



# The Danish Medicines Agency's Guidance on Digital and Decentralised Clinical Trials

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## The Danish Medicines Agency's guidance on implementing digital and decentralised elements in clinical trials involving medicinal products

### Table of contents

1.	Introduction.....	3
1.1	Purpose.....	3
1.2	Concept of decentralised clinical trials .....	4
2	General considerations for the implementation of DCT elements .....	4
2.1	The impact of limited physical meetings with trial participants .....	4
2.2	The impact of DCT elements on trial data integrity .....	5
2.3	Justification for implementation .....	5
2.4	Adoption of new technologies .....	5
2.5	Investigators and sponsor's oversight of their statutory responsibilities .....	6
2.6	Requirements for Applications Submitted to the Danish Medicines Agency .....	7
2.7	Cross-border participation .....	7
3	Delivery of investigational medicinal products and self-administration at home .....	7
3.1	Considerations.....	7
3.2	Expectations for implementation.....	8
3.2.1	Dispensing of IMP by pharmacy .....	8
4	Adverse event reporting.....	9
4.1	Considerations.....	9
4.1.1	Collection of adverse events in clinical trials with medicinal products .....	9
4.2	Expectations for implementation.....	10



5 Monitoring performed remotely..... 10

5.1 General considerations ..... 10

5.2 Remote access to electronic medical records..... 11

**Definitions**

<b>Term</b>	<b>Definition</b>
Decentralised elements (DCT elements)	Decentralised elements in a clinical trial are those trial-related activities conducted outside the investigator’s location. These may include trial visits and/or protocol-related procedures conducted at the trial participant’s home, local healthcare centers or mobile medical units. They also encompass remote interactions, such as video calls or the use of digital health technologies (DHTs) to conduct visits, perform procedures and collect data
Decentralised Clinical Trial (DCT)	A clinical trial in which some or all protocol-specified activities occur without requiring physical site visits. Fully decentralised trials require no on-site visits; hybrid trials combine onsite and remote elements.
Hybrid trial	A clinical trial using a mixture of decentralised procedures (e.g., tele-visits, home visits, remote assessments) and traditional site visits.
Remote visit / remote consultation	A trial-related assessment performed via phone or video call, allowing investigators to evaluate adverse events, symptoms, or trial progress remotely.
Home visit	An in-person visit conducted at the participant’s home by delegated trial personnel. May include examinations, blood sampling, IMP administration, or observation.
Remote Source Data Verification (rSDV)	Verification of source data through secure remote access to electronic health record systems or permitted remote viewing of paper sources, following necessity and proportionality principles.

## 1. Introduction

Decentralised elements in a clinical trial are defined in ICH E6 R3 annex 2 (draft) as those trial-related activities conducted outside the investigator’s location (e.g., trial visit is conducted in the trial participant’s home, local healthcare centre or mobile medical units or when data acquisition is performed remotely using digital health technologies (DHTs).

Clinical trials involving medicinal products have rapidly advanced in their use of digital tools and the decentralisation of trial processes. Examples are the use of electronic informed consent, electronic consultations, electronic data acquisition tools including wearables, and medical devices. These innovations reduce the need for trial participants to attend physical appointments at hospital sites compared with traditional clinical trials. This development promotes greater equity in healthcare by enabling patients—regardless of mobility limitations or distance from hospitals—to participate in clinical trials. These tools and innovative protocol designs may also support broader representation among trial participants and, when implemented appropriately, are likely to enhance both recruitment and retention. Furthermore, the digitalisation of tasks and processes can reduce burdensome activities, creating efficiencies that benefit sponsors, investigators, and trial participants alike.

In December 2022, the EU guideline “Recommendation paper on decentralised elements in clinical trials” was published. The DKMA has contributed to the recommendation paper, and this DKMA guidance serves as a national supplement to the EU document. This guidance does not introduce any additional requirements; rather, it refines and highlights the opportunities available in Denmark.

Furthermore, the Medical Research Ethics Committee has provided [guidance](#) on decentralised clinical trials (DCT), which can be read in conjunction with this guideline.

