Aspects décentralisés et dématérialisés des recherches

Colloque CNCP Toulouse Juin 2023

Claire Bahans

European Medicines Regulatory Network (EMRN)

DCT recommendations published in Eudralex Vol. 10: – CTR, Q/A and other CT guidance documents
'EMRN' document

European Commission
Regulations, Directives and guidances
- CT: EudraLex Volume 10

CTEG and CTAG (clinical trials experts)
Medical Device and IVD area
…

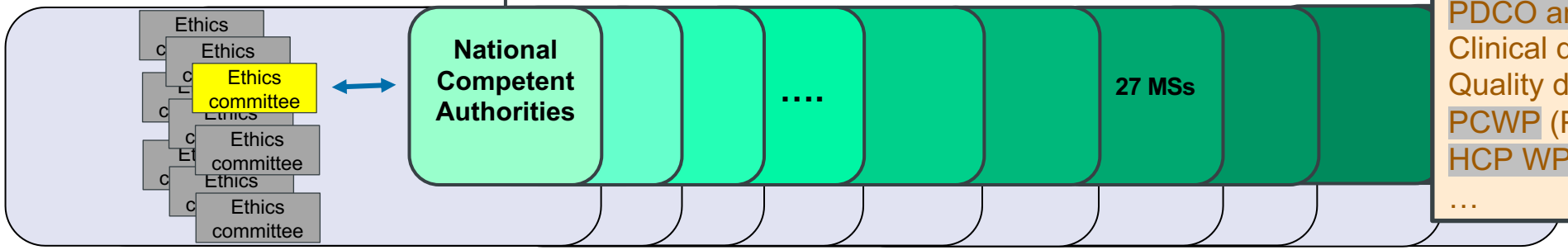
EU DCT project

HMA
Heads of Medicines Agency
Collaboration between National Competent Authorities (NCAs)
- Guidance documents

CTCG (clinical trials coordination group)

EMA
European Medicines Agency
Coordinate authorisation of medicinal products
- Guidance documents, Scientific advice, CTIS

CHMP (Marketing authorisation)
SAWP (scientific advice)
GCP IWG (GCP inspectors)
MWP (methodology, data experts)
Non-clinical WP (safety)
PDCO and Enpr-EMA (paediatrics)
Clinical domain
Quality domain
PCWP (Patients and consumers)
HCP WP (Health care professionals)
…



Recommendations on decentralised elements in CTs
from European Medicines Regulatory Network (EMRN)

RECOMMENDATION PAPER ON DECENTRALISED ELEMENTS IN CLINICAL TRIALS: Published Dec 14th 2022 on Eudralex Vol. 10

DCT Recommendation paper

Direction of EMRN harmonisation

National provisions overview

Member state specific provisions, where national legislation does not currently allow for alignment

First step towards EMRN harmonised DCT approached

Best practice for EU CT authorisation and inspection

Updated as knowledge and experience evolve

Continued information exchange

- Lancet letter published
  [Decentralised elements in clinical trials: recommendations from the European Medicines Regulatory Network - The Lancet]
- Internal Best Practice and tracker

CNRIPH

Groupe de travail national France

. 3 SG (Bonnes pratiques, données, outils)
. Comité de coordination
. Recommandations nationales
. Phase pilote

Decentralized Clinical Trials for Drugs, Biological Products, and Devices

FDA – May 2023

EMRN DCT recommendations

The DCT approach seeks to take advantage of the technological and scientific progress to introduce **new methodologies** to the conduct of clinical trials with the aim to make clinical trials **more easily accessible and participation more convenient for trial participants.**

It is at the discretion of the MS involved in the assessment of a clinical trial whether the use of certain decentralised elements is acceptable in a specific clinical trial.

This is on basis of a case-by-case review, including the EMRN DCT recommendations, EU regulatory framework and national legal provisions.

EMRN DCT recommendations – Table of content

1. Introduction, scope and **general considerations**
2. **Clinical trial oversight**: roles and responsibilities
3. **Informed consent process**
4. **Delivery of medicinal products** and administration at home
5. Trial related **procedures at home**
6. **Data collection and management** including defining and handling **source data**
7. **Trial monitoring**

General considerations (1)

Basic principle that **right, safety and well being** of trial participants to be **protected** and **prevail** over all other interests.

The implementation of decentralised elements in the conduct of a clinical trial should **not result in increased risks to the safety, rights, and well-being** of trial participants.

