GUIDELINES FOR UNDERTAKING DECENTRALIZED ITEMS IN CLINICAL TRIALS

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TABLE OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
SAE	Serious adverse event
AEPD [Agencia Española de Protección de Datos]	Spanish Data Protection Agency
AEMPS [Agencia Española de Medicamentos y Productos Sanitarios]	Spanish Agency of Medicines and Medical Devices
ASM [Asistencia Sanitaria Móvil]	Mobile Healthcare
GCP	Good Clinical Practice
CS	Collaborating site
ERB	Ethical Review Board
IC	Informed consent
CTIS	Clinical Trials Information System
DCT	Decentralized Clinical Trials
DE	Decentralized element
eIC	Electronic informed consent
eCRF	Electronic Case Report Form
CT	Clinical trial
EMA	European Medicines Agency
EudraCT	European Union Drug Regulatory Authorities Clinical Trials Database
FDA	Food and Drug Administration

PIS – ICF	Patient information sheet and informed consent form
PI	Principal Investigator
ICH	International Council for Harmonization
LOPDGDD [Ley Orgánica de Protección de Datos Personales y garantía de los derechos digitales]	Organic Law on Personal Data Protection and Guarantee of Digital Rights
IMP	Investigational medicinal product
HCP	Healthcare professional
REEC [Registro Español de Estudios Clínicos]	Spanish Clinical Study Register
GDPR	General Data Protection Regulation
SEM	Search Engine Marketing
SI	Sub-investigator

1 INTRODUCTION

Decentralizing clinical trials means closing the gap between study procedures and participants by using different activities that combine technology, services, and processes, while maintaining participant safety and data reliability.

The purpose of this document is to describe the main characteristics to leverage when conducting decentralized or hybrid clinical drug trials in Spain. Thus, these guidelines will discuss the processes to be employed for each decentralized element, thereby standardizing their implementation and thus ensuring participant safety and data quality.

Progress in using digital media and telemedicine in recent years, which was accelerated by the COVID-19 pandemic, has greatly increased the demand for technology use by the general population in many aspects of daily life. Technology applied to the field of medicine and, in particular, clinical trials should also be considered by all stakeholders involved in the process.

Decentralized clinical trials (DCTs) can become a viable alternative to traditional clinical trials since decentralizing elements offers participants greater flexibility by transferring some or all of the clinical trial activities to their home through visiting healthcare professionals or to sites other than the main research site. Similarly, DCTs can contribute to expanding the group of eligible participants and assist in their participation in the trial, and furthermore increase access to innovative therapies for populations that may be underrepresented because they live in places far from the main research sites and have mobility issues or travel constraints.

These elements should always be used on a voluntary basis and taking into account the digital divide that may be more present in some specific populations. Therefore, it is important that potential participants can, for example, through their associations, provide their opinion on using these decentralized elements and assess how their use could affect their participation in the trial.

DCTs must fulfill all applicable regulatory requirements, especially those related to privacy and data protection in all cases, as well as those in which digital transmission is involved.

By relying on the technological infrastructure, including data transmission and storage systems, telemedicine platforms, and portable medical devices, it is necessary to ensure that proper technology is used, that adequate risk identification, analysis, management, and control are undertaken, and that there are necessary plans to prevent or to handle risks.

Finally, while decentralized elements may expand the group of participants eligible for clinical trials, they may also require greater cooperation and commitment from all parties involved in the trials.

1.1 Concept and objectives

The main decentralized mechanisms we consider key for clinical trials and addressed in these guidelines are the following:

- Participant recruitment using virtual channels, including digital pre-screening platforms.
- The possibility of an electronic informed consent process (which could include using digital media).
- Using telemedicine for remote follow-up of participants, thereby reducing research site visits.
- Use of mobile nursing services to perform certain procedures at the participant's home.
- Drug and clinical trial material delivery directly to the place indicated by the participant outside the research site.
- The possibility of involving collaborating sites to assist in participation.

This document provides the procedures to be followed to guarantee their proper use in clinical trials conducted in our country.

Please bear in mind some key aspects for conducting decentralized clinical trials:

1. The responsibility for interpreting and making trial-related medical decisions is solely that of the investigator, just like in traditional trials.

2. Healthcare professionals delegated by the principal investigator must always be qualified and trained to perform their specific tasks. This delegation does not free the investigator from his/her responsibility overseeing the trial in accordance with current legislation.

   In keeping with the regulatory authority's instructions and as a means of contributing to clinical trial reviews, the sponsors will list the decentralized elements described in the protocol in the cover letter or through an appendix to said trial.

3. It is necessary to add the possible decentralized elements, additional risks these may entail, and a guarantee of participant privacy by the involved professionals in the information sheets and informed consent forms.

