Vorwort zur 41. Aktualisierungslieferung

Die 41. Aktualisierungslieferung enthält im nationalen Teil zwei neue Dokumente des Arbeitskreises Blut, darunter das aktualisierte Votum zum Verfahren zur Rückverfolgung (Look Back) (gemäß § 19 Transfusionsgesetz) (V48) und die Stellungnahme zum Beratungsergebnis der gemeinsamen Arbeitsgruppe aus Vertretern des AK Blut, des Ständigen Arbeitskreises „Richtlinien Hämotherapie", des Wissenschaftlichen Beirats der Bundesärztekammer, des Robert Koch-Instituts, des Paul-Ehrlich-Instituts und des Bundesministeriums für Gesundheit „Blutspende von Personen mit sexuellem Risikoverhalten".

Im Bereich der EU wurde seit der letzten Lieferung die Guideline zum Management klinischer Prüfungen während der Corona-Pandemie revidiert. Außerdem wurde eine neue EU-Leitlinie zur Qualität, nichtklinischen und klinischen Aspekten von Arzneimitteln mit genetisch veränderten Zellen publiziert. Auch die alphabetische Liste zu Produkt-spezifischen Bioäquivalenzleitlinien wurde wiederum aktualisiert.

Darüber hinaus gibt es neue Verlautbarungen der Europäischen Arzneimittelagentur (EMA) über die regulatorischen Anforderungen an Impfstoffe zum Schutz vor SARS-CoV-2-Varianten und zur Zulassung von COVID-19 Impfstoffen.

Eine neue ICH-Leitlinie befasst sich mit nichtklinischen Sicherheitstests zur Unterstützung der Entwicklung von pädiatrischen Arzneimitteln. Außerdem wurde die ICH-Leitlinie zu Lösungsmittelrückständen in Arzneimitteln revidiert.

Im Bereich Tierarzneimittel wurde die Liste der Substanzen, die nicht von der Verordnung über die Festlegung von Grenzwerten für Tierarzneimittelrückstände in Lebensmitteln ((EC) No. 470/2009) erfasst sind, auf einen neueren Stand gebracht. Weiterhin wird in dieser Aktualisierungslieferung die neue VICH-Leitlinie zur Harmonisierung der Kriterien für Waiver bezüglich der Chargenprüfung mittels Sicherheits-Tierversuchen für Tierimpfstoffe berücksichtigt.

Ferner wurden sieben aktualisierte oder neue europäische Pflanzenmonographien (European Union/herbal monographs) aufgenommen und es gibt einen aktualisierten Überblick über die Produkt-spezifischen Leitlinien für die staatliche Chargenprüfung (EU Official Control Authority Batch Release) für biologische Humanarzneimittel.

Einen wichtigen Mehrwert schafft das Kompendium durch Register. Diese wurden mit der vorliegenden Aktualisierungslieferung ebenfalls überarbeitet und ergänzt.

Remagen, im August 2021 Die Herausgeberin und Bearbeiterin

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Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic

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Contents

The European Medicines Agency (EMA), Good Clinical Practice (GCP) Inspectors Working Group (GCP IWG), the Clinical Trials Facilitation and Coordination Group (CTFG, a working group of the Heads of Medicines Agency (HMA), the Clinical Trials Expert Group (CTEG, a working group of the European Commission representing Ethics Committees and National Competent Authorities (NCA)) and the European Commission (EC) acknowledge the impact of COVID-19 on the health system and broader society, and the impact it may have on clinical trials and trial participants[1]. Extraordinary measures may

1 The word "trial participant" is used in this text as a synonym for the term "subject", defined in Directive 2001/20/EC as "an individual who participates in a clinical trial as a recipient of the investigational medicinal product or a control".

need to be implemented and trials adjusted due, among others, to trial participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infection, and health care professionals being committed to critical tasks.

The COVID-19 pandemic is rapidly escalating putting national health care systems under continuously increasing pressure. In some Member States the capacity of the health-care system has already reached its limits. Against this background, pragmatic and harmonised actions are required to ensure the necessary flexibility and procedural simplifications needed to maintain the integrity of the trials, to ensure the rights, safety and wellbeing of trial participants and the safety of clinical trial staff during this global public health crisis. The points mentioned below are intended to provide guidance and clarity for all parties involved in clinical trials during this time. **It should be noted that the simplification measures proposed in this document will only last during the current public health crisis until the revocation of this Guidance, when there is a consensus that the period of the COVID-19 outbreak in the EU/EEA, has passed.**

Sponsors[2] and investigators should note that due to the rapidly evolving situation further updates to this guidance are possible and likely.

