LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Decentralised clinical trials

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Conducting clinical trial in a decentralised setting could facilitate subjects' participation. Procedures in the trial could then be carried out outside the traditional trial site and with use of digital tools.

Decentralised elements

A decentralised clinical trial (DCT) includes elements conducted outside the traditional trial site and/or where data collects remotely and often with help of different digital tools. Examples are electronic signature of the informed consent, sending investigational products directly to participants and study visits in his/her home. Some DCT elements have been used for some time, but new elements of great importance could together with the general digitalization change the set-up of future clinical trials. Just as for any clinical trial, the safety and rights of the participants together with the reliability and robustness of the data generated are central.

Questions and answers about DCT

The content is a summary of the information based on the experience and knowledge the agency has about decentralised trials at the moment.

Planning +

Planning for decentralised elements in a clinical trial requires a careful and study-specific risk-benefit assessment.

Factors to consider are for example:

- type of study
- study design
- study population
- characteristics of the investigational medicinal product
- indication.

The reasons for performing decentralised elements must be based on a scientific basis and may, for example, be an increased opportunity to include a relevant study population, collection of additional relevant data or reduced risk or burden for patients. Cost efficiency is not an acceptable reason to introduce decentralised elements.

The same requirements regarding ICH GCP, GMP, the scientific value of the study and the safety of subjects, apply to decentralised trials as to traditional trials. Seeking advice from agencies may be appropriate before submitting an application for clinical trials with decentralised steps for approval.

The investigator's overall responsibility in the study applies, even if different procedures are carried out at locations other than the trial site itself.

DCT is considered as a new approach and therefore, sponsors are encouraged to describe these elements in more detail compared to traditional study protocols. The DCT elements planned for should be clear from the cover letter of the application. A description of the elements (what task is performed by whom and how) as well as a benefit-risk assessment of DCT elements should, as a rule, be included in the protocol (or other protocol related document).

Consent process +

Is it possible to obtain informed consent remotely?

Yes, provided that ICH GCP(R2) and other applicable regulations are complied with, it may be possible to obtain informed consent remotely. The procedure needs to be described in detail in the study protocol and justified.

What are the requirements for a remote consent process?

The subject must always be informed and given the opportunity to ask questions as stated in ICH GCP(R2). This can be done in a digital meeting between the subject and the investigator in real time. The parties should be able to both see and communicate with each other via audio and video, and the investigator should be able to ensure that the subject is the right person or, if necessary, check his/her identity, i.e. contact only via telephone/e-mail/chat is not considered sufficient.

That informed consent has been obtained must always be documented in the subject's medical record.

Is it possible to electronically sign an informed consent?

Yes, it is possible, provided that the electronic system used is appropriate and validated for the purpose. For example, signatures must be possible to be verified and different versions of the consent must be stored. As usual in clinical trials, the subject signs first and then the investigator.

How should the informed consent be saved and how should the copy be distributed to the subject?

The signed consent can be sent via, for example, a link with a password or regular mail. Note that consent should not be sent unencrypted via email.

Signed consents can be saved in paper form or in another format as long as any changes can be traced, and readability can be guaranteed throughout the archiving period. As with all clinical trials, filing consent is the responsibility of the investigator.

Who can hold a digital consent process?

The same requirements as in a conventional clinical trial apply. Informed consent must be obtained from the investigator or delegated co-investigator who must be a licensed doctor or, where applicable, a licensed dentist. Signing of the consent cannot normally be delegated to a nurse. The nurse, on the other hand, can preferably be involved in informing the subject about the trial.

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Remote visits

Can some or all visits to a clinical trial be made remotely?

Yes, provided that the sponsor can show that there are prerequisites for collected efficacy and safety data to be of the same quality as during conventional study visits and that the safety of the participant must not be compromised. By remote visits is meant here, for example, different types of digital contact, visits to a location other than the trial site such as a primary healthcare provider or visits to the subject's home.

It is important to initially clarify the roles, responsibilities and tasks that the sponsor, investigator and others involved (such as other healthcare personnel or providers of system used) have in the trial.

What are the general requirements for remote visits?

ICH GCP(R2) and other applicable regulations apply to all clinical trials.

