



The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products

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Changelog, version 1.0 to 2.0:

Version 2.0 of this guidance includes the following updates:

- Typographical updates throughout the document.
- Section 2.1: Change of wording in regards to investigators delegation of tasks and new highlight about continuity in home visits.
- Section 2.2: New section about the impact on trial data integrity.
- Section 2.4: New wording of mitigation plan requirements.
- Section 2.5: Alignment with ICH E8.
- Section 2.6: New wording of contractual agreements and a new sub-section regarding the integrity of the trial participants medical records.
- Section 2.7: Requirements changed for applications.
- Section 4.2 (6): New references.
- Section 9: New possibility of implementing rSDV.



1. Introduction

Clinical trials with medicinal products have made rapid advances when it comes to digitalisation and decentralisation. By this is meant the use of digital tools (digital consent, electronic consultations, electronic data collection systems, wearables and other medical devices, etc.), which reduce the need for trial participants to attend physical appointments at a hospital unit compared to a traditional clinical trial (Decentralised Clinical Trials, DCT).

This development helps ensure equality in the health service because patients regardless of mobility and physical distance to the hospitals can participate in clinical trials. These designs may also ensure a wider representation of trial participants and are likely to facilitate the recruitment and retention of patients in clinical trials.

The Danish Medicines Agency support this development and has therefore launched a project with the aim of ensuring a contemporary and robust regulatory framework for decentralisation of clinical trials. Our focus is that DCT elements are not implemented at the expense of the rights and safety of trial participants, the data integrity, nor increase the burden on the investigator sites.

Please also see our [COVID-19 guidelines](#) and the specific exemptions granted during this pandemic in relation to DCT.

1.1. Purpose

The purpose of this document is to provide guidance on the implementation of decentralised elements in clinical trials with medicinal products and to highlight challenges. This guidance will remain in force after the expiry of the above-mentioned COVID-19 guideline.

The legislation on clinical trials with medicinal products and associated guidelines generally do not prevent the conduct of decentralised trials, but sponsors are encouraged to seek scientific advice and consult the EMA and other regulators regarding the use of specific decentralised elements (e.g. choice of digital endpoints) and its impact on a potential marketing authorisation application.

This guidance reflects upon the challenges raised in clinical trial applications, scientific advices, our dialogue forum on decentralised clinical trials, other inquiries as well as challenges emerging in the ongoing collaboration with national, European and international partners. We encourage all interested parties to contact us at kf@dkma.dk with questions and input. In addition, we recommend to seek scientific advice prior to applying for a decentralised clinical trial if the trial contemplates using elements where there is little experience.

Please note that we expect to update this guidance frequently. DCT is an area undergoing significant and rapid development, and we consider a learning approach to be the best way forward whereby new knowledge and feedback are published continuously.



1.2. Concept

Decentralised clinical trials¹ cover a multitude of elements which reduce, or in some cases even eliminate, the need for the trial participants to go to the clinical trial sites. In this guidance the decentralised elements are placed into the following categories:

- General considerations
- Recruitment
- Electronic informed consent
- Delivery of investigational medicinal products and self-administration at home
- Remote monitoring of trial participants' safety
- Adverse events reporting
- Choice and validation of endpoints
- Remote access to source data
- IT systems and electronic collection, handling and storage of data

In a fully decentralised design, the trial participants never set foot in the clinical site. This is not possible for all trial types; for example, because the trial participants cannot be sufficiently monitored remotely, or there are trial procedures, such as scans or assessments of important parameters/endpoints that require the physical attendance of trial participants.

A decentralised clinical trial is termed a hybrid trial if the trial adopts decentralised elements in parallel with the physical attendance of the trial participants at the clinical site. Clinical trials with medicinal products have for years already adopted some decentralised elements such as electronic diaries, delivery of the investigational medicinal product (IMP) via the site to the trial participant and phone calls or online appointments.