The appropriateness of decentralised elements depends in particular on (but not limited to) **the specific trial population, its disease, type of assessment and characteristics of investigational medicinal product (IMP)** including its stage of development and efficacy/safety profile.

Involvement of **patients and investigators** in an early and sustained manner – implementation of DCT elements **according to patient and investigator needs**.

General considerations (2)

Any **transfer of burden to trial participants or investigators** should be weighed against the **potential benefits** of using decentralised elements in the clinical trial.

Trial specific **risk-benefit assessment**, focused **on selected decentralised elements** which may have an impact on scientific validity, patient safety, benefit/risk ratio or protection of participants rights.

General medical rules to protect patient's/trial participant's safety should **be upheld**, in particular when patients/trial participants are **separated from traditional patient care centers.**

Assessment of **individual patient's risk profile** by responsible investigator with the required qualifications: exception on this should **be justified**.

General considerations (3)

Generating **reliable and robust data** fit for use for regulatory decision making and/or publication in peer-reviewed journals. **Protocol** should **describe potential limitations** introduced by decentralised elements to ensure scientific quality of the clinical trial.

IT devices/technologies developed and utilized should be **fit for purpose**. Use of computerised systems or creation/capture of electronic data should be compliant with **GCP-IWG Guideline on computerized systems and electronic data** in clinical trials ((EMA/INS/GCP/112288/2023 – published 9 March 2023).

Medical devices, including in-vitro diagnostics, should be compliant with the applicable medical device legislation.

A **summary** of the **decentralised elements** planned in the clinical trial should be provided in **the cover letter** of the clinical trial application.

Clinical trial oversight - challenges

↓ On site visits

↑ Involvement of service providers

↑ Use of electronic systems

↑ Amount of incoming data: wearables, home nursing, patient reported outcomes, etc.

More tasks delegated - responsibilities same (ICH E6 GCP)

Mitigate: **Ensure that sponsor and investigator are able to keep oversight on trial paticipant safety and well-being.**

Clinical trial oversight: Clear roles and responsibilities

→ **Document** which tasks are conducted at what place, when, and by whom and how oversight is maintained.

→ Clear **communication plan** between involved parties: sponsor, investigator, participants, service providers.

→ Trial **participants informed** on information flow and how to make contact for acute safety concern, device malfunction or other questions.

Clinical trial oversight: Oversight of incoming data

→ **Digital tools**: Validated and fit for purpose with training of users - participants, investigators, service providers.

→ Procedures to handle **information flow** so investigator has appropriate oversight.

Use of **Data flow diagram** so all involved parties have overview of data flow

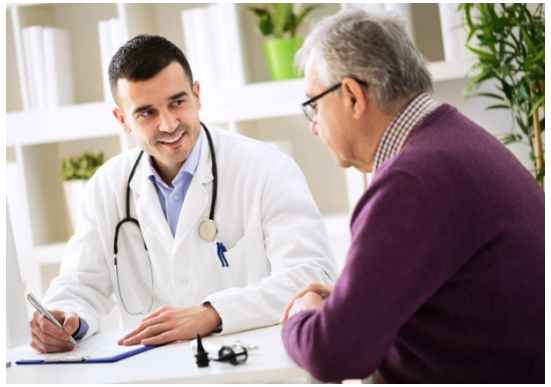
→ Anticipate **critical safety alerts** with risk-based approach. Ensure focus on and risk-mitigation plan for digital tools generating critical safety data.

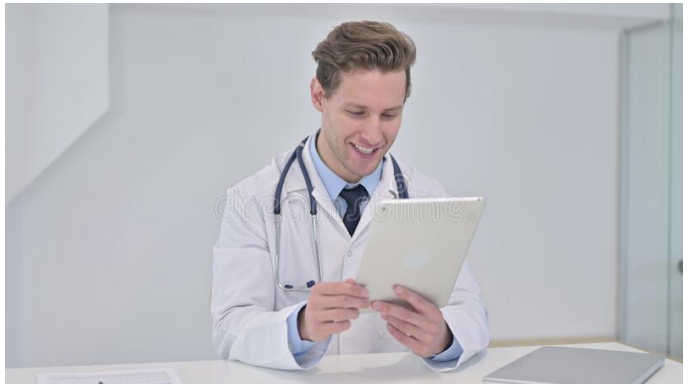
Informed consent process

National provisions overview with country specific requirements

Hybrid forms – many shapes:

