
Article:
Chinnery, PF, Bonnet, M, Cave, A et al. (9 more authors) (2021) Choosing drugs for UK COVID-19 treatment trials. Nature Reviews Drug Discovery. ISSN 1474-1776

https://doi.org/10.1038/d41573-021-00203-7

Choosing drugs for UK COVID-19 treatment trials

*UK Covid Therapeutics Advisory Panel Due Diligence team**

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In early Spring 2020, an alarming number of people in the United Kingdom were found to be infected with SARS-CoV-2, leading to an escalation of hospital admissions. The new virus had a poorly understood pathophysiology leading to severe complications and a high mortality in at-risk groups; particularly the elderly, those with a high body mass index (BMI) and in some ethnic minority groups. At the time, no treatments were known to be effective at altering the disease course.

Given the urgent public health crisis, clinicians and researchers around the world responded briskly and initiated clinical research, facilitated by rapid funding calls. In the UK, the National Institute for Health Research (NIHR) and UK Research Innovation (UKRI) gathered resources to fund scientific studies and clinical trials aimed at having an impact on COVID-19 and its complications in order to shape NHS practice and government policy. Several charities also led funding calls with a COVID-19 focus, including the British Heart Foundation and LifeArc. There was a profusion of ideas with many creative solutions being proposed as potential therapies, with funding panels responding to the ideas presented by investigators across the country. This led to duplicated efforts and, in some instances, competition between trials: normally both enhance scientific excellence and provide validation, but neither are optimal in an emergency, when new treatments need to be discovered and shown to be effective as fast as possible.

Central Coordination

As spring 2020 progressed, a suite of national platform trials emerged in the UK to evaluate new treatments for COVID-19. These began by repurposing and activating Phase III studies in hospital (RECOVERY) and the community (PRINCIPLE), alongside several Phase II platforms (ACCORD 2, CATALYST, TACTIC, DEFINE and then RECOVERY+ (see web resources). The portfolio expanded with the later introduction of the first in-man/first in COVID-19 Phase I platform (AGILE), post-hospitalisation complications (HEAL-COVID) and prophylaxis in specific groups: PROTECT-C in care homes and PROTECT-V for vulnerable patients who are immuno-compromised, followed by Long-COVID in 2021. Central co-ordination of COVID-19 studies supported by the NIHR Clinical Research Network (CRN) was provided by the NIHR Urgent Public Health prioritisation process, which included observational studies and clinical trials. A central tenet of the national platform trials was the coordinated identification of candidate drugs to be tested in the different studies, endorsed nationally and by the trial Chief Investigators who were ultimately responsible for their delivery on behalf of the study sponsors (usually a university or NHS Trust). Here we explain how this was achieved across the therapeutic landscape.

Open and transparent process

Professor Chris Whitty, Chief Scientific Advisor (CSA) to the Department of Health and Social Care (DHSC), invited the Clinical Director of the Medical Research Council, to assemble the UK COVID-19 Therapeutics Advisory Panel (UK-CTAP) in June 2020 (**Figure 1**). UK-CTAP included seven clinical scientists with relevant experience who were not directly involved in the COVID-19 RECOVERY or PRINCIPLE trials, ensuring that recommendations were independent and impartial.

UK-CTAP established an open web portal to allow any individual worldwide – be they a health-care professional, scientist, from the pharmaceutical industry, or the general public – to nominate treatments that they thought should be tested in COVID-19. A minimal amount of data was required as part of the submission process, but it needed to be sufficient to allow further evaluation. The scope was limited to pharmacological interventions, as opposed to non-pharmacological interventions such as ventilation.

Due diligence established the knowledge base for a given candidate, UK-CTAP specialist subgroups then contextualized that knowledge with expert opinion, and finally UK-CTAP considered the knowledge base and expert opinion to deliver a balanced portfolio that did not err to one particular class of drug or mechanism of action. These three layers mitigated against unconscious biases, including familiarity and specialist scientific expertise.