2. General considerations for the implementation of DCT elements

The hybrid model is the most used approach when it comes to decentralised clinical trials with medicinal products. Consequently, this guidance is divided into the different decentralised elements that can be included or excluded according to the trial population and design.

There are too many variables in clinical trials to provide specific guidance on cases justifying the adoption of DCT elements. For this reason, the use of DCT elements must be justified in relation to the specific clinical trial. Accordingly, a trial-specific risk assessment is required to implement decentralised elements (section 2.2).

- The processes described in this guidance assume that it has been assessed that these can be safely implemented without compromising the safety and rights of trial participants.
- Any reference to the investigator in this guidance explicitly means the investigator or delegated staff.

¹ The concept of DCT is not synonymous with virtual trials. The Danish Medicines Agency considers virtual trials to be retrospective data processing without the involvement of trial participants and prospective interventions. Virtual trials are not covered by this guide.



2.1. The impact of limited physical meetings with trial participants

One significant challenge of decentralised clinical trials is whether sufficient safety monitoring of the participants can be maintained. So far, telephone conversations with trial participants have been accepted in connection with follow-up periods or as a supplement to the usual safety monitoring at physical visits.

The development of decentralised clinical trials reduces the need for physical visits as it can now take place by telephone conversations, via video conference or other communication platforms. The Danish Medicines Agency has not been presented with convincing evidence that the trial participants' safety generally can be ensured just as effectively in a completely decentralised setup versus physical meetings. We recognise that the extent of decentralised elements may depend on the specific trial population, disease, assessment type, type of medicinal product and development stage.

- The Danish Medicines Agency encourages the undertaking of studies to identify the weaknesses and strengths of decentralised trials, comparing decentralised aspects with traditional trial designs, including the impact of the reduced face-to-face visits between healthcare professionals and participants.

In this respect, especially the medical observations could be challenged by the lack of physical meetings, more specifically the investigator's possibilities of forming a general impression of the participant by assessing such things as appearance, colour, gait, odour, etc. As a result, the investigator might overlook symptoms that should be assessed further or could misjudge endpoints. In addition, matters of a subtler nature is challenged by lack of physical visits, e.g. building a trusting relationship between the investigator and trial participant to create a safe environment that promote openness.

- These challenges can be met through home visits (section 2.5). Continuity in visits at home should be ensured to the extent possible i.e. the same healthcare professional to visit the trial participant.

Furthermore, an objective and possibly also a neurological examination are usually performed at inclusion and as part of the ongoing monitoring of the trial participant. These examinations must as a general rule be performed by a physician during a physical visit at home or at the trial site. These assessments should generally not be delegated to other healthcare professionals.

In some cases, conducting physical visits is of less importance, e.g. trials planned to be close to real world evidence, when the diagnosis is easy to make (or given beforehand), if there are relatively few and straightforward inclusion and exclusion criteria, and if medical observations/objective examinations are required to a lesser extent or where assessment of the endpoint can be readily ascertained/collected.

- The investigator should obtain evidence of previous important diagnoses (conditions to be examined, diagnoses affecting the inclusion and exclusion criteria, etc.) if these are not performed/have not been performed by the investigator.

2.2. The impact of DCT elements on trial data integrity

Different implementation of DCT elements across trial sites in different countries may occur due to differences in national legislation or other factors. This means that certain procedures are carried out in different ways/settings which may potentially introduce confounding variables which jeopardises the reliability and validity of the trial. Sponsors should very



careful assess these kinds of challenges to ensure the data integrity of the trial. At the same time, comparisons between traditional and corresponding DCT assessments may be relevant, which should be carried out by the trial sponsor beforehand or be robustly justified by literature.

In relation to this, we stress the importance of consulting and receiving scientific advices from the EMA and other regulators.

2.3. Justification for implementation

The Danish Medicines Agency finds that decentralisation will be an important tool in future clinical trials and that many physical visits are generally well suited to the decentralised environment, provided it is thoroughly thought through and adjusted to the specific trial.

