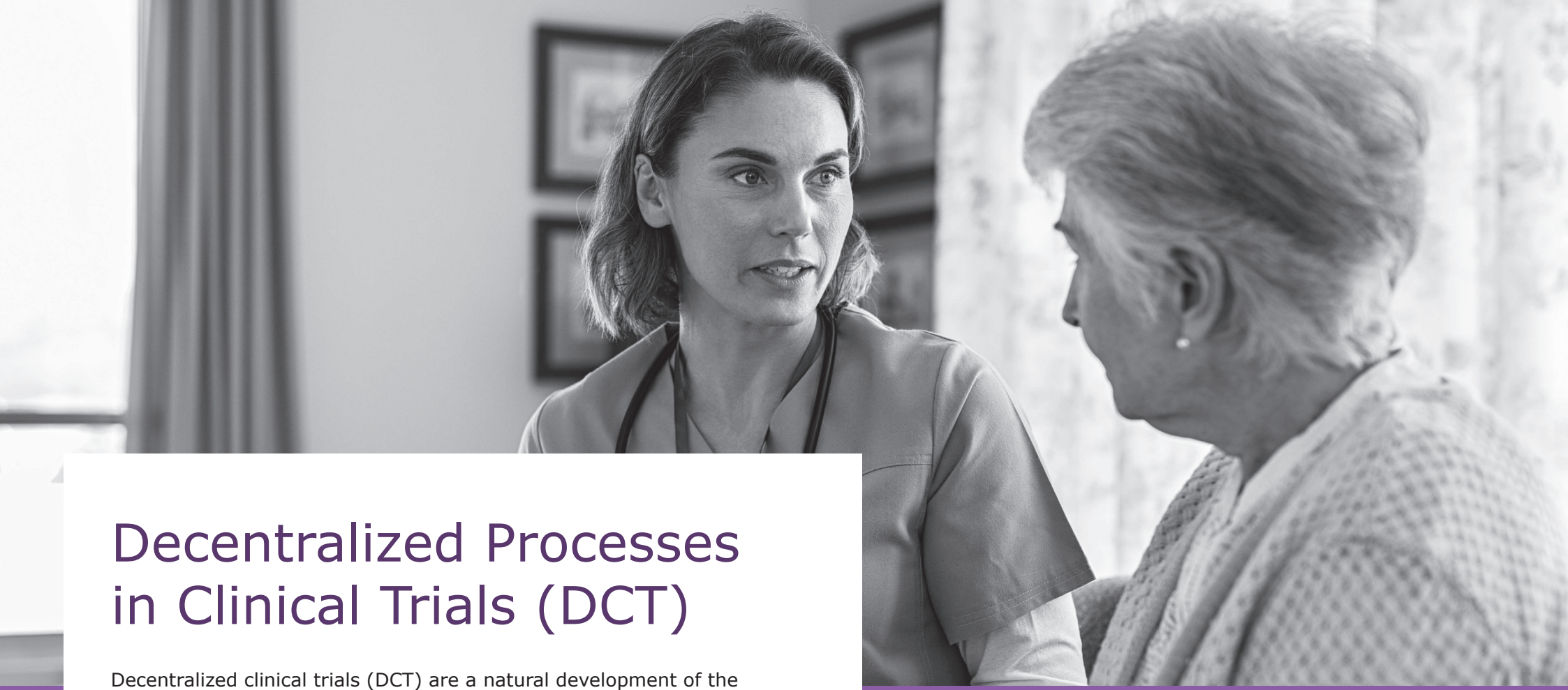


Decentralized Processes in Clinical Trials (DCT)

Decentralized clinical trials (DCT) are a natural development of the methods we already use in clinical trials of medicines. This means that patients do not have to visit the trial unit to the same extent or in some cases not at all.

Knowledge base from the DCT working group with representatives from Uppsala Clinical Research Center, Region Stockholm and the pharmaceutical industry.

Table of Content

Abbreviations/Glossary

AE – Adverse Event

CTIS – Clinical Trial Information System

CRF – Case Report Form

DCT – Decentralized Clinical Trial

DTP – Direct to Patients

eConsent – Electronic informed consent

eCRF – Elektronic Case report Form

EU-CTR – European Clincal Trials Regulation

GDPR – General Data Protection Regulation

Home Nursing – When mobile healthcare team/staff visit trial patient at home

ICH-GCP – International Council for Harmonization – Good Clinical Practice

PI – Principal Investigator

RBC – Regional Biobank Center

SAE – Serious Adverse Event

TMF – Trial Master File

Introduction

Clinical drug trials are dependent on patients and subjects wanting and being given the opportunity to participate. Therefore, the trials need to be made available to as many people as possible, while ensuring scientific robustness and resource and cost efficiency.

In traditional clinical trials, it is often challenging that all participants are required to visit the trial unit, sometimes on multiple occasions.

Decentralized clinical trials (DCT) are a natural development of the methods we already use in clinical trials of pharmaceuticals. For example, in a DCT patients do not have to visit the trial unit to the same extent or in some cases not at all.

Incorporating decentralized elements into clinical trials has the potential to facilitate and improve implementation, enabling choice and flexibility for patients and investigators. Decentralization helps participants adapt a clinical trial to their own lifestyle. Advances in technology, IT maturity and digital infrastructure mean that today there are good opportunities for decentralizing parts of clinical trials.

