EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 April 2020

Submission of comments on Points to Consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials (EMA/158330/2020)

Comments from:

Name of organisation or individual
EFPIA + European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) + Association of Clinical Research Organizations (ACRO) + European CRO Federation (EUCROF) + EUROPA-BIO + Vaccines Europe (VE)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The organisations listed above welcome the release of this Point to Consider (PtC) document, and the opportunity to comment on this important and much needed document. In addition to the main points as detailed below, we have more specific comments on the text as detailed in section 2. • **Flexible and pragmatic approach**: in the context of the unprecedented and fast evolving COVID-19 situation, we would like to seek reassurance that during the assessment process inevitable deviations that will have occurred will be approached in a flexible and pragmatic way. This message would benefit from being further emphasized in the PtC. • **Scientific Advice:** the recommendation to seek scientific advice is very much appreciated in these challenging times. It would be helpful to have text clarifying how CHMP/SAWP/BSWP anticipate this should be done considering that multiple studies are likely to be impacted by the pandemic, and how the agency intends to prioritise between requests for timely advice on specific trials. If possible an expedited process (e.g. in writing or via teleconference) by which to seek scientific advice on Covid-19 related issues would be helpful. • **Patients affected versus unaffected by COVID-19:** identification of patients affected versus unaffected by COVID-19 related measures seem inadequate to address impact on estimated treatment effects. Patients will be affected at different times, both assessed in calendar time and study follow-up, and in different ways. Hence a discussion on how intercurrent events caused by COVID-19 related measures should be approached would be welcomed. • **Data Monitoring Committee (DMC):** the draft PtC suggests a major role for a DMC in making important decisions in ongoing trials. Many of these responsibilities belong to sponsor trial management personnel, as the associated issues can be addressed without access to unblinded data. If important decisions are advised by unblinded data, this should be done through a DMC. If a DMC does not exist already, it may not be operationally feasible to establish one as	

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	suggested. We advise that the document be revised to indicate that assessing trial integrity remains the responsibility of the sponsor with DMC input and consultation as appropriate.
	
	• **Topics not addressed in the draft PtC:** there are additional topics related to the COVID-19 pandemic that are not currently addressed in the document, but it might be helpful to receive some guidance from the agency on:
	  • **Observational studies:** the scope of the guidance may be broadened to include observational studies for certain aspects.
	  • **Documenting changes:** in documenting changes resulting from the pandemic, there is concern that Clinical Trial Units at National Competent Authorities might be overwhelmed by protocol amendments. Does the Agency consider introducing streamlined processes for interactions / seeking scientific advice with its working parties (SAWP, PDCO, …) and / or in the documentation of changes to estimands and statistical analysis (or can those changes be documented only through amendments to the trial SAP)?
	  • **Modifications to success criteria:** some trials might formally fail statistical testing only because recruitment to the trial or collection of data for recruited patients' needs to be terminated due to the pandemic. Can modifications to success criteria be considered and, if so, what methods and justifications would be supported?
	  • **To compensate for information lost because of the pandemic**: it might be envisaged to increase sample sizes, extend follow-up times in time to event trials, or treat beyond the primary timepoint so that assessments can be made once site visits are again possible in order to validate assessments made remotely at the primary timepoint, or to facilitate modelling of outcomes that would have been observed at the primary timepoint. Are there other approaches to compensate for lost information that would be supported by BSWP?
	  • **Remote monitoring:** should there be any mention of trial monitoring in the document (e.g. central monitoring) to assess the completeness of safety data collected? This may be particularly relevant if sites switch to video consultations for trial visits, where it would be difficult to collect samples for lab tests.
	  • **Need for a glossary:** It would be beneficial if the PtC document could include a glossary of definitions of some of the terms used (e.g. "exposed	