A trial-specific risk assessment must always be carried out together with justification for the selected decentralised elements, which, in principle, should be part of the protocol (section 2.6). The sponsor must have reflected on the implementation of decentralised elements in the context of:

- Trial population, including special conditions, e.g. children/elderly.
- The type of medicinal product, its route of administration and safety profile and development phase.
- The required handling of the medicinal product, e.g. mixtures and other regimens of a complex nature.

2.4. Adoption of new technologies

Another focus area is the use of new technologies such as apps, wearables and medical devices supporting at-home medical processes and data collection. The advances in electronic collection, handling and storage of data impose requirements on the validation of systems and data security (section 10).

- Please note that the Danish Medicines Agency can help manufacturers of medico-technological devices with clarification of the [current rules and standards applicable in the area](#).
- The adoption of IT technological solutions presents new vulnerabilities to the conduct of clinical trials, and the sponsor is expected to effect mitigation plans in case of system failure and to assess the risk in relation to the individual remote contact with the trial participant.
- In the EU, qualification opinions on the use of new methodologies are presently being implemented. These are published on the [website of the EMA](#).

The use of artificial intelligence may also be considered in a decentralised clinical trial. In such cases, the sponsor must specifically draw attention the use of any such systems and is advised to contact us or to seek scientific advice prior to such use, especially if critical data or decisions are involved. In this connection, the Danish Medicines Agency has [published suggested criteria for using AI/ML algorithms in GxP](#).



2.5. Involvement of patient population and investigators

As mentioned earlier, the DCT design is to ensure equality in the health service and should facilitate access to and participation in clinical trials. Therefore, it is essential that DCT elements are developed in collaboration with relevant and potential trial participants to shed light on the needs of the targeted patient group.

We have seen several cases where inappropriate design of patient diaries, for example, has severely affected the data integrity or increased the workload for the clinical site or the trial participants.

The involvement of trial-specific participants can help strengthening the trial design. Consulting with patients and/or patient organisations in the design, planning and conduct of clinical trials either during the trial, program or element development helps to ensure that all perspectives are captured. Patients' views can be requested on all phases of drug development. Involving patients at the early stage of trial design is likely to increase trust in the trial, facilitate recruitment, and promote adherence. This involvement may also uncover design challenges, e.g. the DCT design may introduce selection bias on technological maturity why the sponsor is expected to have assessed the need for offering alternative procedures.

- The sponsor should consider where relevant including trial participants' needs in the development. An example of this could be the feasibility of appointments between the investigator and trial participant which are planned to be carried out by videoconference, but where the participant is given the opportunity to choose a physical visit at the clinical site if they find it necessary. The investigator should have the same option, i.e. calling in trial participants for a physical visit if needed.

The above-mentioned involvement and flexibility will allow a more far-reaching DCT design.

In the planning of a decentralised clinical trial, healthcare professionals/investigators should also be involved in the development of the protocol. The expertise of the investigators should be included in the reflections on how to best ensure sufficient monitoring of the safety of trial participants and identification of the consequences of having less or no personal contact.

Reference is also made to [ICH E8](#) regarding the general reflections on clinical trials, including design and involvement of stakeholders.

2.6. Investigator's and sponsor's overview of their statutory responsibilities

Any implementation of decentralised processes must always ensure that the investigator and sponsor can fulfil their legal obligations as laid down in sections 4 and 5 of [ICH GCP](#). This means that the sponsor cannot assume the responsibilities of the investigator and vice versa. In certain cases, the sponsor can use independent committees or central laboratories to save the investigator from using resources unnecessarily or to ensure a higher data quality by involving specific expertise for assessment of endpoints, etc. In such cases, this must be justified based on data integrity and trial participants safety, including considerations regarding the need for independence between sponsor and investigator.

The typical responsibility areas of the investigator could be the inclusion of trial participants, drug dispensing/administration, sampling, efficacy and monitoring of adverse events, etc.



