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Human Medicines Division

# Draft responses to stakeholder comments on the Points to consider on the impact of COVID-19 on methodological aspects of ongoing clinical trials

The Biostatistics Working Party (BSWP) would like to thank all stakeholders for their valuable comments. Comments from 31 stakeholders were received during the public consultation phase (https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials). Due to the high volume of comments, it was not possible to address all comments individually. However, a summary of the main points raised is presented by common themes along a brief outline how BSWP addressed the comments in the updated version of the document (published on 26 June 2020).

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# 1. Comments related to the scope of the document

- Widen the scope to other pandemics and future trials
- Widen the scope to new trials and prevention of COVID-19 disease
- Widen the scope to include safety data
- Provide guidance on possibility to modify success criteria
- Provide guidance which approaches to compensate for lost information are supported by BSWP
- Provide guidance for management of PIPs and PIP modifications/compliance checks
- Provide guidance on recruitment overall
- Include section on conversion of existing trials into adaptive trials
- Reflect on the role of RWD (observational studies), i.e. used to address missing data
- Narrow the scope on key measures affecting the conclusion of trials
- Address impact on estimands
- Provide guidance whether regulators should be consulted about study/site closures
- Provide guidance and align opinion on processing of personal data

***BSWP response:***

The points outlined in this document address in particular the impact on ongoing clinical trials, which are also applicable to future pandemics and future trials. Although the points raised can be taken into consideration for newly planned trials for treatment or prevention of COVID-19, no specific guidance on addressing these can be provided in this document.

This document is intended to provide high-level reflections and Sponsors are encouraged to seek dialogue with regulatory authorities through appropriate channels (e.g. scientific advice) should they feel changes to existing protocols or analysis plans are needed and to discuss specific aspects such as, but not exclusively, modification of success criteria, impact on estimands and conclusion of trials, compensation for loss of information, recruitment, adaptive designs, role of RWD to address missing data, study or site closure, implications for safety data, impact on PIPs and PIP modifications and use of additional Real World Data.

# 2. Comments related to identification of exposed/infected/affected patients, trials, or study sites:

- Sponsors to reflect about which data on impact of trials is needed in real-time and how to collect it (in contrast to data that can be collected retrospectively)
- Ensure text/comment fields already available in CRF
- Distinguish between quarantine measures and patients having contracted COVID-19 disease
- Distinguish between collective measures and individual decisions
- Ask for clarification and report on how pandemic measures impact trials

- Provide guidance on appropriateness of trial adaptions:
  - What if risk assessment leads to IA of efficacy?
  - Ask for compelling rationale for changing IA
- Discuss the impact on statistical power and probability of success
- Discuss the acceptability of delayed/postponed analyses
- Discuss data integrity related to un-/monitored data (source data verification)
- Use risk-proportionate approach to documentation
- Provide guidance on how to define/assess diverging populations:
  - Age distribution of COVID-19 confirmed cases distinctly different to age distribution of fatality rate. Evaluate effect of age on CT participants and on missing values in CRFs
  - How to differentiate/assess impact on trial, country, region, study site, patient, data point level (i.e. representativeness)
  - How to set dates (e.g. intrinsic/extrinsic), if at all possible, and recommend common definition (e.g. region specific or general)
    - Even if dates defined, not all patients affected the same way
  - Determination of exposed/non-exposed is unclear and difficult
    - Ill-defined and inconsistent criteria
    - Date of infection must be taken into consideration
    - Proposal to use confirmed terminology infected/confirmed negative/unknown
    - Effort better spend collecting pertinent info on pandemic related measures
    - Impact on control group unclear
    - Clarify need for testing, who pays and whether additional consent needed
  - Define "interpretability" of treatment effect
  - Assumption of consistency of treatment effects pre- and post-pandemic, and rationale for comparison of treatment effect
  - Analytical approaches to combine data
  - Adaptive designs accounting for unplanned changes
  - Relation to guidance on subgroup analysis on post-hoc defined groups
  - "Moving window" analysis to show changes in treatment effect
  - Granularity (e.g. suspected infection, start/end data of symptoms)
  - Gauge impact on all data
- Not helpful to continue data collection when too high proportion disrupted
- Timeframe for data collection different for efficacy and safety
- Patients need to be informed about risks linked to participation in trials and their changed B/R should be investigated

