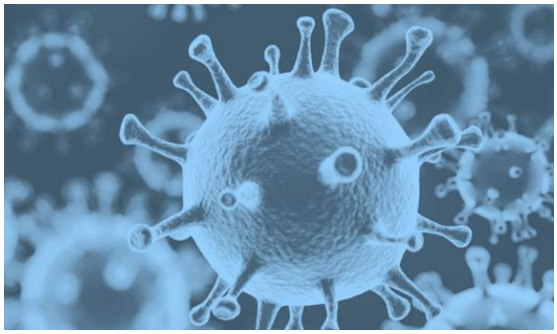
THE IMPACT OF COVID-19 ON RANDOMIZED CLINICAL TRIALS

AN IDDI WHITE PAPER



The COVID-19 pandemic has a major impact on the conduct of most on-going clinical trials, in particular on the treatment of patients and the schedule of their planned protocol visits. General guidance is available from both FDA and EMA on measures to be taken to minimize the impact of COVID-19 on on-going trials; these measures are assumed to have been implemented by Sponsors.

IDDI has published an interview with Marc Buyse, Chief Scientific Officer, and Everardo Saad, Oncologist and Medical Director at IDDI on the impact of the pandemic on the statistical analyses of randomized clinical trials. The podcast with the interview is available at https://www.iddi.com/resources/podcasts/the-impact-of-covid-19-on-randomized-clinical-trials/ .

Here are some key considerations Marc and Everardo discussed during this podcast.

PROTOCOL DEVIATIONS AND MISSING DATA

- A randomized clinical trial (RCT) is, in essence, very robust to protocol deviations. If there is a treatment benefit of the experimental treatment over control, that benefit will survive many of the issues created by the pandemic. The intention-to-treat (ITT) analysis, which usually is the primary analysis of any RCT, will remain valid and will survive many of the deviations that could occur.
- Any factor that affects both treatment arms of a trial equally may dilute the treatment effect but does not create a systematic bias in this treatment effect.

- The protocols are NOT going to be completely ruined by COVID-19. They might be affected by it, but the statistical estimate of the treatment effect will remain valid if deviations are assumed to occur randomly in all trial arms.
- Missing data will in general be missing at random, since the pandemic is an external cause that bears no relationship to the disease or treatment under investigation. Missingness at random is dealt with by likelihood-based methods, or by imputation methods that are valid under the missingess-at-random assumption.

SO, ALL IN ALL, WITHOUT TRYING TO MINIMIZE THE IMPACT OF COVID-19 ON THE CONDUCT OF ON-GOING TRIALS, THOSE TRIALS THAT ARE RANDOMIZED ARE NATURALLY PROTECTED AGAINST EXTERNAL FACTORS SUCH AS THE COVID-19 PANDEMIC, AS LONG AS ALL TREATMENT ARMS ARE AFFECTED APPROXIMATELY EQUALLY.

BEST PRACTICES

- Patients who have symptomatic COVID-19 infections should NOT be removed from trials of other indications. Censoring is wholly unjustified and should not be done other than at the patient's request.
- Some data is generally better than no data. Even if assessments taken at home are less reliable than those taken in the clinic, the loss in efficiency in detecting a treatment effect may be quite small if indeed there are no systematic differences between the randomized treatment groups.

MEDICAL ISSUES AFFECTING TRIAL RESULTS

- In oncology, treatment arms can be differentially affected by the pandemic. In a trial comparing chemotherapy with a non-cytotoxic intervention, say, a targeted agent or placebo, the incidence of COVID-19 may be higher in the chemotherapy arm.
- If COVID-19 is also a risk factor for one or more of the endpoints (such as overall survival), an association may be created between the treatment and this endpoint, thus confounding the analysis. It is advisable to perform competing-risk analyses for the outcome of primary interest in the trial and COVID-19 infection

IDDI's team is available to answer any question you might have on the impact of COVID-19 on your clinical-trial data, not only from a statistical standpoint but also from a data management standpoint. Do not hesitate to contact us at info@iddi.com or simply drop a message in our website.

7751 Brier Creek Parkway, Suite 204
Raleigh NC 27617 - USA
Tel. : +1 984 227 8599
Fax : +1 866 329 4334

Avenue Provinciale, 30
1341 Ottignies - Louvain-La-Neuve - Belgium
Tel. : +32 10 61 44 44
Fax : +32 10 61 88 88

185 Alewife Brook Parkway, Suite 410
Cambridge, MA 02138 - USA
Tel. (Toll-Free): +1 866 835 4334
Fax (Toll-Free): +1 866 329 4334

www.IDDI.com