15 April 2020
EMA/204136/2020
Human Medicines Division

Overview of comments received on 'Points to consider on implications of Coronavirus disease 5 (COVID-19) on methodological aspects of ongoing clinical trials' (EMA/158330/2020)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Giorgio Reggiardo - Head of Biostatistics and Data Management Unit at Medi Service - World Trade Center (WTC) – Genoa - Italy
2	Natacha Bolaños - Lymphoma Coalition Europe
3	José Delgado Alves, MD, PhD - ECRIN Scientific Board Member
4	Leo Pharma A/S
5	The Medical Research Council Clinical Trials Unit (MRC CTU) at University College London (UCL), London, UK
6	Agios Pharmaceuticals, Inc
7	Nevine Zariffa, Founder NMD Group LLC (former SVP Biometrics and Information Sciences at AstraZeneca) and Frank Rockhold, Professor of Biostatistics and Bioinformatics, Duke University Medical Center
8	AstraZeneca

Stakeholder no.	Name of organisation or individual
9	Novartis
10	Takeda Development Centre Europe Limited, United Kingdom / Takeda Pharmaceuticals Inc., United States
11	Galapagos NV
12	The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) - Belgium
13	Mylan Health Care, Hannover
14	Medicines and Healthcare products Regulatory Agency (MHRA), UK
15	Staburo GmbH
16	Ipsen Innovation, France
17	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)
18	European Association of Hospital Pharmacists (EAHP)
19	IQVIA
20	Merck Sharp & Dohme
21	Regeneron Pharmaceuticals, Inc.
22	NextraResearch S.r.l., Italy
23	European Organisation for Research and Treatment of Cancer (EORTC)
24	Cytel Inc.
25	International Society for Clinical Biostatistics, ISCB
26	SQA
27	Alliance for Regenerative Medicine
28	UKCRC Registered CTU Network
29	European Alliance for Vision Research and Ophthalmology (EU EYE)
30	Prof Stephan Harbarth, Geneva University Hospitals, Switzerland, Dr Marlieke de Kraker, Geneva University Hospitals, Switzerland, Julien Sauser, Geneva University Hospitals, Switzerland, Prof Martin Wolkewitz, Freiburg University, Germany, Prof Kit Roes, Radboud University, Netherlands Dr Aaron Dane, DaneStat, UK - STAT-Net, Statistical pillar of the IMI-funded COMBACTE program coordinated by Geneva University Hospitals
31	NIHR – MRC Trials Methodology Research Partnership, UK

1. General comments – overview

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1	As expected one aspect of the COVID-19 infection is confirmed: the age distribution of COVID-19 confirmed cases (1#, the proportion of confirmed cases in younger *age classes* was *greater*: 20-29 years equal to 29.3 % of the total confirmed cases) is *distinctly different from the age distribution of COVID-19 fatality rate* (*1#,* the fatality rate was highest among the age group of 80 years or older). This finding is also supported by the European Centre for Disease Prevention and Control analysis (2#) in the European countries. For this reason it is understood the importance to evaluate a possible effect of age on the clinical trial participants reporting data related to the impact of the methodological aspects of ongoing trials during the COVID-19 disease. (1#) "Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020". J Korean Med Sci. 2020 Mar 16; 35 (10). Doi: 10.3346/jkms.2020.35.e112 (2#) Coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK – seventh update, 25 March 2020. Stockholm: ECDC; 2020.
4	The treatment effect of interest may change as a result of the measures put in place due to COVID-19. A thorough re-assessment of the anticipated intercurrent events and the selected strategies for handling their occurrence should be considered along with accounting for the potential occurrence of unforeseen intercurrent events due to COVID-19. As an example of intercurrent events arising due to measures put in place to mitigate the spread of COVID-19, changes in data collection methods, e.g. switching to virtual assessments should be discussed and addressed within the estimand framework. Given the pragmatic approach many companies have taken in defining intercurrent events, perhaps a reminder is warranted, that the ICH E9-(R1) addendum allows for the necessary level of granularity required, in order to identify intercurrent events.

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	Along those lines, methods for handling missing data and their potential impact in light of pandemic should be re-assessed, along with the pertinent sensitivity analyses.
5	We acknowledge that, at this stage, this is a high-level document that aims to get trial investigators thinking about how this crisis will impact on their trials, particularly in relation to any interim or final analyses. We applaud the EMA for initiating this process. We felt that the document could be structured better and would benefit from the addition of sub-headings that draw attention to key issues for consideration. For example, the document could start with an introduction on the purpose of the document and this could then lead to sub-headings relating to patient safety, drug supply, data collection, statistical considerations, the handling of protocol deviations etc. We were unsure of the emphasis being placed on the Independent Data Monitoring Committee (IDMC) or Data Monitoring Committee (DMC) for much of the advisory decision-making associated with fall-out from the COVID-19 crisis. The structure of oversight committees varies across Europe and the role of other committees should be considered. In the UK, we use a Trial Management Group (TMG), the IDMC and a Trial Steering Committee (TSC) – with independent members who represent the Sponsor[1]. The IDMC is an advisory body to the TMG and TSC. The IDMC will sometimes have seen accumulating, comparative data and thus, some of the actions assigned to the IDMC in the document might be considered inappropriate and should be ascribed elsewhere. Each trial should consult across their committee structure in a way that is most appropriate for their circumstances. The important point to get across is that review of any data (particularly by randomised group) that could undermine later interpretation of the trial results should be by an appropriate independent group. This may be the IDMC but if feasible, it could also be handled by a specialist group, independent of the trial investigators who are convened specifically for the purposes of reviewing the impact of COVID-19 on the trial. We suspect the document could be developed for generic pandemic circumstances, rather than COVID-19 specifically. Other pandemics are likely to occur in the future and these may affect the conduct and analysis of clinical trials. At this premature stage in the crisis, we felt that much of the important data required to assess the impact of COVID-19 on each specific trial (eg. The extent of stopping of trial treatment) would be available for collection retrospectively, once local staff capacity has returned to a point when such data collection can be reasonably requested. However, if there are important data relating to the COVID-19 crisis that need to be collected in real-time (during the crisis), that will not be retrievable once the crisis has passed, trial

[1] Lane JA, Gamble C, Cragg WJ, Tembo D, Sydes MR. A third trial oversight committee: Functions, benefits and issues. Clin Trials. 2019:1740774519881619.

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	investigators should consider how it can be collected. It may be that no real-time data are needed, but consideration of the issue should be undertaken now. For example, if data collected during the pandemic are likely to need subsequent validation for accuracy, it may be necessary to collect other real-time data for validation purposes and this should commence now as part of the current data collection procedures. Similarly, data capture of any changes to the methods for follow-up, such as by telephone or via the internet, may need to be collected in real time.
7	At this junction in the COVID19 pandemic, regulators are faced with an important challenge as regards ongoing clinical trials being disrupted due to a 'Force Majeure' event. The EMA guidance entitled 'Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic' [guidanceclinicaltrials_covid19_en.pdf] was issued in the spirit of maintaining a high degree of quality in data packages in support of new medicines while avoiding a wholesale discounting of years of effort. As such, the EMA guidance on Management of Clinical Trials during the pandemic expressed a willingness to identify practical solutions in the best interest of patients. The points to consider document from the biostatistics working group is focussed uniquely on ongoing trials rather than COVID-19 trials. The biostatistics working group's document highlights an openness on the part of regulators to engage with sponsors which is most welcome. Some of the proposals are well intentioned but impractical (e.g. 1 – redirecting DMCs as described and 2- having individual scientific advice for each trial as there are so many). Other elements are very reasonable and most helpful if applied to all trials. The document mentions a number of complexities – all realistic challenges. Organising these in a framework would be even more helpful to sponsors. There may even be a way to categorise the types of disruption and types of trials so that there is a unified approach to the analysis and interpretation. We envisage the biostatistics working group collaborating with clinical researchers/trialists as critical partners to ensure a common set of standards are used across all trials affected by COVID 19. We anticipate the biostats working group membership and operational procedures may need to be enhanced to cope quickly and well with this unprecedented challenge. In this regard, we encourage engagement with PSI and other cross-industry groups (e.g. EFPIA and PhRMA) where biostatisticians continue to come together around methodological issues of this type. Also, the academic community should be engaged as they provide almost all the resource for IDMC's.

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	Last, the EMA guidance on Management of Trials during the pandemic includes considerations for COVID019 trials (treatment and prevention). It would be valuable to share the statistical considerations for those trials quickly as trials are already underway.
8	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, and how the agency intends to prioritise between requests for timely advice on specific trials.
9	The guidance suggests a major role for Data Monitoring Committees in making important decisions in ongoing trials. Many of these responsibilities might more naturally seem to belong to trial management personnel, as the associated issues can often be addressed fully adequately without access to unblinded data; this might involve sponsor personnel, Steering Committee, etc. If important decisions are advised by unblinded results, then of course this should be done through a DMC. But many of the decisions mentioned seem at first glance to not require unblinded access. Some, including initiating a sample size re-assessment or updating a study's final SAP, could be very problematic in terms of validly interpreting final analysis results if initiated by a party with access to unblinded interim results such as a DMC. In current practice and supported by prior regulatory guidance, such decisions are generally initiated by parties remaining blinded. Of course the DMC should be kept fully aware of any changes implemented in a trial, and should comment if they have any concerns. But for actions taken based upon blinded data, there are generally not confidentiality concerns, and sponsors can enlist any experts who can help arrive at the best decisions. It would be helpful if the document can provide clarification on how unblinded analyses might lead to some of the actions mentioned, and otherwise why a DMC would play such a major role in decisions that seem more naturally and validly made by blinded personnel. It could be helpful to more fully align the guidance with the ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials. The COVID-19 pandemic will lead to many types of unforeseen intercurrent events. Guidance on appropriate strategies to address certain intercurrent events would be very welcome. For example, it is conceivable that the original trial objective and treatment effect of interest will remain unchanged in most settings. Might clinical questions of interest therefore be framed using a hypothetical estimand strategy for intercurrent events that are documented to be related to the pandemic, with methods of analysis modified to align to the resulting estimand? Collecting information on the intercurrent events and other COVID-19 related events is important to enable an informed estimand discussion. The current document calls for "a systematic way to record protocol deviations and capture related reasons" and "sufficient amount of information on pandemic-related measures". 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?