All visits during the trial are primarily the responsibility of the investigator. The investigator's control over the trial (PI oversight) must be ensured and proven even when the trial takes place at a location other than the trial site. For example, it is important that the investigator has sufficiently close contact with the staff who perform study tasks or treatment in a study.

Anyone who performs study-specific tasks, which is not a clinical routine, needs, as with all investigational clinical trials, training in GCP and study-specific training.

The sponsor should consider whether the clinical assessments in a particular trial are suitable to be performed remotely, taking into account what type of data is collected and how the results are to be used (screening/inclusion, primary variable, incidents et cetera).

Related information

EMA's Q&A (GCP matters), question 10 and 11(https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp)

Safety monitoring +

What is required for safety monitoring in a decentralised trial to comply with regulatory requirements?

In general, descriptions relating to safety monitoring need to be very detailed when activities and data collection in the trial are carried out at a remote visit and when the subject is not present at the trial site.

Collected safety data must be monitored according to a risk-based approach so that the examiner can act and report to the sponsor and authority in the same manner as if the data collection had taken place at the trial site.

It is important that the collected data is taken care of continuously and does not remain on a server until the results are compiled. They must be analyzed in accordance with the requirements for patient safety and ICH GCP(R2).

From the study protocol and its appendices, it must be clear that the sponsor has established routines for how the requirements are to be met.

Distribution of investigational medicinal products +

Can investigational medicinal products be sent to a subject's home?

Yes, provided that it is deemed appropriate for the trial in question, based on for example the safety profile, route of administration, and storage requirements of the investigational medicinal product, and that it is described in the clinical trial application.

Sponsor must not know the identity of the subject. Home delivery to a subject must thus take place from the trial site or from a Swedish pharmacy with which the investigator or sponsor has established an agreement for the trial in question. It shall be clear from the agreement that it is the trial site who provides the courier with the subject's address and contact details and that this information must not be passed on to the sponsor. In addition, quality requirements and other requirements for the transport shall be clear from the agreement. It may also be acceptable for home care staff to collect investigational medicinal products at the trial site, which they then hand over to the subject. In case home delivery means that the subject's identity is disclosed to an additional party, this shall be described in the written subject information.

It is the investigator who must initiate all deliveries of investigational medicinal products. Routines for the handling of investigational medicinal products shall be established, and the handling must be carefully documented and be traceable in the study documentation in the investigator's file.

It must be ensured that the right investigational medicinal product in the right quantity is delivered to the right person. These products must not be left in the mailbox, outside the door or similar. Deliveries must meet the requirements specified for storage of the product. It may also be appropriate for the trial site to follow up with the subject after delivery (for example by telephone) to ensure that the investigational medicinal product has been received.

Computerised systems +

What are the requirements for the computerised systems used for data collection/handling in a decentralised clinical trial?

It is sponsors responsibility that the computerised systems used for the collection and/or handling of data in a clinical trial are, based on a risk-based approach, validated for the purpose and meet the requirements of ICH GCP(R2) 1.65 and 5.5.3 including Addendum.

Related information

EMA:s "Guideline on computerised systems and electronic data in clinical trials"(https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-electronic-data-clinical-trials_en.pdf)

EMA:s "Notice to sponsors on validation and qualification of computerised systems used in clinical trials"(https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf)

EMA:s Q&A (GCP matters), questions 8 och 9(https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp)

Monitoring +

How are decentralised trials monitored?

The sponsor must decide for each individual clinical trial on the scope and type of monitoring based on a risk-based approach.

Performing remote monitoring has been brought to the fore with the COVID-19 pandemic. According to the Patient Data Act, direct remote access to the patient's electronic medical record is currently not permitted in Sweden which means that on-site monitoring (at least to some extent) is required for all trials.

DCT in EU

Swedish MPA is represented in the EU-group that in December 2022 published "Recommendation paper on Decentralised elements in clinical trials". The paper is created as part of ACT EU and aims at a harmonized approach to DCT within EU. The document can be found at the EU-commission webpage Eudralex.

EudraLex - Volume 10 (europa.eu) >

(https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en#set-of-documents-applicable-to-clinical-trials-authorised-under-regulation-eu-no-5362014)

Advice from Swedish MPA

In addition to scientific advice, MPA provides regulatory advice with regards to decentralised elements in clinical trials.