This document refers to the following related documents:

- ICH E6 R3 Guideline, principles, annex 1 and annex 2
- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use
- Recommendation paper on decentralised elements in clinical trials
- EMA Guideline on computerised systems and electronic data in clinical trials

### 1.1 Purpose

The legislation on clinical trials with medicinal products and associated guidelines generally allows the use of digital or decentralised elements. However, sponsors are encouraged to seek scientific advice and consult the EMA and other regulatory authorities regarding the use of specific elements (e.g., novel digital endpoints) and their potential impact on marketing authorisation applications.

This includes statistical considerations on how digital and decentralised methodologies are translated into relevant evidence for both drug development and regulatory decision-making.

This guidance focuses exclusively on operational aspects and on compliance with GCP and other regulatory requirements for clinical trials. It reflects challenges identified in clinical trial applications, scientific advice procedures, discussions in our dialogue forum on decentralised clinical trials, inspections, other enquiries, as well as issues arising from ongoing collaboration with national, European, and international partners. We encourage all interested parties to contact us at [kf@dkma.dk](mailto:kf@dkma.dk) with questions and input. Additionally, we recommend seeking scientific advice before applying for a clinical trial that intends to use digital or decentralised elements for which experience remains limited.

## 1.2 Concept of decentralised clinical trials

Decentralised clinical trials encompass a range of elements that reduce, or in some cases even eliminate, the need for participants to visit clinical trial sites at hospitals or clinics.

In a fully decentralised design, trial participants are never required to be physically present at a trial site. However, this is not feasible for all trial types. For example, physical attendance may be necessary when participants cannot be adequately monitored remotely, or when trial procedures—such as imaging or assessments of critical parameters or endpoints—require onsite evaluation.

A decentralised clinical trial is referred to as a hybrid trial when decentralised elements are combined with physical attendance of the trial participants at the trial site. Clinical trials with medicinal products have, for years, incorporated certain decentralised elements such as electronic diaries, delivery of the investigational medicinal product (IMP) from the site to the trial participant or visits via phone calls or online appointments.

## 2 General considerations for the implementation of DCT elements

The hybrid approach is anticipated to be the most applied approach. Consequently, this guidance is structured around the various decentralised elements that may be included or omitted depending on the trial population and overall design. As this document serves as a supplement to the EU recommendation paper, it addresses only those aspects that are not covered in the EU document or require further national specification. It is stressed once again that this guidance do not introduce any additional requirements compared to the EU DCT guidance.

### 2.1 The impact of limited physical meetings with trial participants

One significant challenge associated with decentralised elements in clinical trials is ensuring that adequate safety monitoring of participants can be maintained.

The use of decentralised elements in clinical trials may reduce the need for physical visits as interactions can occur through telephone calls, video conference or other communication platforms. The Danish Medicines Agency recognises that the degree of decentralisation may vary depending on the trial population, the disease area, the type of assessments involved, the characteristics of the medicinal product, and the stage of development.

In this respect, medical observations may be particularly affected by the absence of physical meetings—specifically the investigator’s ability to form an overall clinical impression of the participant by assessing factors such as appearance, complexion, gait, and odour.

Consequently, symptoms that require further evaluation may be overlooked, and endpoints may be misjudged. In addition, more subtle aspects—such as establishing a trusting relationship between the investigator and the trial participant to support openness—may also be challenged by the absence of physical visits.

- These challenges may be addressed by incorporating home visits.
- These challenges may be considered less significant in clinical trials utilising marketed IMPs with well-established safety profiles.

An objective physical examination—and, where relevant, a neurological examination—is typically performed at inclusion and as part of the ongoing monitoring of the trial participant. Such

examinations should generally be conducted by a physician during a physical visit, either at the participant's home or at the trial site.

In certain cases, however, physical visits may be less critical. This may apply to trials designed to approximate real-world evidence, trials where the diagnosis is straightforward or already established, where inclusion and exclusion criteria are simple, where the need for medical observations or objective examinations is minimal, or where endpoints can be easily assessed or collected without onsite evaluation.