Due Diligence

UK-CTAP assembled a team of scientists with relevant expertise to carry out due diligence on all of the proposed treatments. The team included pharmacology, immunology and infection expertise, regulatory expertise, pharmacokinetic and pharmacodynamic modelling, and clinical expertise. UK-CTAP was hosted by UKRI with a transparent governance structure accountable to the DHSC CSA, and through the National Core Studies group established by the Government Chief Scientific Advisor, Sir Patrick Vallance. The diligence team was assembled through rapid secondments from Universities, the NHS, regulatory authorities and the private sector, all within a matter of weeks.

The team gathered data from diverse data sources including published scientific literature, pre-prints on bioRxiv and medRxiv webservers, and international databases. They established close links with international agencies including the US National Institutes for Health, Wellcome, the European Clinical Research Infrastructure Network, and the World Health Organisation, and directly contacted study teams in academia and industry when required. The proposed candidate treatments were triaged based on the likely mechanism of action, and in-depth briefing documents were prepared to inform decision making.

Key data informing decision making

From September 2020 to July 2021, UK-CTAP received 336 nominations and made 30 recommendations into trial, published on the web (see Web Resources). The recommendations were based on the following principles:

Scientific rationale

Candidate drugs needed to have a well-defined mode of action relevant to the pathophysiology of COVID-19 based on *in vitro*, pre-clinical and clinical data. Ideally, evidence was available from non-clinical models or from patients affected by COVID-19, but other relevant non-clinical and clinical data were also incorporated. Mechanisms of action of particular interest included antiviral, anti-inflammatory, immunomodulatory, anti-thrombotic, and antifibrotic activity. During the first year, our understanding of the pathophysiology of COVID-19 evolved substantially. This information was assimilated into the rationale for each candidate drug as it became available. A critical issue that was re-visited repeatedly during deliberations was whether drugs acting on a particular mechanism were relevant at a particular stage of the disease. For example, antiviral activity would be most likely to be beneficial earlier in the

disease course, but might benefit some patients with severe disease if there were a persistent viral burden. On the other hand, specific immunomodulatory drugs could have been detrimental during the early stages, but beneficial at a later stage when patients were closely monitored in hospital and suffering from a pro-inflammatory 'cytokine storm'.

Both re-purposed drugs and new drugs were considered for recommendation into clinical trials. Immuno-modulatory drugs with well-described mechanisms of action were repurposed from a different indication where the same anti-inflammatory activity was likely to be relevant for the COVID-19 hyperimmune pathology; whereas known antiviral drugs were repurposed based on pre-clinical evidence of anti-COVID19 activity. For example, several high-throughput *in vitro* and *in silico* screens identified putative inhibitors of SARS-CoV-2 proteins in libraries of Food and Drug Administration (FDA) approved compounds that were subsequently tested for inhibition of viral growth *in vitro*[1].

Pharmacokinetics and pharmacodynamics

Published and commercially privileged data were combined with in-house pharmacokinetic and pharmacodynamics modelling to predict whether a treatment was plausible and at what dose. A critical issue was whether therapeutically relevant drug concentrations would be achieved in the lung, and over what time period.

When considering possible antiviral drugs, the average number of cells infected by a single infected cell at the beginning of the infection is ~10 (R_0, the basic reproduction number), and the lung tissue concentration needs to exceed the level needed to achieve at least 90% reduction of viral load (Inhibitory Concentration, IC_{90})[2]. This criterion was consistently applied to evaluate antiviral treatments. If the lung concentration was unknown, and the treatment target was on the cell surface (e.g. umifenovir inhibits both entry and post-entry stages of the viral cycle [3]), then plasma concentrations were used as a surrogate. For treatments intended to modulate intracellular targets (e.g. favipiravir), the intracellular concentration was modelled to support the selection of a dosing regimen. For example, the antimalarial drug atovaquone was shown to bind in the SARS-CoV2 Mpro substrate-binding pocket and inhibit viral growth at micromolar concentrations[4]. However, in-house PK modelling predicted that plasma levels would be insufficient when using standard oral doses due to its high plasma protein binding.