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	The guidance stresses the importance of interpreting "the treatment effect in light of the pre-, during and post-pandemic measures phases". Additional guidance on this aspect would be very welcome, e.g. • Can the Agency advise how to set dates to define these phases? Specifically, is there a plan to develop criteria for determining pre-pandemic, peri-pandemic and post-pandemic data collection periods? Would it be perceivable for the Agency to determine these dates based on objective criteria? If not, is it then useful or necessary for regulatory review of different dates to be specified for each region, country or site? • Assessments of "consistency" of treatment effects pre- and post-pandemic might be foreseen. In this scenario, consistency of results pre- and post-pandemic might not be expected, e.g. when study treatment intake is interrupted due to drug supply issues. Can the Agency provide guidance on what might be requested for the consistency assessment and interpretation of trial results? • Are particular analytical approaches preferred to combine information across phases (e.g. pre / during / post-pandemic)? For example, under what circumstances might adaptive design methods allowing for unplanned changes be acceptable? Might it be acceptable to give greater weight in the trial analysis to data collected pre-pandemic? There are additional topics related to the COVID-19 pandemic that are not currently addressed in the document, but it might be very helpful to receive some guidance from the agency, for example: • 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)? • Some trials might formally fail statistically 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 should be developed? • 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

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	would have been observed at the primary timepoint. Are there other approaches to compensate for lost information that would be supported by BSWP? • Currently, both of the Agency's documents 'Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials' and 'Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (Ver 2)' do not discuss paediatric investigation plans (PIPs). Additional guidance on the following two questions would be very welcome: 1. Does the Agency envisage a streamlined process for sponsors to seek and obtain PIP Modifications that result directly from COVID-mediated clinical trial impacts that alter agreed aspects such as: initiation dates/completion dates, assessments, analyses which may impact approaching Compliance Checks (near-term) for linked regulatory submissions requiring PIP Compliance Checks (partial or full) in order to pass validation? 2. Does the Agency envisage or anticipate release of guidance on the management of PIPs during the COVID-19 pandemic?
10	There multiple references to pre-, during, and post-pandemic phases. In order to avoid inconsistent reporting between Sponsors, it would be helpful to have guidance on how these periods should be defined. For example, should they be defined internationally, by country/region, or locally?
11	Galapagos thanks the Agency and welcomes the opportunity to comment on this document.
12	EUCOPE would like to thank the European Medicines Agency (EMA) for compiling this Points to Consider (PtC) document. The document provides more certainty to a topic that is immersed in unpredictability and we acknowledge the EMA's willingness to work with sponsors and MAHs to support clinical research in these difficult times. EUCOPE would like to provide the following general comments: **Documenting Deviations** Regulatory agencies acknowledge that an increase in protocol deviations is expected to result from the COVID-19 pandemic and sponsors are encouraged to define a systematic way to record protocol deviations and capture related reasons. Guidance on expectations for documenting deviations would be useful, as the example from the FDA guidance (link): *"(…) if visits are to be conducted by telephone/video contact rather than at the investigational site as specified in the protocol, documentation that provides*

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	a listing of all study visits that are deviations from the protocol due to the current COVID-19 situation (i.e., study reference number, patient ID, date of visit) generally would be acceptable". **Data Monitoring Committee** The PtC recommends an independent Data Monitoring Committee to analyse accumulating trial data to preserve trial integrity as far as possible. Consideration should be given to including flexibility for sponsors to determine whether a DMC is needed on a trial specific basis. COVID already increases trial complexity and it could add to the complexity by instituting external DMCs, without clear benefits. Trials impacted early in conduct may have suspended recruitment and trials nearing end of study are not likely to require a DMC. Adding to that, setting up a DMC can be challenging for all trials affected. In many cases, the damage caused by COVID-19 can be assessed in a blinded way. However, if independent unblinded analyses of the accumulating data are indeed performed by a DMC, and suggestions regarding sample size adjustments made based on that, then this would amount to an informal adaptive design which could be detrimental to the regulatory decision making. Adding to that, alternative approaches may be appropriate, e.g. Independent group within the Sponsor with or without external expert consult. Sponsors should have the flexibility to reach their own judgment, based upon the scientific, operational and clinical issues each study faces as to whether the "*potential*" actions a DMC may propose are on balance justified, and outline their reasons in the clinical study report. It would be helpful to clarify whether the DMC review is intended to be blinded or unblinded; unblinded efficacy and safety is the more valuable review. The PtC notes the purpose of the DMC analysis is risk assessment and advice on follow-up actions and not an unplanned formal interim analysis for efficacy. Consideration should be given to the situation where the extent of accumulated data may result, unintentionally, in an interim analysis of efficacy. **Statistical Analysis** The PtC suggests additional analyses may be needed to understand the impact of the three phases (pre-, during, and post-COVID-19). The approach to determining impact of measures introduced may be more complicated, e.g. whether different measures were applied to respond to local conditions. Determining appropriate analyses will depend on review of accumulating data but also the operational and clinical issues within each study. Many protocol deviations to improve patient safety will reduce the interpretability of

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	study results. Bias, such as missing values, is addressed in the PtC. Consideration should be given to other sources of variability/bias, e.g. assessment of patients at home versus in clinic. **Missing Data** Changes in study visit schedules, missed visits, or patient discontinuations due to COVID-19 pandemic may lead to missing information. It is of utmost importance to flag the reason for missingness of data, as "*COVID-19 related*" as this would be helpful for both the Health authorities and companies at a later stage during analysis. This should be highlighted in the guidance document. Expectations for retrieval of missing data should be flexible to allow for optimization of the parameters most critical to the statistical analysis needs of each study. We urge the Agency to consider providing additional guidance on how to handle primary and key secondary analyses considering anticipated increased missing data with COVID-19, since these would be helpful for further planning. Guidance might also be useful at one point to replace patients whose data are too damaged by COVID-19, if those decisions are made in a blinded way (i.e. exclude those patients from ITT and replenish the ITT pool post-COVID-19). **Data Interpretability** The PtC discusses reviewing accumulating data regarding ability to interpret the treatment effect and whether the trial will deliver interpretable results. It would be useful if the document includes additional guidance on how best to define "*interpretable*" and clarify what is expected from the sponsors in terms of assessing the likelihood of interpretability of trial results. It would be useful if the PtC also includes considerations in relation to safety data as well as efficacy to permit evaluation of benefit risk. **Risk Assessment** The PtC indicates risk-assessment of the impact of COVID-19 on trial integrity and interpretability. It is also important to consider how COVID-19 has altered the risk-benefit for the patient to continue participating in the trial. The modification to the risk-benefit will depend on the seriousness of the disease, study population (age group and co-morbidities to COVID-19), stage of clinical development (e.g. pre-approval versus post-market studies where the efficacy is well understood; phase I versus phase III where there is clear evidence of efficacy and knowledge of optimal dose), and other factors.

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	Role of real-world evidence and scope for observational studies The Agency should consider the role of real world data analytics to accompany a clinical trial impacted by COVID-19: particularly if the comparator arm (placebo/standard of care) has incomplete assessments or follow-up data, real world data can provide additional context to the active treatment arm. The scope of the guidance may be broadened to include observational studies for certain aspects.
14	This is an important document and the contents are generally agreed. The only strong concern is that we would not want this guidance to unintentionally give license for additional analyses based upon unblinded treatment groups, when the strong need for such analyses is not seen (see also specific comments below).
15	The guidance should also discuss the impact of COVID-19 on estimands.
16	The Points to consider (PtC) on implications of Coronavirus disease (COVID-19) on methodological aspects (EMA/158330/2020) document focuses on ongoing clinical trials. Although an end of the pandemic situation is expected, it can't be excluded that similar considerations would also apply to future clinical trials, we therefore suggest that the scope of the guideline is extended accordingly.
17	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.

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	• **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 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?

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	• **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 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.
18	Overall, EAHP agrees with the content of the document. EMA may ask for an explicit report on how COVID-19 interfered with a clinical trial. Other specific comments have been provided below.
19	**1. COVID-related missing data** More explicit suggestions on analysis of COVID-related missing data would be welcome, e.g.: a. The value to regulators of an analysis of the estimand "treatment effect had COVID not occurred" (e.g., via censoring at start of COVID and imputing to end of scheduled follow-up); it would be helpful to understand the conditions under which such an analysis would be useful. b. The inclusion of COVID-related baseline covariates in imputation (e.g., age, other COVID risk factors); c. Strategies for taking account of sites with almost no data because closed down due to COVID – would it be mandatory to include such sites in the primary analysis?; are there circumstances when it could be proposed to drop these from the primary analysis (perhaps with a sensitivity analysis imputing probable outcomes based on outcomes from other sites)? d. Estimands that take the "composite" approach often count a missing outcome as a failure or as in some sense a poor outcome. This may not be appropriate if missing outcomes are associated with the pandemic. Guidance on this point (e.g. circumstances in

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	which it would be acceptable to modify the planned "composite" approach, perhaps treating COVID-related missingness separately) would be welcome. e. With COVID-related missing visits, time-to-event outcomes may suffer from interval censoring (e.g. the true time to the event could be shorter than that observed, because of a missed visit just before which the event occurred). Guidance on this point would be welcome. **2. Other COVID-related statistical items** a. If certain countries show signs of controlling COVID-19, an unusually high proportion of sites may be expected to be selected from such countries during the period of the pandemic. This may affect the representativeness of a study's findings. Guidance on this question would be welcome. b. Guidance would be welcome as to whether regulators should be consulted about COVID-related site and/or study closure. c. Suggestions would be welcome for supportive or sensitivity analyses that could be helpful to regulators in taking into account the changing clinical environment during the pandemic. Would a "moving window" analysis, showing how estimates of treatment effect change over time during the pandemic, be helpful? d. Guidance would be welcome regarding the inclusion of potentially post-baseline covariates, such as a time-varying indicator of site close-down, in imputation of missing data. These could bias the analysis and it is not clear in what circumstances such a strategy would be useful to the regulator.
20	We welcome the release of this Point to Consider (PtC) document, and the opportunity to comment on this important and much needed document. **Perspectives on the feasibility of modified intention-to-treat population** replacing or excluding some randomized subjects who were significantly impacted by the pandemic would be greatly appreciated. While it is acknowledged that randomization should be preserved to the best extend possible, are there any situations where the trial participations for certain subjects are irreparably impacted by the pandemic, such that the clinical question of interest should be best answered by data from those who are not impacted by the pandemic?

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	A hypothetical example can be found in a neoadjuvant/adjuvant trial for solid tumour, where the surgery closely following neoadjuvant treatment is the critical component of the treatment strategy. These surgeries may be significantly delayed or cancelled due to pandemic mitigation measures. Data collected for these impacted subjects do not meaningfully contribute to the clinical question of interest, and the delay of surgeries may be due to systematic impact of the healthcare system not related to the subjects' disease conditions. **The results of clinical trials should be assessed for their applicability in future clinical settings**. When considering the censoring or missing data induced by the pandemic-related intercurrent events before the trial endpoint is observed, it is helpful to understand whether the treatment effect that would have been observed in the absence of pandemic-related impact is of primary clinical interest. This consideration determines the appropriate statistical methods to be used to quantify the treatment effect. It is understood that the **COVID-19 risk assessment should not focus on confirming the likelihood of success for the trial**. However, if **a maturing trial close to the planned final analysis** is determined to have substantial risk with the interpretation of additional data accumulated during the pandemic measures phase, the sponsor may consider conducting the final analysis earlier than planned. The trade-off between reduced power and increased bias needs to be carefully balanced. The sponsor and the DMC if involved should document the evidence and considerations to justify that such a decision does not compromise the trial integrity. **Further guidance on the appropriateness of different trial adaptations** based on the pandemic risk assessment for ongoing trials would be helpful.
21	Regeneron is committed to helping ensure the safety of its trial participants during the COVID-19 pandemic, and to safeguard the integrity of the data from its studies. Therefore, we welcome the Agency's initiative in releasing this document on the implications of COVID-19 on methodological aspects of ongoing clinical trials. Regeneron recognizes that the COVID-19 pandemic is a fast-evolving crisis, which poses substantial challenges when providing recommendations on aspects related to its impact on clinical trials. Despite this, it is our position that the guidance (when developed) will allow Sponsors to understand better the Agency's expectations, thereby informing more practical decisions that would best align with the EMA's recommendations. We would encourage the Agency to consider expanding the topics to be covered in a future guidance on the methodological implications of COVID-19 on ongoing clinical trials, and to continue revisiting the guidance as more information becomes available – similar to actions taken with the *Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic (EMA/141885/2020).*

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	To help strengthen a future guideline on this topic, Regeneron proposes the following changes: 1. Clarify how the Agency will evaluate whether efficacy procedures specified to be conducted at a particular time point but conducted beyond the defined visit time point windows allowed in the protocol could be included in the analyses of the said time point – including cases where the data relates to efficacy endpoints 2. Clarify considerations the Agency will use to determine if data obtained remotely (e.g. from video or phone call monitoring 'visits') would be considered as equally robust as 'traditional' datasets 3. Clarify if data gaps related to COVID-19 restrictions on study visits/procedure may be considered missing completely at random (MCAR) 4. Under the assumption of MCAR/MAR: a. This document requires clarification as to when it would be helpful to perform a sensitivity analysis that excludes data that is affected by the COVID-19 pandemic b. The Agency should also provide suggestions on options for imputation approaches to handle missing data (e.g. intermittent or monotone pattern) Expanding the current recommendations would guide Sponsors by assisting them in adopting robust strategies to optimally manage the impact COVID-19 may have on clinical programs and analyses of data, contributing to protecting the integrity of clinical trials. It is very likely that Sponsors will encounter protocol deviations/missing data incurred by COVID-19 restrictions on study visits/procedures. Therefore, Regeneron would welcome additional discussion on the level of flexibility Sponsors should anticipate when the Agency reviews clinical data from studies with protocol deviations related to COVID-19 – including deviations that were properly documented and necessary to safeguard patient safety. We would particularly welcome guidance on this topic as it relates to data supporting the study's primary endpoint(s). Further guidance on these aspects would help Sponsors to understand fully EMA's expectations and avoid undue delays refining analyses and data submitted in study reports. Finally, Regeneron would encourage the Agency to consider aligning its recommendations around methodological aspects of ongoing clinical trials during COVID-19 with recommendations from other major Health Authorities, whenever possible.

