

The impact of Covid-19 on clinical trials in Neuroscience Comments and proposals of the European working group on estimands in Neuroscience

European Working group on estimands in Neuroscience sponsored by EFSPi and PSI



Overview

- General thoughts
- Current observations
- Potential impact of Covid-19
- Immediate and later Mitigation steps
- Some recommendations
- Summary

We consider this a living document supporting discussion on Covid-19 pandemic impact

General thoughts (1)

- Covid-19 pandemic currently impacts all clinical trials
- Covid-19 pandemic can have direct and indirect impact on clinical trial conduct and outcome
 - Direct impact on AEs and deaths by additional events due to Covid-19
 - Indirect impacts:
missed doses
missed visits and missed assessments due to pandemic (ie patient not observed),
missed doses and missed visits (ie patient not treated and not observed);

We need to distinguish between these different patterns of missingness as much as possible, and on the reason of missingness (Patient choice, investigator choice, pandemic lockdown).

We may want just one reason (due to pandemic) and this would be sufficient when there are no differential missingness pattern. If we see differential missingness then however the additional details are needed to further mitigation

- Covid-19 can also have further indirect impact on standard of care in a country or the level of monitoring due to pandemic. Especially PRO endpoints may be affected due to the additional emotional burden. This indirect impact is hard to measure but can include changing the primary outcome of clinical trials, especially in indications like depression, sleep disorders etc.

General thoughts (2)

- Most important: Documentation of the direct and indirect impact of Covid-19 on a clinical trial
 - Documentation of Covid-19 related events
 - Documentation of missing doses, visits and assessments due to Covid-19 pandemic
 - Documentation should be easily accessible in the clinical database for adequate reporting
 - Documentation should be simple as possible while enabling differentiation between the different categories of impact. Documentation should be transparent for health authorities how the situation lead to an impact and what the impact is. The easiest would be to document just as “due to pandemic”. But this may be risky in presence of differential missingness. Then, additional information as “patient choice”, “investigator choice” or “pandemic lockdown” is needed
- Need to differentiate between impact of the general situation (Covid-19 pandemic) and special impact on patients being infected (Covid-19 infection AE or death)
- Need to assess what the best way of involving DMCs is, to help assessing the potential direct and indirect impact of covid-19 including deciding independently on first mitigation measures in blinded trials without compromising the integrity of the trial.
Also, we need to understand how to support DMCs to make planned decisions that are affected by the pandemic (missing data, missing visits, bias,...)

General thoughts (3)

- Not every study is the same. Not every indication is the same
- Some studies are hit in the beginning, some at the end, some in the mid of their life cycle
- In many ways the studies which are in the mid of their life cycle are likely to be hit more as impact occurs for some patients in the beginning, in the mid and at the end of treatment cycle; studies that are relatively short in duration are also likely to be hit more than long term studies
- Studies in elderly patients, chronic patients and patients at specific risk are expected to be specifically impacted. This may also be true for neurodevelopmental indications where assessments may depend heavily on PROs sensitive to the general Covid-19 pandemic situation
- Studies with a complex route of administration or a route of administration which requires a site visit or medications for which there is potential substance abuse can also specifically be impacted
- Studies in emergency patients and life-threatening diseases (e.g. Oncology) are likely less affected
- Special attention should be given to non-inferiority trials (could lack assay sensitive) and trials at sites and hospitals which may be completely occupied by treating/preparing for the pandemic

Current observations

- Neuroscience have often non-life threatening chronic disease indications; and therefore generally a higher impact of Covid-19 is expected
 - We can see this specifically in indications as depression, Alzheimers Disease,... or other diseases in elderly patients
- We observe missing dosing, missing visits and missing assessments
 - Currently the extent of missingness is still difficult to estimate. Teams focus on immediate mitigation steps and documentation of missingness
 - Covid-19 specific events (like AE or death) are not yet that frequent or a focus of teams; when such events occur, additional questions need to be addressed by teams, eg. should experimental drug for COVID-19 be allowed (this is usually an exclusion under normal circumstances)
 - It is also unclear when centers return to normal. For multicenter trials an additional complexity is that different centers, different regions and different countries are differently affected at different times
 - For multiregional trials this may be specifically important as impact of Covid-19 may happen at different times and to different extent in different regions

