



## Risk and mitigation actions for clinical trials during COVID-19 pandemic (RiMiCOPa)

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### ABSTRACT

The COVID-19 virus diffusion is, nowadays, global and any clinical trial is potentially affected by the direct and indirect consequences of the COVID-19 during the pandemic. Any step, from protocol design to result's disclosure, needs to be revised to assess the impact of the COVID-19 on the study, evaluate the potential risks, and establish a mitigation plan. We have developed a series of recommendations, belonging to our experience in any aspect of clinical trials.

We hope that the Risk and Mitigation actions for clinical trials during COVID-19 Pandemic (RiMiCOPa) will help all clinical trial professionals, patients, auditors, and assessors to ensure effective data management, statistics, and medical writing standards while conducting clinical trials in the pandemic.

### 1. Introduction

To date the clinicaltrials.gov clinical trials registry records about 55,000 clinical trials enrolling or recruiting patients, more than 18,000 active studies not recruiting and more than 157,000 completed or suspended, without results posted [1]; more than 18,000 ongoing studies are recorded on the EU Clinical Trials Register [2], with thousands of professionals actively involved in any phase and aspect of the trial, and millions of patients enrolled, whom families are heavily impacted [3]. All clinical trials must follow good clinical practices [4] and have to be conducted following the Declaration of Helsinki [5]. The COVID-19 pandemic is impacting the conduct of clinical trials of medical products. Challenges as quarantines, site closures, travel limitations, the supply chain interruption for the investigational products, could be faced as well as other issues including site personnel or trial subjects COVID-19 infection. In March 2020, 170 company sustained clinical trials were suspended worldwide; furthermore, new patient enrolment dropped 65% on a year-on-year basis [6]. As none of these studies have been scrapped, the hope is that much of this clinical work will resume. However, it seems probable that this analysis understates the disruption because updating clinicaltrials.gov is voluntary. Sponsors must be conscious that actions taken during the pandemic have to be recorded. Patients and their families are deeply involved in clinical trials; their

contribution is commonly considered fundamental for conducting effective trials [7]. The RiMiCOPa document, based on EMA and FDA guidelines [8,9], provides advice to evaluate how the different aspects of clinical trials should be handled to mitigate the impact of COVID-19 pandemic on data management, statistics, and medical writing activities, maintaining the required quality standards.

### 2. Development of the RiMiCOPa statement

The statement was developed by extensively experienced professionals on clinical trial data management and statistics (AB, PM), and medical writing (AR). The urgency of facing the COVID-19 pandemic has pushed the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) to issue specific guidelines [8,9] with their recommendations as fast as possible. The RiMiCOPa statement recommendations are compliant with these guidelines with the focus on data management-, statistics-, and medical writing-related matters. They have been developed and subsequently revised by the authors and other experts in different areas. Their development was driven by the need of ensuring study quality and patient centricity in today's environment of uncertainty and fear approaching health care structures.

These recommendations should be used, as a minimum set of mitigation actions for potential risks, for the studies conducted in Countries/

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Regions impacted by the COVID-19 pandemic. A Study Contingency & Risk Mitigation Plan (SCMRP) should be written by the study sponsor or the company managing the relevant aspects of the study, involving Clinical Operations, Data Management, Statistics, and Medical Writing representatives. The sponsor has the responsibility to approve and ensure the SCMRP application. Each SCMRP must be study-specific, should cover all areas of risk, and might follow the structure of this document as a starting point.

### 3. Checklist items

The final recommendations are subdivided into 4 main categories: [a]general; [b] data management; [c]statistics; [d] medical writing. The recommendations are contained in user-friendly tables (Tables 1–4) to aid users who wish to follow them. Each task has a title in the 1st column, followed by the general description of the risks, suggested mitigation actions, and urgency.

#### 3.1. General

General topics that should be considered during the COVID-19 pandemic are summarised in Table 1. Study managers and sponsors must check the presence of any guidance on the management of patients eligible for the study, according to inclusion and exclusion criteria, to be applied in any of the centers involved in the study. Study documents that could be affected by this guidance have to be modified accordingly and any action needed to mitigate its effects should be taken, documented, and safely stored.