If some of these tasks do not take place at the site, this must both be justified and described clearly in the trial protocol. Furthermore, the tasks to be conducted in a decentralised setup must still be controlled by the investigator and performed by qualified staff. In case these tasks are not handled by healthcare professionals from the clinical site but by external healthcare professionals, contractual arrangements should clarify how the investigator maintains control over external healthcare professionals performing trial related tasks under their responsibility and how effective lines of communication between the investigator and the party handling the task are established. Furthermore, procedures should be in place to ensure this.

In addition, it must be ensured that the performed tasks are documented, and that all parts of the investigator's Trial Master File are stored pursuant to the GCP rules. Please also see [Q&A nos. 10 and 11 on the website of the EMA](#).

In continuation of the above, the trial participants medical records shall continuously be updated with protocol-specific information that is clinically relevant to other healthcare professionals involved in the patient's current and future treatment². Robust procedures should be implemented in DCT trials ensuring the integrity of the medical records so that it remains an effective way of communicating necessary and important information. Also, the information should be easily accessible in a timely manner and overly burdensome procedures e.g. to transfer information from trial specific data collection tools to the medical record in order to achieve this should be avoided. Please be referred to the published [guidance of journaling](#) by the Danish Patient Safety Authority (in Danish).

2.7. Application requirements of the Danish Medicines Agency

In order to ensure that it is clear to which extent decentralised elements are used in a trial, it is important to mention the DCT elements in the application's cover letter with reference to the trial-specific risk assessment (section 2.2):

1. The cover letter must mention the DCT elements adopted in the clinical trial and confirm that implementation of the elements in question is made pursuant to this guidance.
2. Any GxP use of AI/ML algorithms should be clearly stated in the cover letter.
3. The DCT processes must be described in the protocol and the informed consent.
4. The use of trial specific apps, wearables or other medical devices must be described in the cover letter, and the sponsor must declare if this is assessed to be medical devices or in vitro diagnostics together with their development status.

It is similarly expected that the DCT elements are highlighted in the submission to the Health Research Ethics Committees. Please note that further guidance on the application requirements and the trial protocol may be provided in individual sections of this guidance.

² Danish law on medical records, BEK nr 1225 af 08/06/2021 (in Danish: "Bekendtgørelse om autoriserede sundhedspersoners patientjournaler (journalføring, opbevaring, videregivelse, overdragelse m.v.)")



In addition, we are aware that some DCT elements may give rise to questions by the rules governing personal data (GDPR). Please be advised that it is the sponsor's responsibility to ensure that DCT elements are implemented in accordance with the GDPR together with any requirements or interpretations published by the Danish Data Protection Agency and the data controllers at the clinical sites.

3. Recruitment

3.1. Considerations

Considerations regarding decentralised recruitment and pre-trial screening of trial participants, e.g. via social media and established databases, should include acceptance by the Health Research Ethics Committees regarding the recruitment method prior to implementation. Likewise, compliance with GDPR must be ensured.

3.2. Expectations for implementation

1. Recruitment and screening methods must be clearly described in the trial protocol, and the processes must be verifiable based on the generated documentation with a view to verifying, for example, a possible selection bias.
2. If trial participants are included from another country, this must be described in detail and specifically approved by the Health Research Ethics Committees. Please note that special requirements may apply to the processes for patient information and informed consent and ongoing communication with the site, including where applicable the need for an interpreter.
3. Special attention should be paid to ensuring evidence for correct diagnosis.
4. Regardless of the nationality of the trial participants, it is recommended that their general practitioner be informed about the participation.
5. It should be documented e.g. in a pre-screening log and related documentation if trial participants are contacted based on pre-screening from social media or the like.

4. Electronic informed consent

4.1. Considerations

We point out that it is not the Danish Medicines Agency's area of responsibility to approve neither the wording nor the process for the informed consent. Requirements and guidance as well as approval of the informed consent process belong to the Health Research Ethics Committees and reference is therefore primarily made to their guidelines, legislation and [website](#).