Current observations

- Patient safety comes first, even when it leads to protocol violations like missed doses or assessments
- Covid-19 pandemic impact on clinical trials:
 - Missing treatment dependent on the amount of missed doses
 - Missing assessments and visits
 - Covid-19 induced events confirmed or suspected (i.e. AE and death)
 - Indirect effects of Covid-19
- Missing treatment can jeopardize study objectives when it occurs more frequently
 - It is generally more difficult to mitigate
 - It can make the outcome within patients and overall non-interpretable as we no longer test the hypothesis we wanted (i.e. the effect of therapy at a given dose for a given time)
- Missing assessments/visits can also be critical but as long as patients are treated we may have more options available to repair. Follow up visits after the pandemic may help as well
- Covid-19 events are currently not expected to be that frequent and therefore may be less impactful for studies at this stage

Potential impact of Covid-19 and Mitigation

- Indirect effects are present but are difficult to handle
- Clearly larger number of missed doses but also larger amount of missed assessments may impact integrity of a study to such an extent that
 - Results become non-interpretable or dependent on assumptions
 - Results may be interpretable but irrelevant when driven primarily by Covid-19 pandemic
- Therefore, mitigation steps are likely needed
- We need to differentiate between immediate and later mitigation steps
 - *Immediate steps* are steps which we need to do now in order to minimize harm to studies such as planning for alternative methods of assessments to replace site visits
 - *Later steps* are steps to be done in the analysis and reporting to account for Covid-19 such as choosing a different estimand to assess the effect of the treatment

Mitigation. Immediate steps

- Important immediate steps
 - Adequate documentation of missed doses, missed visits and missed events due to Covid-19 pandemic including assessments done remotely
 - Documentation of adverse events related to Covid-19 infection including deaths
 - Protocol amendments to handle impact of Covid-19
- Documentation should be simple as we only need to know if a missed event (dose or assessment) was due to Covid-19 pandemic or something else and a simple categorization of those missed events need to be provided
 - Documentation of missed events important that we can handle such events differently in the analysis. The link of the information to the missed event can however be complex as CRFs are usually not designed for it
 - Currently, preferred solution often to use minor and major protocol violation tools and link those to the analysis datasets but this may be insufficient
 - However, it is unknown at this stage how much sites are following advice and how complex this is for them in a Covid-19 driven environment
 - A simple solution for sites for documentation is definitely preferable as long as solution is sufficient to allow differentiation between different categories of missingness (Patient choice, investigator choice, pandemic lockdown). An even simpler solution (due to pandemic) is possible but insufficient in presence of differential missingness.

Mitigation. Immediate steps

- Protocol amendments may be another important mitigation step. Such protocol amendments may include
 - Sample size changes
 - Changes in the duration of follow up
 - Changes of visit time windows for dosing and assessments
 - Sample size increase just to maintain power assumes a dilution of the treatment effect. A replacement strategy for patients with too many missed events (dosing or assessments) may be more meaningful
 - Prolongation of follow up to cover missed assessments may be meaningful. It would still allow interpolation to estimate the assessment at the planned visit. However prolongation can lead to increased drop out rate
 - Prolongation of follow up for missed doses only may be a meaningful alternative. It would however make the definition of an analysis time point for a chronic study more difficult
 - Change of time windows may help only when we believe that the Covid-19 interruption was rather short or the assessment/dosing intervals were long enough

Mitigation. Immediate steps

- It may be good to have protocol amendments in place allowing more flexibility later on
 - To be able to have enough data at the analysis stage to «repair» the damage by Covid-19 pandemic
 - Or in a situation where we really do not know what we will see at the end
- At the end teams need to think also about combination of elements, for example
 - Sample size allowing patient replacement and prolongation of follow up
- It may be good to consider data collection through virtual visits if traditional visits cannot take place due to Covid-19 pandemic
 - In such a case we should look at the data collected during traditional visits and those data collected during virtual visits and evaluate comparability of these data and whether data from traditional visits and virtual visits can be combined
- Finally, teams should continue to enroll patients during the pandemic only in centers where centers can ensure treatment and safety of patients even when this strategy embarks risk to enroll different patients as originally intended (different regions, centers, age groups etc.). This may make generalization of results more difficult. Otherwise, enrolment interruption may be the better choice

Mitigation. Later Steps at analysis

- Real mitigation steps are likely to come later at the stage of the analysis. They will include
 - How to handle missing doses due to Covid-19 pandemic
 - How to handle missing assessments due to Covid-19 pandemic
 - How to handle Covid-19 related adverse events and deaths
 - Further indirect impact due to the pandemic situation may be indication specific and likely more difficult to repair
- The estimand concept is a good framework to handle this. We need to carefully evaluate the different attributes of the ICH E9 (R1) focusing on the objective of the study and how to best address it. Probably, most important is to answer first what we want:

Treatment policy estimand:

Do we want to estimate a treatment effect with or without presence of Covid-19 pandemic ?

