WHO R&D Blueprint
COVID-19
Clinical Trial Design Protocol - consultation on Immunomodulators

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Geneva, Switzerland, 7th May 2020
# Table of Contents

INTRODUCTION ........................................................................................................................................... 3  
OBJECTIVES OF THE CONSULTATION ................................................................................................... 3  
AGENDA ITEMS ........................................................................................................................................... 4  
WORKING GROUP MEMBERS ................................................................................................................... 4  
OVERVIEW OF THE DELIBERATIONS ...................................................................................................... 4  
PROPOSED NEXT STEPS .......................................................................................................................... 7
Appropriate WHO Confidentiality Undertakings were signed and submitted to WHO by all participating experts

INTRODUCTION

The WHO R&D Blueprint secretariat made a presentation to update the group on the implementation of the solidarity trial.

WHO has received expression of interest from 120 member states, the countries received the core protocol, all related information and guidance with the necessary steps to obtain approvals by ethics review committees and the national regulatory authorities. Twelve countries have already completed the approval process.

A second group of countries is about 12, they are already in the process of recruitment and randomization.

A third group is about 30 countries, they will enter soon in agreement to be part of the solidarity trial.

A fourth group about is 69 countries, they have submitted the protocol to their regulatory authorities and already received feedback from the authorities.

Finally, there are 40 countries which have been in contact with WHO and initiated the process.

Up to date around 2,600 patients have been randomized in among 400 hospitals, in Argentina, Brazil, India, Indonesia, Malaysia, Peru and Philippines

The Solidarity protocol allows the DSMC to make intermediate analysis anytime along the study, however, still we don’t have enough data to make and interim analysis with high level of confidence.

OBJECTIVES OF THE CONSULTATION
The Therapeutics Prioritization WG is currently discussing which therapeutics are in the pipeline and if it should be considered for further evaluation in the solidarity trial. The discussion on 6th May was on immunomodulators. Consequently, the main objective of this teleconference is to review the protocol and discuss whether there is a need to adjust the protocol if a new arm with an immunomodulator will be added to the solidarity trial.

Questions to guide the discussion:
1- If we add an immunomodulator to the solidarity trial, what additional safety information should be collected (being considered by the prioritization WG as well)
2- If we add an immunomodulator, what is the most efficient way? An additional study arms or factorial design?
3- What are the implication for the sample size calculations?

This working group should mainly focus the discussion in questions number 2 and 3.

**Agenda items**

1) Welcome and Goals of the Ad Hoc Consultation  
2) Overview of different immunomodulators therapies  
3) Discussion on what need to be adjusted in the Solidarity protocol if an immunomodulator were to be added to the trial  
4) Recommendations and next steps

**Working group members**

Chair: Peter Smith  
Members: Ira Longini, Marco Cavaleri, John Marshal, Frederick Hayden, Thomas Fleming, Richard Peto, Natalie Dean, Martha Nason, Yunda Huang, Jacob Cramer, Elizabeth Higgs, Michael Jacobs, Andrea Antinori, Vicente Estrada.

WHO Secretariat: Alejandro Costa, Ana Maria Henao-Restrepo, Uli Fruth

**OVERVIEW OF THE DELIBERATIONS**
Overall considerations

WHO secretariat (Dr Uli Fruth) presented a pre-selection of different immunotherapeutics to facilitate the discussion, the list was presented and discussed during the Therapeutics Prioritization Working Group on May 6th 2020.

Products to consider are:

1- Biologicals: the following cytokine antagonists are under consideration: anti-IL-6; anti-TNFα; anti-IL-1; anti-IFNY; anti-GM-CSF; anti- C5/C5a. etc.

Tocilizumab (Actrema), an anti-L-6 receptor mAb produced by Roche is the cytokine antagonist that has been most used for COVID (off-label; observational studies) in China, Italy and France, followed by Sarilumab (Kevzara) another anti-IL-6 receptor mAb, produced by Sanofi/Renegeron. RCTs are ongoing for both products.

Anti-TNFα mAbs have been used against inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, psoriasis or ankylosing spondylitis for over 20 years. A number of products (mAbs, soluble receptors) are available as well as a number of biosimilars thereof. Therefore it is surprising that little attention is given to these products in the fight against COVID-19 disease.