Stakeholder no.	General comment (if any)
	Many studies, particularly late-stage or Phase III trials, have sites across the globe. Consistent recommendations around these methodological topics, whenever possible, might help avoid delays to clinical programs and to drug approvals, ultimately benefitting patients. One example of a collaborative harmonized approach that should be replicated is the EMA's involvement with the COVID-19 workshops organised under the umbrella of the International Coalition of Medicines Regulatory Authorities (ICMRA)[2,3]. These workshops are currently focused on considerations related to the development of COVID-19 vaccines and therapeutics. However, similar initiatives could be used to support the development of international recommendations for Sponsors on how to best manage the impact of COVID-19 on their other clinical programs and specifically on the interpretation of data derived from impacted programs.
23	EORTC welcomes the issue of this guidance as well as the Guidance to sponsors on how to manage clinical trials during the COVID-19 pandemic (EMA/141885/2020) which is for obvious urgency reasons could not be open to public consultation. EORTC fully agrees that safety of patient comes first. In relation to the above, EORTC regrets that all Member States (MSs) could not align on the way to handle urgent adaptations required in the scope of clinical trials during the COVID-19 pandemic. Consequently, in addition to the EU guidance, almost all MSs issued their own documents putting sponsors of international trials under the huge pressure of having to analyse a huge number of documents in a very short time. Moreover, in terms of compliance, regulatory teams are facing multiple requirements, which differ in the form and time, driving more than valuable and limited resources away from questions directly related to the patient safety. EORTC is willing to share the summary of differences observed with EMA and/or EU Commission and/or MSs for further discussion on possible harmonisation. Last, but not the least, recommendations in relation to the processing of personal data (not specific to, but applicable to clinical trials) in addition to what was planned or in a different way as initially explained to data subjects was addressed by different MSs differently, further hindering sponsors capacity to comply under pressure while not directly related to patient safety.

[2]EMA press release: *First regulatory workshop on COVID-19 facilitates global collaboration on vaccine development*. 18 Mar 2020
[3] EMA press release: *Global regulators discuss observational studies of real-world data for COVID-19 medicines*. 7 Apr 2020

Stakeholder no.	General comment (if any)
24	Can the guidance explicitly clarify at the start what is meant by "methodological aspects". Presumably this guidance is written to focus on the impact on data collection and analysis and not so much on logistical aspects (for example clinical site management and patient management), which, as the guidance later points out is covered elsewhere? The guideline focuses on patients' data for those already included and/or in follow-up period. A point to consider is also with regards to recruitment overall. Should it be stopped/paused to reduce for instance the risk of protocol deviations and what are the implications of this? Is there any guidance depending on the recruitment rate and/or status with regards to the total planned study size? Can the guidance provide additional comments on whether subjects need to be replaced and/or additional subjects need to be included in the study due to missing data or increased variability? Reference should be made to the different attributes listed in ICH E9(R1), namely treatment, population, variable, population-level summary as well as strategies for handling intercurrent events. In fact, a part of the document could be structured according to these topics. This framework works very well when assessing the implications of COVID-19.
26	The terms "patient" and "study participant" seem to be used at random/interchangeably throughout the document. "Subject / trial subject" would seem to be the more appropriate term in the clinical trial context. During the pandemic, source data verification (SDV) may be significantly impaired or may not be possible. As a result, the pandemic may require decisions made based on "unmonitored" (dirty) data versus "monitored" (clean) data. This may also affect Data Monitoring Committee procedures and recommendations. It would be appreciated if the Guidance included procedures on how to address these issues.
27	ARM thanks the EMA for its reactivity in issuing this document and for the opportunity to comment it. Very few comments on this document were received from our members. This could be due to the quality of the draft document in public consultation, the short timeframe left for comments or to the fact that the Covid-19 pandemic has led to an increase and re-prioritisation of activities by our members.
28	The UKCRC Registered CTU Network welcomes the development of this guidance on the impact of COVID-19 on the methodological aspects of ongoing clinical trials and is in agreement with its overarching aims. Having reviewed the draft guidance, the Network would like to raise the following points.

Stakeholder no.	General comment (if any)
29	The global health emergency caused by COVID-19 and the measures taken to address the pandemic will also have an important impact on the proportion of missing data, which can severely compromise a trial's validity. Methods for handling missing data have non-trivial shortcomings with small samples. Furthermore incomplete data induces biases in the results especially in the case of small trials, which are very common for the evaluation of advanced therapies and rare diseases. In this regard, major changes in the conduct of a trial should allow to increase sample size and thus decrease the potential bias of missing data in small studies
30	To be able to use data from ongoing trials to inform management of COVID-19 (through, for example, individual patient-based meta-analysis) or to inform RCTs focused on COVID-19 treatments, harmonized data collection of the COVID-19 subgroup is a unique opportunity and paramount. Therefore, we suggest that ongoing trials that also cover COVID-19 patients collect a minimum amount of information with regards to exposures and endpoints. For exposure, type, duration and start-date of treatment should be registered. For endpoints duration of mechanical ventilation, duration of hospitalization and mortality at discharge would be unambiguous endpoints that are of interest from both a clinical and public health perspective. In the guidance the terms "pre-, during-, and post- COVID-19" are used to indicate different periods during data collection. However, this division is not defined, nor is any mention made of how to approach this in multi-country RCTs, where these periods may be different. To ensure harmonization of data analysis for all ongoing trials, we encourage EMA to provide definitions to identify the different periods, and to provide guidance on how to deal with the fact that these periods may not be aligned in different countries.
31	This is a high-level document that aims to get trial investigators thinking about how this crisis will impact on the trial, particularly in relation to any interim or final analyses. We applaud the EMA for initiating this process and the UK Trials Methodology Research Partnership (TMRP) appreciates that it is late in responding and will look forward to future versions. We felt that the document could be structured better and would benefit from the addition of sub-headings that draw attention to key issues for consideration. For example, the document could start with an introduction on the purpose of the document and this could then lead to sub-headings relating to patient safety, drug supply, data collection, statistical considerations, the handling of protocol deviations etc. The TMRP was unsure of the emphasis being placed on the Independent Data Monitoring Committee (IDMC) or Data Monitoring Committee (DMC) for much of the advisory decision-making associated with fall-out from the COVID-19 crisis. The structure of oversight committees varies across Europe and the role of other committees should be considered. In the UK, we use a Trial Management Group (TMG), the IDMC and a Trial Steering Committee (TSC) - with independent members who represent the

Stakeholder no.	General comment (if any)
	Sponsor[4]. The IDMC is an advisory body to the TMG and TSC. The IDMC will sometimes have seen accumulating, comparative data and thus, some of the actions assigned to the IDMC in the document might be considered inappropriate and should be ascribed elsewhere. Each trial should consult across their committee structure in a way that is most appropriate for their circumstances. The important point to get across is that review of any data (particularly by randomised group) that could undermine later interpretation of the trial results should be by an appropriate independent group. This may be the IDMC but if feasible, it could also be handled by a specialist group, independent of the trial investigators who are convened specifically for the purposes of reviewing the impact of COVID-19 on the trial. The TMRP suspect the document could be developed for generic pandemic circumstances, rather than COVID-19 specifically. Other pandemics are likely to occur in the future and these may affect the conduct and analysis of clinical trials. (We need an opportunity to see whether the rapidly-implemented COVID-19 trials have lessons for the set-up, conduct and delivery of non-pandemic trials in the future. These pandemic trials have moved quickly in a way that most trials could not under the usual structures. Therefore, need to reflect on which aspects of this rapidity should be helpfully kept.) Much of the important data required to assess the impact of COVID-19 on each specific trial (eg. the extent of stopping of trial treatment) would be available for collection retrospectively, once local staff capacity has returned to a point when such data collection can be reasonably requested. However, if there are important data relating to the COVID-19 crisis that need to be collected in real-time (during the crisis), that will not be retrievable once the crisis has passed, trial investigators should consider how it can be collected. It may be that no real-time data are needed, but consideration of the issue should be undertaken now. For example, if data collected during the pandemic are likely to need subsequent validation for accuracy, it may be necessary to collect other real-time data for validation purposes and this should commence now as part of the current data collection procedures. Similarly, data capture of any changes to the methods for follow-up, such as by telephone or via the internet, may need to be collected in real time.