Hypothetical estimand:

Do we want to estimate a treatment effect in the absence of Covid-19 pandemic ?

Mitigation. Later Steps at analysis

- In case of a treatment policy estimand we should strictly follow the analysis plan without special attention to Covid-19. Missing events due to Covid-19 pandemic are the same as missing events not due to Covid-19 pandemic
- In case of a hypothetical estimand we need first to decide what this means. In principle we decide to estimate the treatment effect as if the Covid-19 pandemic did not take place. But then we need to specify further:
 - *What does this mean for missing doses due to Covid-19 pandemic?*
 - *How do we handle missing assessments due to Covid-19 pandemic?*
 - *How do we handle Covid-19 related adverse events or death?*

Mitigation. Later Steps at analysis

Estimand frame work

- We need to introduce new Covid-19 pandemic related intercurrent events (ICE)
 - *Treatment interruption due to Covid-19 pandemic*
 - *Treatment withdrawal due to Covid-19 pandemic*
 - *Treatment withdrawal due to Covid-19 infection or suspected infection*
 - *Death due to Covid-19 infection or suspected infection*
- In addition we need to differentiate for missing assessments/visits if they are due to Covid-19 pandemic or not
 - Non Covid-19 pandemic related missing data are handled according to the analysis plan for the estimand chosen generating the missing data
 - Missing data caused by Covid-19 pandemic related intercurrent events as above need to be handled according to the Covid-19 pandemic specific estimand
 - Therefore, we need to have as complete as possible documentation on Covid-19 related intercurrent events and missing data
- These events may need further specification (patient choice, investigator choice or pandemic lockdown)

Some initial recommendations

- Generally, in most cases we might **not** be interested in a treatment policy estimand for Covid-19 related intercurrent events and missing data. That is not what we should be interested in (assuming that the Covid-19 pandemic does not become permanent)
 - The result of such a choice could make the result difficult to interpret after the pandemic
- Often, the estimand of interest is a hypothetical estimand with the attempt to estimate what we would have observed without Covid-19 pandemic
 - This approach will usually have weaknesses in the estimation procedure. But as long as sufficiently unaffected data are available it could work
 - There is an ethical reason to keep study results as much as possible to the original hypothesis
 - We need to explore when such a hypothetical estimand can no longer be estimated. Knowing such limits now would help defining adequate protocol amendments for patient replacement
 - Estimation procedures for hypothetical estimands will likely be study or at least indication specific

Some initial recommendations

- We also need to think about how to handle Covid-19 related events, i.e. primarily adverse events and deaths due to confirmed or suspected Covid-19 infection
- Given the difficult situation in testing for Covid-19 we should not differentiate between confirmed and suspected infections
- For the analysis we can summarize such events separately, for example
 - Censor such events in the main time to event analysis in case further patient specific causes can be ruled out
 - Ignore them in the main summary frequency table in case further patient specific causes can be ruled out
- Such rules however should always be thought by the study team and are generally study specific.
- General procedures/standard outputs for the reporting of Covid-19 events may be useful as well.

Summary

- The Covid-19 pandemic affects studies at different degree. Studies in chronic diseases and elderly patients are specifically prone to be seriously affected including many studies in Neuroscience
- We need to differentiate between immediate mitigation steps required now and later mitigation steps required specifically at the analysis stage
- Immediate mitigation steps include adequate documentation of Covid-19 pandemic related intercurrent events and missing data as well as Covid-19 induced events like AE and death. Specific protocol amendments to prolong follow up or increase of sample size may also be needed
- Later mitigation steps are recommended to be based on the estimand frame work where hypothetical estimands are recommended for Covid-19 pandemic related intercurrent events and missing data. Since such hypothetical estimands will come with uncertainties in the estimation procedure early discussions with HA are recommended. Covid-19 related events (AE and death) have to be handled separately