The sponsor should assess the impact of the regulations on clinical trials from the relevant regulatory authorities that apply to the study to evaluate if to set up a DMC for the study, if not already constituted. The DMC should assess the impact of COVID-19 and new regulations, if any, on the study. Any activity and decision of the DMC must be documented and appropriately stored in the Trial Master File (TMF).

The interventions to manage the COVID-19 pandemic in different countries have deeply changed the possibility of participating and conducting clinical trials. Any influence of this new unplanned and unexpected way of living on the clinical trial, both in terms of study feasibility and timelines, must be rigorously evaluated by all the actors of the clinical trial (sponsor, CRO, clinical operations, data management, statistics, medical writing, investigator(s), patients, etc.). The potential

and real consequences should be clearly and objectively evaluated to take the appropriate mitigation actions in place. Any delay or change in the study conduction must be clearly stated and communicated to all the clinical trial's actors and regulatory authorities. The record in the clinical trial registry(es) where the study is recorded must be promptly updated. The background and any action taken must be properly documented and stored in the trial master file (TMF).

#### 3.2. Data management

Data management topics to be considered during the COVID-19 pandemic are summarised in Table 2. The safety of patients involved in any clinical trial is paramount of any decision taken in any phase of the study. All safety data must be collected as stated in the study protocol. Any mitigation action must allow the proper collection of the appropriate Adverse Events (AEs). The study sponsor should enhance the most appropriate processes for the collection, management, and communication of AEs and must train any relevant stakeholders accordingly. The balance between patient safety and data validity should be considered, always prioritising patient's safety in case of conflict.

Contingency measures should be needed, including study protocol amendments (and approvals if they are substantial), case report form/electronic case report form (CRF/eCRF) and/or data management plan/data validation plan (DMP/DVP) modification, study timelines re-evaluation, data collection and management processes re-design and reconciliation. All these measures must be recorded, together with the reasons and rationale that drove to the decided outcome, after their approval in the TMF.

Patients might need to be asked to provide a new informed consent. The need for an amended informed consent should be evaluated, too. Any discussion and decision must be documented and recorded. This possible re-consent should be documented as well as stakeholders' training.

Protocol deviations and missing data will likely increase, when compared to the study plan, because of the patients and investigator issues previously described. Any issue should be collected on the CRF/eCRF. The most appropriate instructions should be provided to the investigators. Because of the increased number, more time should be needed to collect, describe, and store them; modifications in the data management process consequent to the increased protocol violations

**Table 1**

Study Contingency & Risk Mitigation Plan (RiMiCOPa) statement for studies conducted in the COVID-19 pandemic – General aspects.

Area	Risks	Mitigation actions	Urgent (Yes/No)
General			
Guidance documents in addition to EMA and FDA guidelines	Certain Countries/Regions may have issued their guidance documents. A certain disease may require specific guidance; for example, the International Society For Heart And Lung Transplantation (ISHLT) has issued a document on patients with chronic lung/heart disease and transplant, mechanical circulatory support, and pulmonary vascular disease [11].	Check the existence of guidance documents specific to COVID-19 impact/management in the therapeutic area. Check also the existence of specific national legislation and guidance. These documents, if any, should be consulted and used to complete mitigation actions.	Yes
Data Monitoring Committee (DMC)	A DMC may be already in place or not.	If a DMC is not in place, consider implementing an independent DMC, as recommended by both EMA and FDA, with the responsibilities detailed in the "EMA - Points to consider on implications of COVID-19 on methodological aspects of ongoing clinical trials" [12]. If a DMC is already in place, revise the DMC charter, including the responsibilities mentioned above.	Yes
Delay in study timelines	Delays in study timelines are expected as a consequence of many factors: EC meetings canceled, administration offices closed and not able to revise or sign CTAs, delays in protocol and IC amendment implementation, delays in patient recruitment, delays in data entry/cleaning/query resolution, backlog when the situation will be back to routine, etc.	The impact of these delays on the scheduled activities and their financial implications have to be carefully evaluated. An appropriate plan has to be stated. Publicly available data on clinical trial registries must be updated. The specific impact on different areas is discussed below.	Yes

Abbreviations: DMC = Data Monitoring Committee; EC = Ethical Committee; CTA=Clinical Trial Application; IC=Informed Consent.