- Informed consent interview: remote video or physical on-site
- Patient information (leaflet): paper, digital or video
- Signature: electronic or ‘wet ink’ by post

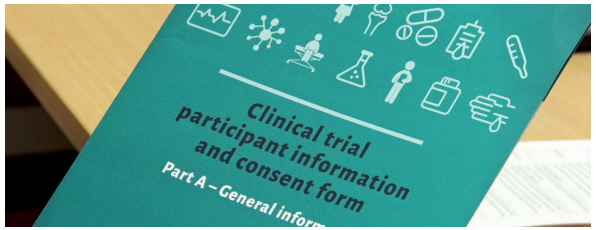




Informed consent process – the interview

Participant-centered approach: Tailor to trial and population

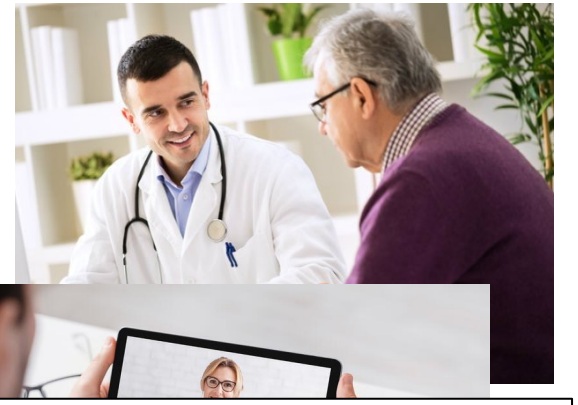
→ICH E6: **trial participants fully informed** and able to ask questions.



→**Step-by-step description** of procedure including selection and evaluation of eligibility. This in general, includes a **physical meeting**. Remote interview may be justified depending on vulnerability of trial population, knowledge on efficacy/safety profile and complexity of trial – then face-to-face real-time videocall.

Informed consent not only of ethical and legal importance: good communication between investigator and trial participant creates mutual trust and promote trial compliance

Informed consent process
- digital information leaflet and signature



→ **Awareness of participants** who cannot or prefer not to use electronic technology - non-digital methods available, unless justified.

→ **Site agrees** to use and store electronic records for consent process. Reconstruction possible with proportionate security levels.

→ Trial participant to **retrieve information** and signed/dated informed consent form.

Guideline on computerised systems and electronic data in clinical trials (europa.eu)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 March 2023
EMA/INS/GCP/112288/2023
Good Clinical Practice Inspectors Working Group (GCP IWG)

Guideline on computerised systems and electronic data in clinical trials

for release for consultation	4 March 2021
ation	18 June 2021
eadline for comments)	17 December 2021
by the GCP IWG	7 March 2023
ffect	6 months after publication

the 'Reflection paper on expectations for electronic source data and data c data collection tools in clinical trials' (EMA/INS/GCP/454280/2010).

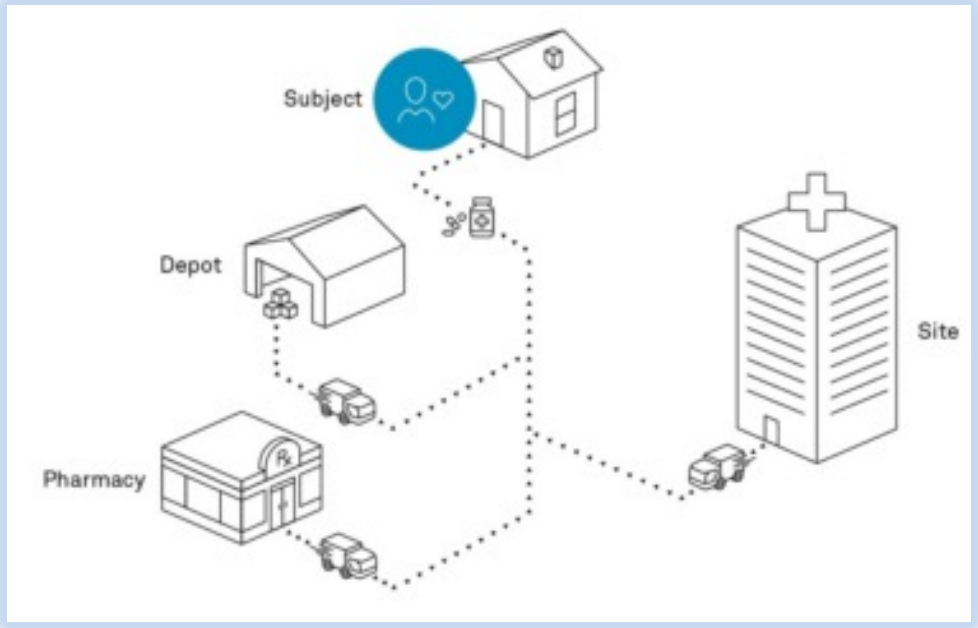
Computerised systems, electronic data, validation, audit trail, user management, security, electronic clinical outcome assessment (eCOA), interactive response technology (IRT), case report form (CRF), electronic signatures, artificial intelligence (AI)