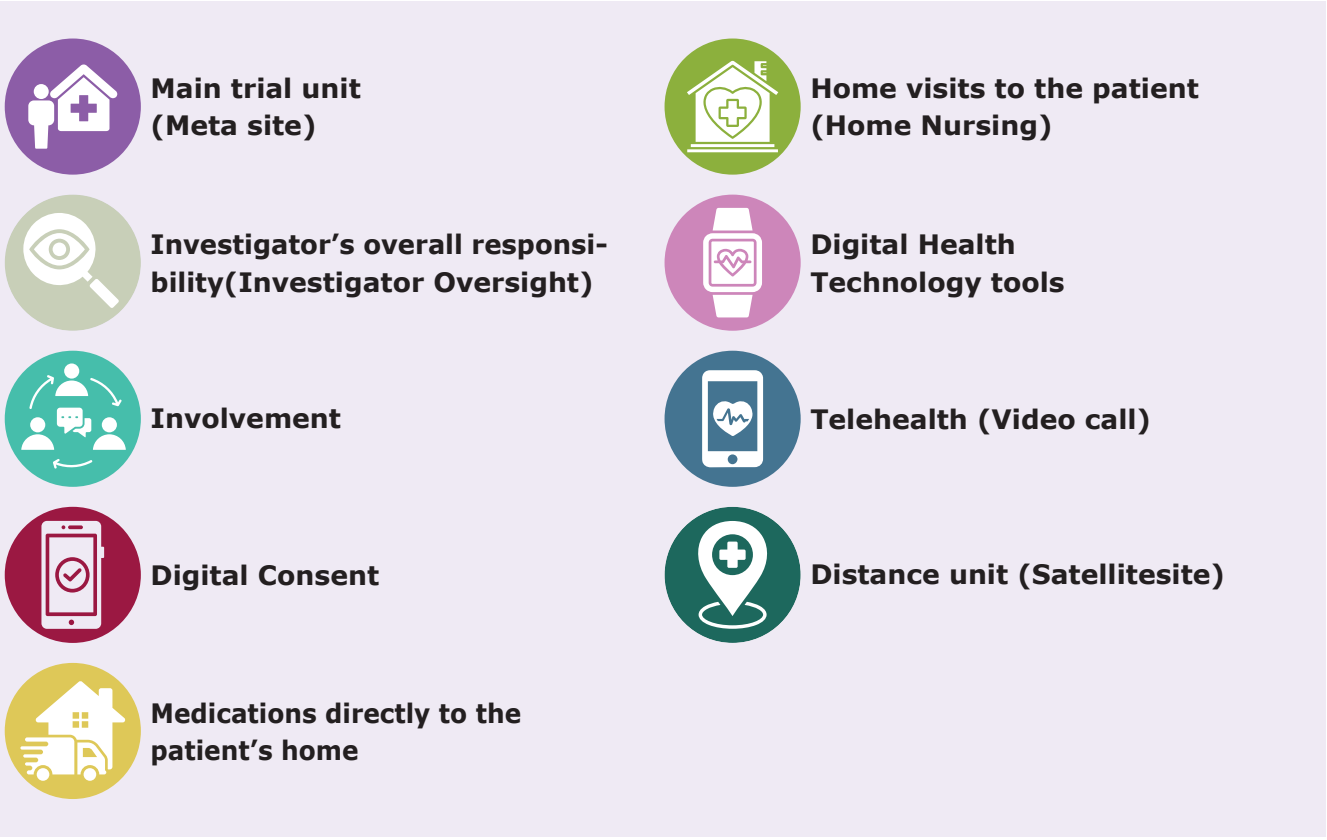
The fact that precision medicine is becoming increasingly common, where trials are often conducted with relatively few patients with rare health conditions, is one reason for the increased need for DCT elements in the trials. Increasingly avoiding long time-consuming journeys can facilitate the recruitment of patients. In a large sparsely populated country like Sweden, there are special benefits if some or all elements of a trial can be conducted remotely.

A decentralized trial is defined by pharmaceutical authorities in Sweden and in other countries as a clinical trial that has activities that are performed elsewhere than the traditional trial site. In a decentralized trial thus, not everything needs to be done remotely. In many decentralized trials, at least some visit will likely still take place at the clinic.

A key issue is to assess the benefits, opportunities and challenges of DCT compared to DCT and a hybrid with traditional trial and DCT elements may be the possible solution.

This is also crucial for the selection of and requirements for the Principal Investigation Unit, as well as the ability to ensure the investigator's overall responsibility (PI oversight).

In this knowledge base, we refer to the activities within a trial that can be performed remotely as DCT elements. Common elements are:



in Sweden to use any of the DCT elements. However, it is important to have a good knowledge of current regulations, especially around digital management and sharing of data, for DCT elements to be used correctly and safely. Since relatively little practice is established in the field of DCT, it is especially important that elements that differ from traditional trials are described in detail in study protocols and applications. This is to make it easier for authorities to assess new approaches when evaluating DCT.

The contributors to this knowledge base have extensive experience working with clinical trials. We also have experience with implementation of various DCT elements in clinical trials. Our working group includes representatives from academia, healthcare and industry. We have deliberately chosen to write in this document about clinical trials that include individuals with a specific diagnosis and a trial medicine. But the concept is of course applicable even to clinical trials that include healthy individuals. In addition, the concept can be applied to other studies that are non-trials.

DCT is an area that is developing rapidly and our purpose with the knowledge base is to provide support to relevant actors with different roles in clinical trials. Sweden is well placed to develop into a leading country for trials with DCT components, and such a development can also increase attractivity for international research investments. The knowledge base should be seen as a current summary of our experiences and has no claim to be comprehensive.

In our effort to make this knowledge base as readable as possible and at the same time use accepted concepts and be consistent, we have chosen to use this vocabulary:

- Clinical trial/trial: Most things that relate to DCT are usually relevant also for other types of clinical studies.
- Patient: In the knowledge base, this includes all types of research subjects/subjects.
- Hospital/clinic/caregiver: This also encompasses research centers that do not conduct care outside of research.

The knowledge base describes in the following the different DCT components mentioned above and what different actors need to consider when DCT components are used in a clinical trial.

Working group knowledge base DCT

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Main trial unit (Meta Site)

A main trial unit means a central trial center that can conduct a clinical trial remotely regardless of where the trial patient is physically located. This includes offering digital solutions for recruiting trial participants, distributing the trial intervention (drug, medical device, etc.) to the trial patient, monitoring, collecting data and communicating with trial participants remotely.

The trial unit should strive to have dedicated project managers, trial coordinators and data controllers with DCT competence. The trial unit should, in collaboration with the sponsor, develop standardized processes for DCT, including the use of digital/technological systems (either internally within the meta site or through an external system provider), risk mitigation strategies, and contract templates for home visit personnel, remote laboratories, home delivery of investigational medicinal products, and other DCT components.

The DCT planning phase

The main trial unit and the principal investigator must agree that the trial design, including any planned remote visits such as video calls, sample collection/measurements, data collection, and communication channels, is sufficient to ensure patient health and safety, as well as the required level of investigator oversight during the course of the trial. The DCT elements must be clearly

described and justified in the protocol. The risk/benefit evaluation for the selection of DCT should be clearly described.

The sponsor's and the principal investigator's responsibility

The same responsibilities for the sponsor and the principal investigator apply in DCT as in traditional trials, in accordance with the Swedish Medical Products Agency's information on EU Regulation 536/2014 (Clinical Trials Regulation, CTR).

