World Health Organization

WHO ad hoc consultation
COVID-19 therapeutics: Knowledge gaps and research priorities

Virtual Meeting
3 March 2021

Meeting report

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R&DBlueprint
Powering research to prevent epidemics

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Acronyms List

ACT Accelerator	Access to COVID Tools (ACT) Accelerator
AVAREF	African Vaccine Regulatory Forum
ACTT	Adaptive Covid-19 Treatment Trial
ACTIV	Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)
COVID-19	Coronavirus disease 2019
GloPID-R	Global Research Collaboration for Infectious Disease Preparedness
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IL-6 inhibitors	Interleukin-6 Inhibitors
LMICs	Low- and middle-income countries
ReFRAME	Repurposing, Focused Rescue, and Accelerated Medchem
REMAP-CAP	Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
UK-CTAP	United Kingdom COVID-19 Therapeutics Advisory Panel

Preface

Over the past year, management of COVID-19 has greatly improved and mortality has been markedly reduced. Platforms have been rapidly established to evaluate potential therapeutics, initially focusing on repurposing of existing medicines. Some effective treatments have been identified and widely introduced.

Despite these successes and the recent rollout of COVID-19 vaccines, new and improved therapeutics are still required. The WHO ad hoc consultation on 3 March 2021, held under the umbrella of the WHO R&D Blueprint, sought to take stock of the current status of therapeutic development and to explore potential future directions of travel. Its specific objectives were:

- To identify knowledge gaps and research priorities for COVID therapeutics.
- To discuss when patients might benefit most from different treatments, using current understanding of COVID.
- To discuss how best to identify promising treatments, and how best to evaluate them.
- To propose actions to enhance international collaboration and coordination in support of identified research priorities.

The meeting was introduced by Dr Soumya Swaminathan (Chief Scientist, WHO) and Dr Michael J Ryan (Head of the Health Emergencies Programme, WHO), with an introductory presentation by WHO Director General Dr Tedros. It was chaired by Dr Sir Michael Jacobs (Royal Free London NHS Foundation Trust UK), with Professor Sir Nick White (University of Oxford, UK/Mahidol University, Thailand), Dr K Srinath Reddy (Public Health Foundation of India) and Dr Mirta Roses (WHO COVID-19 Special Envoy, Argentina) acting as session chairs. After each session, a group of panel members were invited to provide comments. An agenda including the names of panel members is provided in Annex 1.

This report is a summary of presentations and panel discussions. It does not necessarily reflect the views of the organizers, participants or panel members.

Executive Summary

The rapid spread of COVID-19 in 2020 led to a huge demand for treatments. Many repurposed therapeutics were initially used, generally on the basis of unreliable data

The rationale for interventions was based on a model of viral infection in which transient viral replication in the lung triggers an immune response that can clear infection but may also run out of control, causing the most severe symptoms. Interventions are thus generally aimed at viral replication early in infection and host immune responses late in infection. It was also discovered that inflammation increases the risk of thrombus formation, leading to increasing use of antithrombotics.

The pandemic led to the rapid creation of research networks and platforms able to undertake high-quality, large-scale evaluations of potential therapeutics. Initially focusing on repurposed medicines, platforms such as the global SOLIDARITY trial, the UK RECOVERY platform, the European REMAP-CAP network, and US ACTT and ACTIV networks have generated vital data on the safety and efficacy of COVID-19 therapeutics.

These platforms have provided strong evidence of the clinical benefits of steroids such as dexamethasone in severely ill patients, and of immunomodulators targeting interleukin 6 (IL-6), such as tocilizumab.. Although several promising therapeutics have proven to be ineffective, by demonstrating their lack of impact, the trials are ensuring that healthcare resources are used on treatments of proven efficacy.

The platforms are now evaluating a wide range of therapeutics, including antiviral medications, immunomodulators and antithrombotics. The scale of these platforms ensures that specific patient populations can be studied – a key goal of COVID-19 therapeutics research is to identify which therapy works for which patient at which stage of disease.

It is likely that individual COVID-19 therapeutics will have moderate effects. Future treatment will therefore probably involve the use of multiple agents. This could include drug combinations targeting specific aspects of infection (such as viral replication, as in combination therapy for HIV), as well as suites of treatments targeting different disease processes (such as antivirals, immunomodulators and anti-coagulants).

Over time, clinical studies will begin to focus more on newly developed therapeutics. Development of a pipeline of COVID-19 therapeutics will go hand in hand with research on the mechanisms of viral infection and host responses, which will help to identify target molecules and pathways. In addition, such research may identify biomarkers associated with disease progression or response to therapy, which will also aid patient management.

Each trial platform has established mechanisms to prioritize agents to be evaluated. These share common features, including open submission processes, assessment and triaging by expert groups, and final prioritization by overarching committees and triallists.

National, regional and global collaboration and coordination have been essential to create the platforms able to carry out large-scale randomized studies. Some trials also incorporate factorial designs, to maximize the numbers of interventions being evaluated. There may be opportunities to extend coordination between platforms to minimize duplication of efforts and to focus attention on agreed priorities. Further standardization of methods and endpoints would facilitate synthesis of data from multiple sources.

Opportunities also exist to strengthen coordination of pre-clinical and early clinical research, for example through prioritization of targets, greater sharing of data and standardization of research methodologies. Coordinated clinical development could help to build the COVID-19 therapeutic pipeline and support decision-making on entry into phase III trials.

There are also calls for greater sharing of information and trial data, including individual patient data. Potentially a global data platform could be established, with appropriate data governance and access mechanisms, to facilitate analysis of individual patient data from COVID-19 trials.

