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DG PRE authorisation

Guidance on the Management of Clinical Investigations during the COVID-19 (Coronavirus) pandemic

Version 1 (30.04.2020)

The Belgian competent authority acknowledges the impact of COVID-19 on the health system and broader society, and the impact it may have on clinical investigations and participating subjects. Extraordinary measures may need to be implemented and investigations adjusted due to e.g. subjects being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks. Based on the EU Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic we developed this guidance to mitigate the negative effects of the COVID-19 pandemic on the conduct of clinical investigations.

The situation is evolving, and pragmatic actions may be required to deal with the challenges of conducting research, and in ensuring the rights, safety and wellbeing of participants. The points mentioned below are intended to provide guidance for all parties involved in clinical investigations during this time.
Due to the urgency, this guidance is issued without prior public consultation. The sponsors should note that due to the rapidly evolving situation further updates to this guidance are possible and likely.
Sponsors and investigators need to take into account that this document has been drafted by the Belgian competent authority, there might be other specific national legislation and guidance in place in other Member States.

Introduction

Various challenges exist which result in restrictions of visits to healthcare facilities, increased demands on the health service and changes to investigation staff availability. Participants may also be required to self-isolate, which introduces difficulties for investigators to maintain their medical oversight. These challenges could have an impact on the conduct of trials, such as the completion of investigation assessments, completion of investigation visits and the provision of investigational medical devices.
The impact of COVID-19 on ongoing investigations, on opening a new investigational site in an existing investigation, ongoing recruitment and continued involvement of subjects in the investigation, or on starting of new investigations needs to be considered. This evaluation should take into account other national Belgian recommendations including travel restrictions and confinements of investigation subjects and investigation staff and the availability of investigation staff to perform visits, enter data in the Case Report Form (CRF), notify serious adverse events and, more generally, follow the clinical investigation plan. The ability to confirm eligibility and to conduct key safety assessments and investigation evaluation is of particular importance. Actions should be proportionate and based on benefit-risk considerations, on contingency provisions taken nationally and locally by the Belgian authorities with priority given to the impact on the health and safety of the subjects. Where a subject is unable to attend the site, other measures, such as home nursing, if possible given social distancing needs, or contact via phone or telemedicine means, may be required to identify adverse events and ensure continuous medical care and oversight. However, the limitations and risks of such methods and the requirements for data protection should be taken into account and such alternative arrangements need to be adequately documented.

Initiating new investigations
The feasibility of starting a new clinical investigation or including new subjects in an ongoing investigation not related to COVID-19 should be critically assessed by sponsors. The current situation on sites, not only in Belgium but also in other countries, needs to be taken into account if you need to for example import some devices or consumables for the study.

Changes in ongoing investigations
The sponsors should consider in their risk assessment whether the following measures could be the most appropriate during COVID-19. Measures should generally be agreed with investigators and could be:

- Conversion of physical visits into phone or video visits, postponement or complete cancellation of visits to ensure that only strictly necessary visits are performed at sites;

- A temporary halt of the investigation at some or all investigation sites;

- Suspension or slowing down of recruitment of new participants;

- Extension of the duration of the investigation;

- Postponement of investigations or activation of sites that have not yet been initiated;

- Closing of sites. In case it is not feasible for a site to continue participation at all, the sponsor should consider if the trial site should be closed and how this can be done without compromising safety and well-being of patients already participating and data validity;

- If unavoidable (it should be justified that this is a truly exceptional situation based on the personal risk-benefit ratio for the individual subject), transfer of subjects to investigational sites away from risk zones, or closer to their home, to sites already participating in the investigation, or new ones could occur. Initiation of new sites is generally not expected in the current situation unless no other solution exists for the subject. If there is an urgent need to open a new investigation site for critical visits for example outside the hospital, this may be implemented and documented, and sent as a substantial amendment to the ethics committee (and notified to the FAMHP). The exceptional situation could involve e.g. an investigation participant who urgently needs to stay in the investigation and for whom no other sites are available. In such cases, it is important that investigation participants as well as investigators (both receiving and sending) are in agreement for a safe pragmatic approach about the transfer and that the receiving site has the possibility to access previously collected information/collected data for the trial participant and that any eCRF can be adjusted accordingly to allow the receiving site to enter new data. The impact on investigation participants should be considered and arrangements made to e.g. appropriate transportation.

