Coronavirus (COVID-19): impact on the conduct of clinical trials under the Medical Research Involving Human Subjects Act (WMO)

Note: If needed, the information given below may be adjusted. Please check our website and the information given by other parties (see hyperlinks below) regularly for updates. The information below is valid during the COVID-19 pandemic until the situation is normalised and this is stated on the website of the Health and Youth Care Inspectorate (IGJ).

Version 5 (8 February 2021)

- Changes compared to version 4 (22 June 2020): integration requirements (re)start clinical trials into one document, document on the website of CCMO is redundant, remote source data verification
- Changes compared to version 3 (20 May 2020): (re)start clinical trials, monitoring
- Changes compared to version 2 (28 April 2020): Phase I trials
- Changes compared to version 1 (8 April 2020): Phase I trials, remote source data verification

The COVID-19 pandemic affects health care services and the society in general. The conduct of clinical trials and also trial participants in clinical trials might be affected as well. The situation evolves and pragmatic measures might be required to manage the situation regarding the conduct of clinical trials and to ensure the rights, safety and wellbeing of trial participants. These measures should be proportional and based on a risk analysis (benefit-risk assessment). The impact on the rights, the safety and wellbeing of trial participants should prevail.

On the websites of the Government and the National Institute for Public Health and the Environment (RIVM) general information can be found regarding measure taken due to the COVID-19 pandemic. In order to mitigate the negative impact on the conduct of clinical trials during the period of the COVID-19 pandemic, a European Guidance has been developed. Additionally, the Central Committee on Research Involving Human Subjects (CCMO) formulated several recommendations on her website.

In addition to the European Guidance, IGJ emphasises that Dutch legislation (such as the WMO and Medicines Act) might prevail on some issues over the European Guidance. Below you will find several relevant issues.

(Re) start of clinical trials

At regular intervals the current COVID-19 situation is evaluated by the Dutch Government and, under conditions, relaxing measures are announced. These relaxing measures are only possible as long as the spread of the virus decreases, following less hospitalisations and/or (COVID related) deaths. In case of an (eventual) increase of the spread of the virus an earlier relaxing measure for more room might be revoked.

Based on the current situation, for clinical research units (CRU) and health care institutions it might be possible to gradually restart trials that were put on hold or start new trials provided requirements are complied with as they are formulated by the CCMO and the IGJ (with input of relevant stakeholders)

NOTE: The above national requirements 'border' the extra possibilities/loosening of restriction as still applicable on the European level.

Investigational medicinal products (IMP)
The Medicines Act cites specific requirements regarding distribution and handing over of IMP. It might occur that IMP, as a result of the current COVID-19 measures, cannot be handed over per regular practice to the trial participant.

During the COVID-19 situation, the IGJ allows:

- IMP to be send by courier from the (hospital) pharmacy to the trial participant;
- IMP to be send from the hospital pharmacy to the public pharmacy. Please refer to additional information on the website of IGJ (in Dutch only);
- Verbal consent by trial participants to use personal information necessary for sending IMP. The obtained verbal consent should be documented and, if possible, be confirmed by the trial participant via e-mail; there is no requirement to obtain written consent retrospectively.

The IGJ emphasises that shipment of IMP by the sponsor to the trial participant is **not** allowed.

Signals have been noted that shortages of certain registered medicinal products might occur because those are prescribed in clinical trials for COVID-19 patients. This might affect regular treatment, ongoing clinical trials and clinical trials for COVID-19. More information regarding shortages of registered medicinal products can be found on the IGJ website (in Dutch only). Advice what to do in case this results in a (temporary) halt or premature suspension of a clinical trial can be found on the CCMO website (see the link above).

In case of urgent questions, you can contact the IGJ (gcp@igj.nl). The IGJ will adjudicate on a case-by-case basis whether deviation of regulation might be justified.

Informed Consent
Obtaining (re) consent of trial participants for clinical trials can be hampered by the physical condition of the trial participant and/or the COVID-19 measures.
In case a trial participant is unable to provide (re)consent in an emergency situation for a clinical trial, obtaining consent can be deferred under specific conditions. The applicable conditions are cited in the memorandum and flow chart "Deferred Consent" of the CCMO. To be able to use the possibility of deferred consent it is mandatory to obtain approval by an independent ethical committee (METC/IEC) in advance. On the website of the CCMO, information can be found regarding accelerated procedures (fast track) for review of research dossiers.

Note: the memorandum and flow chart are only available in Dutch.

Monitoring
The IGJ emphasises that in European and national legislation cite on-site monitoring and central monitoring are defined. Given the COVID-19 situation, on-site monitoring will not or hardly be possible.