Please be aware that requirements set by the Danish Medicines Agency upon approval and in connection with inspection of the informed consent processes may differ from the requirements set by the Health Research Ethics Committees. The following is thus the Danish Medicines Agency's interpretation and guidelines regarding compliance with ICH GCP and must be read as a supplement to the guidelines of the Health Research Ethics



Committees. During inspections, the Danish Medicines Agency's inspectors will focus on verifying the processes approved by the ethics committees.

In this context, an electronic informed consent means the use of a digital medium (e.g. text, images, video, audio, websites, etc.) to deliver information to prospective trial participants and obtaining a written informed consent by means of a smartphone, tablet or computer, etc. The steps in the process include the communication of information, the possibility to ask questions about the trial and signing of the consent form.

4.2. Expectations for implementation

Special attention should be paid to the following:

1. The use of digital media may deter less tech-savvy trial candidates from participation, thus introducing a selection bias. Alternative procedures should be an option.
2. The confidentiality between the trial participant and investigator must be preserved, implying the use of secure media and without sponsor involvement/access.
3. The sponsor must generally not have access to the communication between the trial participant and the investigator, other than for the fulfilment of their monitoring and audit obligations. This must be ensured through user access control to the systems storing the information.

The communication method must enable unambiguous identification of the trial participant or guardian if relevant. The informed consent must be documented and personally dated and signed using systems ensuring the above-mentioned identification.

4. The documentation must be generated and archived pursuant to the investigator's Trial Master File, and version control must be used.
5. The trial participant should have the possibility to download and print the informed consent/information and should continue to have access to these documents throughout the course of the trial.
6. The electronic systems used must satisfy the general requirements for electronic systems in clinical trials. They must be validated for the purpose, change control must be implemented and user control and methods for sufficient IT security must be implemented. The method used for electronic signature must comply with the applicable standard. Please also refer to ICH GCP guidelines, section 5.5, and to the GCP Inspectors Working Group's reflections and coming guideline on electronic systems and data.
7. Close (real-time) communication between the investigator and the potential trial participant is expected regardless of whether this is by way of physical visits or, for example, video conferences (if approved by the Ethics Committees). The communication must take place on the terms of the trial participant.



5. Delivery of investigational medicinal products and self-administration at home

5.1. Considerations

The considerations and the procedures to be followed for the delivery of the investigational medicinal product (IMP) and self-administration at home depend highly on the route of administration and the safety profile of the IMP concerned.

In the case of a marketed drug with a known and acceptable safety profile, without complex storage conditions, which can be administered by the trial participants themselves (e.g. oral formulations, injection pens, etc.), starting the treatment at home may be acceptable. However, other medicinal products are less appropriate for home treatment e.g. for drugs in the early stages of development, where the safety profile is partially unknown and might require professional handling, administration and possibly observation (e.g. biological drugs for injection).

Pursuant to section 2.6, the points below must be specifically considered in connection with the delivery and self-administration of the IMP and must be reflected and justified in the cover letter, protocol or associated annexes in clinical trial application:

- Knowledge of the IMPs safety profile (phase, known/possible adverse reactions, etc.), including the risk of serious adverse reactions that demand acute treatment.
- The IMPs route of administration and need for healthcare professional's assistance and subsequent observation.
- Whether the trial participant is stable on the IMP before self-administration at home.
- Which criteria the investigator uses to assess if self-administration at home is safe for the trial participant. These criterions should be part of the trial protocol.
- What process is in place for the handling of adverse reactions in home-settings if, for example, allergic reactions occur after injection. This process should be included in the trial protocol.

5.2. Expectations for implementation

It is currently not possible for the sponsor to carry out the delivery of the IMP to the trial participants' home address pursuant to section 23(2) of the GDP Executive Order³. Thus, the investigator must carry out the delivery of IMPs to the trial participants. The sponsor has overall responsibility for the process and can facilitate the drawing up of contracts, which must, however, reflect the principal investigator's areas of responsibility pursuant to ICH GCP (see section 2.5).