Annex 5 Additional consideration to specific systems

A5.1 Electronic clinical outcome assessment.....
A5.2 Interactive response technology system .....
A5.3 Electronic informed consent .....

A5.3.1 Provision of information about the clinical trial
A5.3.2 Written informed consent
A5.3.3 Trial participant identity
A5.3.4 Sponsor notification on the consent process
A5.3.5 Trial participant confidentiality
A5.3.6 Trial participant access
A5.3.7 Investigators responsibilities
A5.3.8 Version control and availability to sites
A5.3.9 Availability to the investigator's part of trial master file
A5.3.10 Withdrawal from the trial

Delivery of medicinal products and administration at home



Basic principles:

→ The **investigator request and initiate shipment** of investigational medicinal product (IMP)

→ **Feasibility** with regard to storage conditions and administration? Clear instructions to participants.

→ Highly **restricted access** to trial participants contact details.

- From a depot
- From pharmacy of investigator's site
- From a local pharmacy (close to participant's home)

National provisions overview with country specific requirements

Many national provisions due to national pharma legislations..

Delivery of medicinal products and administration at home

RISK ASSESSMENT

⇒ To determine if a **direct to patient delivery is appropriate**

- Knowledge & uncertainty of the IMP
- Safety profile of IMP
- Route of administration
- Trial population

Delivery of medicinal products and administration at home

- Observation period required?
- Need for emergency plans?
- Preparation of the final IMP for administration
- Stability of the IMP
- Storage conditions
- Robustness of IMP delivery logistics (the risk of an inadvertently IMP delivery to a non-intended recipient).

The arrangements for delivery of IMP to the trial participant should be described in the CT protocol or IMPD

Delivery of medicinal products and administration at home

PROCEDURES should be in place for the **whole IMP delivery process**:

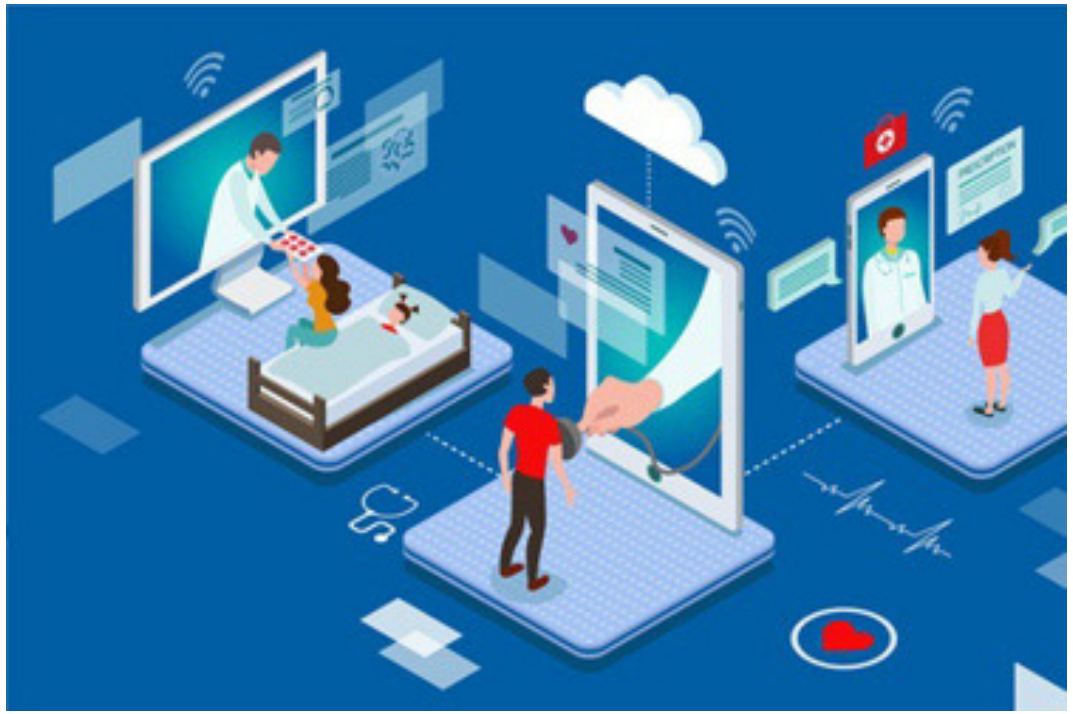
- Shipment
- IMP accountability
- Treatment compliance
- Recalls