Based on the current situation , the IGJ and the CCMO (with input of relevant stakeholders), formulated requirements to (re)start clinical trials, not being clinical trials in CRUs (see also paragraph **(Re)start of clinical trials**).
With respect to monitoring, it should be clear that this can only be implemented after careful consideration by, agreement from and under control of the health care institution. Moreover, the official policies of the institution and the measures of the Government applicable at that time regarding the control of the COVID-19 situation should be complied with. In accordance with the European Guideline and the documents published previously by the CCMO and the IGJ, a (re) assessment needs to be made of which data are considered critical in this phase of the COVID-19 situation. In addition, it should be evaluated to what extend on-site monitoring can (and needs to) be conducted. This should be a proportional process and all considerations should be risk-based (benefit-risk) and adequately documented. The impact on the rights, the safety and the wellbeing of trial participants, but also the safety of other patients and staff should prevail.

Remote source data verification (SDV)

During the COVID-19 situation, the IGJ allows, like most other European countries, remote SDV provided that they follow strict requirements and for a selection of clinical trials only. The IGJ does **not** allow remote SDV in general. The clinical trial should be, in accordance with the European Guidance:

- involving COVID-19 treatment or prevention;
- investigating serious or life-threatening conditions;
- where the absence of SDV for critical data may likely pose unacceptable risks to participants' safety or the reliability/integrity of trial results;
- involving particularly vulnerable participants such as children or those temporarily (e.g. trials in emergency situations) or permanently (e.g. trials in patients with advanced dementia) incapable of giving their informed consent or in pivotal trials.

Remote SDV should focus on the quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data may be monitored simultaneously, provided this does not result in a need to access additional documents and therefore in an increased burden for trial site staff. Remote SDV is only allowed based on the outcome of the evaluation of a risk assessment per clinical trial, including the motivation of the critical data that needs to be verified. The health and safety of the trial participant prevails.

Direct remote access to the electronic health record (EHR) is temporary (during the COVID-19 situation) and allowed only when adhering to requirements to verify critical data relevant for clinical trials by monitors/CRA's. It is recommended that this takes place at the office in accordance with the following requirements and/or restrictions:

- Using a specific, access controlled space (1 person, logged etc.);
- Using a logged PC/laptop (Who, What, When);
- Upfront a screenshot/short video impression (**not** while having access to the EMD!) regarding the setting/arrangement (office and/or home situation);
- In no way recordings (video, screenshot, screen-capture) will be made; moreover the functionality to do so should be disabled;
- Adequate documentation; the agreed method and requirements are put down in writing and confirmed.

The IGJ strongly recommends, if feasible (technical, safe, burden for the research team etc.), to conduct remote SDV where the hospital/research centre is in charge. This means that the monitor/CRA is able to review the EMD and other relevant source documents by means of reading along/on the screen of the person at the hospital/research centre. The platform to be used should be safe and workable for both parties involved (see also the recommendations of the Data Protection Authority (DPA) on privacy and video calls (in Dutch only)).
If the method mentioned above is not feasible due to the burden for a hospital/research centre, direct remote access to the EMD by the monitor/CRA can be an alternative method. Access to the EMD should be assigned on name and function (already assigned accounts should not be used).

In addition, in general:

- The monitor/CRA should be able to access EMDs of trial participants only and, only those parts that are strictly necessary to verify the critical data. Which data is to be considered critical and which (data) as a consequence needs to be accessed, should be reasoned and documented in a complete/correct manner. Access to more than the critical data should be requested with due motive. Unauthorised access to more than the documented critical data is considered a data protection breach and should be reported to the DPA as such.
- Per clinical trial it should be documented which monitor/CRA has been granted access to the EMDs and which ones. The number of monitors/CRA's should be limited to a bare minimum.
- The trial participants should be informed, by means of an updated PIF, regarding the remote access to the EMD in order to, if required, refuse consent thereof or withdraw consent at all.

In case of the start of a new clinical trial, i.e. started after the outbreak of the COVID-19 pandemic, trial participants are informed regarding the remote access to the EMD by the initial PIF. See also section on Informed Consent above.

- The IGJ does **not** allow data verification conducted by means of copies from the medical dossier. These copies could be insufficiently pseudonymised ('redacted') and in addition, it could contain information that is not strictly necessary to evaluate the data described in the protocol. Furthermore, issuing of such copies, and where necessary de-identifying those, are considered a disproportional extra burden for hospitals/research centres. In addition, the trial participant consents to review his medical dossier, not to copy parts thereof and send those via and to third parties. This method is potentially violating the rights of the trial participant.
- The IGJ does **not** allow reading aloud (by site staff) source data via telephone contact. This is considered an inadequate method with a potential for a high margin of error, no factual verification of source data and moreover a significant extra burden for investigators and their team.

In case of urgent questions, especially concerning this document, you can contact the IGJ (gcp@igj.nl). The IGJ will adjudicate, on a case-by-case basis, whether deviation of the current opinion (following strict conditions) might be justified.