This means that in a DCT it can be extra important to ensure the investigator's overall responsibility, as well as processes for safety reporting and follow-up including role distribution. Furthermore, a documented distribution of responsibilities between the meta site, satellite sites, home visit staff and other trial personnel is needed.

A communication plan must be in place between the principal investigator, the meta site, any satellite sites, and other trial personnel (such as home visit staff) who interact with trial participants, as well as a clear allocation of responsibilities and, when necessary, communication channels between the main trial unit and the participant's regular general practitioner/treating physician.

Safety reporting

- PI is (as in traditional trials) responsible for
  - Evaluation of potential (S)AE
  - Documentation of (S)AE in eCRF
  - SAE reporting to the sponsor within the required time frame
- Participants report AE to the main trial unit during scheduled contact or ad hoc by directly contacting the website or systematically through questionnaires
- All trial personnel may capture relevant information that must be made available to PI. This applies to all obvious (S)AE that, for example, occurs during trial visits at home or participants who spontaneously report an (S)AE during the home visit.

Checklist

- Ensure the overall responsibility of the investigator
- Processes for safety reporting and follow-up
- Documented distribution of responsibilities between the meta site, satellite sites, home care
- Communication plan between all parties involved
- Distribution of responsibilities and communication routes between the main trial unit and the regular treating physician

References

https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/medicinal-products-for-human-use/clinical-trials-regulation-eu-536-2014/sponsor-and-investigator

Investigator's overall responsibility (Investigator Oversight)

All visits and procedurs during the trial are primarily the investigator's responsibility – also in decentralized trials. This is usually called investigator oversight and means that the investigator has overall responsibility for everything that happens in the trial. You must be able to show that the investigator takes their overall responsibility and therefore all activities that relate to this need to be documented.

In decentralized clinical trials, it becomes especially important to have a plan for investigator oversight. Partly because much of the performances in DCT differ from traditional trials and partly because the patient less often or not at all visits the trial unit and physically meets the investigator.

If home visits are used or the patients are to visit a distance unit, the investigator retains overall responsibility for these as well. It is reasonable to expect a greater time commitment to ensure and document investigator oversight in DCT, until more routine procedures are established for DCT elements and as more parties become involved in the trial.

Checklist

- Clear agreement and communication between the principal investigator and staff carrying out home visits
- Contact between the trial unit and the home visit staff prior to each home visit
- Trial unit available, by phone or video call for home visit staff during ongoing home visit
- Source data collected during home visits as soon as possible available to the trial unit
- If AE/SAE is suspected in connection with home visits, the investigator should be contacted as soon as possible for initial assessment

Involvement

In DCT, early involvement is particularly important, as patients, healthcare providers, and other stakeholders can actively participate in the planning of the trial, for example in the selection of the meta site or medical devices. Within DCT, it is particularly important that patients are involved in the use of digital platforms for reporting symptoms, conducting surveys and virtual visits. This is particularly important given that some responsibility will be placed on the individual patient. Therefore, it should be easy for patients to do the right thing. This promotes patient-centered research, increases access to clinical trials and improves implementation.
To involve healthcare providers effectively in DCT the following measures might be taken:

- **Training and information:** Provide healthcare providers with the necessary training and information on the current trial, including trial protocols, patient criteria, treatment methods, goals and follow-up procedures with a particular focus on DCT components. Inform them of how they can identify and refer potential participants.
- **Clear communication:** Ensure that there are established communication paths and regular communication between the trial team and healthcare providers.
- **Collaboration:** Create a collaborative environment where healthcare providers feel involved and valued in the conduct of the trial. Discuss their views and experiences in order to improve the trial's implementation.
- **Resources and support:** Provide the necessary resources and support to healthcare providers to facilitate their participation in the trial, including access to technical platforms, patient education materials and support from the trial team.
- **Feedback and follow-up:** Gather regular feedback from healthcare providers about their experiences and challenges after the start of the trial. Use this information to improve the process and maintain engagement.

By involving healthcare providers in an active and engaging way, you can ensure a smooth implementation of DCT and improve the quality of patient care and research.

Digital Consent

Electronic informed consent at a distance (Remote eConsent)

To be able to carry out a decentralized trial, where the patient is not physically present at the trial unit during recruitment, the informed consent must be obtained remotely. To avoid paper handling, the consent can be signed electronically.

When obtaining consent remotely, the same requirement applies as during a physical meeting: the patient must be properly informed and given the opportunity to ask questions. The investigator must be able to verify the patient's identity and assess whether the person has received and understood the information. Therefore, the visit is best done in a video meeting between investigator and patient. According to the Swedish Medical Products Agency, phone calls alone are not considered sufficient.

By using an electronic consent system, researchers can streamline the process of obtaining consent. It can also be more practical and convenient for the patient to give their consent electronically.

The requirement for the electronic patient information does not differ from what applies in traditional trials, but it is good to describe the DCT components included in the trial extra clearly.

Ensure that there is a process for archiving the electronic consents in a secure way for future review and compliance with laws and guidelines.