- The possibility of allowing the sponsor to undertake the task of delivering the IMP directly to the trial participant is being investigated/considered.

³Please also see the Danish Medicines Agency's COVID-19 guidance on clinical trials, which grants exemption from the GDP Executive Order during the pandemic.



Delivery of the IMP is subject to the following conditions:

Transport

1. Proof that the IMP's storage conditions are observed throughout the supply chain must be provided. It should furthermore be considered if it is necessary to perform a control of the storage conditions at the home of the trial participant.
2. The trial participant or a guardian must be home to accept receipt of the IMP. It must be documented how it is handled if the trial participant or guardian is not at home. As a general rule, the IMP should in such cases be brought back by the courier.

Training and communication

3. Manual packaging and release of the IMP should be double-checked.
4. An extra check should be made after the IMP has been received by the trial participant (e.g. by telephone). This is done to ensure that principal investigators meet their obligations of ensuring that the IMP is used in accordance with the protocol, that they explain the correct use of the IMP to each trial participant. Furthermore, the investigator should follow-up on the use at regular intervals to ensure the IMP is still taken according to instructions (ICH GCP 4.6.3, 4.6.5 and 4.6.6).
5. The investigator must ensure that the trial participant has received proper instructions on the use/administration of the IMP, and it should be considered if further instructions should be enclosed or given orally in addition to the instructions appearing on the labelling of the IMP. This should be adapted to the needs of the individual trial participant. This is especially important with administrations of a complex nature or if mixture is needed.
6. Alternatively, trained, experienced and qualified healthcare professionals must handle the administration of the IMP. This is especially relevant in cases of complex administrations, special handling requirements or handling of serious adverse reactions. In case the healthcare professionals does not bring the medicinal product with them, but it is sent separately, it must be made clear to the trial participant that the medicinal product is not to be administered before the visit of the healthcare professional.
7. Clear lines of communication should be established between the investigator and trial participant, e.g. in connection with obtaining the informed consent and by handing out ID cards with contact details.

Drug accountability and compliance

8. Procedures must be in place for keeping account of the IMP and controlling the compliance of trial participants. Records on the pharmacy's dispensing of the IMP to the trial participant are not an accepted measure of compliance, unless it has been thoroughly justified for the trial in question. The compliance of trial participants is generally checked by counting returned packages in combination with conversations with the trial participant if relevant.



5.2.1. Dispensing of IMP by pharmacy

In open trials (non-blinded IMP), the IMP can be dispensed by the pharmacies in Denmark under the following conditions:

1. The IMP must be marketed and used according to the authorised indication (pursuant to the summary of product characteristics).
2. A simple process for reimbursement of the trial participant's expenses must be established, or an agreement must exist with the pharmacy to dispense the medicinal product free of charge.
3. It must be ensured that the label will be printed with the name of a Danish-speaking sponsor or investigator and a reference code enabling identification of the clinical site, investigator and trial participant.
4. There must be procedures for keeping account of the IMP and checking the compliance of trial participants, cf. item 8 above regarding drug accountability and compliance.

5.2.2. Trial participants connected to Danish sites but residing abroad

In Denmark, there is no restriction on sending an IMP directly to a trial participant who is connected to a Danish site but resides abroad. However, it is important that the sponsor consults the authorities of the country in question to ensure compliance with local requirements.

6. Remote monitoring of trial participant safety

6.1. Considerations

In a decentralised design, it is possible to carry out more trial-related procedures at home, such as blood sampling, administration of the IMP and monitoring thereof, including follow up on adverse events. The investigator can delegate these tasks to trained staff pursuant to section 2.5. Certain tasks may require medical expertise, which must be ensured.

If trial participants are having trial activities such as routine blood tests performed at a local medical health centre/laboratory these facilities must be authorised/certified to perform the sampling/analyses in question. Documentation must be available to the investigator and archived in the Trial Master File.