[4] Lane JA, Gamble C, Cragg WJ, Tembo D, Sydes MR. A third trial oversight committee: Functions, benefits and issues. Clin Trials. 2019:1740774519881619.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
18	19	**Comments:** "BSWP" **Proposed change:** Expand abbreviation on first use
22-31 and 47-49	29	**Comments:** The two parts conflict each other particularly as the lines 47-49 appear to encourage the continuation of trials. It may be that the general message is "to continue the trial if this is safe for the patient" but this has to be made clear to prevent misinterpretation. **Proposed change:** Data collection should continue only if it is deemed appropriate and does not compromise the safety of the participants in any way. Potential risks for study participants etc.
34	8	**Comments:** "Impact on the data collection, analysis and interpretation of results for each trial will need a thorough case-by-case assessment". This statement is true but any guidance that can be given on the acceptability of changing the primary estimand in a trial due to COVID-19 would be appreciated.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
34	9	**Comments:** To align with the ICH E9 (R1) addendum, it might be helpful to add the possible change in the trial's scientific objective / estimand
34-35	14	**Comments:** "Impact on the data collection, analysis and interpretation of results for each trial will need a thorough case-by-case assessment." The impact on patient and study site recruitment, should also be considered. **Proposed change:** "Impact on patient and study site recruitment, the data collection, analysis and interpretation of results for each trial will need a thorough case-by-case assessment."
35	22	**Comments:** Metadata and Additional Documentation: • Full statistical analysis plan (SAP), which includes all amendments and all documentation for additional work processes (including codes, software, and audit of the statistical workflow) • Analytic code describing the clinical and statistical choices made during the clinical trial. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		to add "Metadata and Additional Documentation should be organized and managed during all the pandemic phases"
35	22	**Proposed change:** to add "An independent Data Monitoring Committee (DMC) as a group of experts external to a study that reviews accumulating data from an ongoing clinical trial might serve such tasks as described on "GUIDELINE ON DATA MONITORING COMMITTEES" - Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr
38-40	12	**Comments:** Related to capturing systematic deviations, a common approach is to identify the protocol deviation and traditionally patients with major protocol deviations are excluded from per-protocol analyses. Given that it is likely that majority of patients may be affected by COVID-19, does the agency have any suggestion to deal with per-protocol analyses in terms of interpretability of the results? **Proposed change:** We kindly request the Agency to clarify this in the final document.
38-40	21	"- *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"* **Comments:** As currently written, the Agency's recommendation for Sponsors to pre-plan the capture of systematic deviations related to COVID-19 warrants clarification. Sponsors typically pre-plan to capture protocol deviations,

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		even outside the scenario of a pandemic, and will surely aim to capture deviations that are specific to COVID-19. Therefore, Regeneron asks EMA to state if expectations around the recording of protocol deviations during the COVID-19 pandemic differ from what is generally done and considered best practice under normal circumstances (i.e. outside the pandemic). A clearer recommendation on this topic would better inform Sponsors of the Agency's expectations regarding the management of deviations thereby supporting increased compliance.
38-46	12	**Comments:** Given the fact that not all protocol deviations are able to be pre-planned and/or systematically defined, the guidance needs to acknowledge and provide general advice to sponsors on how to handle them in the CSR. **Proposed change:** We kindly request the Agency to clarify this in the final document.
38-46	6	**Comments:** It is important to acknowledge that, beyond protocol deviations, safety data will also be impacted (irrespective of protocol deviations); patients who become infected with COVID-19 are likely to experience a sleuth of adverse events and sequelae, concomitant medications or interventions, and abnormalities in laboratory/ECG/vital sign and other safety measures due to COVID-19 alone but the attribution of whether these are solely due to COVID-19 will be a matter of clinical judgement and cannot be definitely determined. As noted in this "Points to Consider" it will be important to distinguish between 'affected' and 'unaffected' data and there are 3 index dates that can help determine up to which point data are 'unaffected' by the pandemic or whether the pandemic had an impact on the data collected for a patient in the trial. Two of these dates are intrinsic to the patient (date of suspected COVID-19 diagnosis, date of confirmed COVID-19 diagnosis) and one is extrinsic

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		(date when the patient's participation in the trial was first impacted by the pandemic (which can be due to operational disruptions due to the pandemic or any other pandemic-related circumstances that impacted the patients' participation in the trial per protocol). Agios suggests that these are important points to acknowledge and include in this section. **Proposed change:** 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. In addition, patients who become infected with COVID-19 are likely to experience a sleuth of adverse events and sequelae, concomitant medications or interventions, and abnormalities in laboratory/ECG/vital sign and other safety measures due to COVID-19 alone but the attribution of whether these are solely due to COVID-19 will be a matter of clinical judgement and cannot be definitely determined. To assist the assessment of the impact of COVID-19 infections on the safety results of the study, Sponsors are encouraged to capture the index dates associated with suspected and/or confirmed COVID-19 for each patient. The identification of 1) protocol deviations associated with the COVID-19 pandemic, 2) safety data collected after a patient was infected with COVID-19, and 3) date after which the patient's participation in the trial was first impacted by the pandemic (which can be due to operational disruptions due to the pandemic or any other

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		pandemic-related circumstances that impacted the patients' participation in the trial per protocol) will prove valuable in the assessment of the impact of the COVID-19 pandemic on the conduct of the trial, statistical analyses and interpretation of study results and in distinguishing between 'affected' and 'unaffected' data.
38-46	7	**Comments:** this is a very useful idea. A unique standard applied across all trials (presumably driven by CDISC which is currently working on this). **Proposed change:** At the end of the paragraph, add a sentence such as: As a common standard emerges from CDISC, these should be applied across all trials, thereby ensuring the data generated is interpretable across trials.
38-46	21	"*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. (…) 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.*" **Comments:** As presently written, the Agency's recommendations are not completely clear. Regeneron requests that EMA consider revisiting this section to clarify its expectations of Sponsors. We would suggest the Agency to streamline its recommendations and encourage Sponsors simply to identify data that were obtained complete and intact before the COVID-19 pandemic or, perhaps in the future, after COVID-19. By revising these

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		recommendations, EMA would strengthen a future guideline on this topic and better inform Sponsors of its expectations.
38–46	26	**Comments:** Sponsors should already have an established protocol deviation documentation and reporting practice. Why would something different be required just for the COVID-19 situation? **Proposed change:** These decisions were by nature not planned before the start of the trial and should be captured in the systematic way by the sponsor. Additionally, the potential impact of these decisions on the trial outcome 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 add whether the data were affected or unaffected to their deviation recording method.
39	4	**Comments:** Sentence should be re-phrased to remove wording "pre-plan" **Proposed change:** "proactively evaluate/address"
39	15	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Replace the work 'systematic' by 'protocol' **Proposed change:** to pre-plan how protocol ~~systematic~~ deviations …
39	27	**Comments**: "Sponsors are advised to pre-plan how systematic deviations resulting from the measures and 39 individual decisions related to the COVID-19 pandemic are captured." As the recommendation concerns ongoing clinical trials, it more appropriate to mention "to plan" instead of "pre-plan". **Proposed change**: "Sponsors are advised to <u>plan</u> how systematic deviations resulting from […] are captured".
39-40	17	*"Sponsors are advised to pre-plan how systematic deviations resulting from the measures and individual decisions related to the COVID-19 pandemic are captured."* **Comments:** 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 'measures'.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		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…
39-40	27	**Comments**: "[…] systematic deviations resulting from the measures […]". It may be worth clarifying that the "measures" hereby mentioned refer to "collective measures" versus "individual decisions" mentioned in line#40. **Proposed change:** "systematic deviations resulting from the collective measures put in place at national/regional levels and individual decisions […]"
40	4	**Comments:** remove "individual" as decisions may be addressed separately or together depending on how best to address the clinical question of interest.
40	4	**Comments:** Since above line refers to measures and decisions, measures should also be included here as well. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		”These measures and decisions….”
40	26	**Comments:** The guidance limits the handling of departures from the trial protocol because of COVID-19 to protocol deviations. **Proposed change:** Where possible, issue a protocol amendment to include requirements for COVID-19 to obviate the need to document deviations.
40-41	4	**Proposed change:** remove “… by nature…” as it is redundant text.
41-42	14	**Comments:** “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.” Need to clarify data affected/unaffected by COVID-19 **Proposed change:** “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 COVID-19 pandemic.”

Line no.	Stakeholder no.	Comment and rationale; proposed changes
Paragraph from line 41 (41-43)	22	**Comments:** "It would be useful to have an App or an EDC, easy to use, available for all sponsors, public and private, who must develop clinical protocols for the treatment of COVID-19"
41-46	17	"*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*." **Comments:** 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). **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		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***.
42	4	**Comments:** Text is imprecise. **Proposed change:** "assessment of the impact of these implemented measures and decision on the trial outcome…"
43	4	**Comments:** Dichotomizing data as either "affected" or "unaffected" is likely to be a gross oversimplification. The priority should be to gauge the impact on all data.
43	12	**Comments:** Can the agency clarify the current thinking on "*affected*" and "*unaffected*" data and what will be a meaningful way to distinguish at a group level? **Proposed change:** We kindly request the Agency to clarify this in the final document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
43-46	23	**Comments:** EORTC welcomes the use of the word protocol deviation (as opposed to protocol violation) provided the context;, indeed upon the termination of the crisis, sponsors shall carefully evaluate all deviations occurred. Monitoring of protocol deviations is part of the standard responsibilities of the sponsor as per ICH GCP. However, in later phase trials (e.i. phase III intent to treat trials) sponsors would typically record only major deviations. EORTC would propose to emphasise that the purpose of this guideline is to stimulate sponsors to record more thoroughly deviations that occurred because of COVID-19 pandemics in a way to be able to single them out from other deviations that may take place at the same time. **Proposed change:** … "Sponsors are encouraged to define a systematic way to record protocol deviations <u>having occurred because of or in relation to COVID-19 pandemics</u> and capture related reasons"
45	4	**Comments:** Given that the protocol deviations and the reasons for the deviations were not foreseen at the outset of the trial, capturing them in a systematic way will likely require CRF change requests. Such change requests would introduce a time-lag in capturing the required data. Rather, sponsors may need to make use of text/comment fields already 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 needing to make use of the information. Additionally, it will be necessary to distinguish between protocol deviations due to general quarantine measures and those due to patients having contracted the COVID-19 virus.
45	14	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"Sponsors are encouraged to define a systematic way to record protocol deviations and capture related reasons." GCP Inspectors would already expect sponsors to have this in place! **Proposed change:** Replace with "Sponsors should already have a robust and systematic way to record protocol and GCP deviations and capture related reasons, if not, this should be implemented"
47	7	**Comments:** If treatment has been disrupted to a high proportion of patients within a trial, then it may be unhelpful to continue data collection. **Proposed change:** Sponsor should consider the type of disruption and if appropriate to primary hypothesis of the trial, continue data collection. The period of time for Collection of safety data may be different than that for efficacy data.
47	12	**Comments:** With reference to the statement that data collection should preferably not stop and should continue as long as possible, can the agency agree that, for statistical analysis purposes, missing data related to the COVID-19 pandemic can usually be considered as missing at random? **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		We kindly request the Agency to clarify this in the final document.
47-49	17	*"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."* **Comments:** 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 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

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		undergoing study-specific procedures, take priority in decisions taken by patients***, sponsors,*** and health institutes.
47-49	23	**Comments:** EORTC agrees data collection shall ideally not stop. However, site's priorities may be temporarily driven to other tasks to the detriment of the timely transmission of data to trials sponsors. EORTC recommends nuancing between data collection by sites and transmission of that data to trial sponsors and encouraging alternative ways of data collection (e.i. phone interviews rather than physical visit). **Proposed change:** "… patients and health institutes. Collection of data at the health institutes (including by alternative methods such as oral communication e.i. phone interview) shall be prioritised by the health institutes. Transmission of data to the trial sponsors (with exception of safety information and data required to further decide on patient treatment) may occur upon the end of the pandemic situation where this way of working does not impact patient safety and integrity. Specifically in relation to the follow-up data, priority shall be put to the collection of the data (where possible) at the time point foreseen by the protocol and as advised by the trial sponsor by the most pragmatic means, while the completion of the case report forms make take place later.
47-49	24	**Comments:** "*However, potential risks for study participants when undergoing study-specific procedures, take priority in decisions taken by patients and health institutes*". It is difficult to understand who does what in this sentence