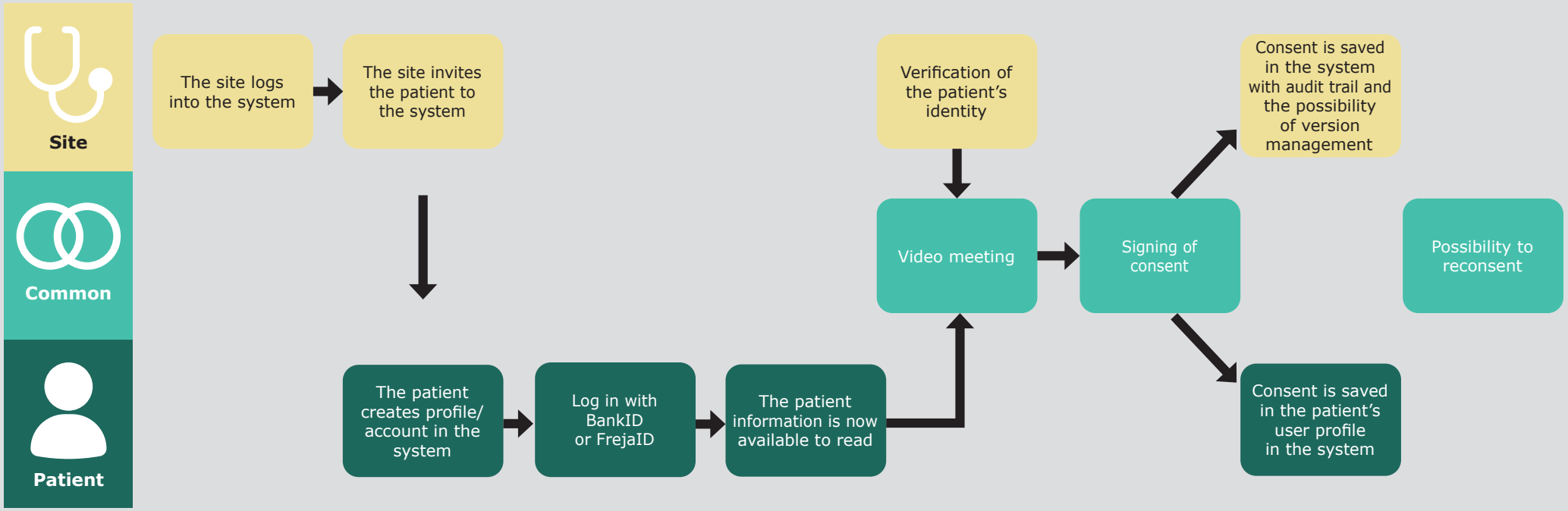
Selection of electronic system

It is the sponsor's responsibility to ensure that the electronic system to be used is appropriate and validated for the task, and that it complies with applicable laws and security requirements to protect participants' privacy and personal data.

It is common to use some form of trial platform where it is possible to set up a profile for the participant with personal information and unique login. There are several systems that handle signing of digital consents. The example below is from a system that our working group has experience using.

The patient's identity must be verified via BankId, Freja eID+ or two-factor authentication (i.e. both with personal password and a personal code generated with each login and sent by email or text message to the patient). This is to ensure that the consent and associated signature come from the correct person.

The video visit can take place in the same system as the signing of the consent, as a trial-specific platform, or in a separate system such as the hospital's medical record system.



Checklist

- Validated systems are required
- Identification of patient and investigator via BankID, Freja eID+ or 2 factor authentication
- Describe in the protocol how consent will be obtained electronically
- Phone calls are not considered sufficient. Video visits are required, this can be done in a separate system
- Signed consent must not be sent by email
- Archiving for 25 years!
- Important with version management

Medications directly to the patient’s home (DtP)

General

In Sweden, investigational drugs must be distributed via pharmacies. The sponsor cannot send the drug directly to the clinic or to the patient’s home.

It is sufficient to contract one pharmacy for the trial in Sweden.

There must be an agreement between the sponsor and the pharmacy, specifying and agreeing on quality and transport requirements based on the handling instructions for the investigational medicinal product.

Responsibility for investigational drugs at the trial site lies with the investigator/institution, according to ICH-GCP 4.6.1.

The general requirements for responsibility regarding medicinal products, as described in ICH-GCP 4.6.3, also apply when investigational medicinal products are shipped to the patient’s home, including documentation verifying which batch was shipped, the number of packages, delivery times, temperature conditions, etc.

At an early stage of the trial, it is important to contact the pharmacy to discuss the specific requirements for the investigational medicinal product and its storage conditions, as well as the pharmacy's ability to enter into an agreement with a transport company/courier for shipment. It is recommended that the pharmacy makes an agreement with the transport company/courier to avoid the sponsor being involved in the patient's contact details. The carrier/courier must be able to maintain the transport requirements and the patient's confidentiality and this shall be specified in the contract between the pharmacy and transport company/courier.

During the course of the trial

Examples of a direct-to-patient process for medicinal products in a trial:

1. The investigator prescribes the investigational medicinal product and other relevant medications in accordance with the local procedure at the trial site or the trial-specific procedure.
2. The trial coordinator orders the drug from the pharmacy
3. The pharmacy organizes transport to the patient's home with the help of the trial coordinator.
4. The pharmacy orders a courier and gives them the patient's address and contact details. The sponsor must not have access to the patient's address. The pharmacy ensures that the patient's details and the patient's confidentiality are upheld and this is described in the pharmacy agreement between the sponsor and the pharmacy.
    a. The pharmacy contacts the patient to organize the transport. This is done to ensure that the patient is at home when the shipment arrives.
5. If the patient is not at home when the shipment arrives, a backup option is discussed with each patient, for example, a relative. The backup plan should be in place for each patient.
6. The handling of the investigational medicinal product during transport and upon delivery, as well as its quality and quantity, will be confirmed by the home visit staff at the next visit before the patient begins treatment. If the patient handles the investigational medicinal product independently without any home trial visits, they must have received instructions on how to store the investigational product and on the applicable documentation requirements.
7. How returns can be handled if you use a mobile trial team for home visits: The home visit staff can perform drug accountability before returned medication is transported back to the pharmacy. The trial coordinator contacts the courier to retrieve the trial drug for delivery back to the pharmacy. If home visit staff are not used in the trial, the patient can return medication by courier or mail. It should be traceable mail.
8. Prescriptions for other drugs are handled electronically by investigators. According to common practice, electronic prescriptions are sent to all pharmacies that patients can visit and collect their medicines.

Document management

Drug accountability logs and documentation should be stored at the clinic and at the pharmacy for monitoring as the monitor cannot visit the patient's home due to confidentiality.

References

ICH-GCP (guidance for good clinical practice E6 (R2), EMA/CHMP/ICH/135/1995

EU-CTR 536/2014

HSLF-FS 2021:109

Checklist

- Agreement between Sponsor and Pharmacy
- Specify transport conditions and confidentiality in agreements
- Ensure that there is a back-up person for the patient who can receive medicines at home.
- Train any home visit staff and patient in the handling of investigational medicinal products
- Documentation according to ICH-GCP for investigational medicinal products also in the patient's home

Home Nursing

Home nursing here means that trial staff come to the patient at a location other than the trial site, usually in the patient's home. The staff who will perform the home visit may be the trial unit's own staff or a hired organization that specializes in making home visits to patients.

Before deciding to have home visits in the trial, a risk assessment must be carried out and documented. The benefits to the patient should be weighed against the need for and access to equipment and facilities, such as proximity to the trial unit or other care unit.

The process described below is an example of how this can be carried out in cases where trial staff not belonging to the trial unit have been engaged and are specialized in conducting home visits with patients.

Establish a written agreement between the trial unit and the organization that will make the home visits. The agreement must include, among other things, the allocation of responsibilities between the trial unit and the organization, communication channels, and assurance that the staff conducting the home visits possess the appropriate competencies (see Appendix 1 for an example of such an agreement). This agreement thus manages the cooperation between the trial unit and the home visit organization and contains no financial terms. An assignment agreement with financial terms is drawn up between the sponsor and the home visit organization.