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	and non-exposed"; "infected" and "non-infected"; "pre-, during and post-pandemic measures ") as these can be interpreted in different ways by different stakeholders. See further comments on individual paragraphs below. • **Add references to other relevant EMA guidance documents,** e.g. the 2005 guideline on DMC (EMEA/CHMP/EWP/5872/03 Corr/: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf) might be helpful.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Lines 32-35		*'At this point in time it is not possible to give general applicable advice on how the different aspects manifold. Impact on the data collection, analysis and interpretation of results for each trial will need a thorough case-by-case assessment.'* **Comment:** This statement is true but the text "*not possible to give general applicable advice*" could be worded rather more positively as it seems there are general points that can be given (and that's the purpose of this document). Also impacts should be included such as on intercurrent events and estimands. **Proposed change:** Impact on the ***intercurrent events, estimands,*** data collection, analysis and interpretation of results for each trial will need a thorough case-by-case assessment; ***impacts may differ depending upon the status of the trial when the pandemic started, nature of the target population, perceived risk/benefits of the IMP and types of endpoints.***	
Lines 39-40		*"Sponsors are advised to pre-plan how systematic deviations resulting from the measures and individual decisions related to the COVID-19 pandemic are captured."* **Comment:** Please clarify whether pre-planning is recommended for all trials or only those where implications are expected. In addition, it is suggested to remove "individual" as decisions may be addressed separately or together depending on how best to address the clinical question of interest. Moreover, the following sentence should also include	

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		'measures'. **Proposed change:** Reword sentence as follows: "Sponsors are advised to pre-plan how systematic deviations resulting from the measures and ~~individual~~ decisions related to the COVID-19 pandemic are captured ***for trials where implications can be expected***. These ***measures and*** decisions were by nature…	
Lines 41-46		"*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*." **Comment:** The eCRF may not be designed to accommodate a change to introduce a time-lag in capturing the required data. Rather, sponsors may need to make use of text/comment fields available in the CRF in order to avoid delays in capturing this data. The use of text fields will have obvious implications for any analysis. Additionally, it may be necessary to distinguish between protocol deviations due to general quarantine measures and those due to patients having contracted the COVID-19 virus. Feasible and pragmatic methods are called for, but can some guidance be given on methods for this recording that would be acceptable, considering that developing and rolling out new CRFs in the current situation, and data collection in full compliance with GCP, will not be possible for all trials? Consider adding examples of reason for protocol deviations (see proposed change).	

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		Proposed change: Sponsors are encouraged to define a systematic way to ***either manage prospectively deviations or*** record protocol deviations and capture COVID-19 related reasons, ***e.g. self-isolating, appointment cancelled, diagnosed with COVID-19***.	
Lines 47-49		*"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."* **Comment:** As recommended by the French agency, ANSM, and highlighted in EMA 'Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic' data completion by teleconsultation could be considered as a mitigation for missing data, and particularly for safety. Will the EMA PtC include details relating to the use of data outside visit windows or handling of variations in planned course of treatment? For example, when is an alternative data collection method acceptable to replace originally planned method (e.g., local lab vs. central lab), is it acceptable to collect patient report outcome (PRO) data remotely by sites via subject interview? Also, "*priority in decisions taken by patients and health institutes",* also refer to decisions taken by sponsors. **Proposed change:** ***Sponsors are expected to continue safety reporting according to EU and national legal frameworks (Directive 2001/20; CT-3). When per protocol physical visits are reduced or postponed, it is important that the investigator continue collecting adverse events and key efficacy data where possible from the participant***	

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		through alternative means, e.g. by phone. Other 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***, sponsors,*** and health institutes.	
Lines 49-52		*"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."* **Comment:** It is now acknowledged that COVID-19 was circulating in the population before its impact was recognized. Consequently, it is very difficult to define the start of the pandemic in individual countries. Similarly, it will be very difficult to define the end with strict accuracy. We therefore recommend that the guidance explains how sponsors should define the start and end of the pandemic, in order to establish harmonized criteria across EU competent authorities and sponsors. Add language to explain how sponsors should define the start and end of the pandemic. Are the "*associated measures*" mentioned here, measures associated with COVID-19, and if so would this include measures affecting them personally (e.g. treatment of COVID-19 if they were affected), or more general measures affecting the study site (e.g. quarantine, staff availability etc)? Also patients may have already completed their participation in the trial. **Proposed change:** … some patients ***were participating in, or had already***	

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		completed their participation in the trial…"	
Line 53		*"Measures taken in relation to the COVID-19 pandemic may interfere with study treatments."* **Comment:** It is not just the treatments that can be affected but also timing of visits, possibility of taking blood tests for lab tests etc. **Proposed change:** ..may interfere with study treatments ***and scheduled assessment procedures and times.***	
Lines 55-58		*"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. "* **Comment:** Sponsors are requested to provide information on exposed and non-exposed patients (in addition to reporting 'infected' confirmed and suspected cases of COVID-19). This comment relates to data on exposure. In general, it is not clear how it is possible to establish whether or not a patient has been exposed to the virus. While we could record patients that have been exposed to confirmed COVID-19 cases, in many countries less than 1% of the population are tested and not all individuals who are ill/or exhibiting mild symptoms are tested given the decision trees for testing are different in each country /State. In addition, patients could be exposed unknowingly (e.g. when coming into contact with hospital/clinic staff for clinical trial visit, in the supermarket, etc). Hence it may not be possible to confirm if a patient has	