Despite the great success of COVID-19 vaccine development, therapeutics are still urgently required. Greater investment is needed in therapeutic development globally, alongside mechanisms to ensure that populations in low-resource settings have access to effective treatments. Funders have a key role to play in promoting coordination, for example through updating of the COVID research roadmap, and in building clinical trial capacity.

Key messages

- Large-scale randomized trials have generated robust evidence on the efficacy and safety of candidate COVID-19 therapeutics, including steroids such as dexamethasone, IL-6 inhibitors such as tocilizumab

- It is likely that therapeutics will work best in particular types of patient and at particular stages of disease, and that treatment will be based on combinations of antivirals, immunomodulatory drugs, and anti-coagulants.

- National and international platforms are providing an infrastructure to evaluate multiple treatments simultaneously.

- Greater international coordination across trial platforms could ensure the most efficient evaluation of candidate therapeutics.

- Greater coordination in early-stage drug discovery and development could help to accelerate development of a COVID-19 therapeutics pipeline and prioritization of therapeutics for phase III trials.

- A global platform could be established to support sharing of clinical data, including individual patient data

Introduction

In February 2020, a WHO-convened meeting developed a roadmap to guide the research response to COVID-19(ref). The roadmap identified key knowledge gaps and research priorities, taken forward by nine thematic working groups and multiple sub-working groups. It has provided guidance for a collaborative and coordinated research response to COVID-19, including the rapid assessment of multiple potential therapeutics for COVID-19. Over the past year, mortality rates for COVID-19 have fallen markedly, due to improvement in care and use of evidence-based therapeutics.

Nevertheless, many interventions have shown disappointing efficacy against COVID-19, and few effective therapeutics are available. Even as vaccines are more widely rolled out, additional treatments are required at different stages of disease – to prevent disease progression as well as to save lives in those severely affected. In addition, actions are needed to ensure that therapeutics reach all those in need, building on the work of the Access to COVID Tools (ACT) Accelerator[1].

The WHO ad hoc consultation in March 2021 was designed to take stock of progress over the past year, to identify lessons learned, and to discuss potential future directions of travel.

[1] The Access to COVID-19 Tools (ACT) Accelerator (who.int)

The magic of randomisation

Early in the COVID-19 pandemic, many possible treatments were suggested and often widely used in the absence of reliable data on their safety and efficacy. Randomized controlled trials are the gold standard approach for assessing efficacy, but are often long, complex, expensive and focused on single agents.

Platform trials were established to rapidly collect safety and efficacy data on multiple potential therapeutics to inform public health practice. Embedded in routine practice, they incorporate randomization, to address the risk of bias, and large sample sizes to minimize the risk of random effects – of particular importance as it was anticipated that effect sizes would be small. To achieve speed, platform trials such as UK RECOVERY or WHO SOLIDARITY, were kept simple and practical, with broad eligibility criteria, a focus on important outcomes such as mortality, and simple randomization and data collection processes, which enabled every acute hospital in several countries around the world to participate.

For hydroxychloroquine, lopinavir, subcutaneous interferon beta 1-a, remdesivir, azithromycin and convalescent plasma, little or no evidence of any beneficial effect on mortality was identified. For dexamethasone, the RECOVERY trial found good evidence for mortality benefits in those receiving supplemental oxygen and on mechanical ventilation, but not in those with less severe disease . This compelling evidence led to changes in practice the same day that the results were unveiled. A WHO meta-analysis has confirmed the beneficial effects of steroids .

Furthermore, although multiple small studies had suggested that tocilizumab also had beneficial effects, the RECOVERY trial was able to provide large-scale data – the trial was four times larger than all other trials combined – confirming a 14% relative risk reduction for mortality as well as benefits in reducing progression to mechanical ventilation . These effects were additional to those provided by dexamethasone treatment – together, mortality was nearly halved among patients needing mechanical ventilation.

A further advantage of platform trials is that they can be readily adapted and can incorporate factorial designs (simultaneous assessment of multiple treatments) – of particular importance when understanding of COVID-19 infections is growing so rapidly. These platform trials are now evaluating a range of antiviral, immunomodulatory and anti-thrombotic treatments (see below).

Natural history of COVID-19 infections

Therapeutic development needs to consider the stage of infection when an intervention is likely to be effective. In the 'standard model' of viral infection, initial infection is followed by a pre-symptomatic phase of viral replication, accompanied by the launch of innate and then adaptive immune responses, the development of mild to moderate symptoms, and potentially then progression to severe disease or death.

This model implies that viral replication is most significant early in disease, with severe symptoms reflecting the impact of over-zealous immune responses. However, some uncertainty surrounds the dynamics of viral replication. Most studies measure viral shedding detected by polymerase chain reaction (PCR) technology, which may or may not reflect viable virus (detected by culturing), which is generally taken as a surrogate marker of infectivity or viral replication.

Viral shedding is apparent later in infection than detection of viable virus by culturing[2], and viral shedding is still seen after culture-positive cases are no longer detected[3]. Persistent viral shedding is also seen for several months in immunocompromised patients[4]. In addition, there is also evidence that high viral loads and longer periods of viral shedding are associated with more severe disease[5] and higher ICU mortality[6]. This may indicate the presence of replicating virus at later stages than is generally assumed, which would have implications for the timing of antiviral treatment.

After an early pre-symptomatic phase, the virus migrates deeper into the lower respiratory tract, infecting alveolar cells. While an immune response is important for clearing virus, it can also drive pathological reactions. Inflammation may also interfere with the blood coagulation system increasing the risk of microthrombi and cardiovascular complications.