Carrying out the home visits shall be delegated by the investigator to the home visit staff. These staff should be included on the delegation log where it should also be stated which tasks are delegated. The delegation log must be continuously updated as soon as any home visit staff is changed. A tip is to have one log per person to simplify when updating the log.

The home visit staff will carry out tasks that are specific to the trial and must therefore be trained on these tasks and the related parts of the trial protocol and GCP. Regardless of the tasks to be performed, the home visit staff must know what applies to routines for AE/SAE reporting.

Before any home visit is conducted, the home visit staff should meet with the staff at the trial unit to discuss the procedures to be performed at the patients' homes, the allocation of responsibilities, and how communication between the parties will be handled. Before visiting the patient, the home visit staff and the trial unit should be in touch with each other to coordinate. This may be relevant information about the patient that has emerged during scheduled video visits or other contact with the patient, and whether there is anything specific to consider before the home visit.

During the home visit, the trial unit should be available for contact. All activities and relevant observations shall be documented. This documentation constitutes the source data and shall as soon as possible be transferred to the trial unit. One option is that the home visit staff is connected to the same healthcare information system or trial platform as the

trial unit. If this is not possible, and the documentation is done on paper, it should be sent by regular mail to the trial unit as soon as possible. In such cases, it is advisable for the home visit staff and the trial unit to have a phone call immediately after the home visit to ensure that relevant patient information is not delayed before reaching the trial unit. Medical record entries and other identifiable patient data must not be sent by email.

If the home visit staff is informed by the patient of an AE/SAE, or if it is obvious to the home visit staff during the home visit, the trial unit should be contacted promptly. It should preferably be done during the ongoing home visit. The investigator must then contact the trial patient as soon as possible to assess AE/SAE. The same routines for reporting AE/SAE apply, of course, in DCT as in traditional trials.

An alternative to having healthcare personnel to conduct home visits could be to engage healthcare units located near the patient to perform tasks of a less specialized nature. These may include procedures such as blood sampling, blood pressure measurement, and similar. A healthcare provider with good coverage in the geographic area where trial participants are expected to be recruited could then be engaged (see also the section on Remote Unit/Satellitesite).

Things to consider when planning the trial

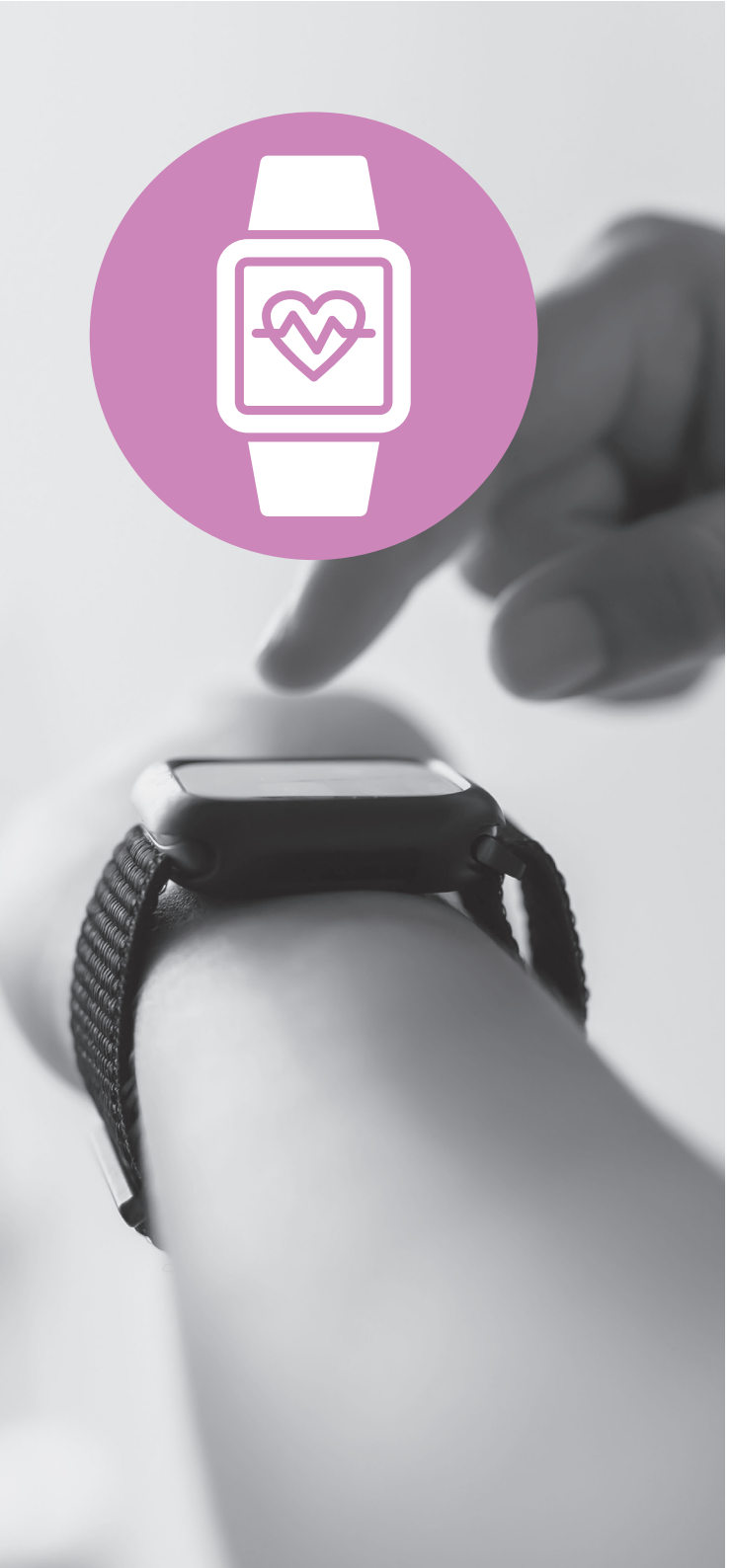
- Plan to have an open and clear communication between the trial unit and the home visit staff.
- The home visit staff is informed if there is anything specific to consider before each home visit.
- The home visit staff should be able to contact the trial unit before, during and after each home visit for information and to share relevant information about the patient.
- The home visit organization must have insured staff. PI must ensure that they assume this responsibility.
- Set up a process for how source data should be transferred to the trial unit and document the process.
  - This can be done by recording the visit notes on paper, which is sent by regular mail to the trial unit.
  - If the home visit staff and the trial unit are connected to the same IT platform, the home visit staff can enter visit notes in this, provided that the trial unit has full access to the notes. If it is described in the trial protocol, the easiest way is to enter the data directly into the eCRF.
- When visiting the patient's home, blood sampling is common. According to the Biobank Act, new samples are registered directly in the sponsor's biobank without the need for a biobank application to RBC or the healthcare provider's biobank. The sponsor is responsible for documentation and for ensuring compliance with the Biobank Act. For access to existing samples such as biopsies, the biobank application and biobank agreement with each affected biobank is required.