***BSWP response:***

The text throughout the document was amended to acknowledge the stakeholders' concerns that the impact of COVID-19 on trials and patients are expected to unfold in a great variety. It is not possible to give specific advice on how and when to collect which information that would be applicable to all trials. Instead, Sponsors are encouraged to reflect upon how their trials could be affected, to record the necessary information to their best ability to be able to assess the expected impact. It is recommended that scientific advice is sought before implementing changes to the study protocol or statistical analysis plan. Such collected information will allow for an informed discussion with regulatory authorities on the necessity to amend study protocols or analysis plans.

# 3. Comments related to the ICH E9 (R1) Addendum on estimands:

- Align document with E9(R1) framework
- Clarify that trial monitoring does not assess probability of trial being successful
- Scenarios from risk assessment should inform strategies for intercurrent events (IE), methods of estimation and sensitivity analyses
- Clarification whether pre-specified plan needed for all trials or only those expected to be impacted by COVID-19
- Emphasis that aim is to single out COVID-19 related deviations
- Provide more examples and how to address them
- Provide guidance on how to record protocol deviations:
  - CDISC works on unique standard
  - in relation to FDA guidance
  - deviation from established GCP
  - App or an EDC would be useful
  - request metadata and codes
- How to handle PP analyses
- Reminder that E9(R1) allows for granularity to identify intercurrent events (IE)
- Provide guidance on re-assessment of:
  - scientific question
  - estimand of interest
  - primary and secondary endpoints
  - success criteria
  - treatment effect of interest as it might change
  - methods for handling missing data and potential impact on estimand (e.g. reasons of missingness, validity of MAR/MCAR assumptions, inclusion of baseline or post-baseline covariates, exclusion of affected centres, suitable imputation methods, composite

strategies (missing=failure), interval censoring in T2E endpoints, role of RWD to address missing data, replacement of patients)

  - sensitivity analysis
  - population (modified ITT)
  - intercurrent events (IE) and strategies to handle them
    - appropriateness of hypothetical strategy for IE related to pandemic
  - new IEs
    - switching to virtual assessments
    - discontinuation due to safety risk (e.g. exclusion of such observations)
  - Streamlined process to assess such changes
- Clarify role of data monitoring committees (DMC) as only Sponsor should define statistical approach to IE and missing data
- Provide recommendations on which alternative data collection methods are acceptable and how to validate assessments
- Mention other sources of bias/variability (e.g. assessment at home vs at clinic, laboratory measurements)

***BSWP response:***

Stakeholders are encouraged to consult the frequently updated GCP guidance for further information on the recording and reporting of protocol deviations.

It is not possible to provide detailed advice on how to handle COVID-19 related impact on methodological aspects (e.g. on endpoints, analysis method, handling of missing values, intercurrent events and strategies to handle them) as this will be different for each trial. However, Sponsors are encouraged to carefully reflect how certain COVID-19 might impact their trial and should seek advice to discuss the need for potential changes to the protocol or analysis plan. The estimand framework might prove helpful to discuss the implications of COVID-19 measures on ongoing trials.