[2] Wölfel R, Corman VM, Guggemos W et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-469. doi: 10.1038/s41586-020-2196-x.

[3] Kim MC, Cui C, Shin KR et al. Duration of Culturable SARS-CoV-2 in Hospitalized Patients with Covid-19. N Engl J Med. 2021 18;384(7):671-673. doi: 10.1056/NEJMc2027040.

[4] Aydillo T, Gonzalez-Reiche AS, Aslam S et al. Shedding of Viable SARS-CoV-2 after Immunosuppressive Therapy for Cancer. N Engl J Med. 2020;383(26):2586-2588. doi: 10.1056/NEJMc2031670.

[5] Cevik M, Tate M, Lloyd O et al. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe. 2021;2(1):e13-e22. doi: 10.1016/S2666-5247(20)30172-5.

[6] Bitker L, Dhelft F, Chauvelot L et al. Protracted viral shedding and viral load are associated with ICU mortality in Covid-19 patients with acute respiratory failure. Ann Intensive Care. 2020;10(1):167. doi: 10.1186/s13613-020-00783-4.

Despite the growing understanding of COVID-19 disease mechanisms, many questions remain unanswered about both viral replication and host responses.

Appropriate guidelines for clinical studies

Notwithstanding the need for speed, it is essential that COVID-19 clinical studies are carried out in accordance with the principles of Good Clinical Practice (GCP). This has two key aims: to protect study participants and to ensure the reliability of trial data.

The most commonly adopted guidelines are the International Conference on Harmonization (ICH) E6 guidelines. However, there are concerns that the guidelines are being overzealously applied, leading to expensive and complex trials, and may be too inflexible to accommodate recent innovations in clinical trial design, having been established for trials designed to facilitate regulatory submission. Updated guidelines (the R2 addendum) were developed in 2016 and an R3 revision is underway.

Leaner and more flexible guidelines now need to be developed, with input from a wider range of stakeholders, that are more appropriate for the full range of clinical studies. They need to address the growing size of consent forms, which often reflect 'defensive' approaches to minimize the risk of litigation rather than a true desire to inform participants. They should also recognize that data do not need to be perfect, and fit-for-purpose data can be obtained if core principles are followed, such as randomization, comprehensive follow up, full ascertainment of outcomes and no premature unblinding.

The Good Clinical Trials Collaborative[7], funded by Wellcome, the Bill & Melinda Gates Foundation, and the African Academy of Science, is consulting globally in order to develop widely applicable and proportionate guidelines that provide opportunities for innovation in trial design and practice and discourage defensive practices. They are intended to promote good science and ethical practices, to be clear and concise, inclusively developed, and progressive and durable. Surveys have sought to gather input on innovative practice in COVID-19 trials and the barriers that investigators have faced. Implementation is planned for July–September 2021.

[7] https://wellcome.org/what-we-do/our-work/good-clinical-trials-collaborative

Treatments

Antivirals

The standard model of viral infection, with viral replication critical over the first few days of infection and pathology linked to aberrant immune responses at later stages, may be an oversimplification in COVID-19. High viral loads are sometimes seen late in infection and aberrant immune responses early. Viral shedding can be detected at up to 17 days (although it is not clear if this represents viable virus)[5].

Moreover, conflicting evidence has been published on the relationship between viral load and severity of symptoms. Despite analysis of specimens from multiple sites, no useful prognostic information can be obtained from viral load measurements. Even less information is available on viable virus, particularly in the sickest patients.

In terms of antiviral treatments, unpromising overall findings from the regimens tested in large trials suffice to refute early hopes, based on smaller or nonrandomized studies, that any of these regimens will substantially reduce inpatient mortality, the initiation of mechanical ventilation, or hospitalization duration.The potential for antivirals remains unrealized, considering both disease and drug factors, and accelerated pathways are needed for the clinical development of new drugs and combinations.

Immunomodulators

Early immune control of SARS-CoV-2 is dependent on the innate immune system, particularly the interferon response. Genetic association studies identified variants in an interferon receptor as a risk factor for severe disease8, while the presence of autoantibodies against IFN- α have been found to predispose to severe disease9. Inhaled IFN-β has been suggested as a possible treatment[10].

Other potentially critical elements of the innate response include neutrophils and monocytes. Large numbers of both types of cell, and abnormal cell types, are commonly seen in severe disease[11]. Increased

[8] Pairo-Castineira E, Clohisey S, Klaric L et al. Genetic mechanisms of critical illness in COVID-19. Nature. 2021;591(7848):92-98. doi: 10.1038/s41586-020-03065-y.

[9] Bastard P, Michailidis E, Hoffmann HH et al. Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. J Exp Med. 2021;218(4):e20202486. doi: 10.1084/jem.20202486.

[10] Monk PD, Marsden RJ, Tear VJ et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med. 2021;9(2):196-206. doi: 10.1016/S2213-2600(20)30511-7.

[11] Mann ER, Menon M, Knight SB et al. Longitudinal immune profiling reveals key myeloid signatures associated with COVID-19. Sci Immunol. 2020;5(51):eabd6197. doi: 10.1126/sciimmunol.abd6197.

levels of inflammatory markers such as CXCL-10/IP10 are also seen, and may be associated with an elevated risk of coagulatory symptoms.

Prospective studies have identified immune profiles characteristic of different disease trajectories[12]. Mild disease is associated with early and robust innate and adaptive immune responses, with no systemic inflammation. By contrast, hospitalization is associated with a delayed immune response and high levels of inflammation. The presence of immunopathology at admission suggests that early immunomodulatory treatment may be required.