## 2.2 The impact of DCT elements on trial data integrity

Implementation of specific DCT elements may vary across trial sites and countries, for example due to differences in national legislation. An overview of national provisions in EU Member States is provided in the EU Recommendation Paper on Decentralised Elements in Clinical Trials.

As a result, certain procedures may be performed in different ways or settings, potentially introducing confounding variables that could compromise the reliability and validity of the trial. Sponsors should very carefully assess these challenges to ensure the data integrity of the trial. Additionally, comparisons between traditional and corresponding DCT assessments may be relevant and should either be conducted in advance by the sponsor or supported by robust literature.

## 2.3 Justification for implementation

### Identification and mitigation of risks

Remote visits or home visits should be thoroughly justified and tailored to the specific trial. The use of other decentralised elements or digital tools should be supported by robust and secure processes.

A trial-specific risk assessment should always be conducted, and the justification for using novel digital or decentralised elements should be included in both the protocol and the submission cover letter, clearly outlining their added value.

The sponsor should reflect on the implementation of the elements in the context of:

- The intended trial population, including any special conditions, e.g. vulnerable populations.
- The type of medicinal product, its route of administration, safety profile and development phase.
- The required handling of the medicinal product, e.g. regimens of a complex nature.

## 2.4 Adoption of new technologies

The use of new technologies such as apps, wearables and medical devices can support at-home medical processes and data collection. The advances in electronic collection, handling and storage of data impose requirements on the validation, user management and IT security of systems.

It is recommended that representatives of intended participant populations and healthcare professionals are involved in the design of the system, where relevant, to ensure that computerised systems are suitable for use by the intended user population. The involvement should be described in the protocol in accordance with clinical trial regulation.



- The requirements can be found in the [EU Guideline](#) on computerised systems and electronic data in clinical trials
- 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](#).

In the EU, qualified opinions on the use of new methodologies are currently being implemented.

These are published on the [website of the EMA](#).

Where artificial intelligence is used for processes of higher criticality in a clinical trial, the sponsor should describe the use of such systems and is advised to contact the DKMA or seek scientific advice prior to implementation, particularly when data or decisions of higher criticality are involved.

## 2.5 Investigators and sponsor's oversight of their statutory responsibilities

Any implementation of decentralised elements in a trial must ensure that both the investigator and the sponsor are able to fulfil their respective legal obligations as outlined in ICH GCP. As a general principle, the sponsor cannot assume the responsibilities of the investigator, and vice versa. However, the sponsor may facilitate certain processes that fall under the investigator's responsibility, such as home nursing services or the handling of IMP.

Examples of typical responsibility areas of the investigator are inclusion of trial participants, drug dispensing, administration and accountability, assessment of efficacy and monitoring of adverse events.

Although the sponsor may facilitate some of the processes, this should be justified and described clearly in the trial protocol. Furthermore, the investigator should continue to exercise oversight for areas under their responsibility, and all tasks should be performed by appropriately qualified personnel. How investigator oversight is ensured should be clearly described in agreements or alternative arrangements to which the investigator has agreed.

The sponsor and the investigator should ensure oversight of their respective service providers. The range and extent of oversight should be tailored to the complexity of and risks associated with the trial.

Use of DCT elements in clinical trials does not change requirements for documentation. The sponsor and the investigator respectively should ensure that their clinical trial processes are appropriately documented and that their part of the Trial Master File is maintained. Where data acquisition, tools are used to collect trial data in accordance with the protocol, such as trial participant or physician reported outcomes, the investigator should ensure that medical records for trial participants contain the information relevant to other healthcare professionals involved in the trial participant's current and future treatment as required by local law. Robust procedures should be implemented in trials with decentralised elements ensuring the integrity of the medical records, so it remains an effective mean of communication. The information should also be readily accessible in a timely manner, and overly burdensome procedures—such as transferring information from trial-specific data acquisition tools to the medical record solely to achieve this—should be avoided.



## 2.6 Requirements for Applications Submitted to the Danish Medicines Agency

To ensure clarity regarding the extent to which decentralised elements are used in a trial, these DCT elements should be explicitly described in the application's cover letter, with reference to the trial-specific risk assessment.