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		been exposed to COVID-19 or not, and possibly prudent to expect 100% of patients have been potentially exposed. Signs and symptoms of COVID-19 and confirmed cases, where known, will be added to the list of AEs, however there is a large risk of under-reporting unless every subject in a clinical trial is tested for antibodies after the pandemic is over. Any classifications of patients into these sub-populations for data analysis purpose may be inaccurate, and additional analysis will be required to explore different classifications and treatment effect evaluations. This will need the trial SAP to be amended. Would it be possible to precise how to define the subpopulation of patients exposed to pandemic associated measures? **Proposed change:** We would recommend removing the recommendation for collecting pandemic exposure information or alternatively request further guidance how to manage this, given the data on exposure may be highly unreliable. **Comment:** To have the most complete data set possible to determine impact of COVID-19 on treatment outcomes, real world data options such as retrospective review of electronic health records (EHRs), subject self-monitoring tools, and/or claims data should be leveraged to identify COVID-19 impacts - as well as to help fill COVID-19-caused data gaps in patient clinical trial records. The information should be collected in such a way as to ensure the privacy rights of the patient (e.g. de-identified before reaching the sponsor). Such data could be used to substitute for or supplement trials that are failing to enrol. Can the Agency provide guidance on acceptable alternative methodologies that can be used to address missing data or gaps such as the use of real-world data or historical controls?	

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		Proposed change: Sponsors should collect ~~this~~ information to the extent feasible and in a pragmatic manner***, for example through retrospective review of real world data sources such as electronic health records (EHRs), subject self-monitoring tools, and/or claims data***	
Lines 59-62		*"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."* **Comment:** While it is acknowledged this risk assessment is the sponsor's responsibility, since the future acceptability of the clinical study data will be dependent of Agency's review, any specific expectations in terms of impact that the Agency has for this risk assessment would be appreciated, illustrated with examples, to guide sponsors and thus help risk assessment's standardisation. Impact of COVID-19 should also be assessed on main assessment criteria. Consider adding a 3rd point (see proposed change). Consider including examples of reason affecting participants (see proposed change). ***Proposed change:*** (i) COVID-19 potentially affecting trial participants directly ***(e.g. diagnosed with COVID-19, self-isolating)*** ~~and~~ (ii) COVID-19 related measures affecting clinical trial conduct on trial integrity and interpretability is recommended ***and (iii) COVID-19 related measures affecting main assessment criteria.***	
Lines 62-65		"*Sponsors are advised to contemplate an analysis of the*	

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		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." **Comment:** Rather than **contemplate** this activity provide more details for what sponsors should consider. This also supports sponsors conducts these analyses rather than a DMC as discussed above. Moreover, in multinational trials the consideration of pre-, during and post-pandemic phases as regards of impact on the trial might not be possible as in different countries these phases have different timing. Even the consideration of a country effect might not be possible as the disease spreads differently in different regions of one country. In addition, there might be seasonal effects (we really don't know yet) that impact the severity of the outbreak at different times in different countries. For a very small regional trial, it might be possible to define pre-, during and post-pandemic phases, but for larger and/or multinational trials, this will not be possible. Should the pandemic phases be defined by region (country) or overall or rather it may be more valuable to simply use additional analyses (see proposed change) **Proposed change:** Sponsors are advised to ~~contemplate~~ ***conduct*** *… to interpret the treatment effect* ~~*in light of the pre-, during and post-pandemic measures phases*~~ *using* ***additional analyses that are associated with various changes in study implementation, for example modality of endpoint assessment or alternative methods to compensate for missing data***.	