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		and why, and how it relates to the following sentences. Is the patient that takes a decision a study participant, and how is the health institute related to the study? Is it a "should" statement or a factual statement? **Proposed change:** Delete the last 8 words and keep: "*However, potential risks for study participants when undergoing study-specific procedures, take priority"*. Start a new bullet point afterwards.
47-49	26	**Comments:** The draft says that data collection should continue as long as possible. It is unclear if this includes all data, including exploratory endpoints that will not impact the conclusions of the study. **Proposed change:** Please clarify if all data points should be continued, or if there should be a determination which assessments are absolutely required for the study.
47-58	12	**Comments:** Data collection process might be impacted, switching from global laboratories to local laboratories and during home visits for example. Consistency of endpoints assessment, data processing and laboratory measurements is not always possible to guarantee, which might create different biases. This might result in non-comparability in data at different time points of this study. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		We kindly request the Agency to provide additional guidance on how to present local and central laboratory assessments.
47-58	27	**Comments:** As data might be affected by the health status of the patients in regards to Covid-19 (exposed/non-exposed; infected/non infected), is the Agency recommending to perform to the possible extent tests (virological; serological) on all patients included in a given trial?
47-58	28	**Comments:** The proposal of dividing populations into "pre/peri/post COVID19" is sensible. It is also worth considering whether some studies would benefit in collecting additional data on whether individuals have suspected or confirmed COVID-19. Ensuring that any additional data that is collected is limited to the data that is required and for a specific purpose. This might include information on the start and end dates of symptoms, a positive test and any hospitalisations. This would give a more granular idea of the impact on an individual level. If this information is not being captured through adverse event reporting, then procedures may need to be changed to capture it. **Proposed change:** Addition of suggestions above.
48-49	2	**Comments:** The document proposed to take priorities in decisions taken by patients and health institutes on potential risks for study participants when undergoing study-specific procedures but does not ask sponsors to inform patients about the associated risks. Patients should be provided with up-to-date information about potential risks during

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		the COVID-19, particularly those linked to their participation in the ongoing trial. The document should consider patients not as passive subjects of research.
49	27	**Comments:** "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." Decisions can be made also by national or regional authorities in Europe and should be followed as well. **Proposed change:** "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, health institutes and national or regional authorities."
49-51	7	**Comments:** The notion of "before", "during" and "after" COVID 19 would benefit from a common definition. We assume the definition applies to the pandemic, not to each individual patient. One could have a single set of dates for each region of a country. The list would be maintained centrally and accepted by all regulatory authorities worldwide. **Proposed change:** See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
49-51	19	**Comments:** "The external validity" **Proposed change:** "The population to which inference can be made"
49-52	6	**Comments:** Patients may have been enrolled in the trial prior to the start of the pandemic but during the trial have been impacted by the COVID-19 pandemic. Further, the impact of COVID-19 pandemic may not have an end date for a trial or a patient as patients may continue to have clinical sequalae due to COVID-19 infection well after restriction measures associated with COVID-19 have been lifted. As a result, the classification of patients into three trial sub-populations is not feasible. **Proposed change:** ~~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.~~
49-52	17	*"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."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Comments: 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 completed their participation in the trial***…"
49-52	26	**Comments:** Trial subjects may fall into more than one category of "before pandemic," "during pandemic" and "after pandemic" populations, e.g. starting "before pandemic" and completing "during pandemic," or starting "during pandemic" and completing "after pandemic," or even starting "before pandemic" and completing "after pandemic."

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Rephrase for increased clarity.
51	4	**Comments:** When considering different trial populations, it may be relevant to assess how the measures introduced to slow the spread of COVID-19, affect the patient population present in the trial during the pandemic.
51	12	**Comments:** Patients in pre-pandemic period are easy to identify but not so much for the "*during*" based on the geographical location. Not every patient in a trial may be affected even if the pandemic started in a specific location, especially the patients who are at near completion of the trial. Grouping such heterogeneous patients will risk the interpretability of the treatment effect. **Proposed change:** We kindly request the Agency to clarify this in the final document and providing the current thinking on this.
52-58	24	**Comments:** It is difficult to understand how to act on this possibly because "*measures taken*" is very vague. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Categorizing measures by e.g. a) who made the decision to implement the measure, b) the timeframe, and c) the local extension, would already provide some basic structure on how to collect the information.
53	17	*"Measures taken in relation to the COVID-19 pandemic may interfere with study treatments."* **Comments:** 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.***
53	18	**Comments:** In case measures taken in relation to COVID-19 interfere with study treatments, it would be important to establish that the patient safety/survival is a priority. In case of interference was caused by the need to save the patient, it should be possible to evaluate the exclusion of the patient from the clinical trial. All the decisions made have to guarantee the patient's safety first.
53-56	23	**Comments:** Collection of the data suggested is not part of any non-COVID trial at present. Moreover, different countries have different strategies in relation to COVID testing. Not all patients will be tested for COVID and not regularly (as infection can occur at different time points). Therefore, any of such information collected would not be of a

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		quality required for any analysis. Moreover, this guideline shall not be understood in the sense that sponsors would have to support the costs and/or to ensure testing. In any case, EORTC would propose to avoid the need to collect additional consents and to have a consensus among all MSs that the legal basis for processing of this additional data would be public health interest (of course data controller will have to provide the complement of information to data subjects). Indeed, managing consents (even oral forms) in this situation proves extremely difficult as compared to the provision of information as it appears very difficult to be able to prove consent was given thereafter (unless oral communication is recorded, which exposes data subjects to additional risks, unnecessary in EORTC view). **Proposed change:** EORTC suggest not to impose systematic collection of data on infection with COVID, unless there is a strong scientific rationale for doing so (based on the type of trial and/or treatment). EORTC suggest integrating a consolidated (one) legal basis for all EU for the collection of these additional data.
53-57	6	**Comments:** Determination of exposed/non-exposed to COVID-19 will be challenging and likely not implementable for most patients. Given that patients that were infected with COVID-19 may also have a substantial amount of data in the clinical trial prior to the pandemic and/or prior to the infection, it may not be meaningful to separate the patients into subpopulations simply based on whether or not they were infected; the date of infection must be taken into consideration. **Proposed change:**

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		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 (taking into account date of infection) / non-infected patients will be necessary to study the impact on the treatment effect.
53-57	11	**Comments:** The guidance makes reference to exposed/non-exposed and infected/non-infected subpopulations. While definition of infected/non-infected is relatively straightforward, definition of exposed/non-exposed is challenging. There are multiple definitions of community-related exposure associated with different levels of risk as defined by WHO (Ref: WHO/2019-nCoV/SurveillanceGuidance/2020.6 and WHO/2019-nCov/HCW_risk_assessment/2020.2). Additionally, establishing community exposure relies on detailed information regarding duration of contact, the health status of the infected contact, the distance from the contact, the use of infection prevention and control measures that are difficult to obtain and are likely to lead to an inaccurate assessment. Hence, in our opinion, it is not useful to analyse subpopulations based on ill-defined categories of exposed/non-exposed. **Proposed change:** "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."
53-58	8	**Comments:** 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,

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		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, we are testing less than 1% of the population and not all individuals who are ill/or exhibiting mild symptoms are tested. 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 been exposed to COVID-19 or not, and possibly prudent to expect 100% of patients have been potentially exposed. We would recommend removing the recommendation for collecting exposure information or alternatively request further guidance regarding exposure data, as it is unclear how to manage this, given the data on exposure may be highly unreliable.
53-58	21	"*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.*" **Comments:** Based on the limited medical resources including the accurate knowledge (e.g. epidemiological data) of COVID-19 infection rates in the general population (e.g. community spread) outside the scope and control of studies, it is difficult, at present, to identify exposed or infected patients who are asymptomatic but carry the SARS-CoV-2 virus. More robust definitions of exposed and infected patients are expected in the future, as testing becomes more widely available and knowledge of the SARS-CoV-2 virus expands. Therefore, Regeneron requests that the Agency clarify its current expectations regarding the identification of subpopulations (e.g. exposed / non-exposed, and infected / non-infected patients). Alternatively, we would propose a different set of subpopulations to be considered in this impact analysis: confirmed infected, confirmed negative, unknown (which would include suspected cases, like symptomatic but not confirmed infected with a diagnostic test). We hope our suggestions

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		will help strengthen EMA's guidance, providing Sponsors with a pragmatic approach while allowing flexibility to adequately study the impact of COVID-19 on treatment effects, as estimated by clinical trials.
55	9	**Comments:** "exposed / non-exposed": Can this sentence be further clarified to distinguish between patients who have been exposed to COVID-19, and patients not necessarily exposed or infected but impacted by virus-related aspects (e.g., curfew, unavailability of investigator, etc.)?
55-58	12	**Comments:** We would urge the Agency to provide clearer definitions and further explanation on how best to define "*exposed/not exposed*" in the context of the current pandemic. This does not seem to be something ever easily known without a test for all patients at various timepoints during the duration of a study. **Proposed change:** We kindly request the Agency to clarify this in the final document.
55-58	17	*"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. "* **Comments:** 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,

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		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 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. **Comments:** 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-

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		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? **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***
56	4	**Comments:** Prudent to also consider those who infected and recovered.
56	4	**Comments:** Given the various testing strategies that have been implemented, collecting reliable data on the sub-populations exposed/non-exposed and infected/non-infected seems a tall order. Perhaps effort is better spent collecting pertinent information regarding pandemic related measures affecting trial sites including the dates of implementation and cessation.
56	12	**Comments:** The interpretation of treatment effects is most meaningful when subgroups are defined at baseline: there is a risk involved in terms of interpretability by grouping patients (infected/non-infected and exposed/non-exposed)

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		based on post-randomization findings. Can the agency elaborate on the regulatory implication of performing such subgroup analyses? **Proposed change:** We kindly request the Agency to clarify this in the final document and to elaborate on the above.
56	16	**Comments:** The PtC document is suggesting to consider subpopulations such as exposed versus non-exposed or infected versus non-infected. Would it be possible to get clarity on how to define such subpopulations? The status of each subject will be difficult to ascertain due to asymptomatic cases and this applies for both exposed and infected subpopulations.
59-62	4	**Comments:** The scenarios from the risk assessment should be used to inform the selection of strategies for handling intercurrent events, methods of estimation and pertinent sensitivity analyses.
59-62	12	**Comments:**

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		Not all measures are equally important and given the limited resources, the guidance should emphasize on key measures affecting the conclusion of the trial. Trial integrity and interpretability are very broad, and the guidance should provide more narrowed scope and advice. **Proposed change:** We kindly request the Agency to clarify this in the final document.
59-62	17	*"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."* **Comments:** 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).