As the inflammatory response during COVID-19 becomes better understood, potential new targets and therapeutics are emerging. Possible approaches include targeting of the complement system, pivotal inflammatory pathways, or neutrophil and monocyte activation. Immune profiling could also support patient stratification and guide choice of immunomodulatory therapeutic.

Antithrombotic therapy

COVID-19 is associated with an increased risk of multiple thrombotic conditions, including deep vein thrombosis, pulmonary embolism and myocardial infarction. This is believed to reflect increased systemic inflammation, leading to platelet activation and coagulopathies. D-dimer, a fibrin breakdown product, can be used as a biomarker of coagulopathy and shows a strong correlation with COVID-19 disease severity.

While these findings highlight the potential benefits of antithrombotic therapeutics, questions such as choice of drug, dosing and timing of treatment remain unanswered. A further key issue is whether antithrombotic treatments should be used prophylactically or therapeutically, and whether biomarkers such as D-dimer can be used to guide dosage[13].

Observational studies have suggested a survival benefit associated with antithrombotic use, especially in patients on mechanical ventilation14. However, randomized trials are needed to provide more

[12] Bergamaschi L, Mescia F, Turner L et al. Early immune pathology and persistent dysregulation characterise severe COVID-19. MedRxiv. 2021. doi: https://doi.org/10.1101/2021.01.11.20248765

[13] Tassiopoulos AK, Mofakham S, Rubano JA et al. D-Dimer-Driven Anticoagulation Reduces Mortality in Intubated COVID-19 Patients: A Cohort Study With a Propensity-Matched Analysis. Front Med (Lausanne). 2021;8:631335. doi: 10.3389/fmed.2021.631335.

[14] Paranjpe I, Fuster V, Lala A et al. Association of Treatment Dose Anticoagulation With In-Hospital Survival Among Hospitalized Patients With COVID-19. J Am Coll Cardiol. 2020;76(1):122-124. doi: 10.1016/j.jacc.2020.05.001.

robust evidence. Three large-scale platform trials – ATTAC, ACTIV and REMAP-CAP – are collaborating to harmonize approaches and address a range of key questions. Interim data analyses suggest that therapeutic use is superior to prophylactic use, although few if any benefits are seen in intensive care unit settings. Further studies are needed on choice of drug and use at different stages of disease, including before hospitalization and after release.

Discussion

Panelists emphasized that COVID-19 treatment will likely be multimodal, including antivirals, immunomodulators and anticoagulants as appropriate. Use of such combinations will need to be stratified by stage of disease, with antivirals predominantly used in early disease and immunomodulatory drugs later. It was also noted that other aspects of patient care, such as oxygen delivery and ventilation, should not be neglected.

As more potentially effective therapeutics are identified, many detailed questions about dosing, timing and appropriate combination treatments will need to be answered. It is likely that therapeutic use will need to be targeted to specific stages of disease, highlighting the need for biomarkers to guide use of different treatment strategies. There may be different 'critical windows' when particular treatments are most effective.

Opportunities may also exist to explore possible synergistic effects between therapeutics. Efficacy against emerging variants also needs to be assessed. In the longer term, drug development could also focus on broad-spectrum agents active on a wider range of coronaviruses.

The need to ensure that treatments are practical for use in low-resource settings was also stressed. In such settings, complex approaches for patient stratification may not be feasible. The importance of community engagement and strong communication was emphasized, to raise awareness of evidence-based treatments but also to manage expectations, as many treatments are likely to have modest benefits (while still delivering major public health benefits).

As well as research, regulatory evaluations also need to be carried out swiftly but without compromising rigour. Again, clear messaging around decision-making and the supporting evidence is essential.

Prioritization

ACT-A

The ACT-A therapeutic partnership was set up to accelerate research on COVID-19 therapeutics and ensure their availability in all countries. It was convened by Wellcome and UNITAID and includes multiple other partners.

ACT-A has adopted an end-to-end perspective on therapeutic development and implementation. Its six streams cover strategy and coordination; rapid evidence assessment; market preparedness; procurement; costing and preparedness; and oxygen supplies. Selection of candidate therapeutics spans the rapid evidence assessment and market preparedness streams.

Landscaping analyses are carried out to identify potential assets, existing and novel, which currently number in excess of 600. These have been whittled down through more intensive assessments and with expert input, with around 60–70 assets being actively tracked, 30 on a 'watchlist' undergoing preliminary market assessments, 15–20 undergoing prioritization, and 5–8 being subject to extensive market assessment. The assessments are used to identify potential points at which specific interventions might be required to advance the development of candidates.

ACTT/ACTIV

ACTT is a single trial platform carrying out large-scale phase III evaluations of COVID-19 therapeutics, as illustrated by its work on remdesivir. The ACTT-2 trial reported that use of baricitinib alongside remdesivir further reduced recovery time in hospitalized patients[15]. The ACTT-3 trial is evaluating remdesivir in combination with an immunomodulator, interferon- α 1a. Selection of drugs rests primarily with the US National Institutes of Health (NIH), in discussion with the triallists and other experts.

ACTIV is a multi-partner 'platform of platforms' undertaking a range of studies mostly in hospital settings. These include ACTIV-1 on immunomodulators, ACTIV-3 on antivirals and monoclonal antibodies, and ACTIV-4 on anti-coagulants. ACTIV-2 is a study of monoclonal antibodies, IFN-β and camostat mesilate (a serine protease inhibitor that blocks viral entry) in outpatients, while ACTIV-5 is a phase II study platform that assesses candidates for the phase III trials.

