EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 June 2020
EMA/158330/2020 Rev. 1
Committee for Human Medicinal Products (CHMP)

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

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| 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 |
| Update agreed by Biostatistics Working Party | 11 June 2020 |
| Adopted by CHMP | 26 June 2020 |


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| 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

The Biostatistics Working Party (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 COVID-19 pandemic on methodological aspects of ongoing trials. It is foreseeable that the COVID-19 pandemic will interfere with the conduct of many ongoing trials, not limited to the collection, analysis and interpretation of clinical trial data.

Most importantly, safety of study participants is paramount and must be 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 so that the efforts taken by study participants and physicians can benefit drug development and inform 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, medical, and methodological perspective into decision making about the future conduct of a trial while carefully considering advice from regulatory and healthcare authorities responsible for study participant and employee safety. Reference is made to other guidance related to the COVID-19 pandemic, including (Guidance on clinical trial management during the COVID-19 pandemic).

At this point in time it is not possible to provide general advice on how the different aspects related to the COVID-19 pandemic should be handled, as implications on clinical trials are expected to be manifold. Impact on recruitment, 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 study participant 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 the 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 data 'affected' and 'unaffected' by the COVID-19 pandemic. In order to assist efficiently with the identification of deviations related to the COVID-19 pandemic that are of major importance for interpretation of trial results, Sponsors should ensure that their existing systems are able to record pandemic-related 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 study participants and health institutes. Measures taken in relation to the COVID-19 pandemic may interfere with study treatments, study assessment schedule and individual participants' observation time. It can be expected that study participants within a certain trial will be unequally affected by such general (i.e. external to the trial) COVID-19 pandemic measures: some study participants may already have completed all study relevant activities and recorded measurements before pandemic-related issues started impacting the trial; for other participants, the main individual study phase might fall during a time when it can be affected by the COVID-19 pandemic. Where preparation for the pandemic situation is

still possible, investigators should consider which information is essential for the interpretation of the trial and whether an alternative method of data collection might be warranted.

- In a pandemic situation, capability and willingness to follow the trial protocol is expected to vary between and within trial participants. All aforementioned issues are assumed to be of particular relevance in multi-centre and multi-regional clinical trials. Any attempt to address those issues at the time of study reporting will require information external to the trial concerning COVID-19 pandemic measures per region and per study site. Such information pertains for example to dates and duration of (partial) lockdowns and travel restrictions, as well as any further measures which would affect recruiting study sites. On the individual participant level, any available information concerning COVID-19 testing or infection status should be recorded in trial documentation whenever possible.

  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 study participants during the trial, ability to record data and ability to interpret the treatment effect. It is understood that risk assessment should be part of the central trial monitoring activities and should primarily be performed by the Sponsor 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. Risk assessment should focus on quality and reliability of the data from a trial conduct perspective and should consider the impact of intercurrent events (e.g. treatment discontinuations) and missing data arising from the COVID-19 pandemic on the analysis and interpretation of the data. The estimand framework provides a comprehensive approach to articulate this impact analysis.

  A more thorough analysis based on blinded review may be warranted, but the use of unblinded data is not recommended. Any analysis that bears the risk, however small, of unblinding should be specified a priori and conducted independently of the Sponsor supervised by an independent Data Monitoring Committee (DMC). The purpose of any thorough review should be risk assessment and to advise on follow-up actions, not to perform an unplanned formal interim analysis for efficacy to claim trial success. The grounds for the decision for performing this typically blinded review should be documented and properly justified. Detailed justifications are required for any resulting amendments to the trial protocol, e.g. reasons for proposals to modifying the timing of any planned analysis.

  If not yet in place, an independent DMC should preferably be established for all trials affected by the COVID-19 pandemic, following the necessary approval procedures regarding interaction with Ethics Committees and relevant competent authorities. This will ensure that the Sponsor can preserve trial integrity to the greatest extent possible, even though the final decision about modifications of the trial are under the responsibility of the Sponsor. If a DMC is already in place, it might be indicated to revise the DMC charter accordingly, including considerations to ensure necessary methodological expertise for its mandate.

- Potential follow-up considerations based on the risk assessment may include the following:

  - proposals to deal with any identified potential sources of bias comprising identification of newly emerging intercurrent events or missing values, or other unforeseeable required changes to trial elements;

- the need to adjust the trial sample size;
- recommendations from a trial participant's safety perspective on how to stop, pause or re-start the trial;
- recommendations of additional measures when completing the trial after the pandemic (e.g. validation of outcomes that were measured differently).

Substantial changes in the design and conduct of a trial should follow the local regulations and be approved by Ethics Committees and the relevant competent authority unless directly mandated by the need to assure the safety of participants. 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 if substantial modifications to the original protocol are considered necessary. Further and updated information on dedicated support to COVID-19 related aspects can be found on the EMA website. Sponsors should also rest assured that these aspects related to impact on recruitment, data collection, analysis and interpretation of results will be thoroughly reflected upon during the assessment of affected clinical trials data submitted to EMA for Marketing Authorisation Application.