Supplemental Appendix for Challenges in assessing the impact of the COVID-19 pandemic on the integrity and interpretability of clinical trials

Mouna Akacha\textsuperscript{a*}, Janice Branson\textsuperscript{a}, Frank Bretz\textsuperscript{a,b}, Bharani Dharan\textsuperscript{c}, Paul Gallo\textsuperscript{c}, Insa Gathmann\textsuperscript{a}, Robert Hemmings\textsuperscript{d}, Julie Jones\textsuperscript{a}, Dong Xi\textsuperscript{c}, and Emmanuel Zuber\textsuperscript{a}

\textsuperscript{a}Clinical Development & Analytics, Novartis Pharma, Basel, Switzerland;

\textsuperscript{b}Section for Medical Statistics, Medical University of Vienna, Vienna, Austria;

\textsuperscript{c}Clinical Development & Analytics, Novartis Pharmaceuticals, East Hanover, NJ, United States of America

\textsuperscript{d}CONSILIUAM Salmonson & Hemmings, London, United Kingdom

Provide full correspondence details here including e-mail for the *corresponding author

Mouna Akacha

mouna.akacha@novartis.com

Novartis Pharma AG,

Clinical Development & Analytics,

Postfach CH-4002 Basel,

Switzerland

**Appendix**

We provide a list of concrete questions that may help in the decision process for the impact assessment, such as whether to stop, halt or continue the trial, with or without changes to the protocol and trial conduct.
The list of questions below is not exhaustive and rather meant to serve as a guiding principle to support cross-functional discussions that need to occur during the pandemic and thereafter. As the COVID-19 situation is changing rapidly, the impact on trial integrity needs to be assessed repeatedly over time.

The questions are categorized into some general considerations with regard to trial conduct and statistical aspects. In addition, more specific considerations pertaining to endpoints, study treatments and trial populations are provided. Some of these questions aim at triggering an estimand discussion by identifying relevant unforeseen intercurrent events. As many of these considerations are interrelated, there is some overlap in the questions.

**General impact**

- Is the trial predominantly conducted in regions/sites severely impacted by COVID-19?
- Is the randomization of the study stratified by region or country?
- How many subjects are enrolled so far, and yet to be enrolled?
- How many subjects are impacted by COVID-19-related issues?
- How long will it be before the trial ends, perhaps relative to recruitment as well as the planned follow-up time or overall observed number of events?

**Impact on therapeutic context**

- Were subjects hospitalized during the COVID-19 pandemic and, if so, for which reasons?
- Do some subjects have a lung disease history?
• Does the disease area of interest in the trial share disease characteristics with COVID-19? How to identify whether symptoms are due to COVID-19 or the underlying disease of interest? Are COVID-19 diagnostic tests available for all subjects in a given trial? Do they differ across regions or countries?

• Is the nature of disease/condition under investigation affected (e.g. impact on symptom scores in depression trials or quality of life scores due to isolation)?

• Will the medical practice after the pandemic be different from the medical practice prior to the pandemic (e.g. systematic COVID-19 diagnostic tests prior to start of treatment)? Can some of these differences be anticipated in the trial, or will that possibly affect the interpretability or relevance of trial results?

Impact on trial conduct

• Should COVID-19 testing be done as part of screening procedures prior to start of treatment? Would this have an effect on the population of interest?

• Does treatment need to be delayed, interrupted or stopped for subjects with a positive COVID-19 test, or only for those subjects who show symptoms, or subjects showing symptoms without having been tested? What is the impact on the treatment regimens and the interpretability of efficacy and safety data?

• Considering site access restrictions/quarantine, is there a need to change methods for monitoring subjects (e.g. conduct visits via phone, virtual visits) regarding safety, efficacy, patient reported outcomes? Can direct remote communication with investigators adequately replace in-person visits, and in such cases, can investigator assessments be made sufficiently accurately? Would the collected data be interpretable and address the same scientific question?
• Is there a shortage of drug supply at specific sites? What is the impact on the treatment regimens and the interpretability of efficacy and safety results?

• If subjects are supplied with medication at visits, can there be alternate arrangements for delivery, and does this ensure identical treatment?

• What is the visit frequency for the trial; perhaps relative to the length of time in which the current concerns will be present?

• For the near future while the pandemic continues, are uncompromised visits possible at all?