**Table 2**  
RiMiCOPa statement for studies conducted in the COVID-19 pandemic – Data Management.

Area	Risks	Mitigation actions	Urgent (Yes/No)
Data Management Impact of COVID-19 pandemic on patient safety	Patient safety is paramount and at the heart of every decision, regardless of any potential consequences for an ongoing trial.	The Investigators must continue collecting adverse events and other protocol-specified safety data (depending on the study) from the participants through alternative means, e.g., phone contact, virtual visit, alternative location for assessment, local labs, or imaging centers. <u>Possible implications:</u> Consider alternative ways of collecting safety data, evaluating patient's safety vs. data validity. Patient safety is the priority, in case of conflict. Revise the CRF/eCRF. Amend the DMP/DVP, for example for including local labs. Revise the procedure for SAE reconciliation. Evaluate the need for new training. Evaluate the need for a formal protocol amendment. Evaluate the impact of changes on data protection requirements. <u>Auxiliary tasks:</u> Support Clinical Operations on writing procedure(s) for new data collection, for example, for AE recording by phone. A procedure should guide the Recorder on how to mitigate the risk for over-reporting of AEs.	Yes
Other changes in study conduct	Contingency measures, such as delay of scheduled visits, withdrawal of trial participants, implementation of new methods for data collection (see more detailed list under Statistics) may be needed.	It is important to collect pragmatically and systematically information on pandemic-related measures and whether and how trial patients or trial conduct were affected, as well as on the sub-populations of exposed/non-exposed, and infected/non-infected patients. Sponsors and clinical investigators should document and report in CSR how restrictions related to COVID-19 led to the changes in study conduct and duration of these changes. <u>Possible implications:</u> Evaluate the impact of changes in data processing/study duration. Make sure an efficient system to distinguish between "affected" and "unaffected" data is in place. Establish a minimal set of information to collect on patients who get COVID-19 infection. Revise the CRF/eCRF. Amend the DMP/DVP. Evaluate the preparation of new periodic report(s) to be shared during the study, for monitoring purposes. Evaluate the need for new training. Evaluate the need for a formal protocol amendment. Evaluate the impact of changes on data protection requirements.	Yes
Protocol deviations	COVID-19 pandemic is likely to introduce more protocol deviations than normal.	Pre-plan how systematic deviations, due to the measures to face with the COVID-19 pandemic, are captured. Given the large expected number of such deviations, consider the use of <i>ad hoc</i> documentation approaches, for example, through specific listings. <u>Possible implications:</u> Make sure an efficient system for documenting protocol deviations is in place. Consider that, because of the pressure on sites caused by the COVID-19 pandemic, and delays of on-site visits, identification of protocol violations may be delayed. Evaluate the creation of new periodic reports, to be generated through the study, for monitoring purposes. Amend the DMP/DVP.	Yes
Missing data	An increase in missing data is expected.	It is important to capture specific information in the CRF explaining the reason(s) for the increased number of missing data, including the relationship to COVID-19. <u>Possible implications:</u> Revise the CRF/eCRF. If it is not possible to record such information in the CRF, develop <i>ad-hoc</i> processes that enable systematic capture of these data across the sites. Evaluate the need for new training(s).	Yes
Availability of technological tools at sites	IT systems and any other technological tools or the support for these systems may become temporarily unavailable.	Assess the continued availability of, and support for, information technology systems and any other technological tools that are needed to support the trial. <u>Possible implications:</u> Consider the creation of back-up plans.	Yes