Project conducted

During 2020-2021, the Swedish Medical Products Agency carried out a feasibility study and a subsequent project about decentralised clinical trials. The project aim was to establish conditions for how clinical trials can be carried out decentralised in Sweden. Five clinical trials with decentralised elements were included as pilots in the project. Below follows information about the elements approved by the Swedish MPA and the experience that sponsors, investigators and other study staff have shared. The pilots represent all clinical trials phases and both academic and commercial sponsors. Indications include diabetes, COVID-19, and breast cancer et cetera.

The decentralised elements in one or more of these trials include:

- remote electronic consent
- home sampling administered by the patient himself

- remote visits within the framework of the trial
- medical device solution to capture symptoms of possible side effects
- distribution of investigational medicinal products
- medical device solution to register compliance to treatment.

Trial 1

In this register-based interventional clinical trial, there are various ways in which subjects can be included. To increase the inclusion rate and enable patients who, for geographical reasons, would otherwise not have been able to participate in the trial, the option of remote consent process, inclusion and randomisation is available. The investigator has a video conversation with the patient and, using an electronic tool, the consent document can be signed by the subject via Swedish BankID and by the investigator with his/her SITHS card (an e-identification system within the healthcare).

Health centres across the country may be involved in different ways. Some health centres that, for example, do not have the resources to be involved in clinical trials, may find suitable subjects and ask if the patient would like to be contacted by a study coordinator from the trial site in Uppsala that uses video meeting for inclusion and consent. The study coordinator will then provide details of the trial by telephone and send a link to the subject information document and, if the patient is still interested in participating, can arrange a video meeting with the investigator. In these cases, the health centre can provide the investigator with the data (from samples and physical examinations) needed for inclusion. The study coordinator report that it may take some extra time to check that all data are being reported from the health centres. Their experience is that these subjects are positive about taking the samples when visiting their regular health centre.

Other health centres participate as independent trial sites.

The idea behind the electronic consent tool is that it should be compatible with the systems used in all health care regions and free of charge for academic researchers to use. The tool will be further developed with new functionalities. For example, the subject will be able to access his/her copy of the signed consent document directly in the system in the future. Other types of e-identifications may also be included in the system.

Trial 2

All subjects in the trial, regardless of the randomisation arm, receive their medication in a bottle whose lid registers each time it opens. The investigator explains that they put this lid on at the first visit and that it is easy to handle in practice. The aim is to see patient's compliance with the treatment with the assumption that an opened lid correlates with the subject taking their medication, as well as to help with accountability.

Data from the lid is transferred to a database and a signal is sent to the investigator if the frequency of the lid opening deviates. The investigator emphasizes the positive aspect of being able to contact the subject if it appears that he/she is not taking the medication. The subjects seem to see this as a service rather than that it would be a feeling of being watched. To gain a deeper insight into the patients' experience, a separate sub-study is

ongoing in which a researcher uses qualitative research methodology with in-depth interviews with some of the subjects involved in the trial.

Both the investigator and sponsor emphasize the importance of new technology that is being introduced to be robust and that subjects are well informed about how the technology works. In this case, connectivity to a network where the subject is located, which is required for the lid to send data, may be limiting.

The trial also includes an app for subjects to use. It is voluntary to use and, in addition to information about the study and contact details, contains quality-of-life aspects and questions about symptoms and events. Based on what is reported through the app, an email and a notification are sent to a portal where study staff have access to the reported information. The sponsor is using this app as additional information and sees it as a way to gain experience for using similar data collection methods in future studies.

There is technical support linked to the lid and the app. However, in the sponsor's experience, there are often other issues related to the study and treatment at the same time as the technical issues. Therefore, it is important to keep the study staff involved in this contact with the patients.

Trial 3

Screening and the first visit in the clinical trial take place at the trial site, where the subject meets the investigator and other study staff. At this point the subject is screened, and at the second visit the first doses of the investigational medicinal products are administered and the subjects are trained to use the blood glucose meter and app, linked to a telemedicine platform, which the subject will then use from home.

For the following study visits, the subject visit the treating physician, who performs physical examination and treatment based on routine care. The investigational medicinal products are approved and used according to the summary of product characteristics. The subject can choose between having the intramuscular investigational medicinal product administered when visiting his/her treating physician or by a nurse from, for example, a health centre who comes to the subject's home. In both cases, the trial site sends the investigational medicinal product to the subject's home. This is done via the courier with whom the region has an agreement. It is important that the storage conditions for the medicinal product are met with throughout the entire chain.