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		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.***
59-62	28	**Comments:** We would strongly advocate a risk-proportionate and efficient approach to the documentation of the impact of COVID-19 which focusses only on those which are of major importance for the interpretation of trial results. The statistical analysis plan may need to be adapted to address planned design and analysis issues related to COVID-19 and these changes will be on a trial by trial basis. **Proposed change:** Addition of a risk-proportionate and efficient approach that focuses only on those which are of major importance for the interpretation of trial results.
59-69	24	**Comments:**

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		Risk assessment is a new topic. **Proposed change:** Add a new bullet point
61	12	**Comments:** It would be valuable if the EMA could provide additional details on "*COVID-19 related measures*" aspects. **Proposed change:** We kindly request the Agency to clarify this in the final document.
62 and 91	25	**Comments:** Interpretability and any unforeseen changes to trial elements, missing data and intercurrent events. It would be helpful in the Points to Consider to refer explicitly to the trial estimand, as any action required due to a Covid-19 related change to the trial will differ depending on whether or not it impacts on the estimands of interest in the trial.
62-63	13	**Comments:**

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		The timing and goal of "analysis of the accumulating trial data" is unclear. Pragmatic actions, like assessing the amount of missing data, would be done under normal circumstances any way and be performed without any additional analysis. Further, when shall these analyses being done? **Proposed change:** Remove the proposal
62-64 and 87	24	**Comments:** The guidance mentions "*the implications on recruitment, loss of patients during the trial*" (lines 62-64) and later with regards to the DMC "*The need to adjust the trial sample size*" This could be expanded further. In fact, all the topics listed in this sentence could be expanded on. **Proposed change:** After lines 62-64 add "*The proportion of screening failures, those who discontinue assigned study treatment and those who withdraw from the study might be higher than initially expected. The ability of the study to meet its objectives should be assessed, and if necessary the planned sample size modified."*
62-65	12	**Comments:** We assume that there may be a practical difficulty to define "pre, during, and post pandemic" status on a "study" basis. The spread of COVID-19 outbreak varies depending on the regions, countries and even cities. It would not disappear suddenly, either. As it stands, this definition may become quite arbitrary, which would ultimately affect the interpretability of the data. We think detailed guidance from the regulators on this point would be helpful so that all sponsors could take as consistent approach as possible. If decision to define the post-pandemic period is taken by a global, regional or national authority, there is a risk that not all sites are

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		able to resume all protocol-defined activities at the same time. Please note that the timing of the declaration by the organisations could also be politically influenced. Therefore, it is highly unlikely that the same rules/regulations can be applied to all sites universally. In addition, even after the declaration of "post-pandemic" status, the sites would still be affected in various degrees because COVID-19 infection is unlikely to disappear suddenly, i.e., will continue for several months (or years) at least sporadically. This means that even at the same site, each patient enrolled can be affected to a different extent; some patients cannot proceed with screening, some cannot complete more than half of planned visits, some have just missed the follow-up visit, some missed dosing for a certain period, etc. The impact of COVID-19 would ultimately be different in each patient. **Proposed change:** Including illustrative examples on how sponsors can define and justify the definitions referred above would be useful, noting that it would still be sponsors' responsibility to define key aspects (e.g. cut-offs, percentage of impacted patients and its classification) on a trial-by-trial basis. See below an illustrative example which might apply to a longitudinal study with several on-treatment assessments: "COVID-19 status" would be best assessed on a trial-by-trial basis by considering the proportion of subjects affected by COVID-19 and using the following criteria related to the assessment of the primary endpoint(s): • The patients who have missed >XX% of scheduled assessments or dosing due to COVID-19 are classified as "critically" affected. • The patients who have missed YY-XX% of scheduled assessments or dosing due to COVID-19 are classified as "majorly" affected.

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		• The patients who have missed <YY% of scheduled assessments or dosing due to COVID-19 are classified as "minorly" affected. • The patients who were not affected by COVID-19 are classified as "not" affected." In case of blinded studies, these classifications should be done prior to unblinding. If a large proportion of enrolled patients are classified as "critical" or "major", such a study cannot be analysed in a "usual" way; it would lead to the modification of the Statistical Analysis Plan including a review of the power calculations and the handling of protocol deviations. Please also note that each study has its own primary objective. The "primary objective" of the study should also be taken into consideration and should be the main driver for the scientific justification to assess impact to patients in different pandemic phases. In the studies whose primary objectives are the "efficacy" assessments, missing dosing and/or missing efficacy timepoints would be more critical. On the other hand, in the studies whose primary objectives are the "safety" assessments, missing safety timepoints would be more significant.
62-65	17	"*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*." **Comments:** 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

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		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 changes:** 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*****.**
62-65	21	"*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*" **Comments:** We would welcome the Agency to add a new section to this guidance focused on a scenario where the treatment effects in the pre-, during and post-pandemic phases are found to have some differences. In some situations, it may be appropriate to restrict the analysis to the pre- and post-pandemic data. The Agency should propose flexibility in considering such post-hoc changes to the analysis plan. Perhaps the Agency can also propose certain post-hoc changes that, in general would be considered acceptable (such as the example given above). While we understand these are very complex topics to discuss, any Agency recommendations on these scenarios would be valuable for Sponsors, and for patients. More guidance on this topic might help ensure that useful data

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		will not be negatively impacted by the pandemic, leading to failed studies and needless delays in bringing potentially useful drugs to patients.
62-79	28	**Comments:** **Where it is essential** that the DMC undertake unblinded analyses, it should be agreed *a priori* what analyses will be considered and for what possible scenarios. This would help ensure that the integrity of the trial is preserved. **Proposed change:** Addition of comment above
64-65	15	**Comments:** Why should only the **treatment effect** be interpreted in light of the three phases (pre, during, post)? This sentence is also in contradiction to lines 67- 69 that state that the purpose of the interim analyses should not focus on whether the trial will be successful.
65	23	**Comments:** EORTC believes there is a need to clarify the scope of the word monitoring. Indeed, currently only central monitoring techniques are possible. **Proposed change:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"It is understood that risk assessment should be part of the central trial monitoring activities… "
Paragraph from line 65 (65-69)	22	**Comments:** "the control group must be differentiated between patients in relation to the severity of the disease: 1. Mild type: mild or asymptomatic clinical symptoms, without diagnosis of pneumonia in CT, but positive for SARS-CoV-2 in pharyngeal swabs. 2. Ordinary type: fever, respiratory symptoms, etc., diagnosis of CT report pneumonia. 3. Serious type: which meets one of the following criteria: (1) breathing difficulty, RR≥30 / min; (2) Peripheral oxygen saturation <93% in rest state; (3) Arterial oxygen partial pressure (PaO2) / oxygen inhalation concentration (FiO2) ≤300mmHg (1mmHg = 0.133kPa). 4. Critical type: meet one of the following criteria: (1) Respiratory failure occurs and mechanical ventilation is required; (2) Patients go into shock; (3) ICU required for the insufficiency of other organ systems"
65-71	17	*"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."* **Comments:** 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).

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		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 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."*
65-73	23	**Comments:** There is a recommendation to perform a risk assessment on the likelihood of the trial being able to deliver intended results. While we support this type of assessment, the guidance goes one-step further into

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		recommending that "such an analysis of the trial data is conducted by an independent Data Monitoring Committee". Several aspects shall be considered: - not all trials may be affected to the extent that would require IDMC involvement - the type of analysis required in general may differ from what is usually presented to IDMC; for example, data integrity check may not require unblinding (as indeed mentioned in the line 67); however there may be instances where unblinding may be needed (for example in case of signs of possible interference of the treatment with COVID) - the timing of such an IDMC is also very important and current text does not provide enough clarity on this While we can understand the general recommendation for considering the need for an IDMC, this stronger position poses practical problems. Convening IDMCs, for many trials at once, at a moment when external experts may have other duties, would be challenging. Moreover, an IDMC evaluation is a time-consuming process, whereas many of the measures needed (such as temporary recruitment suspension, allowing assessments off-site, …) require immediate implementation. **Proposed change:**

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		EORTC would propose to clarify that not all trials may need an IDMC and that IDMC involvement shall be feasible and shall not refrain sponsors from taking timely measures. Specifically, EORTC proposes to amend the text: "Nevertheless, a more thorough analysis may be warranted in cases such as: - if such an analysis might disclose information that could jeopardize trial integrity (eg unblinded treatment effect) - if the impact of pandemics leads to the need of major changes to the design and/or analysis plan 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 feasible. Such analysis may take place during and/or post pandemic, but shall not refrain sponsor from taking actions necessary to ensure patient safety and integrity in a timely manner."
66-74	8	**Comments:** If the Points to Consider document is referring to blinded analysis of accumulating data the recommendation that this is performed by the DSMB is not supported. In addition, for ongoing trials without a DSMB the recommendation to set one up is not practical as by the time the DSMB is set up it will be too late in many cases to salvage ongoing trials. **Proposed Change:** It is recommended that any change to design or planned analysis method based on looking at (blinded or unblinded) data from that same trial must take into account any potential impact on trial integrity, and that the

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		use of DSMB is recommended in cases where trial integrity could be called into question if changes were made following the sponsor's look at the data.
67-68	13	**Comments:** the term of "interpretable results" is not commonly defined. It is therefore un-clear what is the aim of any additional analysis. Furthermore, the criteria for deciding whether results "interpretable" are very difficult to define, if at all. **Proposed change:** Remove the "interpretable results"
67-69	15	**Comments:** The term 'interpretable results' is not clear and should be explained. More importantly, it is not clear how to differentiate 'interpretable results' from 'a successful trial'. Example: It can be expected that due to COVID-19, many trials will have fewer evaluable patients and therefore, the power will be decreased. What is the impact if the DMC comes to the conclusion that it is unlikely to show a statistically significant result? Will the trial go on without modifications if the results are still deemed 'interpretable'. **Proposed change:** Please clarify the term 'interpretable' and discuss in more detail the impact of COVID-19 on the power of the trial.

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68-69	7	**Comments:** We are not aware that sponsors run blinded aggregated data reports with the 'usual intent to confirm the likelihood of a trial being successful.' other than for the purposes of tracking elements related to data quality (risk based monitoring) or statistical power to ensure the trial can meets its design objectives. **Proposed change:** remove the text 'usual intent to confirm the likelihood of a trial being successful' to avoid confusion. The important point has already been made. Removing the language avoid mis-interpretation equating 'successful' with 'positive'.
68-69	24	**Comments:** It is not the usual intent of trial monitoring activities to confirm the likelihood of the trial being successful, as the sentence seems to state. This part of the sentence is related to "I". **Proposed change:** Delete: "*, not with the usual intent to confirm the likelihood of the trial being successful. Nevertheless, a more thorough analysis may be warranted."*
69	7	**Comments:** 'nevertheless a more thorough analysis may be warranted.' The first section of the paragraph speaks to routine reports that are produced blinded and aggregated across treatment groups/sites/countries etc. This is emerging as good practice and should continue, with special attention to the "COVID defined" periods of time. One should also need to separate the risk of infection with COVID-19 and the impact on trial operations. What

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		comes next in the paragraph appears to be about this same set of questions though perhaps unblinded…which is generally not necessary. It also encompasses questions which have to do with the ultimate interpretation of the trial data…again ill-advised unless the trial was designed (or is being converted) to an adaptive design, including sample size re-estimation or conditional power.
69	9	**Comments:** Please clarify whether this "more thorough analysis" is intended to convey that this requires unblinded information. Is this possibility what motivates involvement of a DMC?
69	19	**Comments:** "more thorough analysis may be warranted" **Proposed change:** It would be helpful if it were clarified explicitly whether analysis and perusal of unblinded data by the independent DMC is encompassed in this suggestion.
69-70	17	"*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*." **Comments:** 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

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		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 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."
69-71	24	**Comments:** "*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*". It is a bit unclear what "*such an analysis*" refers to in the general context, and even more if the proposed change to Lines 68-69 is followed. **Proposed change:** Replace by: *"All analyses of unblinded trial data for this purpose must be conducted by an independent Data Monitoring Committee (DMC), which may already exist for the trial."*

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69-73	7	**Comments:** Independent of the concerns noted above, as proposed, this is not the best use of a DMC. DMC membership is established prior to the start of the trial and is focussed on very specific responsibilities vis a vis risk-benefit for the patients in this trial. Simply stated, the current DMC (who are experts about the trial) can certainly be queried about the structural integrity and viability of the trial in a manner which does not elicit knowledge about the likelihood of a particular result. It is unclear what new experts not knowledgeable about the trials will add to the mix. In addition, initialising a new or additional 'DMC' for each of the ongoing trials is simply not feasible…there are too many trials and sets up the risk of disparate advice. **Proposed change:** Strike out the entire section and focus uniquely on blinded aggregated data reporting. Include a section on the conversion of an existing trial to an adaptive trial (e.g. modifying the trial with a futility interim analysis conducted by an existing DMC or a blinded assessment by those running the trial).
69-73	10	**Comments:** The recommendation to stand up an independent data monitoring committee (IDMC) may not be feasible for all studies, even when unblinded data review is needed. Setting up IDMC can be a lengthy process given the contracting and compliance issues involved. This process may become be more challenging as the current crisis increases the demand for subject matter experts to serve on IDMCs. Consider allowing an internal data review committee, with appropriate firewalls to protect trial integrity, as an alternative. **Proposed change:**

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		Add following text, "If it is not feasible to set an independent DMC, an internal data review committee may also be considered. If this approach is used, appropriate internal firewalls must be set up to prevent the study team and other trial personnel from gaining access to unblinding data or reports."
69-74	6	**Comments:** The establishment of an independent DMC triggered by the COVID-19 pandemic, if otherwise a DMC would not have been warranted for the trial, is likely to create an undue burden to experts that comprise DMCs. **Proposed change:** It is recommended that the impact of COVID-19 pandemic be discussed with the independent Data Monitory Committee (DMC) for the trial and that additional analysis of the trial data be conducted as deemed necessary. ~~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.
69-74	24	**Comments:** *"It is recommended … is conducted by an independent Data Monitoring Committee… This will ensure that the Sponsor can preserve trial integrity as much as possible."*. This text, and the structure of the section overall implies that any risk assessment that involves analysis of the data is conducted by an independent DMC. Given that sponsors typically have access to at least some blinded data, for example recruitment figures, site monitoring reports, deviation logs etc, they too can perform a risk assessment. Can the guidance be expanded to briefly explain how this can affect trial integrity, as per the guidance suggestion, and so why sponsors should not do this themselves?

