EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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

Written by the EMA Biostatistics Working Party

BBS virtual seminar on Impact of COVID-19 on clinical trials

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Disclaimer

The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties

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- Coronavirus disease and EMA's response to the pandemic
- Draft points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials
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Coronavirus disease (COVID-19) and EMA's response

- *https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19*
- **The European Medicines Agency (EMA) is contributing to global efforts to save lives during the COVID-19 pandemic by expediting the development and approval of safe and effective treatments and vaccines, supporting the continued availability of medicines in the European Union (EU), and providing reliable information to patients and healthcare professionals.**
- Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus.
- On 30 January 2020, The World Health Organization (WHO) declared the outbreak a public health emergency of international concern. On 11 March 2020, WHO characterised COVID-19 as a pandemic.
- There are currently **no authorised vaccines or treatments** in the EU to prevent or treat COVID-19. However, there are ongoing clinical trials evaluating potential treatments.
- The COVID-19 EMA pandemic Task Force is the main tool of EMA and the European medicines regulatory network for enabling EU Member States and the European Commission to take **quick and coordinated regulatory action** during the pandemic.

EMA's response to COVID-19 pandemic

www.ema.europa.eu

Guidance for medicine developers and companies on COVID-19

- Early support for medicine and vaccine developers
- Advice for sponsors of clinical trials for COVID-19 treatments and vaccines
- Guidance on regulatory expectations and flexibility

- Advice for sponsors of clinical trials affected by the pandemic

Guidance is available for clinical-trial sponsors on how they should **adjust the management of clinical trials** and participants during the COVID-19 pandemic. This covers concrete changes and protocol deviations for dealing with extraordinary situations, such as the need for isolating participants, limited access to public spaces and the reallocation of healthcare professionals:

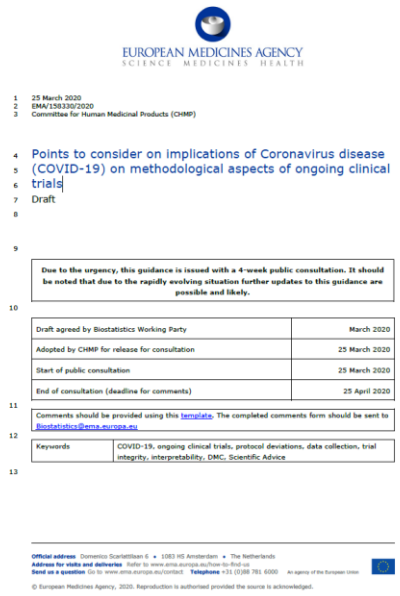
Good clinical practice: Guidance on clinical trial management during the COVID-19 pandemic

Guidance is also available on the **actions** that sponsors of affected clinical trials should take to help **ensure the integrity of their studies** and the interpretation of the study results while safeguarding the safety of trial participants as a first priority:

Implications of coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials

In line with this guidance, EMA will be flexible and pragmatic during the assessment of affected clinical trial data submitted to the Agency as part of marketing authorisation applications.

Draft PtC on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials



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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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25 March:

- Draft agreed by Biostatistics Working Party (BSWP)
- Adopted by the Committee for Medicinal Products for Human Use (CHMP) for a 4-week public consultation

25 April:

- End of public consultation: Comments from 30 stakeholders were received

28 May:

- Release of updated Points to Consider?

Motivation

- 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**
  - Implications on clinical trials are **manifold**
  - **No general advice** how to handle them
  - Thorough **case-by-case assessment** is needed
- But… in this document BSWP **highlights major points** that Sponsors could take into consideration **in case** their trials are affected

Patient safety first

- **Patient safety is paramount**, regardless of potential consequences for an ongoing trial
- Ethical mandate to **proceed with a trial as long as there is an opportunity** to benefit drug development and patient care
- **Integrate all available knowledge**: ethical, medical, **methodological** aspects to be considered in decisions whether to continue, pause or stop the trial

Systematically capture deviations and record related reasons

"Pre-plan how systematic deviations resulting from the measures and individual decisions related to the COVID-19 pandemic are captured and record related reasons."

- Such measures and decisions were **not planned before** the start of trial
  - Record ALL available information; 'pre-plan during trial' is better than react at end of trial
- Information will be **valuable to assess the potential impact** on trial outcome
- Better understand **when** trial data might be affected by imposed measures
- No specific guidance on **how,** Sponsor is free to choose but a **systematic** way will facilitate better analysis, assessment, interaction, etc.

Potential impact on external validity – what else to record?

"The external validity of trial outcomes may be affected by the presence of different trial populations. (…) Measures taken in relation to the COVID-19 pandemic may interfere with study treatments."

- Population: patients present in trial before, during and after end of pandemic
- **Sufficient amount of information** on the following aspects is needed to study the impact on the treatment effect:
  - **pandemic-related measures**
  - **whether trial patients or trial conduct were affected**
  - **subpopulations of exposed / non-exposed, and infected / non-infected patients**

Risk assessment of impact of COVID-19 on ongoing trials

"Assess the impact and risk of COVID-19 potentially affecting trial participants directly and of COVID-19 related measures affecting clinical trial conduct on trial integrity and interpretability."

- **Not an unplanned formal interim analysis for efficacy**!
- Analysis of the accumulating trial data
  - **Evaluate the implications** on recruitment, loss of patients during the trial, ability to record data and ability to interpret the treatment effect.
- Most investigations can be covered by usual **trial monitoring**
- Based on **aggregate and blinded data**

Data Monitoring Committees (DMC)

- In some cases a more thorough analysis may be warranted
- To preserve trial integrity, it should be conducted by an (independent) DMC
- Additional competencies might be needed in an already established DMC
- Establishment of DMC could be considered if necessary

Potential measures to address pandemic impact

- How to re-start usual **trial operations**
- **Additional measures** when completing the trial after the pandemic
  - e.g. validation of outcomes that were measured differently
- Adjust trial **sample size**
- **Additional analyses** to understand the treatment effect as estimated in the trial
  - To be included in the Statistical Analysis Plan
- Deal with any identified potential **sources of bias**
  - E.g. missing values, newly identified intercurrent events, other unforeseeable required changes to trial elements

Next steps

- Updating the points to consider – ***thanks*** *to all who commented !!!*
- Further changes expected
- Interaction with stakeholders
- Continuous scientific discussion expected

Summary

- Convincing scientific reasons needed to implement changes
- Consult COVID-19 related guidance
- Discussion with relevant competent authorities is encouraged (e.g. through Scientific Advice) early in the process

Record, report, assess and seek advice before reacting

Any questions?

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