The investigator points out the importance of interaction with the treating physician, who is not a co-investigator in the study, and that the division of responsibilities between them is established. When reporting adverse events, the subject has the option of sending photos of, for example, skin rashes via the app for assessment by the investigator. The investigator also has the option of contacting the subject via the app and follow up with a video call.

During the clinical trial, subjects measure their blood glucose levels and, to avoid errors when entering these values, they take a photo with their mobile phone of the display and upload it to the app. The sponsor is interested in how subjects perceive the decentralised design of the trial and therefore, with the help of the app, the subjects will be able to answer questions about this on several occasions during the trial.

This hybrid trial ends with the subject, after a series of remote visits, meeting the investigator again at the trial site for the final visit.

Trial 4

As the trial did not start in Sweden, the following case includes a description of the approved decentralised elements in the protocol and the experience from the planning of the study.

Some trial sites planned the informed consent process as a traditional study visit. In addition, one trial site planned to conduct the consent process electronically using a platform that uses Swedish BankID as a signature.

The sponsor emphasizes the importance of a process log for on-site consent, as consent can be obtained in different ways. To obtain electronic consent, the subject receives a link with the subject information and, prior to signing, the subject and investigator are in direct contact via a video link.

The trial involves a number of visits that can be carried out in different ways: at the trial site, at home (by the trial site staff or other healthcare provider) or digitally. The sites chose different procedures depending on their respective circumstances. Offering subjects the opportunity to either participate via traditional visits to a trial site or in a decentralised approach is something that the sponsor is looking favorably on for future studies.

The first study visit, which includes screening and physical examination by a medical doctor, was planned to always include the participation of the investigator. That is, in the cases where the external healthcare provider (with a medical doctor) visits the subject's home, the investigator would participate via video in this first study visit. The sponsor states that this approach is resource-intensive but necessary.

The following home visits includes a nurse from the external healthcare provider who handles the investigational medicinal products and sampling. The healthcare provider has the option of contacting staff at the trial site 24 hours a day. Staff from the healthcare provider should communicate any adverse events and serious adverse events to the investigator via telephone or video call at the end of the home visit. All home visits must be reported within 48 hours. All visits are booked from the trial site and the external healthcare provider does not make any medical decisions, which facilitates the investigator oversight of the study. All staff involved are trained in the study and in ICH-GCP.

Visits with no physical examination were planned to be conducted by telephone or video by a nurse. Video may be preferable if, for example, the subject wants to show something. These video visits take place either via an app or via the clinic's own channels (for example Swedish Vårdguiden).

Trial 5

A study nurse sends the possible subject a link to the patient information and books a video meeting for the subject to meet the investigator. During the video meeting, the investigator can start an electronic consent system that allows the investigator to sign only after the subject has given his/her informed consent. Both the subject and the investigator electronic signatures are given using Swedish BankID.

As the time frame for study screening was tight, it was an advantage to be able to set up this video meeting as soon as both study subject and investigator were available and that the subject did not have to come to the clinic.

If the subjects want additional time to consider about their participation in the study it is possible to schedule another video meeting between the investigator and the subject. It is also possible for the subject to sign the informed consent at a later date but doing this via another video meeting may be preferable, as follow-up questions often arise.

A study nurse from the trial site conducts a home visit and administers the investigational medicinal product, and train the subject how to fill in a diary via an app. An assistant nurse from the trial site makes home visits for sampling. All study staff are trained in both the study and ICH-GCP. The investigator believes that he/she is able to keep the oversight of the study as the visits are clearly scheduled.

A study nurse has a follow-up telephone meeting with the subject. The investigator assesses all adverse events, but there is no continuous follow-up of the diary as it was not considered necessary from a risk perspective for this study.

Study staff use a tablet both to enter medical records and to complete the CRF (case report form) directly at the subject's home.

Representatives of the sponsor summarise that some logistical planning was required regarding the home visits and sample handling. For example, it becomes a little more complicated to handle equipment for samples in a place other than the trial site where procedures already exist. However, it is understood that subjects find the home-visit approach effective. It was clear already in the pre-screening phase that all interactions would take place digitally or at home, which reasonable meant that only those who were positive of such a setup were likely to be interested in participating in this study.

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