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69-75	21	*"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"* **Comments:** Presently, it is not clear if the Agency expects independent DMCs to look at unblinded treatment data. If this is the case, Regeneron encourages the Agency to add to this document a discussion on the concerns of introducing potential bias by allowing DMCs to give advice on a wide range of trial modifications based on knowledge of unblinded data. The Agency's acknowledgement of these concerns and its advice on how to address these factors would help ensure that Sponsors adequately maintain the integrity of their trials.
69-93	14	**Comments:** We have general concern over the points to consider suggesting that an analysis broken down by treatment groups could be performed. The appearance of this proposal in a guidance document could make it a more frequent approach than it would otherwise have been, which would be concerning. As the purpose of this exercise is to look at the impact on the quality and reliability of the data from an operational/trial conduct viewpoint, rather than focussing on results of the trial, it does not seem necessary. It is considered that it can be seen whether suitable data are still being collected on patients without the need to see the treatment comparison, and that decisions on e.g. whether additional patients are needed to replace patients whose data has been ruined by the pandemic, or other possible actions as listed on lines 84-93, can be made without needing knowledge of the treatment effect, or requiring an independent DMC. Allowing decisions to be made based on unblinded data seems to create more disadvantages in terms of potentially compromising trial integrity, even if done by a DMC, than it gives advantages.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Everything from "Nevertheless, a more thorough analysis" on line 69 to "methodological competence" on line 77 could be deleted. Reference to a DMC removed on line 83.
70	9	**Comments:** "is conducted by": Perhaps clarify that this analysis is *reviewed* by a DMC; DMCs rarely conduct an analysis themselves, but rather review analyses performed by an independent statistical center.
70-71	13	**Comments:** Usually a DMC is set-up is to minimise bias and/ or for the benefit of expertise. It is difficult in this context to see, how bias could be introduced and as the challenges which this situation brings are equally unfamiliar to all parties. Therefore, the proposal of adding a DMC for a study, which never planned to include a DMC is in doubt. Since the rational and the operational guidance for DMC is unclear. **Proposed change:** Remove the request implementing DMCs
70-82	12	**Comments:** As an example, if a Phase 3 trial does not have a Data Monitoring Committee (DMC), would that be considered a review issue, even if the study team produces its own risk assessment of COVID-19 on the study without use of

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		such a DMC? Without a nuanced requirement for DMC based on the risk assessment this might be considered an unnecessary burden for many sponsors. **Proposed change:** We kindly request the Agency to clarify this in the final document, particularly to reconsider the level of risk that would require a DMC to be established in studies.
71	8	**Comments:** Establishing DMCs in the current environment may not be feasible; please clarify what could be circumstances that may require a DMC to look at unblinded data in order to make a risk assessment.
71	9	**Comments:** A DMC "may already exist for the trial. If not . . . should preferably be established": The wording suggests that all ongoing trials need a DMC. Can you clarify the scope? For example, does this apply to phase III trials? Is there general guidance based on a trial's size or duration, or current status relative to planned completion, that could be described? Especially in phase II, can this DMC include personnel internal to the sponsor organization?; etc. Establishing a qualified DMC when one was not previously felt to be needed can be challenging and time consuming. Attempting to ensure that they have full understanding of all relevant background for the important tasks that this guidance suggests for them, compared to trial personnel or Steering Committee members who will already have such perspective, could be risky. Unless actions are expected to depend upon unblinded interim results, might this be re-stated to allow some leeway in this?

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		If an unblinded DMC is felt necessary to establish, given the challenges of identifying and implementing such a group quickly, could an internal firewalled group be an option in some cases?
71-73	12	**Comments:** Establishing an independent DMC for studies where one does not currently exist may be challenging and cause potential delay to the required timely decision-making for the COVID-19 situation. Risk assessments of studies should not be delayed due to the initiation of a DMC. **Proposed change:** We kindly request the Agency to clarify this in the final document.
71-73	17	"*If not, an independent DMC should preferably be established, following the necessary procedures regarding Ethics Committees and relevant competent authorities*." **Comments:** 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*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
71-73	21	"*If not [DMC does not exist for the trial], an independent DMC should preferably be established, following the necessary procedures regarding Ethics Committees and relevant competent authorities.*" **Comments:** At present, EMA's recommendation on the potential need to establish an independent DMC (IDMC) to evaluate the impact of COVID-19 on trial integrity and interpretability is not completely clear. An IDMC is not a routine requirement for all trials. Additionally, when they are implemented, DMCs often focus on safety rather than efficacy considerations. Therefore, Sponsors might need to revise their DMC charters to ensure the appropriate level of methodological competence for this COVID-19 risk assessment exercise. Clearer guidance on the topic of trial modifications based on IDMC recommendations after review of unblinded efficacy data would better inform Sponsors on actions they could ask an IDMC to perform beyond oversight of patient safety. Such recommendations would assist Sponsors in optimizing the DMC's scope rather than indiscriminately introducing additional complexity with minimal potential value and further complicating an already challenging pandemic.
71-73	24	**Comments:** "*If not, an independent DMC should preferably be established, following the necessary procedures regarding Ethics Committees and relevant competent authorities.*" Is it realistic to expect DMCs to be established, given the time frames that are being worked to? The impact of COVID-19 needs to be assessed now. The guidance does state "if feasible" but typically it is more likely to not be feasible? Alternatively, the guidance could comment on what to do (and what not to do) if the study does not have an established independent DMC.
73	26	**Proposed change:**

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		Add "Data Integrity" to trial integrity
From line 74 (74-75)	22	**Comments:** "It would be useful to establish a public DMC for each country managed by the CAs of the countries where the clinical trial takes place or from the country in which the PI operates."
75-77	17	**"***If a DMC is already in place, it might be important to revise the DMC charter accordingly, including considerations to increase its methodological competence."* **Comments:** 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:** *… 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.***
77	8	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		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?
77-79	24	**Comments:** There is no explicit statement on circumstances where the analysis may be performed on unblinded rather than blinded data. Indirectly, it is clear that it is recommended to perform these analyses on "aggregate and blinded" data (line 67), though there might be situations where the drug interfers either with COVID-19 or with COVID-19-related concomitant medication, in which case, an unblinded analysis might be important, or the DMC might be indirectly unblinded by additional information. **Proposed change:** Please give explicit guidance on blinded and unblinded analysis.
77-80	12	**Comments:** 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 and to not use the pandemic as a blanket excuse to make changes that may have other motivations. 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.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: We kindly request the Agency to clarify this in the final document.
77-80	17	*"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."* **Comments:** 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."*
80	14	**Comments:** "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." This sentence

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		seems odd. The trials are likely not to be conducted as planned due to operational restrictions due to the pandemic, not for a convincing scientific reason and it is the impact of these changes on the interpretability of results that is being assessed.
83	11	**Comments:** We propose an additional clarification to avoid potential misunderstandings on the role of Data Monitoring Committees (DMCs) in the conduct of clinical trials. **Proposed change:** "Potential follow-up considerations or advises of the DMC **with regards to patients' safety and study integrity** may include the following:"
83	17	"*Potential follow-up considerations or advises of the DMC may include the following:"* **Comments:** 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.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Potential follow-up considerations ***for the Sponsor (with*** or ***without*** advises of ***a*** ~~the~~ DMC***)*** may include the following:
83	18	**Comments:** In case measures taken in relation to COVID-19 interfere with the trial, more emphasis has to be put on the risk assessment plan and the sponsor needs to specify how the interference was managed.
83	27	**Comments**: With regard to "Potential follow-up considerations or advises of the DMC", could it be clarified whether the trial termination can be considered before the planned end of trial date if the current data available are acceptable and sufficient to allow the DMC to make a clear conclusion on the trial ?
83-93	1	**Comments:** During the COVID-19 infection period it is expected that trial participants may not be able to come to the investigational site for protocol-specified visits. Missed visits, or patient discontinuations may lead to missing or incomplete information in the case report form with the consequence to increase missing data in the statistical analysis. Considering the COVID-19 specific age distribution it is possible that these missing data will be not equally distributed in the cohort of patients enrolled in the trial. The rate of trial participants that may not be able to follow correctly the study protocol could be influenced by the age of the patients. For this reason the missing protocol-specified information can be influenced by age. To verify this hypothesis a new potential consideration could be included in the point to consider document.

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		Proposed change (add a new item): Recommendations of additional analyses to evaluate the impact of a potential age-related bias in patients' reporting data during the pandemic measures phase.
83-93	12	**Comments:** We acknowledge that the established role of the DMC is to guide clinical research and ethical/statistical decisions on study conduct, with the ultimate decision to act on such decisions lying with the Sponsor. Due to the exceptional circumstances and the guidance to use a DMC in COVID-19-impacted studies, would the Agency please confirm that the DMC role would remain unchanged and that any divergence from DMC guidance would still need to be justified by the sponsor as part of the review process? **Proposed change:** We kindly request the Agency to clarify this in the final document.
83-96	28	**Comments:** The draft guidance states that "potential follow-up considerations or advises of the DMC may include recommendations on how to re-start usual trial operations". In the document the DMC is referenced but within a UK setting there are other oversight committees that may need to have input into the recommendations listed (e.g. trial management group and/or trial steering group with guidance from the sponsor). **Proposed change:** Consideration of input from other oversight committees as outlined above

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84	7	**Comments:** 'Recommendations on how to re-start usual trial operations' Once they have seen unblinded data, DMCs should only comment on general trial integrity and data quality.
84	9	**Comments:** Unless the decision is directly impacted by unblinded results reviewed by the DMC, re-starting usual trial operations seems most effectively addressed by the appropriate trial personnel who manage trial operations. Can you clarify the suggested role of the DMC here?
84	12	**Comments:** It is not clear to us why a DMC would have special expertise on "*recommendations on how to re-start usual trial operations*." **Proposed change:** We would request the Agency to please remove the bullet on line 84.
84	24	**Comments:** We question whether the DMC is the best place to advice on "*how to re-start usual trial operations*".
85	12	**Comments:**

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		We believe the current sentence might be confusing to interpret. **Proposed change:** We would request changing to "*Recommendations of additional measures to be taken after the pandemic before completing the trial*."
85-86	7	**Comments:** best done by those running the trial in a blinded fashion.
85-86	9	**Comments:** If this refers to additional measures or analyses that have not yet been produced but the DMC feels would be helpful to see during their ongoing deliberations, then of course they should request these. However if this refers to the final study report and the DMC has already seen related unblinded data, this becomes problematic to implement objectively. Please clarify.
86	17	*"(e.g. validation of outcomes that were measured differently);"* **Comments:** 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?