The general matters related to remote monitoring are discussed in section 2 which, among other things, discuss investigators opportunity to form an overall impression of the trial participant, the involvement of the patients and investigators in the preparation of the protocol and the importance of continuity of the healthcare professionals visiting the trial participants.



6.2. Expectations for implementation

1. The protocol and the schedule of assessments must clearly detail which contacts with the trial participants are physical visits at the clinical site, telephone contact, video contact, home visits or a visit to a local laboratory or the like. It should be clearly noted if there are different options available to the trial participant for each specific contact.
2. In continuation of the above, it is important that the sponsor discusses/justifies each individual decentralised contact in the protocol.
3. The sponsor must have systems in place to ensure data comes from the trial participant.
4. The investigator must have continuous access to the data reported by the trial participants, e.g. in electronic questionnaires. These data must furthermore be under the investigator's control.

7. Adverse event reporting

7.1. Considerations

The robustness of registration and reporting of adverse events can be strengthened by the use of digital platforms, often a central element in a decentralised clinical trial. By means of a digital platform, e.g. a smartphone app, the trial participant is equipped to register adverse events themselves, which means they are instantly available to the investigator. The Danish Medicines Agency acknowledges the strength of this type of registration, which may essentially improve the ongoing collection of data about the trial participants safety. We also acknowledge that the handling of these reports by the investigator (including the frequency of assessment), must be implemented through a risk-proportionate approach balancing the resource consumption/added value in relation to the IMP's safety profile as well as the collection of adverse events in traditional clinical trial designs.

7.1.1. Collection of adverse events in clinical trials with medicinal products

The applicable rules for collection and reporting of adverse events appear from CT-3⁴. The new clinical trial regulation⁵ introduces a risk-proportionate approach, and the following guidelines for handling of adverse events in decentralised clinical trials are based on this.

- Decentralised clinical trials generally do not change the need for the investigator to use non-leading questions to find out if the trial participant has experienced adverse events since the last contact, and follow up on events registered in a digital platform at all physical visits and/or telephone/video conferences.

In a traditional clinical trial, the trial participants can register adverse events continuously by means of diaries that support the conversation with the investigator. In this setup, the investigator will not be informed of adverse events before the next meeting with the trial participant, which is either scheduled in the protocol or requested by the trial participant. However, it is normal practice for trial participants to be encouraged to contact the

⁴ EudraLex Vol. 10, Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ("CT-3")

⁵ Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use



investigator in case of serious adverse events such as hospitalisations. The main difference in terms of the trial participant's registration on a digital platform is that the digital platform makes all adverse events instantly available to the investigator.

7.1.2. Digital platforms for registration and reporting of events.

The use of digital platforms that engage the trial participants and facilitate the decentralised trial processes can also be used to enable the trial participant to register adverse events themselves. It also means that the investigator can receive information about adverse events at any time, 24 hours a day, 7 days a week.

- The trial participant might expect the investigator to respond immediately to adverse events registered on the digital platform. This may deter them from contacting the investigator directly. The possible outcome is that the investigator is informed of events requiring follow-up and/or treatment at a delay. This is to be mitigated in the design of the digital platform and in the instructions given to the trial participant and associated guidance.

7.2. Expectations for implementation

1. The investigator must ensure the continuous monitoring of data reported by the trial participants and, where relevant, to identify adverse events, lack of efficacy, etc. If there are special reasons why the investigator should not have access to these data (e.g. specific unblinding issues), this must be justified in the protocol.
2. The trial participant must receive explicit instructions as to when they should contact the investigator directly. In case, the investigator will not be assessing reports immediately upon receipt, the trial participant should be made aware of this in the system/instructions.
3. It must appear clearly on the digital platform how the trial participant can get in touch and/or make an appointment with the investigator, also in acute situations.
4. A feature must be built into the system which ensures that serious events in the extent possible trigger a notification to the investigator who must then promptly assess and report it to the sponsor within 24 hours.
 - a. In terms of the safety profile of the IMP, the sponsor must include in their risk assessment if there are any other relevant seriousness criteria's or specific events necessitating the immediate notification of the investigator by the system.
5. The frequency of monitoring of data must be justified and established taking the safety profile of the IMP and any other potential risks to the trial participants into account. If necessary, the investigator must contact the trial participant with follow-up questions.
 - a. It must be documented that all registrations have been assessed by the investigator.