- IMP return form trial participant's home + rules for destruction of unused IMP
- Steps taken to avoid that the IMP remains at the trial participant's home beyond the treatment period

Clinical Trial Procedures at Home

What are we talking about?

- Trial related procedures performed at the trial participant home by:
    - Trial participant;
    - Site personnel;
    - Third party
- 'Home' could be more than one place
- What kind of trial procedures?



Clinical Trial Procedures at Home

- Performing trial-related procedures at home should only be done if the procedures do not cause **additional risk** to
    - trial participant; or
    - reliability of the data

- Be aware of **additional burden** for the trial participant and/or the investigator.

Clinical Trial Procedures at Home

- The investigator should ascertain whether the trial participant's **home situation is suitable** to have trial related procedures performed at home.
- Are there personal/social circumstances which could exclude home visits?

- **Inclusion/exclusion criteria** should include provisions related to the adequacy of the trial participant’s home for critical trial related procedures at home.

Clinical Trial Procedures at Home

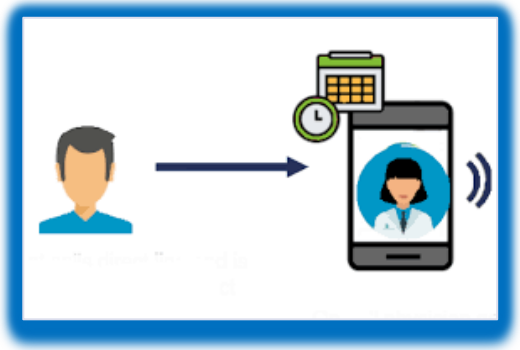
- The sponsor should provide alternatives if a trial participant is unable or not willing to use her/his/their own **private device** to capture trial data.

Clinical Trial Procedures at Home

- Trial participants and/or the delegated person(s) should be properly **trained** to perform trial related tasks at home correctly

- The investigator should monitor **compliance** of the trial participant now that there is a decrease in the number of face-to-face visits or meetings between the trial participant and the investigator.

Clinical Trial Procedures at Home



- The trial participant should be provided with a **direct line of contact** if further support to perform a trial related task is needed.

- The trial participant should be given the opportunity to **visit** the investigator in person if needed or preferred.

Clinical Trial Procedures at Home

- There should be procedures in place for reporting and management of **adverse events** noticed by the trial participant or by any delegated person during home visits.

- The **insurance** or indemnity or a guarantee should be in place to cover any damage resulting from trial related procedures performed at home.

Clinical Trial Procedures at Home

- **Trial specific rationale:** depending on trial population, its disease, type of assessment and characteristics of investigational medicinal product (IMP) including its stage of development and efficacy/safety profile.

- **Assessment:** do all clinical trial procedures at home have to be justified?

Data Collection & Management - Oversight of Incoming Data

→ Procedures to handle **information flow** so sponsor and investigator(s) have appropriate oversight/supervision.

Use of **Data flow diagram** so all involved parties have overview of data flow

Customized training on data collection & handling, incl. **safety data** identification and their reporting lines

→ Plan for handling **critical safety alerts** and their **timely assessment,** based on a risk-based approach: IMP safety profile, indication, population, known and anticipated/potential risks

Defining and Handling of Source Data

↑ data collection outside trial site and by direct data capture
↑ complexity of data flow

Same scientific and ethical principles regardless of data capture locations, methods and data aquisition tools

- ICH E6: data shall be credible, reliable and verifiable.
- Data protection requirements according to the GDPR should be adhered to

→ Data **acquisition tools** configured and valided according to intended use.

→ Determine type and scope of trial participants' **personal data** to be collected – GDPR.

→ **Transfer of data** with irreversible deletion from data acquisition tool: ensure metadata are included.