Furthermore, the following bullets should be included in the clinical trial application:

- The cover letter should mention the use of novel DCT elements that are identified as being critical-to-quality. DCT elements should also be described in the protocol and the patient information.
- For trials with more complex data flows, the trial protocol or a protocol-related document such as a data management plan should include a data diagram. This is to ensure high-level summarised information of the data flows between sponsor/service providers, vendors/investigator and data acquisition tools and other important computerised systems used in the trial.
- Use of AI/ML for functionality of higher criticality should be clearly stated in the cover letter.

## 2.7 Cross-border participation

Cross-border participation in a clinical trial is defined as clinical trial participants who are joining a trial at a site located outside the country where they reside or hold citizenship.

There is no Danish legislation that prevents a patient from another country from participating in a clinical trial in Denmark. Participation is therefore possible, provided that all ethical and regulatory requirements regarding clinical trials in Denmark are met.

Decentralised elements may be particularly relevant for patients participating across borders.

Furthermore, in Denmark, there are no legal restrictions on dispatching an IMP directly to a trial participant who is affiliated with a Danish trial site but resides abroad. Nevertheless, the sponsor is responsible for ensuring compliance with all applicable legislation in the participant's country of residence.

# 3 Delivery of investigational medicinal products and self-administration at home

## 3.1 Considerations

The considerations and procedures for delivering the investigational medicinal product (IMP) and enabling self-administration at home depend largely on the route of administration, the safety profile of the IMP, and the investigator's preferences and ability to maintain appropriate oversight.

For medicinal products with a well-established and acceptable safety profile, no complex storage requirements, and suitability for self-administration by trial participants (e.g., oral formulations, injection pens for subcutaneous use), initiating treatment at home may be acceptable. However, certain medicinal products are less suitable for home use—for example, products in early development stages where the safety profile is only partially known and may require professional handling, administration, and potentially observation (e.g., injectable biological products).

The investigator retains full responsibility for the treatment decision, and this decision must be documented before any investigational product is shipped to the participant's home

The following points should be carefully considered in relation to the delivery and self-administration of the IMP. These considerations should be reflected and justified in the cover letter, the protocol, or the relevant annexes of the clinical trial application:

- Knowledge of the IMP's safety profile (development stage, known and potential adverse reactions, etc.), including the risk of serious adverse reactions requiring urgent medical intervention.
- The IMPs route of administration and whether it requires assistance from a healthcare professional and subsequent observation.
- Whether the trial participant has prior experience with the IMP or the treatment is initiated on-site before transitioning to self-administration at home.
- The criteria used by the investigator to assess if self-administration at home is safe for the trial participant. These criteria should be defined in the trial protocol.
- The process for management of adverse reactions in home-settings such as allergic reactions following injection. This process should be described in the trial protocol.

### 3.2 Expectations for implementation

It is currently not possible for sponsors to deliver the IMP directly to trial participants pursuant to section 23(2) of the GDP Executive Order. Thus, the trial site or a pharmacy should oversee the delivery of IMPs to the trial participants as they are allowed to hand-out medicinal products to end consumers.

The sponsor has overall responsibility for the delivery process and may facilitate the establishment of agreements between principal investigator and service providers; however, these agreements must clearly reflect the principal investigator's areas of responsibility in accordance with ICH GCP.

- The Danish Medicines Agency is currently investigating the possibility of allowing sponsor and sponsor depots (external service providers) to undertake the task of delivering the IMP directly to the trial participant.
- The current draft of the Biotech Act (dated 16.12.2025) includes a provision that will allow sponsors to supply the IMP directly to trial participants.