- There may be a need for critical laboratory tests, imaging or other diagnostic test to be performed for patient safety. In case the investigation participant cannot reach the site to have these performed, it is acceptable that laboratory, imaging or other diagnostic tests are done at a local laboratory (or relevant clinical facility for other tests) authorised/certified (as legally required nationally) to perform such tests routinely (e.g. blood cell count, liver function test, X-ray, ECG etc.), if this can be done within local restrictions on social distancing. The sites should inform the sponsor about such cases. Local analysis can be used for safety decisions. If this is a trial endpoint and the samples cannot be shipped to the central lab, analysis should be performed locally and then explained, assessed and reported in the clinical study report.

The changes above may also be initiated by the investigator sites contacting the sponsor. There might also be cases where the current principal investigator (PI) of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily to e.g. a sub-

investigator. Any permanent changes in PI should be submitted to the National Competent Authority (NCA) and Ethics Committees as appropriate.

When changes in ongoing trials are considered, the overall well-being and best interests of the participant should be also considered, for example in investigations for patients with life-threatening or severely debilitating conditions, when participants require to stay on investigational treatment. In cases, when investigation halt, even if temporary only, can potentially compromise the overall well-being and best interest of participants, all measures need to be considered and taken to avoid this.

Changes should be well balanced, taking into account in particular the legitimate interest of investigation sites in avoiding further burden in terms of time and staffing during the COVID-19 pandemic.

Please note that prospective protocol waivers remain unacceptable and that patients should not be included in investigations without proper eligibility assessment, including performance of planned tests, and written informed consent according to national laws and regulations.

Compliance with the clinical investigation plan should be ensured to such an extent that an ongoing benefit-risk assessment for the clinical investigation and its participants is still possible. The impact of protocol changes on clinical data interpretability needs to be properly assessed by the sponsor.

Risk assessment
The safety of the participant is of primary importance, and risks of involvement in the investigation, in particular with added challenges due to COVID-19, should be weighed against anticipated benefit for the participant and society (ref: principle 2.2 of ICH GCP, article 5 of Law of 7 May 2004, Declaration of Helsinki and ISO 14155).

All decisions to adjust clinical investigation conduct should be based on a risk assessment by the sponsor (ICH GCP section 5.0) in collaboration with the principal investigators. It is expected that the sponsor performs a risk assessment of each individual ongoing investigation and the investigator of each individual participant and implements measures which prioritise subject safety and data validity. **In case these two conflict, subject safety always prevails.** These risk assessments should be based on relevant parties' input and should be documented on an ongoing basis. It is important that sponsors in their risk assessment consider prioritisation of critical tasks in the clinical investigation and how these are best maintained.
The sponsor should reassess risks as the situation develops. This reassessment should also be documented.

It is possible that with the escalation of the pandemic, local circumstances lead to a local change in risk assessment, therefore the need to implement additional measures may arise, and an investigator-driven risk assessment might be necessary (and communicated to the sponsor).

Regarding participants enrolled in ongoing clinical investigations who may be determined as being a risk group for COVID-19 or who are in investigations involving therapies which may increase such risk, the potential impact of COVID-19 on these patient groups should be carefully considered when deciding to start or continue such investigations.

Communication with authorities
Priority is given to any (new) clinical investigation applications for the treatment or prevention of COVID-19 infection, and/or substantial amendment applications to existing clinical trials necessary as a result of COVID-19.

In case the risk assessment leads to actions that affect the investigation as described below in a) and b), the relevant competent authorities and Ethics Committees must be informed in accordance with the Directive and national laws:

a) When a new event is likely to have a serious effect on the benefit-risk balance of the trial, it is possible that immediate actions are required by the sponsor and investigator to protect the subjects against immediate hazard. Under emergency circumstances, urgent safety measures to protect the rights, safety and well-being of subjects may be taken without prior notification, but the information needs to be provided *ex post* to the National Competent Authority (NCA) and the Ethics Committee as soon as possible (ISO14155 point 4.5.4b). In this communication, the sponsor is expected to provide adequate information on the measures taken and the plan for further actions;
a) If changes are likely to affect the safety or well-being of the participants and/or the scientific value of the investigation, but do not require immediate action from sponsor or investigator, it should be possible to submit them as substantial amendment applications.

Unless otherwise advised by relevant authorities, it is recommended to mark any contact clearly with 'COVID-19' in the subject field.