For anti-inflammatory treatments, the main challenge was to select a safe and efficacious dosing regimen for the trials, as the same agents may have been trialled elsewhere with different dosing regimens. Modelling of intracellular PK of colchicine in blood monocytes in non-COVID-19 clinical trials recapitulated the highly nonlinear dose-PK relationship[5], which was used to support the dosing regimen chosen for the RECOVERY trial. Likewise, modelling of the glucocorticoid receptor occupancy by dexamethasone in pemphigus showed a linear

relationship with interleukin 6 (IL-6) release in blood monocytes[6], informing the UK-CTAP recommendation of a higher daily dosage (20mg) of dexamethasone than the previously adopted (6mg) for RECOVERY International trial.

Safety and possible drug interactions

Each candidate was evaluated for its safety profile in healthy volunteers, other relevant disease such as Adult Respiratory Distress Syndrome (ARDS), and COVID-19 where data was available. The panel systematically evaluated compounds for potential drug interactions, either because they were known, or were likely based on the evolving standard of care. Potential safety risks of candidates were juxtaposed with potential clinical benefits to guide decision making. Higher safety standards were required for candidates that were to be tested in community trial platforms, and particularly for prophylaxis studies where the risks of severe COVID-19 were low.

As an example, antifibrotics were considered in a post-hospital discharge setting for patients who had developed lung fibrosis. However, the side effect profile of licenced anti-fibrotic drugs was considered to be too high for use in COVID-19 patients, given reports of the spontaneous resolution of the radiological features of lung fibrosis. Likewise, the antiviral favipiravir was considered for prophylaxis and the treatment of early COVID-19, however, the potential teratogenic effects influenced a decision not to prioritise the drug for the prophylaxis setting because in this context, the *a priori* risk of severe COVID-19 was low.

Availability and supply

Availability and supply were critical considerations, with our sights on potential prescribing across the National Health Service (NHS) if a trial was shown to succeed. This work was done in partnership with the DHSC Therapeutic Task Force and NHS procurement teams. For example, the inhibition of the C5 complement cascade was recognised as a potential therapeutic target for COVID-19, however there was no scientific rationale to prioritise one complement C5 inhibitor from the class of C5 complement modulators. UK-CTAP therefore recommended the class of C5 inhibitors, with the final prioritisation on the basis of availability and supply for UK trials, including cost.

Human studies in COVID-19 patients

The due diligence team continuously surveyed all information sources for evidence of efficacy in COVID-19, including the monitoring of live clinical trials running in parallel across the world listed on Clinicaltrials.gov, and other regulatory intelligence sources, most notably the RAPID C19 oversight group hosted by the National Institute for Heath and Care Excellence (NICE) where there was open bi-directional information exchange. Based on these findings, drugs would be prioritised or de-prioritised over time. Comprehensive and up-to-date oversight of the global trials landscape was essential, primarily to avoid duplicated effort. However, one of the most challenging issues was whether or not to begin a trial in the UK because we were uncertain when ongoing trial would deliver elsewhere in the world.

Panel decisions

The due diligence briefing documents were presented to advisory sub-groups convened with specific expertise to evaluate groups of related drugs. A UK-CTAP member chaired each sub-group and reported back the discussions to UK-CTAP, often within 48 hours of the sub-group meeting, presenting the original drug briefings and a summary of the expert discussions. Following in-depth discussions, UK-CTAP made recommendations about whether to prioritise specific drugs to the DHSC CSA and the study Chief Investigators who had overall responsibility for the trial sponsored by their host organisation. The ranking was based on several factors such as the practicalities of giving the treatment (e.g. intravenous drugs considered potentially useful in the community but impractical at scale), because of an adverse side-effect profile in a standard clinical care setting (e.g. a high likelihood of exacerbating renal dysfunction in patients already severely ill with COVID-19 who were known to have a high incidence of renal failure), because of drug supply issues (e.g. because even if effective, the treatment could not be manufactured at sufficient scale for national roll-out), or because the mechanism of action was highly unlikely to be relevant and was potential dangerous. Occasionally a class of drugs was recommended when it was not possible to separate individual candidates, and the final decision would be influenced by availability and cost. In this way, the group assembled an active list of highly prioritised agents, the ranking of which was reordered over time based on new knowledge summarised under the workflow.