8. Choice and validation of endpoints

The aim of this guidance is not to offer definitions to appropriate endpoints for use in decentralised clinical trials, nor to describe procedures for clinical or technical validation of digital endpoints. It is recommended to seek scientific advice about this.

9. Remote monitoring, including remote access to source data

9.1. Considerations

The use of remote monitoring, including rSDV should be a supplement in the risk-based monitoring plan to enhance data quality and gaining better monitoring of patient safety but can generally not replace the need of on-site monitoring.

The COVID-19 pandemic raised an acute need for monitors to have remote communication and access to source data (rSDV) due to the restrictive access to clinical sites. An extraordinary exemption was therefore granted in the EU, which meant that monitors could gain remote access to source data by different methods.

The continued use of rSDV is allowed under certain conditions and only by using the method where monitor gain restricted electronic access to the trial participants' medical records or other source data i.e. it should not be possible for monitors to get access to medical records of persons not participating in the trial. A key condition is that this method should not impose additional, unnecessary burden on trial sites or undue pressure from sponsors or CROs to change existing site procedures, TMF systems etc.

The sponsor is responsible for ensuring that remote monitoring including rSDV complies with GDPR. A separate risk assessment must be prepared regarding data protection for the implemented procedures. Consideration should be made whether access is contemplated at the monitor's home or office and conditions for this to take place.

The Danish Medicines Agency continuously gather experience from stakeholders and via inspections regarding the use of remote monitoring, including rSDV, and the requirements are subsequently likely to change. For non-commercial trials in which public sector GCP units are monitoring the trial and are employed by the organisation, the institution/investigator (verified by the data-responsible person) may provide access for rSDV.

9.2. Expectations for implementation

1. Establishing remote access must be in accordance with the principles of necessity and proportionality and must always be done in a way that protects the rights of the participants and does not place unnecessary burden on site staff.
2. The sponsor should not put pressure on the investigator to establish remote access to source data.
3. The investigator should always ensure that they can fulfil regulatory requirements and national legislation.



4. The establishment of remote access to source data should be described in the trial protocol and proof should be available at inspections that investigator's institution data-responsible person/department approval have been obtained and furthermore, has implemented systems to ensure restricted access to the relevant trial participant records and data without jeopardising data protection or imposing increased risks to IT security.
5. Remote access to Danish source data may only take place from a location within EU/EEA.
6. Access must be established under secure conditions. This include a secure connection on a machine protected from unauthorized access. The location must ensure that outsiders cannot overlook the process.
7. Monitor must be trained in the process.
8. The investigator and the institutions data officer must assess the necessity for monitors to sign a written confidentiality agreement regarding their remote access to the systems owned and controlled by the institution.
9. The access shall be restricted to read-only. Furthermore, monitors access should be restricted for trial participants only.
10. The IT system must have an event log that shows when the monitor has accessed specific information. Monitor must have personal access to the system and the personal access must be provided with 2-factor authentication.
11. The system should not, to the possible extent, allow the monitor to make local copies. The monitor should not take screen dumps or store personal data about the trial participants on their computer whether pseudonymised or not.
12. The monitors' remote access shall only be granted when necessary and be terminated immediately when the need for remote access is no longer present.

10. IT systems as well as electronic collection, handling and storage of data

Decentralised clinical trials require validated, secure and user-friendly IT solutions.

Regarding these points, reference is generally made to the ICH GCP guidelines, section 5.5, and to the GCP Inspectors Working Group's reflections and coming [guideline on electronic systems and data](#).