Agreement with and communication to sites
Changes to investigation conduct should be agreed with and communicated clearly to investigator sites. To support implementation by sites, it is important that changes and local implications are made clear, including marking of changed documents with track changes. Agreements may be documented as e-mail exchange.

Changes to informed consent
Sponsors should be mindful of the current pressure on the medical profession and should carefully assess the pertinence of adding new subjects in ongoing clinical investigations. Absolute priority should be given to clinical investigations on treatments for COVID-19 and COVID-19 related illnesses, or investigations on serious diseases with no satisfactory treatment option. In case a sponsor plans to initiate an investigations aiming to test medical devices in the management of patients COVID-19, advice should be sought on alternative procedures to obtain informed consent, as it is likely that the physical consent cannot leave the isolation room, and therefore is not appropriate as investigational documentation.

In case of emergency situations, when investigation participants are incapable of giving their informed consent (for example because they are under intensive medical care), sponsors shall adhere to the provisions set out in the Directive and by national law. Informed consent of these patients or their representatives will need to be acquired later, as soon as feasible.

There may be a need to re-consent already included investigation participants. However, avoid the need for participants to visit investigator sites for the sole purpose of obtaining re-consent. If re-consents are necessary for the implementation of new urgent changes in investigation conduct (mainly expected for reasons related to COVID-19), alternative ways of obtaining such re-consents should be considered during the pandemic e.g. contacting the participants via phone or video-calls and obtaining oral consents supplemented with email confirmation. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants will be back at the regular sites.

Any validated and secure electronic system already used in the investigation for obtaining informed consent can be used as per usual practice and if in compliance with national legislation.

Changes to monitoring
Certain sponsor oversight responsibilities, such as monitoring and quality assurance activities need to be re-assessed and temporary, alternative proportionate mechanisms of oversight may be required. The extent of on-site monitoring, if it remains feasible, should take into account national and local restrictions, the urgency (e.g. source data verification can often be postponed) and the availability of site staff, and should only be performed as agreed with investigator sites. The burden of the introduction of any alternative measures for the site staff

and facilities should also be considered in order to strike an acceptable balance between appropriate oversight and the capacity of and possibilities at the site.

Possible temporary, alternative measures could include:

- Cancelling of on-site monitoring visits and extending of the period between monitoring visit;
- Implementing phone and video visits (without unnecessarily increased burden to the investigator site and taking into account participant integrity);
- Adapting the on-site monitoring plan when it is impossible to follow, supplementing it with (additional/increased) centralised monitoring and central review of data if possible and meaningful.

Results of adjusted monitoring/review measures should be reported to the sponsor in monitoring reports and in the clinical study report.

It is essential that robust follow-up measures are planned and ready to be implemented when the situation is normalised. This should likely include increased on-site monitoring for a period that is sufficient to ensure that the impact of the reduced monitoring could be rectified and problems resolved or properly documented for reporting in the clinical study report.

So-called remote source data verification (e.g. providing sponsor with copies of medical records or remote access to electronic medical records) is currently not allowed as it might infringe trial participants' rights. In addition, provision of redacted/ de-identified pdfs files will not be acceptable as it puts disproportionate burden on site staff.

Protocol deviations

We acknowledge that the COVID-19 situation is likely to introduce more protocol deviations than normal. We expect that the sponsor escalates and manages such protocol deviations in accordance with their standard procedures. A proportionate approach will be taken by the GCP inspectors when such deviations are reviewed during inspections, in particular where the best interest of the participant is maintained, and the participant is not put at risk.

Reimbursement of exceptional expenses

Taking into account this exceptional situation, if, in order to implement urgent measures for the protection of participants involved in a clinical trial, expenses may arise which may be borne initially by the participants, these should typically be compensated subsequently by the sponsor via the investigator. If additional financial compensation is provided to sites/investigators, this needs to be documented and performed according to national legislation. Handling of reimbursement of such expenses should follow national legislation and/or guidance.

Initiation of new investigations aiming to test medical devices for treatment of COVID-19

Belgium fully supports the submission of new investigations aiming to test the use of medical devices in the treatment of COVID-19 and absolute priority is given to clinical investigations on treatments for COVID-19 and COVID19-related illnesses.

In order to avoid or minimise any delays, sponsors are recommended to prospectively contact the FAMHP (ct.rd@fagg-afmps.be) to explore the feasibility of an accelerated procedure.

Contact information

Any further questions can sent by e-mail to our general mailbox: ct.rd@fagg-afmps.be