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		Please provide further details of what documentation will be needed to be provided to validate outcomes measured differently.
87	9	**Comments:** For a DMC, or any party that has had access to unblinded results, to recommend adjusting sample size seems very problematic. A number of regulatory guidances strongly advise against design changes proposed by parties who have been unblinded, DMCs included. Could you clarify when this might be warranted?
87	11	**Comments:** The guidance recommends the involvement of an independent DMC to ensure that the Sponsor can preserve trial integrity. We support this recommendation to involve a DMC to help ensure patient safety and data integrity, but we do have a concern to involve the DMC to recommend on the need to adjust the trial sample size, for the following reasons: We believe that the Sponsor should strongly consider a blinded sample-size recalculation due to an expected reduced precision of the efficacy measurements resulting from e.g. loss of patients during the trial, missing data and reduced ability to record high quality data. We therefore prefer not to have an unblinded DMC perform the sample size re-estimation as their main focus is on patient safety and trial integrity. Furthermore, an unblinded sample size re-estimation presents additional challenges in maintaining trial integrity, even more in case it does not concern prospectively planned adaptations. Last but not least the DMC may not have the background information on the original calculation/methodology and/or the required methodological competence on sample size estimation in order to perform this type of analysis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Proposed change: Consider deletion of the following bullet point: "The need to adjust the trial sample size"
87	12	**Comments:** Some caution may be noted that a DMC providing advice on 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. **Proposed change:** We kindly request the Agency to clarify this in the final document.
87	15	**Comments:** The guidance recommends that the DMC can recommend sample size adjustments. These will be based on blinded or even unblinded sample-size reassessments that have a huge potential impact on the inflation of the type-1 error. **Proposed change:** Please discuss critically how potential changes of the trial conduct affect the type-1 error.
87	17	"The need to adjust the trial sample size;"

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Comments: Some caution may be noted that a DMC providing advice on 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.
87	28	**Comments:** We note that there is no mention of analysis populations within the guidance. Whilst the primary analysis for most trials is ITT, the circumstances around COVID-19 are unique and could make this questionable in some settings. In these cases, if a different analysis set were now considered the primary analysis population, this will have implications on the power of the study. The guidance acknowledges this by sample size re-estimation, but re-activating trials that are already in follow-up may not be feasible. **Proposed change:** consideration of analysis populations as outlined above
88-90	4	**Comments:** Specify that it may be relevant to conduct such additional analyses on the impact of the three phases (pre, during and post COVID-19) at the patient, country and trial levels.
88-90	6	**Comments:** Given the fact that long term sequelae are a reasonable possibility after COVID-19 infection, Agios would suggest that determination of a post COVID-19 phase is not possible in a given trial. An index date associated with the earliest date of possible/confirmed COVID-19 infection and date of patient's participation in the trial is

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		first impacted by the COVID-19 pandemic can be used to summarize trial results including all data collected with those after excluding data on or after the index date. **Proposed change:** Additional analyses (to be included in the Statistical Analysis Plan) to investigate the impact of ~~the three phases (pre, during, and post COVID-19)~~ COVID-19 pandemic on the data collected after the index date ~~to understand the~~ and the treatment effect as estimated in the trial;
88-90	7	**Comments:** In the event an existing DMC has already seen informative unblinded results from the trial, they should not be advising the blinded study team on any additional analyses while the trial is ongoing. **Proposed change:** Any changes to the SAP should be made prior to database lock and based on blinded, aggregated data. It is possible that multiple approaches will be required in concert to draw inference – sponsors should include the rational for each proposed analyses and what aspect of the disruption it aims to assess.
88-90	9	**Comments:** One might expect that the motivation to investigate differences across trial phases as part of the final analysis should be apparent to all personnel. Changes or additions to a study's final analysis plan would almost always be motivated by blinded trial personnel. If analysis changes are initiated by a party that has had access to unblinded information, it can be very challenging to be certain that these can be interpreted to be valid. Can it

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		be clarified why the DMC should play such a role, and why this would not raise questions about the validity of those analyses?
88-90	12	**Comments:** As noted in previous comments (see lines 62-65), phases of the pandemic (pre-, during, post-) will differ across regions, and across countries/states within region. The guidance could provide a recommendation to consider this when conducting additional analyses to understand the impact on treatment effect. **Proposed change:** We kindly request the Agency to clarify this in the final document.
88-90	17	"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;" **Comments:** 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.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		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
88-90	21	"*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*" **Comments:** Regeneron would like to suggest the Agency establish a CHMP working group to provide advice on the types of analyses that would be acceptable for investigating the impact of actions taken during the pandemic on assessments of treatment effects in clinical trials, with accelerated timelines for review that would meet the needs of Sponsors who have trials that are nearing completion. Where statistical analyses require some modification versus what is described in a protocol, it would be highly pragmatic if the National Competent Authorities were to consider such as non-substantial amendments that can be documented by the Sponsor in the Trial Master File.

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Such recommendations would help ensure Sponsors conduct all appropriate analyses of these datasets. They would also help avoid undue delays to the conduct of statistical analyses and to any future regulatory filings these datasets may help support.
88-90	23	**Comments:** There is a recommendation (also alluded to in lines 62-65) regarding to assess the treatment effect in 3 phases: before, during and after COVID19 measures. No definition is given how these phases are to be defined: based on the official date of the start and end of the pandemic, on country level, on institution level, patient level or even data point level (when dealing with longitudinal endpoint). Neither is there any specification on recommended methodology, whether analyses need to be adjusted on the population level (subgroups), test statistic (stratifying; adjusting) or even whether this needs to be considered as intercurrent events. **Proposed change:** EORTC suggests to convene a working multi-stakeholder group of expects to address this issue and to provide separate guidelines on this complex matter.
89	16	**Comments:** Would it be possible to clarify how to determine the dates to define the "Pre / during / post" COVID-19 periods? Is there an expectation that "pre/during/post" periods would be region specific or general? If region specific, would it be related to travel restriction/quarantine or circulation of the SARS-CoV-2 within region?
90	12	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Does the Agency consider that "*treatment effect as estimated in the trial*" refers to efficacy or both efficacy and safety? **Proposed change:** We kindly request the Agency to clarify this in the final document.
91	8	**Comments:** The statistical approach to intercurrent events and missing data will determine the interpretation of the treatment effect, which usually does not fall under the responsibility of most DMCs and it is recommended that it is made clear that this is done by the Sponsor.
91-93	4	**Comments:** Relevant to include proposals to handle additional variability introduced through changes in the methods used to collect data, as one of the considerations the DMC may advise the sponsor on.
91-93	9	**Comments:** Missing data and newly identified intercurrent events should be apparent to all. Just as when such unexpected complexities arise in current practice, the preferred approaches to deal with these can and should be identified by blinded personnel. Can the potential DMC role be clarified?
91-93	12	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		In considering trial integrity it would help to clarify if the recommendation is to retain, if possible, the current primary estimands and analysis plans and to consider supplementing these with others to address COVID-19. **Proposed change:** We kindly request the Agency to clarify this in the final document.
91-93	17	*'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.'* **Comments:** 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:

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		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).***
92	9	**Comments:** Suggest adding after "newly identified intercurrent events" something to the effect of "and how they should be reflected in the estimand".
94	3	**Comments:** An additional bullet point should be added highlighting potential changes in safety-related tests, with safety results being potentially altered has a result of a) viral infection, b) viral associated treatment. **Proposed change:** "- Re-definition of possible cut-off values for safety related tests and/or AE and SAE in association with COVID-19 infection or COVID-19 associated treatments"
94	14	**Comments:**

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		"Major changes in the conduct of a trial should follow the local regulations and be approved by Ethics Committees." **Proposed change:** Add "and the national regulatory authority" at the end and change "major" to "substantial".
94-95	12	**Comments:** Propose to also include reference to National Competent Authorities for clarity. **Proposed change:** Major changes in the conduct of a trial should follow the local regulations and be approved by **National Competent Authorities and** Ethics Committees.
94-95	15	**Comments:** It is not clear which major changes need to be approved by regulatory authorities.
94-95	17	*"Major changes in the conduct of a trial should follow the local regulations and be approved by Ethics Committees."* **Comments:** 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

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		opinion by ECs. CAs are missing in the above sentence and ECs do not 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.***
94-95	21	"*Major changes in the conduct of a trial should follow the local regulations and be approved by Ethics Committees*" **Comments:** We request that the Agency clarify the term, "major change in the conduct of a trial" in the context of the COVID-19 pandemic by providing a carve out of types of changes that would be considered typical during the

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		pandemic and would not require review by Ethics Committees. Clarification of the Agency's expectations would help ensure that only appropriate changes would be submitted and reviewed by Ethics Committees, helping avoid an unnecessary burden on these bodies – which are likely facing multiple challenges during the pandemic.
94-95	26	**Comments:** Major changes (if meeting the definition of "substantial amendment" per Directive 2001/20/EC) must also be approved by the Competent Authority (CA), not just the Ethics Committee. **Proposed change:** Please add the requirement for CA approval for substantial amendments.
97	14	**Comments:** "BSWP would encourage Sponsors to take these points into consideration and to seek Scientific Advice on these matters early in the process." Does this mean formal scientific advice from the agency? Encouraging seeking scientific advice may overwhelm the agency in these circumstances? Perhaps instead emphasise the use of guidance and consider setting out what criteria would be appropriate to trigger sponsors to ask for scientific advice?
97-98	6	**Comments:** Will there be enough capacity within the scientific advice process to handle the anticipated bolus of requests? Minor change has been recommended to allow flexibility in timing of meeting conduct.

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		Proposed change: BSWP would encourage Sponsors to take these points into consideration and to seek Scientific Advice on these matters as early as possible in the process.
97-98	7	**Comments:** There would be too many ongoing trials and the Scientific Advice process would grind to a halt. It might be possible to redesign the scientific advice process (or create a public meeting alongside other regulatory bodies) to review 'archetypes' of trials and disruption scenarios. This would provide meaningful advice open to all sponsors involved with such trials. It would require quite an investment but may be most effective overall. **Proposed change:** See above. We strongly encourage implementation of an open-access review process for the common issues affecting protocols without sharing sensitive company information.
97-100	12	**Comments:** EMA is encouraging sponsors to seek scientific advice. Considering that each (on-going or recently started) clinical trial will have to be analysed separately, seeking a formal Scientific Advice might not be the most practical procedure. Clarification is needed on more flexible and dedicated pathways to Scientific Advice and how the EMA would manage the large volume of requests from applicants. We propose that a dedicated channel is established at EMA SA office for sponsors to ask questions and get clarification. **Proposed change:**

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		propose to change the sentence as "*BSWP would encourage Sponsors to take these points into consideration* ***when seeking*** *Scientific Advice on these matters early in the process"*
98-100	17	*"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."* **Comments:** 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.
From line 99 (98-100)	22	**Comments:** "Scientific consultation should be free of charge for all public and private sponsors."