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Table 2 (continued)

Area	Risks	Mitigation actions	Urgent (Yes/No)
Changes in on-site monitoring visits	Monitors may not be able to access the trial sites for on-site visits as planned during the COVID-19 pandemic.	If planned on-site monitoring visits are no longer possible, the sponsor should consider optimizing the use of central and remote monitoring programs to ensure oversight of clinical sites. <u>Possible implications:</u> Define how to document situations where monitors were unable to perform or had to delay monitoring visit(s) at the clinical site(s). <u>Auxiliary tasks:</u> Discuss with Clinical Operations how Data Management can support an alternative monitoring program if any (e.g. the central review of data, how overall data quality can be improved, etc.).	No
Informed Consent	There may be a need to re-consent participants already included in the trial.	Define how to document this re-consent, especially if obtained through alternative ways. For example, if oral consent was obtained by phone, it could be supplemented with email confirmation. Then, normal consent procedures should be applied as soon as the patients can visit the site.	Yes
Impact of changes in IMP distribution on treatment compliance assessment	Changes in the distribution of the IMP may be necessary.	Assess the impact of any alternative shipping/returning of IMP on the evaluation of treatment accountability and patient compliance to treatment administration.	No

Abbreviations: CRF=Case Report Form; CSR=Clinical Study Report; DMP = Data Monitoring Plan; DVP = Data Validation Plan; IMP= Investigational Medicinal Product; IT=Information Technology; SAE=Serious Adverse Event.

should be ensured, tracked, and approved. The DMC should meet and act accordingly if existing. The study sponsor must ensure the appropriate mitigation actions. The sample size should be re-evaluated. Any consequent action will have to be evaluated; any involved stakeholder must be properly updated and trained. All decisions and actions must be tracked and stored in the TMF.

In the COVID-19 period, people increase their use of the internet and technological assets needed for its use. It is, thus, possible that technological assets normally used in the trial will not be fully available as needed and planned due to the increased global use of these infrastructures. The availability of technologies should be re-evaluated; any action needed to ensure the needed technology will have to be identified, implemented, described, and shared with the appropriate stakeholders, and appropriate documentation reported in the TMF.

In this period shipments could be strongly affected, too. Clinical trials materials distribution to centers and patients could, thus, be impacted. The appropriate actions for minimising the impact should be established by the study sponsor. The possible consequences on patient's compliance should be evaluated, tracked, described, and stored.

Monitors may not be able to perform on-site visits as planned during the COVID-19 pandemic. The sponsor should consider optimizing the use of central and remote monitoring programs to ensure oversight of clinical sites. The issues encountered where monitors were unable to perform or had to delay monitoring visit(s) at the clinical site(s) should be identified. The feasibility of an alternative monitoring program (if any) should be discussed with Clinical Operations to identify the proper actions. Any decision should have to be properly recorded, shared with the stakeholders, and stored in the TMF.

### 3.3. Statistics

The first assessment to be done within a team of statisticians and clinicians is whether COVID-19 and/or COVID-19 measures could have had an impact on the ability to meet the trial objectives. Primary and key secondary endpoints will have to be the primary focus of this assessment.

As usual, trial modifications based on data that may introduce bias into the interpretation of the study findings, for example, information that reveals the magnitude of the treatment effect, must be avoided. There are however other modifications to the planned statistical analysis that do not introduce any bias and must be taken into account.

Change in visit's schedule linked with the pandemic could have some consequences including missing visits, missing data, change in the dates when data are collected, laboratories where blood, urine, and imaging tests are performed. The rate of patient withdrawal may be increased by COVID-19 and/or COVID-19 measures. All these changes must be revised with the stakeholders and the most appropriate mitigation actions to ensure the maintenance of the statistical quality requested by GCPs must be taken, integrating them with other mitigation actions.

