EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 March 2020
EMA/158330/2020
Committee for Human Medicinal Products (CHMP)

Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials

Draft

Due to the urgency, this guidance is issued with a 4-week public consultation. It should be noted that due to the rapidly evolving situation further updates to this guidance are possible and likely.

Draft agreed by Biostatistics Working Party	March 2020
Adopted by CHMP for release for consultation	25 March 2020
Start of public consultation	25 March 2020
End of consultation (deadline for comments)	25 April 2020

Comments should be provided using this template. The completed comments form should be sent to Biostatistics@ema.europa.eu

Keywords	COVID-19, ongoing clinical trials, protocol deviations, data collection, trial integrity, interpretability, DMC, Scientific Advice

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Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials

BSWP would like to acknowledge the impact of the Coronavirus disease (COVID-19) on trial participants as well as of the resulting measures taken to address the pandemic on methodological aspects of ongoing trials. It is foreseeable that the COVID-19 pandemic will interfere with the conduct of many ongoing trials, also with the collection, analysis and the interpretation of clinical trial data.

Most importantly, patient safety is paramount and at the heart of every decision taken, regardless of any potential consequences for an ongoing trial. Beyond this, it is an ethical mandate to proceed with a trial that has been started as long as there is an opportunity that the efforts taken by patients and physicians can benefit drug development and patient care. Although it might be desirable from a methodological point of view to continue trials or, in some cases, pause them temporarily, Sponsors are strongly recommended to integrate all available knowledge from the ethical, the medical, and the methodological perspective into decision making about the future conduct of a trial while carefully considering advice from regulatory and healthcare authorities responsible for patient and employee safety. Reference is made to other guidance related to the COVID-19 pandemic, including (Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic (EMA/141885/2020)).

At this point in time it is not possible to give general applicable advice on how the different aspects related to the pandemic should be handled, as implications on clinical trials are expected to be manifold. Impact on the data collection, analysis and interpretation of results for each trial will need a thorough case-by-case assessment.

BSWP would like to raise the following major points for consideration to Sponsors whose ongoing clinical trials are or might be affected:

- In light of the inevitable priority setting due to patient and employee safety and availability, Sponsors are advised to pre-plan how systematic deviations resulting from the measures and individual decisions related to the COVID-19 pandemic are captured. These decisions were by nature not planned before start of the trial. Such information will prove valuable in the assessment of the potential impact of these decisions on the trial outcome and should help distinguish between 'affected' and 'unaffected' data. In order to assist efficiently with the identification of deviations related to the pandemic that are of major importance for interpretation of trial results, Sponsors are encouraged to define a systematic way to record protocol deviations and capture related reasons.

- Data collection should preferably not stop and should continue as long as possible. However, potential risks for study participants when undergoing study-specific procedures, take priority in decisions taken by patients and health institutes. The external validity of trial outcomes may be affected by the presence of different trial populations: some patients were present in the trial before the start of the pandemic; some during the pandemic while possibly exposed to associated measures; and some after the end of the pandemic. Measures taken in relation to the COVID-19 pandemic may interfere with study treatments. In order to be able to identify and address such concerns, sufficient amount of information on pandemic-related measures and whether trial patients or trial conduct were affected, as well as on the subpopulations of exposed / non-exposed, and infected / non-infected patients will be necessary to study the impact on the treatment effect. Sponsors should collect this information to the extent feasible, and in a pragmatic manner.

Risk-assessment of the impact of:

(i) COVID-19 potentially affecting trial participants directly and

(ii) COVID-19 related measures affecting clinical trial conduct

on trial integrity and interpretability is recommended. Sponsors are advised to contemplate an analysis of the accumulating trial data in order to evaluate the implications on recruitment, loss of patients during the trial, ability to record data and ability to interpret the treatment effect in light of the pre-, during and post-pandemic measures phases. It is understood that risk assessment should be part of the trial monitoring activities and could be performed on aggregate and blinded data with the intent to inform the likelihood of the trial to deliver interpretable results, not with the usual intent to confirm the likelihood of the trial being successful. Nevertheless, a more thorough analysis may be warranted. It is recommended that such an analysis of the trial data is conducted by an independent Data Monitoring Committee (DMC), which may already exist for the trial. If not, an independent DMC should preferably be established, following the necessary procedures regarding Ethics Committees and relevant competent authorities. This will ensure that the Sponsor can preserve trial integrity as much as possible. The grounds for the decision of performing such analysis should be documented, as well as the reasons for modifying the timing of any planned (interim) analysis. If a DMC is already in place, it might be important to revise the DMC charter accordingly, including considerations to increase its methodological competence. Emphasis is put on the purpose of the analysis discussed here which is risk assessment and to advise on follow-up actions, and not to perform an unplanned formal interim analysis for efficacy. The latter would come with all well-known concerns and associated precautions. As a general principle, there are strong scientific reasons to conduct trials as planned and implement changes only when there is a convincing scientific reason that it improves interpretability of results.

- Potential follow-up considerations or advises of the DMC may include the following:
    - Recommendations on how to re-start usual trial operations;
    - Recommendations of additional measures when completing the trial after the pandemic (e.g. validation of outcomes that were measured differently);
    - The need to adjust the trial sample size;
    - Additional analyses (to be included in the Statistical Analysis Plan) to investigate the impact of the three phases (pre, during, and post COVID-19) to understand the treatment effect as estimated in the trial;
    - Proposals to deal with any identified potential sources of bias such as missing values, newly identified intercurrent events or other unforeseeable required changes to trial elements.

Major changes in the conduct of a trial should follow the local regulations and be approved by Ethics Committees. Discussion with relevant competent authorities is encouraged and COVID-19 related guidance should be consulted.

BSWP would encourage Sponsors to take these points into consideration and to seek Scientific Advice on these matters early in the process. Sponsors should also rest assured that these topics will be thoroughly reflected on during the assessment of affected clinical trials data submitted to EMA for Marketing Authorisation Applications.