Things to consider at patient recruitment and conduct

- Inform the patient that healthcare professionals will visit their home, how many visits and what procedures will be performed at home.
- Ensure that the patient's home is suitable for the intended procedures.
- All visits during the trial are primarily the investigator's responsibility. The investigator's overall responsibility in the trial (Investigator oversight) must be ensured and be able to be proven.
- Have a clear and frequent communication with the home visit staff.
- The source data generated during the home visit should be made available to the trial unit as soon as possible.
- The patient may feel isolated when not meeting the staff at the trial unit in person. Therefore, allow the patient to contact the trial unit if necessary throughout the course of the trial, just as in all clinical trials.

References

Swedish Medical Products Agency on DCT: https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/medicinal-products-for-human-use/decentralised-clinical-trials EMA Q&A on GCP: https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/compliance-research-and-development/good-clinical-practice/qa-good-clinical-practice-gcp EMA Recommendation paper on DCT: https://health.ec.europa.eu/system/files/2023-03/mp_decentralised-elements_clinical-trials_rec_en.pdf)



Digital Health Technology tools

Digital Health Technology tools and communication tools are commonly used components in DCT to collect data without patients visiting the trial unit. When designing the trial it should be considered whether the technical solution brings any extra value to the participant in the trial or to the trial itself. And also considered whether the technical solution is suitable for the population in the trial and to answer the scientific question. These may include apps on a mobile phone or tablet, such as electronic diaries or questionnaires, or wearable measuring devices such as heart rate monitors.

It is important that the instruments are easy to use both for the participant and that there is good support available if needed. One risk with an overly complex technical solution is that the trial participant may become discouraged and avoid using it.

If an app is used, an agreement is required with the app developer regarding data sharing, how the data will be handled in the trial, and confidentiality of the patient's data. The sponsor is not entitled to have direct access to the data. All digital measuring devices must be validated and CE-marked for their intended use. If they are not CE-marked, a separate trial for the Medical Device may be required.

More information can be found on the Swedish Medical Products Agency's website for what applies to requirements for medical technical products and validation, etc.

Checklist

- Adapt the use of digital measuring instruments to the trial and the patient group.
- Ensure that the tools are also validated and CE-marked for the purpose
- Describe the data management in agreement with the technical solution provider(s)
- Ensure that there is support for the digital measuring instrumen

Telehealth (Video call)

Telehealth refers to video calls via mobile, tablet or computer where the parties can communicate with each other with both audio and video.

In general, one can say that video calls can always replace phone calls, but not vice versa, as the image of the the person you are talking to provides more information such as body language and facial expressions. For this reason, the collection of informed consent is not accepted in the case of telephone calls but may be accepted in the case of video calls.

The data transmission of audio and video must be secure. Major providers of video calling systems, such as MS Teams and Zoom, encrypts data transferred between the parties. If the trial unit routinely uses a system for video calls with its patients that meets the requirements for this, it may be preferable to use. Check whether the clinic or hospital has any guidelines for which systems may be used for video calls with patients. In industry sponsored trials, it is common for the sponsor to use a telemedicine platform, which must then be validated by the sponsor.

Video calls are primarily suitable for telephone follow-ups with the trial patients and during the consent process. Uncomplicated visual assessments can also be made, but is completely dependent on the requirements for these in the trial. Otherwise, the suitability of video calls are determined by the trial population, the type of medicinal product or medical device being studied, and the phase of development of the trial. If an AE/SAE is detected or reported by the patient during the video call, it must be assessed and documented. It is important that a video call is designed so that it does not pose an increased risk to the patient and the quality of the data collected compared to a physical visit to the trial clinic. If this is not possible, a physical visit to the trial unit, to another healthcare provider or home visit should be considered.

When patients are recruited in the trial, they need to be informed that visits will be made by video calls. It is also important to ensure that the patient has the appropriate equipment for video calls and knows how to use it.

The sponsor should be able to provide equipment if the trial patient is unable or does not want to use their own equipment. It is also beneficial if the patient is able to be in a suitable and undisturbed environment during the video call.

There are generally very few guidelines and recommendations when it comes to Telehealth. This is likely because follow-up phone calls have long been used in clinical trials, and video calls may be considered to have a similar function but with slightly expanded opportunities.

References

EMA recommendation paper:
https://health.ec.europa.eu/document/download/2ccc46bf-2739-4b9a-ab6b-6f425db78c61_en?filename=mp_decentralised-elements_clinical-trials_rec_en.pdf
EMA Guideline on computerised systems and electronic data in clinical trials:
https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-and-electronic-data-clinical-trials_en.pdf
Q&A: Good clinical practice (GCP):
https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-clinical-practice/qa-good-clinical-practice-gcp
Swedish Medical Products Agency:
https://www.lakemedelsverket.se/en/permission-approval-and-control/clinical-trials/medicinal-products-for-human-use/decentralised-clinical-trials

Distance unit (Satellite site)

General

To make a clinical trial accessible to patients who are geographically distant from specialized healthcare and to increase their opportunity to participate in clinical trials, visits to a distance unit, such as a primary care center or another healthcare facility, may be an option. The term ”satellite site” can also be used, but there is no actual definition regarding the concept of a satellite site. Cooperation between the main trial unit and the distance unit generally facilitates research activity, as more healthcare units in the country can participate in clinical trials and gain knowledge of new treatment opportunities.

According to the Swedish Medical Products Agency, visits to a remote unit are permitted if the sponsor can demonstrate that the conditions ensure that the efficacy and safety data collected will maintain the same quality as in traditional trial visits, and that patient safety is not compromised. An evaluation should be made as to whether the use of a distance unit is appropriate for the specific trial.

When a suitable distance unit has been identified, the specific trial activities that are appropriate to perform at the distance unit are determined in consultation between the sponsor, the patient, and the selected distance unit.