#### 3.2.1 Dispensing of IMP by pharmacy

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

- The IMP is marketed.
- A simple process for reimbursing the trial participant's expenses should be established, or an agreement should be in place with the pharmacy to dispense the medicinal product free of charge. Alternatively, a waiver may be granted in accordance with Section 15 of the



Danish Act on Clinical Trials with Medicinal Products, that exempts the requirement for the IMP to be provided to the trial participant free of charge. The Danish Medicines Agency may grant an exemption from Article 92 of the Regulation, which stipulates that trial subjects must, as a general rule, be provided free investigational medicinal products, auxiliary medicinal products, and the necessary equipment for the treatment, if: the purpose of the trial would be defeated if they were provided free of charge, or the products are used for an indication covered by the medicinal product's summary of product characteristics, and the trial subject, regardless of participation in the trial, is already receiving treatment with the medicinal product for which the trial subject personally pays. Furthermore in trials conducted at a hospital where the trial subject already receives the medicinal product, etc., free of charge as part of hospital treatment, the sponsor may enter into an agreement with the hospital whereby the hospital covers the costs of the medicinal product, etc., in connection with the trial.

- IMP labels should comply with the requirements in the Clinical Trial Regulation 536/2014, Article 67.
- There should be procedures for keeping account of the IMP and checking the compliance of trial participants, where applicable.

## 4 Adverse event reporting

### 4.1 Considerations

The robustness of adverse event registration and reporting can be strengthened using digital platforms, which often constitute a key component of clinical trials incorporating decentralised elements. By using a digital tool, such as a smartphone application, trial participants can record adverse events themselves, thereby making this information available to the investigator in near real time.

The Danish Medicines Agency recognises the value of this approach, as it can substantially enhance the continuous collection of safety data from trial participants. The Agency also acknowledges that the investigator's handling of such reports—including the frequency and extent of review—should follow a risk-proportionate approach that balances resource use and added value in relation to the safety profile of the investigational medicinal product (IMP), as well as established practices for adverse event collection in conventional clinical trial designs. Introduction of decentralised elements in a clinical trial (e.g. patient diaries) can result in adverse events being recorded and reported via multiple sources. To avoid under or over reporting of adverse events, or variation in reporting approaches among sites, the sponsor should provide clear instructions to investigators and participants and have robust processes in place for the handling of safety-related information (e.g. reported as signs or symptoms, injection site reactions or observations).

#### 4.1.1 Collection of adverse events in clinical trials with medicinal products

The applicable rules for the collection and reporting of adverse events are set out in Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, which introduces a risk-proportionate approach.

The following guidelines for the handling of adverse events in decentralised clinical trials are based on this framework which may also be relevant in trials that include decentralised elements:

- Danish Medicines Agency’s Guidance on Risk-Based Recording and Reporting of Adverse Events in Clinical Trials on Medicinal Products under Regulation (EU) No 536/2014
- CTCTG’s Question and Answers on safety related issues in amendment of the Commission’s Q&A section 7 on safety, Eudralex Vol 10

Clinical trials incorporating decentralised elements do not alter the investigator’s obligation to use non-leading questions to determine whether the trial participant has experienced any adverse events since the last contact. Likewise, the requirement to follow up on events recorded in a digital tool at all physical visits and/or telephone or video consultations remains unchanged.

## 4.2 Expectations for implementation

- In accordance with ICH E6(R3), the sponsor should provide the investigator with timely access to data and the investigator is responsible for the timely review of this data, including relevant data from external sources that can have an impact on, for example, participant eligibility, treatment or safety (e.g., central laboratory data, centrally read imaging data, other institution’s records and, if appropriate, electronic patient-reported outcome (ePRO) data). The protocol may specify justified exceptions to data access, for example to safeguard blinding.
- The frequency of monitoring of data by the investigator should 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 should contact the trial participant with follow-up questions.
- The trial participant should receive explicit instructions as to how and 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.
- The system should include a feature that, to the extent possible, ensures that serious events (that are not exempt from registration or reporting) automatically trigger a notification to the investigator, who must promptly assess the event and report it to the sponsor within 24 hours of becoming aware of it.
- Taking the safety profile of the IMP and the protocol design into account, the sponsor should consider if there are specific events warranting the immediate notification of the investigator.

## 5 Monitoring performed remotely

### 5.1 General considerations

It may be appropriate to fully or partially conduct Source Data Verification (SDV) or Source Data Review (SDR) remotely. This approach may reduce the number of on-site monitoring visits and/or enable enhanced monitoring, depending on the trial and its risk-based monitoring plan. However, rSDV must not impose additional or unnecessary burdens on trial sites—such as requirements for

uploading, translating, approving, or pseudonymising documentation—as outlined in ICH GCP E6(R3) Principle 7.