[15] Kalil AC, Patterson TF, Mehta AK et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021;384(9):795-807. doi: 10.1056/NEJMoa2031994.

An online portal provides an opportunity for commercial or academic groups to submit possible therapeutics for assessment. These undergo an initial assessment by working groups for immunomodulators, antivirals, anticoagulants and monoclonal antibodies. They are assessed against seven parameters, including biological rationale, preclinical data, safety data and manufacturing feasibility. The most promising candidates are presented to an oversight committee and the triallists for consideration.

Experience to date suggests that there are many more candidates than can possibly be evaluated, so a systematic triaging with objective criteria is essential. Existing clinical data and plausible biological pathways are particularly important to consider. With evaluation capacity inevitably limited, collaboration and coordination is essential to avoid duplication of efforts.

Agents under evaluation

- ACTIV-1: Abatacept, cenicriviroc, infliximab
- ACTIV-2: Four neutralizing monoclonal Abs (AZD7442, Brii-196, Brii-198, LY-CoV-555), IFN-β, camostat mesilate
- ACTIV-3: Neutralizing monoclonal antibodies and antivirals (AZD7442, Brii-196, Brii-198, LY-CoV-555, VIR-7831)
- ACTIV-4: Low molecular weight heparin, unfractionated heparin (hospitalized) and low-dose aspirin, high-dose aspirin, and apixaban (pre-hospitalized)
- ACTIV-5: Risankizumab, lenzilumab

UK-CTAP

The UK COVID-19 Therapeutics Advisory Panel (UK-CTAP) has established a transparent and independent mechanism for prioritization of candidate drugs. Proposals can be submitted by any party through the UK-CTAP 'funnel'. Triage and due diligence activities are undertaken to collate evidence on candidates, which is presented to expert groups. Their prioritizations are presented to an overarching panel, which makes final recommendations for consideration by the Chief Medical Officer and triallists.

The UK has established a range of therapeutics testing platforms across the COVID-19 disease spectrum and different stages of clinical development:

- Phase I and II: AGILE: candidate assessment: EIDD-2801, VIR-7831, VIR-7832, niclosamide
- Phase IIb: RECOVERY+: hospital-based: dimethyl fumarate
- Phase III: PRINCIPLE: community-based: inhaled budesonide, colchicine; scheduled: favipiravir, adalimumab

- Phase III: RECOVERY: hospital-based: neutralizing antibodies (REGN10933, REGN10987), aspirin, colchicine, baricitinib; paediatric use: methylprednisolone, immunoglobin, hydrocortisone, anakinra; scheduled: namilumab, infliximab
- Phase III: REMAP-CAP: ICU-based: lopinavir/ritonavir, interferon-beta, anakinra, simvastatin, anti-platelet arm (aspirin, clopidogrel, prasugrel and ticagrelor); scheduled: namilumab, infliximab
- Long COVID: HEAL: community based: scheduled: atorvastatin, apixiban
- PROTECT V: Pre-exposure prophylaxis in vulnerable immunocompromised
- PROTECT CH: Post-exposure prophylaxis in care homes: scheduled: ciclesonide, intranasal heparin

Lessons learned to date include the importance of considering plausibility of targets and proposed mechanisms of action, credible pharmacokinetics/pharmacodynamics at sites of action, and a safety profile appropriate to the proposed setting of use (e.g. ICU, community). Scalability of manufacturing is another important consideration. Preliminary efficacy data are critical, but not always easy to obtain from developers – more openness and rapid reporting would be beneficial.

Having access to a full spectrum of trials (I, II and III) is advantageous, as is the ability of platforms to stratify patients in research settings. Close liaison with flexible regulatory authorities has also facilitated rapid initiation of trials.

SOLIDARITY

The WHO's SOLIDARITY trial platform has established a similar prioritization process. Technical expert panels provide input into a drug prioritization advisory group, which makes recommendations to the trial executive group.

Some assessment criteria are mandatory, including pre-clinical efficacy data, ideally in non-human primates, safety data and GMP data. Prioritization also takes into account factors such as data on efficacy and safety, dosing schedules, routes of administration, and production and supply feasibility.

Interested parties can make contact with the advisory group secretariat. Through the triage procedure, a briefing document is developed, and proposals are placed in one of three 'baskets': (e.g. basket 1: suitable to enter phase III trial; basket 2: one issue to be resolved; basket 3: several issues to be resolved). Data can be submitted to support the movement of products to higher-priority baskets.

REMAP-CAP

The REMAP-CAP platform is an international, multifactorial, adaptive platform spanning nearly 300 hospitals in 19 countries. Focused on community-acquired pneumonia, it has pivoted to study interventions for those seriously ill with COVID-19.

REMAP-CAP has established a core protocol that is adapted to evaluate interventions across multiple domains – antivirals, steroids, immunomodulators, anticoagulants, immunoglobulins, antiplatelet agents, and a miscellaneous category including interventions such as vitamin C and statins. REMAP-CAP studies have confirmed the beneficial effect of steroids16 and identified the benefits of IL-6 inhibitors[17].

Its prioritization process is based on an international committee with members drawn from multiple disciplines. Proposals come from internal team members, external investigators, or from funders. Its selection criteria are simple, including biological and clinical rationale, safety data, compatibility with REMAP-CAP operations and portfolio, and long-term feasibility of the intervention as a practical treatment option globally.

Lessons learned to date include the need for a clear process of prioritization – initially the network was overwhelmed with suggestions. Committee-based decision-making is important, to provide a range of perspectives and to protect individuals. There is also a need to be selective and not to rush into trials without careful evaluation. In addition, coordination is critical when capacity is limited, so as many options as possible can be assessed.