Conclusions

The UK-CTAP model provides an independent rigorous means of prioritising the best possible candidates into clinical trials based on available data in a rapidly evolving landscape. The open web-portal ensured any individual or organisation could propose a new treatment for a

trial through the nationally funded platforms. Prioritisation decisions were made through an open, transparent process based solely on the available scientific data and the logistics of giving the treatment in the NHS. The recommendations are published on-line (see web resources). Importantly, UK-CTAP very rarely rejected candidate drugs. The overall ethos was to prioritise the most promising drugs for specific indications based on the best information available at the time. Non-commercially sensitive data was openly shared with partner organisations in the United States, Europe (ECRIN), and the World Health Organisation to promote a cohesive global approach. This became important, particularly as case numbers decreased in the UK, and our recommendations were taken forward in international trials (RECOVERY International), requiring an additional refinement in our recommendation process to reflect local availability of drugs and cost.

Since August 2020, UK-CTAP has met 16 times informed by 47 expert subgroup meetings (**Figure 2**). These were often scheduled at very short notice and outside standard office hours in response to new data or the need for a new trial drug candidate. The work has only been possible because of the commitment of the panel and sub-group membership, often meeting at unsociable hours because of their many additional responsibilities, including frontline NHS clinical duties. The model of decision-making shows what can be done during a pandemic, made possible through remote video link (none of the groups have ever actually met in person). A similar independent and evidence-based approach could be used to evaluate and prioritise therapeutic candidates for nationally co-ordinated treatment trials in other disease areas.

Acknowledgements

UK-CTAP is funded by UKRI and NIHR. PFC is a Wellcome Trust Principal Research Fellow (212219/Z/18/Z), and a UK NIHR Senior Investigator, who receives support from the Medical Research Council Mitochondrial Biology Unit (MC_UU_00015/9), the Medical Research Council (MRC) International Centre for Genomic Medicine in Neuromuscular Disease (MR/S005021/1), the Leverhulme Trust (RPG-2018-408), an MRC research grant (MR/S035699/1), an Alzheimer's Society Project Grant (AS-PG-18b-022). This research was supported by the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Web resources

DHSC website explaining the national trial platforms and the process for nominating treatments, including the UK-CTAP nomination form:

https://www.gov.uk/government/publications/covid-19-treatments-making-a-proposal-for-clinical-trials/guidance-making-a-proposal-for-covid-19-therapeutics-clinical-trials

UK-CTAP recommendations:

https://www.ukri.org/about-us/policies-standards-and-data/data-collection/uk-covid-19-therapeutics-advisory-panel/recommended-treatments-for-clinical-trials/

RECOVERY: https://www.recoverytrial.net/

AGILE: https://www.agiletrial.net/

REMAP-CAP: https://www.remapcap.org/coronavirus

PRINCIPLE: https://www.principletrial.org/

PROTECT-V: https://www.camcovidtrials.net/trials/view,protect_50.htm

HEAL-COVID:https://heal-covid.net/

ACCORD 2: https://www.accord-trial.org/

CATALYST: https://www.birmingham.ac.uk/research/crctu/trials/catalyst/index.aspx

TACTIC: https://cctu.org.uk/portfolio/COVID-19/TACTIC

DEFINE: https://www.ed.ac.uk/inflammation-research/clinical-trials/define-covid19

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Figure 1. Drug prioritisation into the UK clinical trials platforms and the UK Covid 19 therapeutics advisory panel (UK-CTAP)