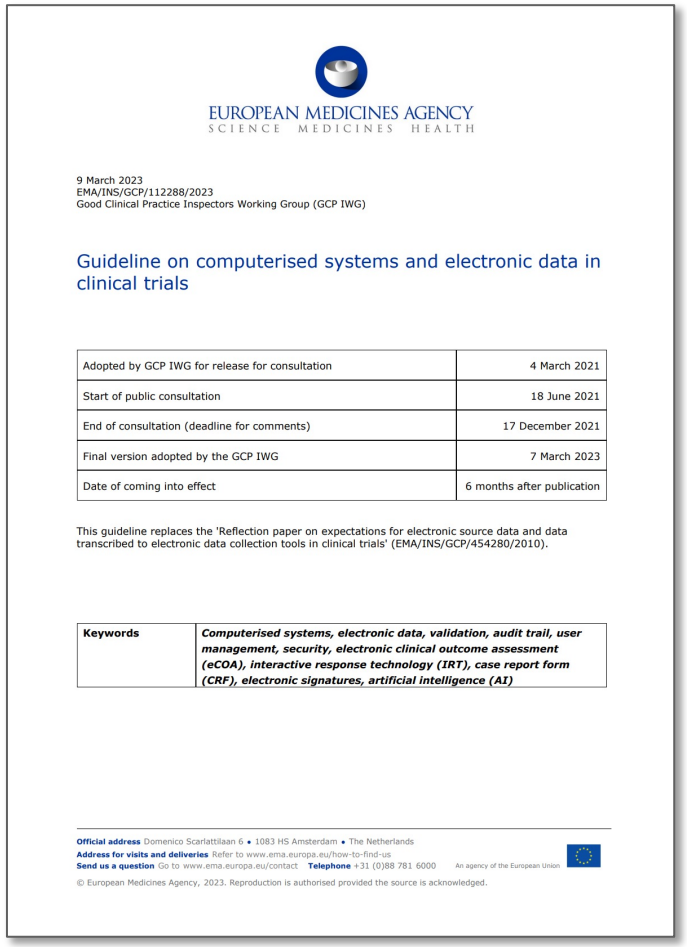
→ Procedures for **preventing unauthorised access** to data.

→ Control of and continuous **access by investigator** to all trial participant-related source data – including those captured off-site.

→ The risk of erroneous **data entry by trial participants**, especially on primary, key-secondary or safety endpoints should be minimised by appropriate measures.

Additional European Guidance To Digital Data Capture

- Guideline on computerizes systems and electronic data in clinical trials, coming into effect 9 September 2023
  https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-electronic-data-clinical-trials_en.pdf
- 'Qualification opinion on eSource Direct Data Capture (DDC) (EMA/CHMP/SAWP/483349/2019)' from the EMA Scientific Advice Working Party (SAWP)
  https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-esource-direct-data-capture-ddc_en.pdf
- 'Notice to sponsors on validation and qualification of computerised systems used in clinical trials' (EMA/INS/GCP/467532/2019)'
  https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf
- GCP IWG Q&A B3 'How and where should source data be defined'
- GCP IWG Q&A B5 'What are the expectations of the investigator's copy of the CRF when using a web based application'.



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 March 2023
EMA/INS/GCP/112288/2023
Good Clinical Practice Inspectors Working Group (GCP IWG)

Guideline on computerised systems and electronic data in clinical trials

Adopted by GCP IWG for release for consultation	4 March 2021
Start of public consultation	18 June 2021
End of consultation (deadline for comments)	17 December 2021
Final version adopted by the GCP IWG	7 March 2023
Date of coming into effect	6 months after publication

This guideline replaces the 'Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials' (EMA/INS/GCP/454280/2010).

Keywords	***Computerised systems, electronic data, validation, audit trail, user management, security, electronic clinical outcome assessment (eCOA), interactive response technology (IRT), case report form (CRF), electronic signatures, artificial intelligence (AI)***

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Trial Monitoring Strategy

- ICH E6: Monitoring strategy shall be adapted to clinical trial specifics –taking into account data collection in regards to processes, tools, locations and individuals.
- Combination of centralized and site monitoring generally appropriate. Site monitoring usually **on-site**, unless **off-site (remotely)** is found suitable and fits purpose.
- The **term 'site'** in this document includes investigator sites and any other site (facility, institution, party), where source data relating to trial-participants are generated and/or collected
- Principle of necessity and proportionality. Monitoring strategy should not unduly burden trial site.