Global coordination

From a global perspective, much has been achieved over the past year. There is global consensus on the importance of large, well-conducted trials delivering robust evidence, and that duplication of efforts wastes resources. Many large-scale collaborations have been established, including the COVID-19 Clinical Research Coalition18, focused on research in low- and middle-income countries (LMICs). Even

[16] Angus DC, Derde L, Al-Beidh F et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. 2020;324(13):1317-1329. doi: 10.1001/jama.2020.17022.

[17] REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Feb 25. doi: 10.1056/NEJMoa2100433.

[18] COVID-19 Clinical Research Coalition. Global coalition to accelerate COVID-19 clinical research in resource-limited settings. Lancet. 2020;395(10233):1322-1325. doi: 10.1016/S0140-6736(20)30798-4.

so, collaboration is not yet optimized; some stakeholders, such as academics and the biotech sector, may yet not be fully integrated into networks.

Effective collaboration and rapid progress are dependent on transparency, as well as timely sharing of information and data. There has been some sharing of protocols, standard operating procedures and other documentation, but even more openness would be beneficial. Large amounts of data have been made available, although further sharing of landscaping and assessment documents would be advantageous. Very little sharing of individual patient data has yet occurred. A lack of standardization remains a major challenge in drawing together evidence from both pre-clinical and clinical data.

More work is needed to understand the natural history of infection, including long COVID, to provide leads for therapeutic development. It was noted that more than 2700 clinical studies have been launched, including nine major platform trials, which are taking a dynamic and flexible approach to evaluate multiple products in different population groups and in different settings.

Collaboration in other spheres is also advantageous. The African Vaccine Regulatory Forum (AVAREF), for example, has been coordinating joint review of research proposals and licensing applications. ACT-A has been serving a valuable role but could bring in additional stakeholders, and its remit could be extended upstream and downstream. For example, it could provide a platform for sharing of individual patient data and coordination of pre-clinical research.

Discussion

As well as new therapeutics, it was noted that tools are needed to support their effective use. For example, biomarkers are needed to identify those at risk of severe disease and those likely to respond to particular treatments.

The need for fully global approaches was identified, for example so that more countries can participate in trials and data can be collected in different settings. It was suggested that an end-to-end approach could be considered, with prioritization of targets as well as treatments. The importance of harmonized regulatory systems was also emphasized.

The potential of natural products as a source of new therapeutics was raised. Resources such as the ReFRAME library, an open source collection of 12 000 compounds, have been screened to identify

those with activity against SARS-CoV-219. Multiple hits have been identified, although activity in primary cell cultures has not always matched that seen in transformed cell lines, contributing to high attrition rates. Even so, such studies can provide important insight into biologically important pathways and potential targets. The possibility of a more systematic approach to pre-clinical studies and a centralized platform for data sharing was raised.

The importance of coordination, transparency and standardization was emphasized. Of particular value are large simple trials with widely applicable solutions. As well as acute disease, the need for therapeutics for pre-exposure prophylaxis and long COVID was also stressed. It was suggested that networks could collaborate more with each other.

A deeper understanding of viral infection and mechanisms of disease is vital for identifying new targets and for establishing the biological plausibility of candidate therapeutics. At a national level, early engagement between academics, clinicians and regulators is important for establishing a shared understanding and to ensure that the data generated in research studies is of value to regulators and can support more agile and flexible decision-making. Large numbers of small, inconclusive studies, with a variety of endpoints and assays, can make regulatory decision-making very difficult.

Clinical trial design

Randomized studies

It is likely that COVID-19 therapeutics will provide moderate benefits, so large-scale trials will be needed to generate reliable data on effects. The need to consider efficacy in subgroups of patients further emphasizes the importance of large sample sizes.

Randomization is critical for minimizing the risk of bias. Data from non-randomized, real-world studies therefore need to be treated with caution because of the risk of bias. The risk of misleading results due to random errors requires very large sample sizes, in the many thousands. Systematic reviews also play a critical role in collating evidence from multiple studies.

[19] Riva L, Yuan S, Yin X et al. Discovery of SARS-CoV-2 antiviral drugs through large-scale compound repurposing. Nature. 2020;586(7827):113-119. doi: 10.1038/s41586-020-2577-1.

Placebo-controlled trials are most informative but may not always be necessary. In general, they are less important when 'hard' endpoints such as mortality are used. Active comparators can be an appropriate alternative to placebo controls in many situations.

Differences in trial design may explain the discrepancy in results on remdesivir obtained in the RECOVERY, SOLIDARITY and ACTT-1 trials. The latter, which was smaller than SOLIDARITY and RECOVERY but placebo-controlled, found larger survival benefits. Systematic reviews have come to mixed conclusions about the survival and other clinical benefits of remdesivir, emphasizing the need for additional high-quality data.

A regulator's perspective

The early days of the COVID-19 pandemic were characterized by widespread use of many therapeutics on the basis of little reliable evidence. As more data have accumulated, use of unproven agents has declined and more use is being made of products that are supported by clinical evidence.

The conventional approach to clinical evidence generation for regulatory approval – large-scale phase 3 trials organized by pharmaceutical companies – could be complemented by pragmatic studies based in routine practice. Although the quality of evidence may not be as high as in large-scale phase 3 trials, data could be generated rapidly, at less cost, and in wider groups of patients.