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Lines 65-71		*"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."* **Comment:** The sentence could be interpreted that for every trial affected by COVID-19 the analysis of the accumulating trial data should be performed by an independent DMC: As this is probably not what the PtC intended, we recommend to amend the sentence (see proposed change). Clarification that an informal analysis of the impact of COVID-19 on the study (blinded by the sponsor, or in more depth by an independent DMC) would not be considered by the Agency to constitute an interim analysis which would impact on type 1 error. Please elaborate on the risk assessment objective to "*inform the likelihood of the trial to deliver interpretable results*". Whether results will be interpretable or not will be highly dependent on the protocol specified approaches to missing data and intercurrent events such as treatment discontinuations. A treatment policy strategy may provide results that are interpretable in terms of treatment effect during a pandemic but otherwise not. Will it be acceptable to adopt a different strategy, such as hypothetical, for intercurrent event related to COVID-19 measures in order to obtain a more generally interpretable treatment effect? It may be helpful to evaluate a statistical power or probability of study success under assumptions on treatment difference independent of these study results (assuming the study is double-blind). A mention that this fact does not contradict	

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		the statement in the guidance will increase the comprehensibility of the sentence. **Proposed change:** *"It is understood that risk assessment should be part of the trial monitoring activities and could 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~~* ***treatment*** *being successful. Nevertheless****, if*** *a more thorough analysis* ***(e.g. of unblinded data)*** *~~may be~~* ***is*** *warranted.~~ It~~* ***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."*	
Lines 69-70		"*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*." **Comment:** Please clarify what kind of analyses could be performed by the independent DCM to help with risk assessment and whether "*a more thorough analysis*" is synonymous with "an analysis based on unblinded data" since the list of potential follow-up considerations is something that study teams should usually be able to discuss based on blinded data. In addition, we believe for an exploratory study, the need for a DMC to do such an analysis is not necessary and in most cases be handled by the sponsor. It is suggested to limit this suggestion to trials with potential registrational intent (see proposed change). In addition, if analyses are made on blinded data, there should be no concerns for trial integrity irrespective of how thorough such analyses might be. Could there be more general guidance on when an unblinded Interim Analysis would be warranted to assess the impact of	

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		COVID-19 measures on the risk of trial outcome? **Proposed change :** It is recommended **<u>for trials with potential registrational intent</u>** that such an analysis of the trial data is conducted by an independent Data Monitoring Committee (DMC), which may already exist for the trial."	
Lines 71-73		"*If not, an independent DMC should preferably be established, following the necessary procedures regarding Ethics Committees and relevant competent authorities*." **Comment:** Establishing DMCs in the current environment, and in particular when the remaining study duration is short, may not be feasible. **Proposed change:** *If* ***there is a need to establish an*** *independent DMC* ***when there isn't one in place****,* ***submit a substantial protocol amendment including the DMC charter and*** *follow****~~ing~~*** *the necessary procedures regarding Ethics Committees and relevant competent authorities*	
Lines 75-77		**"***If a DMC is already in place, it might be important to revise the DMC charter accordingly, including considerations to increase its methodological competence."* **Comment:** Please clarify what is meant by "to increase methodological competence". Does this refer to the composition of the DMC, and whether sufficient expertise is represented in the existing DMC to provide an appropriate risk assessment? Moreover, we recommend adding text to make clear that the fundamental role of the DMC is not changed (see proposed change). **Proposed change:**	

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		… competence. ***Primary responsibility of the DMC is to assure the safety of participating trial participants, therefore the DMC's assessment of the impact of modifications of trial conduct due to COVID-19 on patient safety is important to consider.***	
Lines 77-80		*"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."* **Comment:** Further considerations for unplanned efficacy or futility analyses, such as design and maturity of the study, may be undertaken before precluding these entirely. For example, type I error with group-sequential testing methodology allows changes to the number and/or timing of efficacy interims if not based on study outcomes. With that, it could be noted that sponsors should put forward a compelling rationale for why a change to interim analysis plans is required based on a COVID-19 risk assessment. The rationale should indicate why it is critical to make the proposed changes and argue why they are more appropriate than other options to mitigate the impact of COVID-19 (see proposed change). **Proposed change:** *"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****, unless justified and documented****. The latter would come with all well-known concerns and associated precautions."*	
Line 83		*"Potential follow-up considerations or advises of the DMC may include the following:"*	

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		Comment: Not all of these points should be under the responsibilities of a DMC as they likely lack the information on (changes in) the operational conduct the trial conduct. It would be important to note that sponsors should work closely with the DMC to lay out the deliverables and timelines and to provide them with the necessary analysis plan and codes to perform the needed analyses. We should recognize that DMCs may not have the expertise/capacity to advise on some of these considerations, such as how-to re-start usual trial operations, additional analyses to investigate the impact of the three phases. Therefore, close collaboration between DMC and sponsor is needed. Also, rapid decisions often need to be made and involvement of the DMC (including revising the charter) may be challenging in many situations. **Proposed change:** Potential follow-up considerations ***for the Sponsor (with*** or ***without*** advises of ***a*** ~~the~~ DMC***)*** may include the following:	
Line 86		*"(e.g. validation of outcomes that were measured differently);"* **Comment:** What would be an acceptable level of validation of outcome measures when changed from in-clinic assessment to remotely conducted assessments (e.g. e-systems)? What are the consequences if the required level of validation cannot be obtained? Please provide further details of what documentation will be needed to be provided to validate outcomes measured differently.	
Line 87		"The need to adjust the trial sample size;" **Comment:** Some caution may be noted that a DMC providing advice on	