The distribution of work between the main trial unit and the distance unit has been described by Clinical Studies Sweden (kliniskastudier.se). We therefore refer to their work regarding how to set up and operate distance units, where most activities take place at the distance remote unit, but the main trial unit retains overall responsibility.

Examples of activities that can be conducted at a distance unit include follow-up visits, where deemed appropriate for the trial, dispensing of the investigational medicinal product, blood sample collection, and delivery of samples to the laboratory, as well as other examinations such as weight, blood pressure, etc.

Applications and implementation

It must be clearly stated in the protocol and in the patient information for the clinical trial that distance visits will be included as a component of the trial. New blood samples are registered directly in the sponsor’s biobank, the sponsor is thus responsible for documentation and for ensuring compliance with the Biobank Act. Principal investigators must show that they also have an overview of the distance unit. (ICH GCP 4.2.5).

Principal investigators who delegate tasks to a distance unit must ensure the correct execution of what has been delegated, and the quality of the reported data. (ICH GCP 4.2.6).

We recommend that the main trial unit set up a written delegation plan or a clear delegation from the responsible investigator (Clinical Studies Sweden has support templates for this).

The written plan/delegation must be kept in the investigator site file at the main trial unit and in the Trial Master File (TMF) at the sponsor. It should also be noted that the principal investigator had regular contact with the established distance units.

An agreement on compensation through a financial contract must be established either directly between the main trial unit and the distance unit, or alternatively, the sponsor may establish a contract directly with the distance unit.

If the investigational medicinal product is to be shipped between the main trial unit and the distance unit, there must be a description of the transport process for the investigational medicinal product between these sites. There must be written instructions on how to transport medicinal products, and the sponsor’s SOPs must also be followed in parallel.

In cases where the investigational medicinal product is stored at the distance unit, a clear work instruction must be in place describing how the investigational medicinal product is stored, how any temperature logs are to be completed, as well as reporting pathways and a backup plan in the event of deviations or unforeseen incidents. If a pharmacy manual is available for the trial, it must be followed.

Training and maintaining documentation

Staff at the distance unit must have formal and real competence to perform the tasks required

for the specific trial. The staff specified in the delegation list must undergo training required for the trial and it is the responsibility of the principal investigator and sponsor to ensure that this is complied with.

The usual record-keeping regarding the patient's visits to the distance unit shall be carried out. The written job description from the main trial unit shall specify which trial documentation is expected to be maintained for the trial.

The distance unit shall, in accordance to GCP, report any AE/SAEs to the main trial unit if they become aware of such an event (see safety reporting under the section Meta Site).

Documentation shall be stored at the main trial unit, and, to a certain extent, also at the distance unit. Depending on the tasks and investigations carried out at the distance unit, the following documents may, if necessary, be available on the distance unit:

- Protocol and any amendment
- Regulatory approval and biobank approval
- Investigators Brochure or SmPC
- Delegation Log & Source Data Location List
- Documentation on sites' processe (SOPs) or job descriptions
- Drug accountability logs + temp logs
  - Requisitions of medicines
- Required system manuals
- Relevant correspondence

Monitoring and close out visit

Whether monitoring visits and close out visits are required at the distance unit depends on the scope of the investigations carried out and any storage of medicines at the distance unit.

The Sponsor shall comply with regulations and the internal requirements in the Sponsor's SOPs, as well as the monitoring plan established for the trial.

Checklist

- Satellite site can be used if the specific trial is suitable for this and that this has been preceded by a discussion between the parties concerned.
- Ensure that the patient feels comfortable making certain visits to the distance unit.
- Check that remote visits are described as an opportunity in the protocol and in the patient information and that approval has been obtained from the authorities.
- Ensure that the distance unit has received the training they need to carry out their tasks and that they have the necessary equipment, and that delegation from the main investigator has been made.
- The distance unit must know what to document within the framework of the trial.
- Reporting and contact channels between the distance unit and the main trial unit must be clear and well defined.

References

ICH: E 6 (R2): Guideline for good clinical practice – Step 5 (europa.eu)
Clinical Trials Information System | European Medicines Agency (europa.eu)
Decentralized clinical drug trials | The Swedish Medical Products Agency (lakemedelsverket.se) Clinical drug trials | Clinical Studies Sweden
Research guide – Biobank Sweden – Biobank Sweden

Appendix 1

Example of agreement between trial unit and mobile care giver

between **Trial unit**
with Principal Investigator

and **Mobile care provider** (hereafter referred to as" Provider")

The Trial unit and Principal Investigator have been engaged by the Sponsor, to conduct the study "Study title" with the protocol number xxxxx. Provider has been engaged by Sponsor to support The Trial unit and Principal Investigator in delivery of the study.

Provider and the Trial unit shall perform tasks set forth in this Delegation Agreement in accordance with Good Clinical Practice, applicable laws and regulations and the Clinical Trial Protocol. Principal Investigator authorizes Provider to assume the study tasks listed below, for which Provider and Provider's staff are qualified by training, education, and experience.

Tasks to be carried out by Provider and The Trial unit:

The Trial unit	Provider
Request patient visits by provider in accordance with agreement with the participants	Schedule off-site visit with participant and inform the Trial unit
…	Perform and communicate Handover visit with the Trial unit
…	Perform trial assessments
…	…

As observed during the visit, Provider staff shall, in accordance with the Protocol, alert the Principal Investigator (or medical designee) of any observed changes to the trial subject's health, safety, and any observed or trial subject-reported Adverse Events, Serious Adverse Events, Serious Adverse Drug Reactions, and Unexpected Adverse Drug Reactions, as these terms are defined in ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R2) (ICH GCP). Provider staff shall be available to communicate directly with the Principal Investigator (or medical designee) in the event of safety or any Adverse Event or Adverse Drug Reactions reporting.

Provider will adequately document the activities conducted at the study visits and source documentation will be provided to The Trial unit to be part of The Trial unit's source documents. Source documentation should comply with ICH-GCP requirements and be attributable, legible, contemporaneous, original, accurate, and complete.

Provider shall report to The Trial unit any protocol deviations or potential serious breach incidents.

Principal Investigator shall always retain all responsibilities regarding identification, classification, assessment, documentation, and reporting of all safety issues, and all safety events, including Adverse Events, Serious Adverse Events, Serious Adverse Drug Reactions and Unexpected Adverse Drug Reactions, as these terms are defined in ICH GCP and required to be reported as per applicable regulations, ICH-GCP, and the Protocol.