Such studies could be based on collaborations between industry and the public sector. With a large network of investigators, potentially at a global level, standardized endpoints could be used that are robust, objective, easy to obtain in different settings, and applicable to the full spectrum of disease. By engaging all stakeholders in the design of studies, an agreed set of endpoints would ensure that data generated would serve multiple purposes, including meeting the needs of clinicians, regulators and public health authorities. Some work has been carried out to establish standardized outcomes measures for COVID-19[20].

Discussion

It was noted that development and evaluation of potential treatments was still hampered by a lack of understanding of disease progression. In addition, the risks associated with use of real-world evidence and its potential to mislead were repeatedly stressed. Convalescent plasma, for example, was widely used

[20] WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020;20(8):e192-e197. doi: 10.1016/S1473-3099(20)30483-7.

in 2020, yet data from the RECOVERY trial and a systematic review21 have failed to identify any clinical benefit.

One potential use of real-world studies is to generate hypotheses that can then be tested in a rigorous clinical trial. Pragmatic randomized controlled trials can be seen as a good compromise, having the advantage of large sample sizes and randomization, as well as a real-world context and a wide range of patient types. However, there is also value in phase II studies, which can explore in more detail how therapeutics are acting and help to identify biomarkers of response to treatment.

It was emphasized that trials are important for rigorously and systematically assessing risk–benefit ratios for candidate treatments. Placebo-controlled trials are particularly important for newly developed therapeutics, when effect sizes are likely to be small, and when 'soft' endpoints are being assessed.

It was emphasized that therapeutic evaluation needs to consider stage of disease, as different treatments are likely to be needed at different points. Choice of trial endpoint will therefore depend on the stage of disease being targeted. Selection of endpoints should also reflect the needs of clinical and regulatory decision-making.

More attention may need to be given to mortality after 28 days, given the risk of relapse, re-hospitalization and death. Additional endpoints could be considered to assess impacts on extent and speed of recovery. More attention also needs to be given to the longer-term consequences of COVID-19, including long COVID, neurocognitive sequelae and other disabilities. There may also be potential for nested studies in particular patient groups, such as those on mechanical ventilation.

Based on the experience of HIV, survival and other clinical benefits are likely to be gained iteratively by the addition of new therapeutics each of individually moderate impact. This calls for careful public communication and management of expectations, particularly given the unexpectedly high efficacy of vaccines, which may raise hopes that therapeutics will be similarly effective.

The funders' perspective

The Bill & Melinda Gates Foundation argued that it was important for low-income and middle-income countries (LMICs) both to participate in COVID-19 therapeutic research and to enjoy its benefits.

[21] Janiaud P, Axfors C, Schmitt AM et al. Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis. JAMA. 2021 Feb 26. doi: 10.1001/jama.2021.2747.

Structures such as the ACT Accelerator were developed in light of the chaotic approach to drug repurposing seen in response to the Ebola epidemic, aiming to provide a mechanism for more systematic assessment and generation of reliable evidence to support clinical use.

The importance of pre-clinical research was also emphasized. Resources such as the ReFRAME library and associated assays have facilitated drug screening, notwithstanding some misleading early results obtained in transformed cell lines, and ensuring wide access to these assays and data is critical.

It was also suggested that some assumptions about the clinical capabilities of LMICs should be revisited. Although treatments need to be globally applicable, it was indicated that some centres in resource-poor settings would be capable of using treatment types often assumed to be feasible only in high-income countries.

From a European national funder's perspective, the possibility was raised of a more coordinated approach to early-stage research. While science thrives on competition and diverse thinking, this may not be the best approach in times of crisis. A more coordinated strategy could help to avoid duplication of efforts and focus attention on key questions. Some kind of 'honest broker' would be required to organize coordination, but the result could be a more effective knowledge generation system.

In the short term, collaboration between platforms, greater alignment on endpoints and data sharing are helping to achieve the scale required to answer important questions. Structures such as the COVID-19 Trials Coordination Board, bring together multiple European stakeholders, aim to enhance coordination across trial platforms. Large pragmatic trials and exploratory studies both have important roles to play.

From the LMIC perspective, platforms such as SOLIDARITY have enabled LMICs to take part in clinical trials. It is important that global access is considered during prioritization processes, and that clinical evaluations consider global population diversity, as well as the needs of specific disadvantaged groups. Involvement of LMICs in trials will help to ensure the generalizability of results.

As well as trials, LMICs should be involved in prioritization processes. Trial design should take into account the capabilities of LMICs, and capacity building should be considered to facilitate their greater involvement.

The Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) provides one mechanism to support greater collaboration between funders. In early 2020, it worked with WHO to

develop a roadmap for COVID-19 research. Its COVID-19 Research Tracker database provides a snapshot of global COVID-19 research activity. By the end of February 2021, the database included nearly 8000 projects in 101 countries, representing a total investment of US$3.8 billion.

Before COVID-19, GloPID-R had been considering the feasibility of 'umbrella' funding and clinical trial coordination, and was able to provide support for the SOLIDARITY and RECOVERY networks. It is aiming to bring more funders on board and expand its partnerships with other stakeholders, to promote coordination and consistency in practice.

Conclusions

The devastating impact and rapid spread of COVID-19 in 2020 led to huge demand for treatments. Many existing drugs were proposed as possible treatments, and many were used even in the absence of reliable evidence on their effectiveness and safety.

Several platforms were rapidly established to carry out large-scale and robust clinical trials, some in the settings of routine care. These studies have begun to deliver robust evidence on the efficacy and safety of multiple therapeutics, and have provided flexible and adaptive platforms supporting the clinical evaluation of candidate therapeutics targeting particular patient groups and stages of disease. Although many existing therapeutics have shown little or no clinical benefit in COVID-19, the evidence gained through trials will ensure that healthcare resources are not wasted on ineffective treatments.