2- Chemical drugs: The following products were listed for consideration: inhibitors of protein kinases (Janus kinases, JAK; mammalian target of rapamycin, mTOR; Bruton´s tyrosine kinase, BTK), inhibitors of dihydroxyorotate dehydrogenase, DHODH; inhibitor of phospholipase A2 (Varespladib) and bioactive peptide (Solnatide).

Several protein kinase inhibitors are licensed or under development for a broad spectrum of conditions, including inflammatory diseases (RA, Crohn´s), hematologic malignancies, or as immunosuppressants, etc.

There is hardly any experience with kinase inhibitor in COVID-19, but Lili´s batricinib (Olumiant) has been included as an arm in NIAID’s Phase III Adaptive Covid-19 Treatment Trial.

Chemical drugs have a number of potential advantages over biologicals regarding complexity of production and scale-up, logistics (cold chain), drug delivery (Oral vs s.c. or i.v.) and possibly cost of product. These characteristics would render such drugs interesting for large scale use in LMIC.

Discussion
The discussion focused on the trial design implications of introducing one, two, or more of the above immunomodulators into the solidarity trial. What would be the methodological issues to be considered? Which are the options to introduce the changes?

One option would be to add more arms to the trial, however adding more arms we will slow down the availability of the results. Most likely there will be more potential therapies coming forward. Therefore, the efficiency of incorporating each of these future candidates in individual arms into the solidarity trial was questioned.

A second option would in a factorial design respect to the existing arms of the trial, using the same control arm. This design would clearly provide some advantages, like no or little slowdown to the course of the overall trials and a possibility to evaluate drug interactions in the combination group.

For the calculation of the sample size when arms are added, one should not count on one of the existing arms to be dropped prematurely. It will happen, but not likely in the coming months. Therefore, one would be on the safe side new intervention were added in a factorial fashion, as this will not change the sample size of the already existing arms in the study.

The main issue with combined therapies would their potential drug interactions. Some of them are known to exist, rendering combination such as anti-TNFα and anti-IL-1 a no-go. For others it might be time-consuming to obtain approval by regulatory oversight bodies and ethics committees. A good example was the RCT for therapeutic in the Ebola trial where the committees did not approve combined therapies, so the trial concluded that mAbs114 and Regeneron were better than Remdesivir and ZMapp, but thus it remained unclear whether Remdesivir in combination with other therapeutic would have had benefit.

Factorial design have benefits to gain in efficiency for therapies that may have synergetic effects like an antiviral and an immunomodulators. (e.g. LPV/RTV + IFNβ). If it was decided to add a new immunomodulator it should be with additional 2 arms for example: one arm with the combination LPV/RTV or CQ/HCQ or Remdesivir + the immune-modulator; and another arm with the immunomodulator alone to understand whether the combination is better than the immunomodulator alone, and the immunomodulator alone is better than the control group.

Looking at the list of targeted groups of immunotherapies presented it would be essential to evaluate their complementary and potential interactions given at full dose. A single arm against control, will not be certainly efficient to assess these candidates since they most likely need to be administered with an antiviral.
There are may be some safety concerns about the unknowns were therapies are combined. The question is whether there is a need for separate smaller safety study or we can adjust the protocol to observe potential side effects. We are aware that the NIH trial included an IL-6 inhibitor (Tocilizumab) in a factorial design phase II without going to interim safety studies, similarly, in UK´s RECOVERY trial. However, such an approach may not be possible in some countries in Africa.

If the decision was to evaluate 2 immuno-modulators, the design would have to be discussed whether will be full factorial design for all combinations or other separate arms, depending on the type of therapeutics and whether there may be synergistic or antagonistic effects.

It is anticipated that not all centers will include all arms, each center will randomize with the therapeutics available, however the efficacy analysis of immunomodulators will be compared across different centers.

**Conclusions:**

If it is believe that combined therapies will have additive effects or synergistically positive efficacy, the factorial design is the most inclusive, informative and efficient design, assuming the therapies can be given at full dose.

**PROPOSED NEXT STEPS**

1. Create a sub-group to review the current protocol and propose modifications.
2. In a week´s time the sub-group will present the new version of the protocol to the full group.
4. Next call in a week Friday 15th May, after the prioritization WG call.

**Note that above prioritization decisions are preliminary and may change as further information is provided to WHO.**