182 sites and 14 countries. The aim is to enrol thousands of patients in more than 100 ICUs in the UK[45,46]. This is funded by the European Commission (FP7). Results will be expected around July[45].

PRINCIPLE: Aims to find treatments for COVID-19 for older people, >65 or aged 50-64 years with underlying health conditions, which can help those with COVID-19 symptoms get better quickly and stop them needing to go to hospital[47]. Patients will be tested for COVID-19 where possible, and will receive either the usual care provided plus hydroxychloroquine 200mg twice a day for 7 days, or azithromycin for 3-5 days, or usual supportive care without any experimental treatment[37].

The primary endpoint is hospital admission or death as a result of COVID-19 infection[47]. The trial aims to recruit over 3,000 people, and has been designed to be adaptive, so new suitable treatments can be added into the trial when these become available. The trial is funded by the UKRI/NIHR and has received £1.7 million from the £24.6 million rapid response fund[37]

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