It should be noted that equal requirements apply to rSDV compared to on-site SDV, namely that monitors must be able to understand and communicate in Danish.

Site monitoring (on-site or remotely), on the other hand, encompasses more than SDV and SDR and is an assessment of general protocol and GCP compliance, including an evaluation of site staff competencies and processes to generate source data. Therefore, even if all source documentation is electronic and can be assessed remotely, the need for on-site monitoring remains relevant for most clinical trials.

Remote SDV of electronic medical records in clinical trials is allowed if the process adhere to the conditions set in this guidance<sup>1</sup>. The appropriate method of conducting rSDV is for the monitor to be granted restricted and secure electronic access to the trial participants' electronic health records<sup>2</sup>. Hence, it should not be possible for monitors to gain access to EHRs of persons not participating in the trial.

## 5.2 Remote access to electronic medical records

The electronic medical record systems in Denmark are managed individually by the Danish Regions. The investigator should ensure compliance with EMAs Guideline on computerised systems and electronic data in clinical trials as well as the requirements from the Danish Regions.

Considerations may include, but are not limited to, the following.

### **The EHR system at the investigator site should allow:**

- Read-only access which is restricted to trial participants only. An appropriate ID verification process should be in place when granting an access to the designated monitor.
- An event log that shows when the monitor has accessed specific information.
- The monitor should have personal access to the system, and the personal access should be provided with 2-factor authentication or equivalent strong security.
- The system should not allow the monitor to print, copy, and download information.

The sponsor should ensure:

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<sup>1</sup> The utilisation of rSDV may differ in non-commercial trials in which the public sector GCP units are monitoring the trial and the monitors are employed by the site organisation. In these cases, the rSDV process should comply with the internal processes of the site institution.

<sup>2</sup> Please be referred to the [GCP Q&A](#) in regards to sharing of health records beside the purpose of SDV (“What should be considered when transferring copies of medical records to clinical trials sponsors or their service providers”)



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- That any established remote access to monitors is in accordance with the principles of necessity and proportionality and always in a way that protects the rights of the participants.
- That monitors have access to all relevant content of the electronic medical record. Please also see the DKMA notification about direct [Access for monitors](#).
- That processes do not cause undue burden for sites. While remote access for monitors can reduce the burden of arranging monitoring visits it should also avoid placing unnecessary burden on site staff. Furthermore, the sponsor should not put undue pressure on the investigator to establish remote access to source data.
- That organisational, technical and security measures on remote access (or rSDV) to clinical trial data are implemented to ensure that security practices and access controls are in accordance with EU standards.
- That remote access is established under secure conditions. This includes appropriate security measures such as firewalls, virus and malware protection and other security measures as required according to the guideline on computerised systems and electronic data, and choice of location which ensures that outsiders cannot overlook the process (a private place using privacy screen on the device, always logging out prior leaving the device unattended).
- That monitors are trained in the process. This should explicitly include guidance for monitors not to obtain screen dumps or to store any personal data about the trial participants on their computer whether pseudonymised, and not to share user account and log-in details.
- That compliance with GDPR is ensured
- That user management is performed according to section 4.3.8 of ICH E6(R3) i.e. that procedures are in place for setting, revoking and periodically review accesses to ensure only valid user accounts.



### Changelog, from version 2.0 to 3.0:

Version 3.0 of this guidance includes the following updates:

- Typographical updates throughout the document.
- Added definitions
- General updates to reflect current practices including ICH GCP R3
- Deletion of aspects/guidance already covered in the EU Guidance “Recommendation paper on decentralized elements in clinical trials” throughout the document.
- Section 1: Reference to EU Guidance “Recommendation paper on decentralized elements in clinical trials”
- Deleted section of involvement of patient population and investigators
- Deleted section on online recruitment and screening
- Added section of cross border participation
- Updated legal references
- Added links to relevant guidance’s and removed links no longer valid