# 4. Comments related to the necessity and role of DMCs:

- Blinded analysis of accumulating data by DMC not supported:
  - Trial integrity is paramount (and Sponsor‘s responsibility) but unblinded access not always needed
  - Sample size re-estimation & SAP amendment should not be informed by unblinded data
  - Clarification on recommendations based on unblinded analyses and circumstances requiring DMCs looking at unblinded data
  - Do not allow for additional analyses based on unblinded treatment groups without strong reasons
  - Unplanned analyses need to be justified and documented (defined a priori)
  - Provide specific guidance on blinded and unblinded analyses

- Provide guidance on post-hoc changes to analysis plan
- Discuss acceptability of early termination of trials and conducting final analysis earlier than planned
- Discuss alternatives to DMCs:
  - structures differ in Europe (e.g. In UK also TMGs, TSC)
  - Some decision can be taken by trial management personnel, sponsor personnel (internal firewalled grouped), Steering Committee without access to unblinded data
  - Sponsor is free to choose any expert
- Provide guidance for which trials a DMC should be established but allow flexibility whether to do so
- Additional assessments or creation of new DMCs are impractical:
  - fast decision needed and DMC cannot always be involved
  - new DMC members unfamiliar to trial cannot add much
  - not enough time to set up a new DMCs
  - too many trials that might need a DMC (burden on experts)
  - create public (national) DMCs
  - what to do if cannot establish new DMC
- Clearly describe responsibilities of DMCs (safety, study integrity) and request reasons for divergences of tasks:
  - Points raised not all in remit of DMC (i.e. how to re-start trial operations)
  - Clarify which 'increased competences' a DMC might need

***BSWP response:***

In response to the comments received, BSWP clarified the wording to emphasise that the protection of the trial's integrity is of utmost importance. Hence, necessary risk assessments of COVID-19 impact on ongoing trial should be conducted on blinded data and by independent committees (not necessarily a DMC) if trial integrity is potentially at risk.

# 5. Comments related to Scientific Advice (SA):

- Refer to guidance documents and set out criteria for when to seek SA
- It is impractical to have SA for each trial individually (as too many ongoing trials)
- Will SAWP be able to handle all requests?
- How will EMA prioritise requests for timely responses
- NCAs might be overwhelmed by protocol amendments
- Provide information on how interaction with regulators is anticipated (e.g. SA, pre-submission meetings, meetings with Rapporteurs)
- Provide a streamlined process for interaction and SA

- Redesign SA process to open-access review process for common issues
- Create expedited process
- SA should be free of charge

***BSWP response:***

Sponsors are encouraged to seek scientific advice to discuss planned changes to study protocols or statistical analysis plans. EMA will try to facilitate such requests to the best of their ability and further guidance should be provided if common and recurrent issues are seen.

# 6. Comments related to Marketing Authorisation Applications:

- Reassure a flexible and pragmatic approach to inevitable deviations in assessments and to protocol deviations
- Provide guidance on expectations for risk-assessment
- EMA review of changed SAP before database lock?
- Establish CHMP working group to provide advice on which analyses are acceptable
- Provide accelerated timelines for review

BSWP response***:***

It is not possible to provide specific guidance of which protocol changes might be acceptable as the circumstances will be different for each development programme and trial. Sponsors are encouraged to seek scientific advice for their trials before modifying study protocols or analysis plans. Information on accelerated timelines and further support to developers are communicated on the EMA website, which should be monitored regularly.

# 7. Comments related to editorial changes and clarifications:

- Including sub-headings for better structure
- Provide framework for challenges and categorise types of trials and disruptions so that unified approach to analysis and interpretation
- Add glossary
- Add references (e.g. to DMC Guideline)
- BSWP: Expand abbreviation on first use (l18)
- Risk assessment should be new bullet point it is as new topics (l59)

***BSWP response:***

These comments were considered and reflected in the updated version; clarification of specific terminology and aspects were included, whenever possible.

# 8. Comments related to engagement with stakeholders:

- BSWP to collaborate with stakeholders (e.g. PSI, EFPIA, PhRMA, academics) and enhance its membership and procedures
- Create a public meeting alongside other regulatory bodies to review archetypes and open-access SA review process for common issues
- Align with international health authorities and NCAs (too many guidelines pose too much burden on Sponsors) – stakeholder happy to share summary of differences in guidelines
- Participate in ICMRA workshops
- Create multi-stakeholder group to develop guidance on definition of pandemic phases

***BSWP response:***

BSWP will contemplate these suggestions and inform stakeholders on future possibilities to interact on these aspects.