Member States are encouraged to implement the harmonised guidance to the maximum possible extent to mitigate and slow down the disruption of clinical research in Europe during the public health crisis. At the same time, sponsors and investigators need to take into account that national legislation and derogations cannot be superseded. Member States shall complement this guidance to create additional clarity on specific national legal requirements and derogations to them[3].

This document sets out to include most of the current guidance across Member States with the aim of serving as a harmonised EU-level set of recommendations. Hence, this guidance was drafted and supported by the CTEG, EMA, the CTFG of the HMA and the GCP IWG coordinated by the EMA. Commissioner Kyriakides shared this guidance with the Health Ministers and no Member State has raised any concern with this guidance in the videoconference of Ministers of Health of 27 April 2020.

1. Introduction

Various challenges exist which result in restrictions of visits to healthcare facilities, increased demands on the health service and changes to trial staff availability. Trial participants may also be required to self-isolate, which can make it difficult for investigators to maintain their medical oversight. These challenges could have an impact on the conduct of trials, such as the completion of trial assessments, completion of trial visits and the provision of Investigational Medicinal Products (IMPs).

2 Sponsors should be read in this context as "sponsor and/or CRO".

3 Links to national guidance documents are collected here: https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_03_CTFG_Link_to_National_guidance_on_CT_managmant_during_the_COVID-19_pandemia.pdf

The impact of COVID-19 on ongoing trials, on opening new trial sites in an existing trial, on ongoing recruitment and continued involvement of participants in the trial, or on starting of new trials needs to be considered. This evaluation should take into account national recommendations and measures including travel restrictions and confinements of trial participants and trial staff and the availability of trial staff to perform visits, enter data in the Case Report Form (CRF), notify serious adverse events and, more generally, follow the protocol. The ability to confirm eligibility and to conduct key safety assessments and trial evaluations is of particular importance.

Actions should be proportionate and based on benefit-risk considerations, on contingency provisions taken nationally and locally by the authorities, with priority given to the impact on the health and safety of the trial participant. Where a trial participant is unable to attend the site, other measures, such as home nursing, if possible given social distancing needs, or contact via phone or telemedicine, 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.

The International Committee of Medical Journal Editors has made clear that in the event of public health emergencies, information with immediate public health implications should be disseminated without concern that this will preclude subsequent consideration for publication in a journal.[4]

2. Initiating New Trials

The feasibility and immediate necessity of starting a new clinical trial should be critically assessed by sponsors, in close collaboration with other relevant parties, in particular the investigators. Additional risks to trial participants should be addressed in the benefit-risk section of the protocol along with risk mitigation measures (see chapter 5).

3. Changes to Ongoing Trials

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 trial at some or all trial sites;
- Interruption or slowing down of recruitment of new trial participants – the feasibility of including new trial participants in an ongoing trial needs to be critically assessed;
- Extension of the duration of the trial;
- Postponement of trials or of activation of sites that have not yet been initiated;

4 http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications.html

- 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 the rights, safety and well-being of trial participants and data validity;
- If unavoidable (it should be justified that this is a truly exceptional situation based on the personal benefit-risk ratio for the individual trial participant), transfer of trial participants to investigational sites away from risk zones, or closer to their home, to sites already participating in the trial, or new ones, could occur. Initiation of new trial sites is generally not expected in the current situation unless no other solution exists for the trial participant. If there is an urgent need to open a new trial site for critical trial visits, for example outside the hospital, this may be implemented as an urgent safety measure (USM) first, followed later by a substantial amendment (SA) application (see below in chapter 6) for the approval and initiation of this additional site. In such cases, it is important that trial participants as well as investigators (both receiving and sending) are in agreement about the transfer, that the receiving site has the possibility to access previously collected information/collected data (including necessary medical records) for the trial participant and that any eCRF can be adjusted accordingly to allow the receiving site to enter new data. The impact on trial participants should be considered and arrangements made such as providing adequate transportation;
- There may be a need for critical laboratory tests, imaging or other diagnostic tests to be performed, (e.g. blood cell count, liver function test, X-ray, CT, MRI, ultrasonography, ECG etc.), e.g. for trial participant safety or the integrity of the trial. In case the trial 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 authorised/certified (as legally required nationally) to perform such tests routinely, 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 biological samples cannot be shipped to the central laboratory, analysis should be performed locally and then explained with detailed justification, assessed and reported in the clinical study report following ICH E3. In these cases, it is important that the sponsor is given access to the normal ranges and certification information of any additional laboratory used in order to support the use and evaluation of results.