Remote Monitoring Including Remote Source Data Verification

GCP IWG Q&A - What are the considerations when direct remote access of identifiable personal and health data is required in a clinical trial?

- Direct remote access is any access from an access point (location and/or hardware) that is not under the control and supervision of the investigator/institution.
- Description of the **arrangements** to comply with the applicable rules on the protection of personal data and description of measures in case of data security breach in the **trial protocol**.
- **Data Protection Impact Assessment** strongly recommended; involvement of the sponsor's **data protection officer** (DPO) and the institution(s)/investigator(s)' DPO (if applicable).
- Appropriately informing trial participants about planned remote access, the **trial participants' informed consent** does not relieve the investigator or sponsor of their responsibility to ensure compliance with data protection legislation.

National provisions overview with country specific requirements

Recommandations de la FDA

« **The variability and precision of the data obtained in a DCT may differ from the data in a traditional site-based clinical trial. This would not affect the validity of a finding of superiority in a trial using such data (although it could reduce the effect size), but it could affect the validity of a finding of non-inferiority**. Remote assessments may differ from on-site assessments, particularly when trial participants are responsible for performing their own physiological tests (e.g., home spirometry). Assessments performed by local HCPs as part of routine clinical practice (e.g., evaluation of symptoms) may also be more variable and less precise than assessments conducted by dedicated trial personnel. In non-inferiority trials, when the effect size of an active control drug, for example, has only been determined in a traditional site-based clinical trial, it may not be reasonable to assume that the same effect size would be seen for the active control drug in a DCT. This may present challenges in calculating a non-inferiority margin. »

Aspects méthodologiques

« To account for **multiple sources of data collection** in a DCT, the sponsor should include at least the following in a **data management plan** (**DMP**):

- Data origin and data flow from all sources to the sponsor (e.g., a diagram that depicts the flow of data from creation to final storage)

- Methods used for remote data acquisition from trial participants, trial personnel, and contracted service providers (e.g., local clinical laboratory facilities and local HCPs who perform trial-related activities)

- A list identifying vendors for data collection, handling, and management »

Plan de gestion des données
Circuit des données

- « Sponsors should describe in the **trial protocol** how **operational aspects** of the DCT will be implemented. This description should cover, but may not be limited to, the following:

- Scheduled and unscheduled clinical trial visits (remote and in-person, as applicable)

- Transmission of reports on activities performed at different locations (e.g., medical imaging; clinical laboratory tests; and procedures performed at trial participants' home, work, or other local facility)

- Delivery of IPs to trial participants, if applicable, and accountability for IPs

- Safety monitoring and management of adverse events.

- **Case report forms should identify when and where data were collected and by whom. »**

Aspects opérationnels → protocole
CRF

- « The **safety monitoring plan** should take the decentralized nature of the clinical trial into account and ensure that adverse events are appropriately captured and adequately addressed. The monitoring plan should prespecify if and when telehealth visits or in-person visits (e.g., physical examinations) will be scheduled with trial personnel or local HCPs to collect safety data by.
- As in any site-based clinical trial, the safety monitoring plan should describe how participants are expected to respond to and report adverse events, including where to seek medical assistance locally when necessary and where to receive follow-up care.
- **If significant safety risks emerge because of the remote administration or use of an IP, sponsors must discontinue remote administration or use**; notify FDA, the IRB, and all investigators who have participated in the trial; and determine if the trial should continue.
- If authorized in the protocol, routine safety monitoring involving laboratory testing and imaging may be performed using local clinical laboratory facilities close to trial participants. **Investigators should ensure they promptly receive reports of these services and review them in a timely manner.** »

Plan de gestion de la sécurité

Plan de la recommandation France

Introduction

1. **Champ d'application et définitions**
   - 1.1. Champ d'application
   - 1.2. Définitions
   - 1.3. Les 6 domaines d'essais concernés par la décentralisation
2. **Principes généraux**
3. **Conception de la recherche** (Eléments du 'Gen. Considerations' reco EU)
4. **Lieu, activités et responsabilités**
5. **Information et consentement**

   Annexe dématérialisation transmission information et recueil consentement
6. **Médicaments, produits**
7. **Données recueillies**
8. **Contrôle de qualité et monitoring à distance**

Pièce jointe

En cours de rédaction par PH Bertoye et C Peiffert