• Going forward, what timeframe of disruption of visits would be affordable, for the trial continuation to be viable and to provide meaningful data?

• Will it be possible to identify the relationship of missing assessments, protocol deviations, adverse events, treatment and trial discontinuations as well as mortality due to COVID-19 with the information collected in the trial?

• Could some COVID-19 related procedures or complications lead to unacceptable levels of unblinding in the trial?

**Impact on endpoint**

• In case of COVID-19 related death, can this directly impact the primary or secondary endpoints, e.g., all-cause mortality or composite endpoints including all-cause mortality?

• Is there a risk that assessments could be impacted by the COVID-19 pandemic itself (e.g. quality of life, mobility assessments, neuropsychological scales such as depression or anxiety) due to
o changes in data collection modalities (i.e. same endpoint, but different mode of collection); remote communication with sites rather than in-person; different site or provider?
o subtle changes in the endpoint itself due COVID-19 impact?

- How will the trial estimands be affected if subjects
  o discontinue trial treatment, but stay on trial follow-up?
  o discontinue trial treatment and withdraw consent?
  o miss efficacy assessments?
  o die of a COVID-19 related cause?

**Impact on trial treatment**

- Is there an impact on administering trial treatment (treatment access and safe administration for the general trial population)?
- If treatment is delayed, interrupted or stopped, how will it affect the interpretation of efficacy and safety data?
- Are the trial treatments impacted by medications used to treat COVID-19 symptoms? Can those affect the treatment effects of interest, e.g. can they generate treatment interruptions, or interactions?
- Do the treatments used in the trial act as immunosuppressant, including concomitant therapies (e.g. cancer chemotherapy, corticosteroids)?

**Impact on population**

- Do COVID-19 measures introduce any bias in the trial population, e.g. younger population enrolled, more healthy subjects because they can come to the site, or ethnic/geographic selections? In other words, are the subjects that we
follow/observe during (and potentially after) the pandemic representative for the population of interest?

- Is there a change in trial population before and after introducing changes to the screening procedures (e.g. cohort effect)?

- In the event that a subject has a suspected / confirmed COVID-19 infection during the screening or run-in period, what is the impact in case that: (1) the subject will be excluded from enrolment/randomization? (2) the subject will continue to be randomized/enrolled?

**General statistical considerations**

- Is there reason to expect imbalances between treatment arms with regard to the number of treatment discontinuations and missing assessments (e.g. in open-label trials or trials involving study drugs with a specific mode of action, are subjects in one arm possibly at higher risk of infection)?

- Could subjects with missing assessments be different from those with reported assessments (e.g. progressing subjects more likely to travel to the hospital than responders who feel well; elderly subjects less likely to attend scheduled visits)?

- Should the primary estimand be re-phrased to account for additional intercurrent events?

- If interest lies in a hypothetical strategy to account for unforeseen intercurrent events, how should hypothetical trajectories be predicted? What is the interplay of foreseen and unforeseen intercurrent events?

- Is there a need to assess consistency in terms of treatment effects, regional effects, targeted populations etc. based on data observed before, during and after the COVID-19 pandemic?
- What is the impact on recruitment and timing of read-out for interim and primary analyses?

- In group sequential trials, are interim decisions based on similar conditions throughout the trial?

- Is it necessary to set recruitment on hold and how should the final statistical analysis plan be impacted, especially for a pivotal trial? As time goes by, will enrolment be restarted in recovered regions and what would the impact on the study population be? Should enrolment in recovered regions be capped to protect the integrity of the trial?

- For trials planning to use an external control or to borrow data from an ongoing global trial for a region-specific sub-trial: are populations comparable between external and internal data, between the sub-trial and the overall trial, through the time of the pandemics?

- Is there a need / potential to adjust the sample size to mitigate loss of power? If so, could this be done based on the overall missing proportion of the data or is a formal interim look needed? Would an increase in the sample size mitigate power loss or could it be counterproductive, e.g. lead to increased variability of the endpoint or to a dilution of the treatment effects?

- What are the implications (e.g. on trial power) if the trial was to stop early because of COVID-19? Are there other options that would be appropriate and could be considered to mitigate power lost due to COVID-19 complications? For example: increased sample size (perhaps within an adaptive scheme), extended study duration to obtain more events, change from a fixed-time endpoint to a longitudinal approach, incorporating data from other studies or historical controls, change to a hypothetical estimand strategy, etc.