If the amount of missing data generated by drop-outs is increased or the length of follow up is decreased vs. what was planned in the protocol, the study sample size (or the duration of follow up) should be re-evaluated possibly through blinded methods and evaluating the impact of the re-assessment on the statistical inference (e.g. p-values and confidence intervals). In case sample size re-assessment is already planned, the need for any change to this analysis should be assessed. In case it was not anticipated in the protocol, it should be planned with an amendment. If needed, an interim analysis for futility could be added to the protocol and detailed in the statistical analysis plan (SAP). Additional analyses to include the effect of COVID-19 might be needed to better understand the impact of the pandemic on the study, for example, for evaluating the impact of additional concomitant medications, problems with the supply of the investigational product that could have caused increased use of rescue medications, or differences in baseline characteristics of patients enrolled in different periods (for example in case study enrolment was halted for a long time).

Any option must be evaluated with the study team balancing the increased costs and times with the quality needs. Patient safety must be paramount for any decision.

All the involved stakeholders must be properly updated and trained. Any change to the study protocol, SAP, and any other study document, as well as any decision and training, must be approved according to the study's procedures and tracked and stored in the TMF.

In its recent guideline [10], FDA recommends that "sponsors consult with the relevant FDA review division when considering protocol changes and changes to the statistical analysis plan that may impact the analysis and interpretation of these endpoints".

### 3.4. Medical writing

Any action, intervention, meeting concerning the influence of COVID-19 on the trial must be documented. The document could be

**Table 3**  
RiMiCOPa statement for studies conducted in the COVID-19 pandemic – Statistics.

Area	Risks	Mitigation actions	Urgent (Yes/No)
Statistics Changes in study conduct	<p>Possible measures to be evaluated by Sponsors and Investigators are as follows:</p> <p>Conversion of physical visits into phone or video visits, with possible self-assessment.</p> <p>Delay or cancellation of visits, leaving mandatory visits only to be performed at sites.</p> <p>Stopping the trial at some or all trial sites, temporarily.</p> <p>Suspending or slowing of recruitment of new trial participants.</p> <p>Extension of the duration of the trial independently from the cause.</p> <p>Delay in the activation of sites that have not yet started the study.</p> <p>Closing of sites.</p> <p>Transfer of participants to investigational sites away from risk zones to COVID-19 safe locations (exceptional situation).</p> <p>Critical laboratory tests, imaging, or other diagnostic tests moved from central to local facilities.</p>	<p>The impact of protocol changes on clinical data quality, reproducibility, and interpretability needs to be accurately assessed. All planned modifications and additional analyses should be documented in the SAP before data unblinding.</p> <p><u>Possible implications:</u></p> <p>Assess whether COVID-19 or COVID-19 measures could have had an impact on the ability to meet the trial objectives.</p> <p>Assess external validity and interpretability of study results (for example, are censoring patterns or composite endpoints during the pandemic representative of non-pandemic conditions?).</p> <p>Evaluate the impact of changes in the duration of the study and consequent delays on scheduled activities. In some therapeutic areas, the delay may have a seasonality impact (e. g., in studies on allergy, flu, hypertension, Raynaud syndrome, etc.).</p> <p>Conduct impact analysis of each change in the planned statistical analysis, focusing on the primary efficacy and safety variable(s).</p> <p>Include proposals to deal with any identified potential sources of bias (missing values, newly identified intercurrent events, or any other unpredictable change), to mitigate their effect on the integrity of the study.</p> <p>Consider introducing periodic administrative interim analyses on the data available at different time points, to evaluate the implications on recruitment, loss of patients during the trial, data recording, ability to reach the planned sample size, analysing and interpreting the study results as originally planned. This is especially needed if the study sites are significantly impacted by the COVID-19 infection spread.</p> <p>Revise the SAP. In areas with a significant spread of COVID-19 infection, additional analyses to be included are likely to be the ones needed to investigate the impact of the three phases (pre, during, and post COVID-19) on the study outcomes. However, many other changes/additions to the SAP may be needed to evaluate the study outcomes, for example, analyses for evaluating the impact of increased use of additional concomitant medications or rescue medications, or the impact of differences in baseline characteristics among patients enrolled in different periods (in the case study enrolment was halted for a long time).</p> <p>Plan additional sensitivity, supplementary, ad post hoc exploratory analyses to properly understand and characterize the treatment effect.</p> <p>Assess the need for additional safety analyses on events associated with COVID-19 vs. those non-associated to fully characterize the product safety profile.</p>	Yes
Endpoint definition	<p>It might be necessary to replace in-person endpoint assessment with remote assessment or extend the protocol-defined window of time for assessing the endpoint or include/remove components from a composite endpoint. New intercurrent events [13] may be generated as a result of the COVID-19 pandemic.</p>	<p>The impact of any change in endpoint definition, either through a change in methods or a change in timing, should be carefully evaluated in sensitivity analyses.</p> <p><u>Possible implications:</u></p> <p>If an endpoint has to be measured differently from what is specified in the original study protocol, address the matter of exchangeability of methods and identify the most appropriate strategy to validate the outcomes, if any.</p> <p>In case of time to event endpoints, when the endpoint is defined relative to the date of randomization, if there is a considerable delay between randomization and start of treatment, evaluate the possibility to redefine the endpoint start date as the start of treatment.</p> <p>For an alternative collection of specimens, address reconciliation and verification.</p> <p>Give special considerations to endpoints where patient outcomes could be directly impacted by the pandemic, for example, in respiratory diseases or quality of life endpoints. In case pandemic-related intercurrent events are generated, assess the impact on the trial through the estimand framework [14].</p>	Yes