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 NCA and/or Ethics Committees (in line with chapter 6).

When changes in ongoing trials are considered, the overall well-being and best interests of the trial participants have to be prioritised, for example in trials for patients with life-threatening or severely debilitating conditions, when trial

participants need to stay on trial treatment. When a trial is halted, even if temporarily only, this can potentially compromise the overall well-being and best interest of trial participants. All measures need to be considered and taken to avoid this.

Changes should be well balanced and proportionate, taking into account in particular the legitimate interest of trial sites in avoiding further burden in terms of time and staffing during the COVID-19 pandemic. Alternative arrangements, consistent with the protocol to the extent possible, should be fully documented with a well-reasoned rationale as to how they will ensure trial participant safety, data integrity and protection of personal data.

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

Compliance with the trial protocol should be ensured to such an extent that an ongoing benefit-risk assessment for the clinical trial and its participants is still possible. The impact of protocol changes on clinical data interpretability needs to be properly assessed by the sponsor and the overall evidence generation package could be subsequently discussed within scientific advice with regulatory authorities. A relevant guidance on the implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials by the CHMP Biostatistics Working Party was published on 25 March 2020[5].

4. Safety Reporting

Sponsors are expected to continue safety reporting in adherence to EU and national legal frameworks (Directive 2001/20/EC[6]; CT-3[7]). When per protocol physical visits are reduced or postponed, it is important that the investigators continue collecting adverse events from the trial participant through alternative means, e.g. by phone calls or telemedicine visits, as appropriate.

5. Risk Assessment

The safety of the trial participants is of primary importance, and risks of involvement in the trial, in particular with added challenges due to COVID-19, should be weighed against anticipated benefit for the trial participants and society (ref: principle 2.2 of ICH GCP).

All decisions to adjust clinical trial conduct should be based on a risk assessment by the sponsor (ICH GCP section 5.0). It is expected that the sponsor performs a risk assessment of each individual ongoing trial and the investigator of each individual trial participant and implement measures, which prioritise trial participant safety and data validity. **In case these two conflict, trial participant safety always prevails.**

5 https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials

6 Directive 2001/20/EC (OJ L 121, 1.5.2001) https://ec.europa.eu/health/documents/eudralex/vol-10_en

7 Communication from the Commission ('CT-3'; 2011/C 172/01) https://ec.europa.eu/health/documents/eudralex/vol–10_en

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 trial and how these are best maintained.
The sponsor should reassess risks as the situation develops. This reassessment should also be documented as part of the sponsor's trial master file.
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. This assessment should be documented in the investigator's site master file and communicated to the sponsor.
The potential impact of COVID-19 on trial participants who may be determined as being part of a-risk group for COVID-19 or who are in trials involving treatments, which may increase such risks, should be carefully considered when deciding to start or continue such clinical trials.

6. Communication with Authorities

Priority is given to any (new) clinical trial application 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.
For ongoing trials, the guidance given by EC CT-1[8] on substantial amendments remains applicable. A single submission by the same sponsor with the list of concerned trials and an aggregated list of changes is acceptable and encouraged in case of substantial amendments as well as of urgent safety measures.
Two important aspects need to be taken into account:

1) It is up to the sponsor to assess whether an amendment is to be regarded as 'substantial'. A change is substantial when it has a potential impact on the safety or physical or mental integrity of the clinical trial participant, or on the scientific value of the trial (CT-1 section 3.3, CT-2 section 5[9]). Substantial amendments relate to amendments of documents/information that are part of the clinical trial application dossier.
2) Submission of information is only obligatory if the amendment is a substantial amendment. Directive 2001/20/EC does not require notification, or immediate submission of information on non-substantial amendments. In other words, the only communication mechanism of substantial changes to information in the protocol or clinical trial dossier is through the submission of a substantial amendment. Non-substantial amendments, or changes that do not relate to information submitted in the clinical trial application dossier should be recorded in the documentation when it is subsequently submitted, for example in the subsequent submission of a substantial amendment (CT-1 section 3.1).

8 Communication from the Commission - ('CT-1') (2010/C 82/01) https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52010XC0330(01)
9 Detailed guidance from the Commission ('CT-2') (2006) https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/12_ec_guideline_20060216_en.pdf