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		the need for sample size adjustment may not always be appropriate, for example, if the DMC has previously reviewed unblinded interim data on primary efficacy endpoints.	
Lines 88-90		"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;" **Comment:** In light of potential changes to SAP as mentioned in the PtC, would the EMA be able to review prior to database lock? Is there guidance for sponsors to approach EU regulators? Is there a mechanism where changes that fall within an agreed framework can be made and the sponsors can inform EU regulators vs. asking permission in each case? In the situation where the Statistical Analysis Plan is already finalized for a study and it is not possible to update it, we recommend noting any additional or adjusted analyses in the clinical study report rather than doing an amendment. As trials may be impacted differently, refer to additional analyses investigating the impact of COVID-19. At present, it is not known how the COVID-19 pandemic will evolve and if and when there will be a "post COVID-19" phase. We fully agree with the need to analyze the impact of COVID-19 on the trial but suggest not to mention the three phases. **Proposed change:** Additional analyses (to be included in the Statistical Analysis Plan ***where possible or at minimum described in the clinical study report***) to investigate the impact of ~~**the three phases (pre, during, and post**~~ COVID-19~~**)**~~ to understand the treatment effect as estimated in the trial	
Lines 91-93		*'Proposals to deal with any identified potential sources of bias*	

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		such as missing values, newly identified intercurrent events or other unforeseeable required changes to trial elements.' **Comment:** The statistical approach to intercurrent events and missing data will determine the interpretation of the treatment effect, does not fall under the responsibility of DMCs and it is recommended that it is made clear that this is done by the Sponsor. In light of recent ICH E9(R1) this will warrant a review of the primary and key secondary estimands for ongoing clinical trials. In addition, missing data handling methods, such as non-responder imputations, may lead to study results that are difficult to interpret when there are many subjects discontinuing trials early, and may lead to different assumptions being required. **Proposed change:** Suggest the last bullet is split into: • ***Proposals to clarify strategies for dealing with newly identified intercurrent events in primary and key secondary estimands.*** • ***The need to adjust missing data methods or add additional sensitivity analyses to investigate the root cause of any missing data.*** ***Consider the handling of other unforeseeable changes to trial elements (around visit schedules for example).***	
Lines 94-95		*"Major changes in the conduct of a trial should follow the local regulations and be approved by Ethics Committees."* **Comment:** It is proposed to also include reference to Competent Authorities (CA) for clarity. Major changes require a substantial amendment in the current legislation and have to be authorised by CAs and receive a favourable opinion by ECs. CAs are missing in the above sentence and ECs do not	

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		approve but issue a reasoned opinion according to EU Directive 2001/20/EC. Submission of a permanent protocol modification to CAs should be clarified, as following sentence is written in EMA 'Guidance on the Management of Clinical Trials during the COVID-19 pandemic': '*In case the risk assessment leads to actions that affect the trial as described below in a) and b), the relevant competent authorities and Ethics Committees must be informed in accordance with the Directive 2001/20/EC and national laws*:' (see proposed change). Where are changes documented, i.e. is it sufficient to document any change to the trial elements, estimands, intercurrent events, analyses and sensitivity in the SAP, or should any of them be documented in a protocol amendment for an ongoing study? (see proposed change). **Proposed change:** Add text: Major changes in the conduct of **an ongoing** trial should follow the local regulations ***and be documented in protocol amendment*** and approved by Ethics Committees ***and Competent Authorities. Whilst additional analyses may be documented in the statistical analysis plan, any key changes to the planned primary and key secondary estimands and/or planned analyses should also be documented in protocol amendment where feasible or in the trial SAP.***	
Line 98-100		*"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."* **Comment:** While this statement is welcome further clarification on how sponsors could facilitate this reflection would be appreciated, e.g. pre-submission and/or Rapporteurs meetings, SA.	

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Please add more rows if needed.