Yes

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Table 3 (continued)

Area	Risks	Mitigation actions	Urgent (Yes/No)
Missing data/Increase in drop-out rate/Reduced length of follow up/Increase in variability	An increase in missing data is expected. As a result of the reduced quality of data, variability is likely to increase.	It is important to evaluate these aspects prospectively to assess the need to re-evaluate the trial's sample size. <u>Possible Implications:</u> Perform a risk assessment analysis on these aspects. Evaluate the extent of missing data and the specific reasons for missingness and define the approach to be used in the statistical analysis [14]. Evaluate the need for a protocol amendment for sample size re-assessment (possibly in blind conditions, and always reminding that the analyses based on the knowledge of the magnitude of the treatment difference may introduce bias into the interpretation of the study findings). In case sample size re-assessment is already planned, assess the need for any change to this analysis. In case the situation is extreme, an interim analysis for futility may be the action to recommend.	
Protocol deviations	COVID-19 pandemic is likely to introduce more protocol deviations than normal.	Before locking the database, the sponsors should address how protocol deviations related to COVID-19 will be handled in the pre-specified analyses in the SAP. <u>Possible implications:</u> Evaluate the impact of the expected protocol deviations on the planned statistical analysis. Revise the SAP.	No
Difficulties in obtaining the investigational product at all or selected sites	COVID-19 pandemic is likely to cause problems in the supply of the investigational product.	Unavailability of the study treatment may be considered a pandemic-related intercurrent event (see above). If the study treatment was unavailable for a long time, it may be reasonable to exclude from the analysis all participants potentially impacted. This decision should be based on information such as site location and randomization date and not on post-baseline patient information because this could introduce bias in the analysis. <u>Possible implications:</u> Decide whether the unavailability of study treatment may configure as a pandemic-related intercurrent event and define impact on estimand definition (see above). Evaluate whether to exclude from the statistical analysis the patients who did not take the investigational product due to its unavailability. Evaluate the impact of this exclusion on the sample size.	No
Presence of heterogeneous populations	Three patient groups will be likely created (pre, during, and post COVID-19), at least in the areas with significant COVID-19 infection spread: 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.	The external validity of trial outcomes may be affected by the presence of different trial populations. <u>Possible implications:</u> Revise the SAP. Evaluate the need for a protocol amendment for sample size re-assessment.	No

Abbreviations: SAP=Statistical Analysis Plan.

written by an expert medical writer following current communication standards and stored in the TMF. Any change in the study protocol or any study document must be professionally written, following the same standards used for the development, start-up, and conduction of the study.