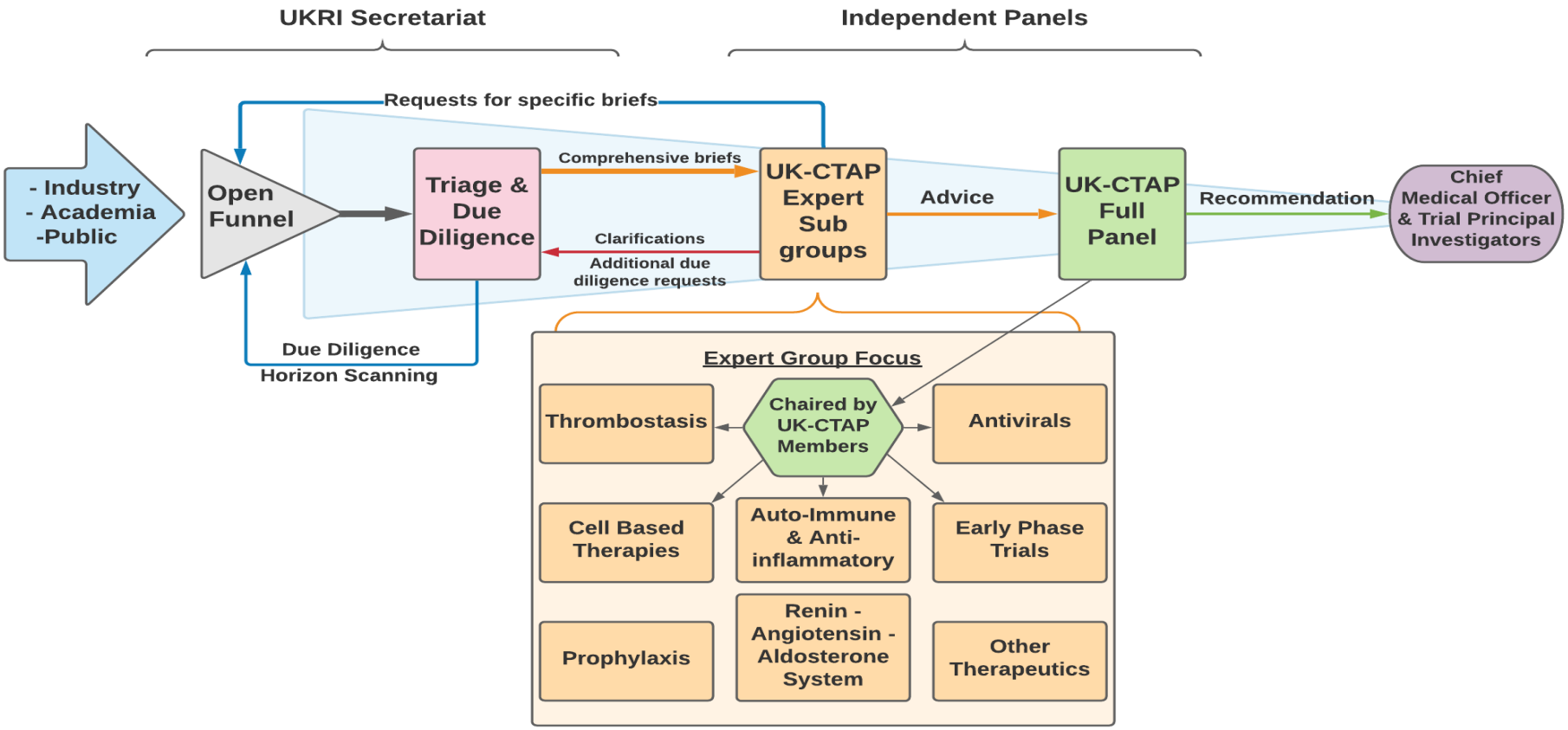

Figure 2. Summary of the work of the UK Covid 19 therapeutics advisory panel (UK-CTAP)