Despite the success of COVID-19 vaccine development, therapeutics are still needed. There is an urgent need to expand the COVID-19 medical armamentarium across all stages of disease, and to identify which treatments work for which patients and at which stage. It is likely that patients will ultimately require multiple therapeutics, targeting both the virus and host mechanisms that drive severe disease.

While efforts to date have focused on repurposing existing products, the therapeutic pipeline will increasingly include newly developed treatments specifically targeting COVID-19. Research to better understand the mechanisms of viral infection and transmission, as well as host responses to infection, will be essential to guide drug discovery and development.

Such work will help to identify biomarkers associated with disease progression or response to therapy. These also have the potential to provide tools to improve patient management, and clinical research is also required on how therapeutics can be optimally introduced into clinical decision-making and the clinical care pathway.

Progress to date has been dependent on unprecedented levels of collaboration, at national, regional and global levels. Though often challenging in the short term, such efforts greatly accelerate progress by ensuring consistency in approaches, facilitating sharing of information, promoting alignment around shared visions, and creating opportunities for large-scale trials delivering robust evidence.

There may be opportunities to achieve further alignment between major platforms, to reduce duplication of effort and to focus attention on shared priorities, although some overlap is important, to demonstrate replication of research findings. Potentially, greater coordination could also be achieved in the pre-clinical space and in early stages of clinical evaluation, to accelerate the development of a global pipeline of COVID-19 therapeutics.

Other possible new initiatives could include a clinical data-sharing platform, with appropriate data governance and access mechanisms, to support individual patient data analysis. A further priority is to ensure that researchers from LIMICs have the opportunity to feed into process that set the global COVID-19 therapeutic research agenda. Funders have a particularly important role to play in promoting coordination, for example through updating of the COVID research roadmap, and in building clinical trial capacity.

Annex 1 – Agenda

WHO ad hoc consultation COVID-19 therapeutics Knowledge gaps and research priorities, Objectives

To identify knowledge gaps and research priorities for COVID therapeutics.

To discuss when patients might benefit most from different treatments, using current understanding of COVID, how best to identify promising treatments, and how best to evaluate them.

To propose actions to enhance international collaboration and coordination in support of identified research priorities.

DRAFT AGENDA

Chairperson - Michael Jacobs

Time	Topic	Speakers
13:30-13:35	Welcoming remarks	WHO
13:35-13:40	Objectives of the meeting	Michael Jacobs
Setting the scene		
13:40-13:55	The magic of randomisation	Martin Landray
13:55-14:10	Natural history of COVID infection and disease	Leticia Kawano-Dourado
14:10-14:20	Facilitating appropriate trials	Christina Reith
Treatments for different phases of disease Chair: Nick White		
14:20-14:30	When might patients benefit from antivirals?	Andre Kalil
14-30-14:40	When might patients benefit from immunomodulators?	Paul Moss
14:40-14:50	When might patients benefit from antithrombotics?	Vicente Estrada Perez
14:50-15:20	Panel o Which treatments for which phases of COVID? o Should combination therapies be a priority? o How to investigate the relevance of variants of concern to treatments effects? o What are the research priorities?	Panellists: John Marshall Marissa Alejandria Mariam Hassan Adolfo Garcia-Sastre Gustavo Mendes
Identification and prioritization of drugs for RCTs Chair: Michael Jacobs		
15:20-16:20	What criteria are being used to select treatments to include in phase 3 trials? Are there any lessons? (maximum 5 slides in 10 minutes)	NIH-ACTIV (Greg Deye) Recovery (Alison Cave) WHO- Solidarity (Uli Fruth) REMAP-CAP (Anthony Gordon) ACT-A (Janet Ginnard) EU- IMI (Yves Lévy) *

Time	Topic	Speakers
16:20-16:30	Is there a need for more transparency and coordination?	Nathalie Strub-Wourgaft
16:30-17:00	Panel o Can we improve the future selection of drugs? o Is it possible to share outputs of selection processes across platform trials? o How to identify promising drugs at an early stage and nurture their evaluation?	Panellists: Reza Malekzadeh Renu Swarup Stefan Pöhlmann Quarraisha Abdool Karim Monalisa Chatterji Marc Blockman
What clinical trial designs are needed? Chair: K. Srinath Reddy		
17:00-17:15	Large-scale randomised evidence	Richard Peto
17:15-17:30	What are the really important trial endpoints?	César Hernández García
17:30-18:00	Panel o When are placebos appropriate, and when are open-label controls appropriate, in RCTs? o What endpoints should be prioritized in Phase 3 randomized trials? o When can "real-world" evidence mislead, and when can it be trusted?	Panellists: Abdel Babiker Sheela Godbole France Mentre Marco Medina Deborah Cook Samba Sow Elizabeth Higgs
Towards a common research agenda Chair: Mirta Roses		
18:00-18:30	Panel o What can donors do to improve collaboration at global and national level? o What can donors do to facilitate appropriately large-scale randomized evidence?	Panellists: **Africa CDC** John Nkengasong **BMGF** Trevor Mundel **EU-RESPONSE & RECOVER (EC projects)** John-Arne Røttingen **Fiocruz** Nísia Trindade Lima **GloPID-R** Charu Kaushic **Indian Council of medical Research** Balram Bhargava **Wellcome** Jeremy Farrar
18:30-18:40	**Conclusions and next steps**	Michael Jacobs WHO

WHO Headquarters in Geneva

Avenue Appia 20
1202 Geneva
Telephone: +41-22-7912111

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