Any change in the timeline and conduction of the study must be promptly included in the study record of the clinical trial registry where the study is registered.

The planned disclosure activities included in the study protocol must be revised to align with other changes required by the COVID-19 pandemic. Any change in the planned disclosure of the results must be included in the study protocol; the approval of this amendment should follow the study guide.

Any amendment to the study protocol and any decision taken because of the COVID-19, recorded in the TMF, must be included in the Clinical Study Report (CSR) by a professional medical writer.

#### 4. Concluding remarks

In this task-driven recommendation, we have attempted to give a simple and practical tool to be used for evaluating the impact of the COVID-19 pandemic on their clinical studies from the point of view of data management, statistics, and medical writing. We know it is not complete or directly applicable to any clinical trial potentially influenced by the pandemic. Any professional or patient involved must provide its contribution and adapting to its peculiar needs, having patient's centrality as their guide. Most of the proposed interventions must be implemented as soon as possible, especially if the risk assessment has revealed critical situations. Mitigations not classified as urgent will have to be addressed when needed in the study process. They can be used as a reminder to ensure patient compliance, protocol violations, and "COVID-19" populations are properly managed and reported, together with all other contingencies classified as urgent.

To facilitate wider dissemination and uptake of this guidance, we



**Table 4**

RiMiCOPa statement Study Contingency &amp; Risk Mitigation Plan for studies conducted in the COVID-19 pandemic – Medical Writing.

Area	Risks	Mitigation actions	Urgent (Yes/No)
Medical writing Clinical Study Report	COVID-19 effects on the clinical trial must be described to let the regulatory authorities able to evaluate how the pandemic has affected the timelines, quality, and results of the study.	All changes and implications related to the COVID-19 pandemic must be described in the appropriate sections of the CSR (or in a separate study-specific document). The following is a list of the main aspects to be addressed: <ul style="list-style-type: none"> <li>Describe all the contingency measures implemented during the COVID-19 disruption to manage the study conduct.</li> <li>Document how restrictions related to COVID-19 led to the changes in study conduct and the duration of these changes.</li> <li>Provide a list of all participants affected by the COVID-19 related study disruption by unique subject number identifier and by investigational site, and a description of how the individual's participation was altered.</li> <li>Describe analyses and corresponding discussions that address the impact of the implemented contingency measures (e.g., trial participant discontinuation from investigational product and/or study, alternative procedures used to collect critical safety and/or efficacy data) on the safety and efficacy results reported for the study.</li> <li>Describe all changes that were needed to the planned protocol analyses as a result of the contingency measures and the following implications (for example, changes in the primary efficacy analysis, sample size re-assessment, etc.).</li> <li>Describe the effects of the measures implemented during the COVID-19 disruption on the quality of the study (if applicable).</li> </ul>	Depending on the stage of the study
Publications from the study	COVID-19 effects on the communication plan must be evaluated.	All changes and implications related to the COVID-19 pandemic must be described in the appropriate sections of any disclosure/publication describing the clinical trial outcomes, to let the reader able to understand the effects of the COVID-19 pandemic on the timelines, results, and quality of the study reported in the disclosure/publication, in addition to GPP recommendations [15].	Depending on the stage of the study
Study protocol	COVID-19 effects on the communication plan must be evaluated.	All changes and implications related to the COVID-19 pandemic must be described in the appropriate sections of the study protocol. If they are significant, a protocol amendment should be written and approved. The appropriate protocol amendment(s) should have to be ranked and, if major, approved according to GCPs.	Depending on the stage of the study

Abbreviations: CSR=Clinical Study Report; GPP = Good Publication Practice.

encourage other journals and groups to consider endorsing RiMiCOPa.

We believe it will be important to evaluate the effects of the implementation of this statement and checklist on reporting in clinical trials performed during and after the COVID-19 pandemic. As the pandemic continues to evolve, it might also be needed to revisit or extend the guidance accordingly.

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