Principal Investigator understands and agrees, that delegation of these tasks to Provider, in no way alters the responsibilities of the Principal Investigator for this study as defined by ICH-GCP.

Provider accepts delegation of these tasks and agrees Provider and Provider's staff will conduct the tasks as directed by Principal Investigator and in accordance with this Agreement, the Protocol, all applicable laws, industry standards, regulations and guidelines including ICH GCP, and data protection regulations for the duration of the study. Provider agrees that Provider staff are qualified by training, education, and experience to conduct these tasks. Provider staff will provide their CV, documentation of qualifications, training, and experience to The Trial unit on request.

Provider retains responsibility for any liability related to professional malpractice or individual misconduct resulting in damage to the trial subject. Provider acknowledges that an insurance policy is in place to cover any potential damages to the trial subject. Such insurance policy can be provided upon request by The Trial unit.

Provider acknowledges that all payments for services rendered as a result of this agreement are to be paid by Sponsor and, therefore, The Trial unit will have no financial obligations with Provider under the Terms of this Agreement.

Trial subject's confidentiality shall be maintained in accordance with applicable personal data protection regulations, ICH-GCP and the clinical trial informed consent form.

The Parties shall otherwise comply with the confidentiality and data privacy provisions concerning Sponsor and/or trial subject information as provided for in the respective Clinical Trial Agreement.

ACKNOWLEDGED AND AGREED:

THE TRIAL UNIT:	PROVIDER:
Name:	Name:
Title:	Title:
Signature:	Signature:
Date:	Date:
Name:	Name:
Title: Principal Investigator	Title:
Signature:	Signature:
Date:	Date:

Appendix 2

PI plan for overseeing the conduct of the clinical study at the satellite sites.

- The PI needs to prepare a plan for overseeing the conduct of the clinical study at the satellite site(s).

The plan addresses:

- Storing and transferring of study documents, Investigational Medicinal Products (IMP), Non-IMP and medical devices, and supplies
- Communicating information in a timely manner (e.g., notification of screened/randomized study participant, faxed and mailed lab results from the Central Laboratory, safety events, updates, and clarifications)
- Handling/shipping laboratory specimens
- Attending to clinical emergencies (e.g., notifying PI, obtaining unblinding information, communicating with the study participants)
- Any other study specific information

Appendix 3

Example of delegation to describe that PI has an oversight of the satellite site

- By this Agreement, the Principal Investigator (PI), XXX, delegates specific tasks to YYY, who will act as a Designated Satellite Investigator (DSI) at Hospital XXX.
- The DSI, YYY, will maintain a separate delegation log at Hospital XXX and will further delegate tasks to their designated investigational staff as appropriate.
- The PI, XXX, and Hospital XXX will be responsible for the overall oversight of the study at the Satellite Site, as well as for all study activities conducted at Hospital XXX. This responsibility will include, from Day XX to Day XX, YYYY, during the conduct of the study, ensuring oversight of subject eligibility, providing training, leading, and supervising the investigational staff at the study site, as further described in the established Clinical Study Agreement with the Sponsor.

Biographies

Mats Thoring

Pharmacist who have worked within clinical trials since the mid-90s. Has led Bayer's clinical trials organization in Scandinavia for 16 years. He has been involved in the planning and initiation of decentralized trials, participated in Bayer's project to develop DCT, is a member of a working group within IMI Trials\@Home, has contributed to the Swedish Medical Products Agency's DCT project, and has served as a stakeholder for EMA in the development of the Recommendation Paper on DCT. Now he works with supporting Bayer trial professionals around the world to implement projects with DCT components

Sandra Funning Schedin

Pharmacist with 16 years of experience working in the pharmaceutical industry, primarily in clinical trials. Now she works as a project manager and is responsible for the review of trials within Clinical Operations at Roche AB in Sweden. Has experience in planning and applying for approval of a fully decentralized oncology trial in Sweden, and through this, along with other trials involving decentralized elements, she has gained her experience in decentralized trials.

Gabriella Seger

Nurse who has worked with clinical trials and medical devices at various trial units in Sweden for about 20 years. She has worked in several trials where use has been made of one or more DCT solutions. Her current work is as a Clinical Research Associate and Study coordinator at the Uppsala Clinical Research Center where she works with clinical trials and DCT projects.

Anna Åhlander

Nurse who has worked with clinical trials at Region Uppsala and Uppsala University for about 10 years. She has worked in various roles in a number of trials where use has been made of of one or more DCT components, including one of the pilot studies included in the Swedish Medical Products Agency's DCT project. For two years, she has worked as a Clinical Project Manager at the Uppsala Clinical Research Center (UCR) with a focus on trials with DCT elements.

Susan Öman

Nurse with a past at Karolinska University Hospital Huddinge as a research nurse. Works at Sanofi AB with clinical trials for 24 years. Has held various positions within clinical trials and currently leads a team of 11 project managers responsible for running Sanofi's trials in the Nordic and Baltic countries, where DCT components are playing an increasingly important role. Today, one or more DCT components are included in all clinical trials that Susan works with.

Elham Hedayati

Associate professor and consultant in oncology at Karolinska Institutet and Karolinska University Hospital. Clinical researcher who early on established an independent line of research focused on personalized breast cancer treatment and trials investigating side effects and long-term complications of conventional breast cancer therapy. Chairman of phase 1 units at Karolinska University Hospital, and chairman of the Council for Good Clinical Research Practice at Karolinska University Hospital. Founder of True Dose AB.

Jonas Oldgren

Professor in coagulation research and consultant in cardiology at Uppsala University and Uppsala University Hospital. Has conducted clinical and randomized trials in cardiovascular diseases, with grant support from the Swedish Research Council (VR), the Swedish Foundation for Strategic Research (SSF), the Swedish Heart-Lung Foundation, and the NIH, or in collaboration with the industry. Head of the Uppsala Clinical Research Center (UCR) 2014-2022, currently general secretary for clinical research at the Swedish Research Council. Aims to enable more patients to participate in clinical trials through the development of pragmatic trial designs such as DCT, in order to reduce resource requirements and workload for both patients and investigators, while maintaining quality.

Decentralized Processes in Clinical Trials

Decentralized clinical trials (DCT) are a natural development of the methods we already use in clinical trials of drugs. This means that patients do not have to come to the trial unit to the same extent or in some cases not at all.

Knowledge base from the DCT working group with representatives from Uppsala Clinical Research Center, Region Stockholm and the pharmaceutical industry.