Perspective

How to Conduct Clinical Trial during an Epidemic : Lessons from the WHO Solidarity Trial

Rudrajit Paul[1], Jyotirmoy Pal[2]

The Covid-19 pandemic has been the greatest challenge facing doctors and scientists over the last one year. This new virus with no known therapy or vaccine wreaked havoc all over the world with high mortality among the elderly and those with certain chronic conditions. In March 2020, the World Health Organization (WHO) started an international trial on treatment options for Covid-19: **Solidarity.** An interim result was published in the NEJM on December 2, 2020. The process of conducting this trial during on emerging pandemic is a good case study for future medical researchers. Here, certain salient points of this trial will be highlighted.

The trial was essentially started with four drugs: Remdesivir, Hydroxychloroquine, Lopinavir and Interferon beta-1a. These are drugs, already in use for other indications, which had been repurposed for Covid-19 based on expert opinion. But design of the trial was adaptive. This means that during the trial, any drug found useless could be dropped and any other molecule found or thought useful could be added. Thus, the end point of the trial was not defined by the clinical efficacy of one particular drug but rather, clinical improvement of the patient (by whatever means) was the sole purpose. This is in sharp contrast to usual clinical trials where the effects of one particular drug is analysed for a long time.

Technology came in handy during recruitment for this trial. A cloud based data management system was used which also factored in local availability of the trial drug(s) before assigning a study subject to a particular arm of therapy. Thus, the need to spend time on procuring a particular drug for the trial was avoided.

Very quickly, it became clear that some of the drugs were useless. Thus, HCQS, Lopinavir and Interferon arms were discontinued on June 19, July 4 and October 16 respectively. So, wastage of valuable time in experimenting with futile therapies could be avoided. During an epidemic, there is no time to do finer sub-group analysis. If anything is not showing significant clinical result within a short time, it must be abandoned and other options looked for.

This trial had no placebos. Participants either received one of the four drugs or they just received standard supportive therapy without any trial medicine. Thus, during a medical emergency, the standard protocol of blinding or using placebo as control was skipped to save time. Since the drugs had different formulations (oral or iv) both the doctor and the patient knew which therapy was being tried. The main aim was to see whether lives are saved, not to eliminate observers' bias.

For any clinical trial, sample size is very important to give the study adequate power. But during an emerging epidemic, when the probable number of persons infected is essentially unknown, this method of calculating sample size is not useful. Thus, in this trial, the WHO steering committee said,

"The larger the number entered the more accurate the results will be, but numbers entered will depend on how the epidemic develops. …"

Finally, during an epidemic or pandemic, different trials are simultaneously conducted at multiple centres. So, another crucial question arises.How to synthesize these data together? Since all the studies are started on an emergency basis, it is likely that there will be very little homogeneity among the study methodology in different countries. In the Solidarity trial, they used inverse-variance–weighted average of $b=\log_e$ rate ratio from each stratum of each trial.

One major impact of this Trial result publication was stopping similar trials elsewhere. Thus, wastage of time and money on futile therapies could be stopped. During an epidemic, when the allocation of funds is of prime importance, the results of such trials are important in choosing the future direction.

References

1 WHO Solidarity Trial Consortium. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. NEJM 2020; [Online First December 2, 2020]. DOI: 10.1056/NEJMoa2023184

[1]MD, DNB, MRCP (UK), Consultant Physician, Kolkata
[2]MD, FRCP, FRCP, FICP, FACP, WHO Fellow, Professor of Medicine, RG Kar Medical College & Hospital, Kolkata 700004