4. A DCT protocol must ensure that adverse events are appropriately reported and treated. Subjects participating in a decentralized trial must receive explicit instructions on how and when to contact the investigator if they suffer a serious health problem. In addition, investigators must follow the instructions for serious adverse event reporting to the sponsor within 24 hours.

5. Remote source data verification must be done according to the guarantees stipulated in the EU guidelines and the requirements established by the AEMPS and AEPD. Remote data monitoring must be done in accordance with the published Spanish Data Protection Agency instructions, specifically with special focus on compliance with the documents "Remote Source Data Verification Monitoring", published on May 27, 2020, and "Spanish Agency of Medicines and Medical Devices instructions for conducting clinical trials in Spain".
6. The clinical trial insurance policy must cover any potential harm resulting from trial procedures, regardless of where they take place, in accordance with Royal Decree 1090/2015, of December 4, which governs clinical drug trials, drug research ethics committees, and the Spanish Clinical Study Register.

2 DIGITAL RECRUITMENT

2.1 Definition

Digital recruitment is understood to be using digital strategies/tools for the inclusion of participants in a clinical trial.

Digital recruitment is reviewed from two aspects: access to clinical trial information (to increase awareness and to expand communication of what clinical trials are and what it means to participate in them) plus information exchange about available clinical trials to improve participant, caregiver and/or family member, and HCP access to them. The idea is to work towards harmonizing the requirements that the platforms, tools, and channels used to broadcast clinical trials must have in order to speed up the approval process and, therefore, to promote their use.

2.2 Considerations

There are public clinical trial registers, such as the following: WHO (trialsearch.who.int), FDA (clinicaltrials.gov), EMA (clinicaltrialsregister.eu), CTIS portal (euclinicaltrials.eu/search-for-clinical-trials), and Spanish Clinical Study Register (REEC) (reec.aemps.es/reec/public/web.html), the latter publishing clinical trials available in Spain. The REEC is a public, free-to-use, and no-cost database for all users, accessible from the AEMPS website, whose purpose is to serve as a primary source of information on clinical drug studies. The level of information in these registers varies, and it is not easy for participants to contact the clinical trial sites.

Moreover, scientific societies, patient associations, cooperative groups, and institutions have their own clinical trial informational platforms. Likewise, many sponsors have virtual educational platforms for clinical trials that can help people find the study that best suits their reality and that can also connect them to site of their choice. In these cases, the platforms usually incorporate the means to facilitate participant pre-screening.

To do this, the person seeking a clinical trial will fill out an online questionnaire about their health status and treatment history. Based on their answers, the system suggests

potential clinical trials that might coincide with the participant's condition. Normally, they can then choose a research site for the potential trial and provide their contact information so the research team can contact them. The final decision about participating in the clinical trial will be made by the research team.

Sites should be able to choose whether they want to be contacted and how they want to be contacted by those seeking a clinical trial (HCP, participant, family member, caregiver); e.g., through a call center or their contact details.

We propose identifying existing barriers and how they can be addressed; e.g., data privacy aspects, aspects related to referring key participants in DCTs.

2.3 Processes

In order to provide a reference for interpreting the legitimacy of using these methods/systems/platforms, the following are the elements that these platforms should have to expedite ERB review and approval:

- **Tool/channel definition:** Sponsor, institution, participant association, and cooperative group platforms, central health service departments, and social networks.
- **Elements that can be included in the tool:** Only public information available on other "websites" or platforms, such as those of the REEC, clintrials.gov, and EUDRACT.
- **Information to be included:** Disease, participant age range, location of the research sites, start and end dates, protocol synopsis for lay persons, type of study drug, means of contacting sites/investigators, etc.

  Principal investigators must be involved and consent to receive referred participants or participants from other geographic areas.

- Data protection **recommendations** from the AEPD; i.e., data storage purpose and time period, server location, cybersecurity requirements, cookies, data transfer, etc.
- **The ERB process** for approving the contents of the materials/platforms, documentation to be submitted (complete material about what will be published on the platform and how and where it will be used), and the requirements to be fulfilled, according to Annex I of the AEMPS instructions ("Documents related to subject recruitment procedures and materials").

  Standardization could positively impact clinical development programs by promoting access to information, increasing access to a greater number of participants, creating a more diverse population and, therefore, shortening enrollment times.

3 ELECTRONIC INFORMED CONSENT (eIC)

3.1 Definition

Electronic informed consent (eIC) means using digital means (e.g., text, images, video, audio, websites, etc.) to provide information to potential trial participants and then to obtain informed consent using a smartphone, app, tablet, or computer, etc. eIC refers to both the patient information sheet and the consent form. The steps in the process include communicating information through an interview between the potential participant and the PI or SI, the possibility of asking questions about the trial, according to ICH GCP(R2), and signing the consent form either electronically or on paper. One or all parts of the process may be done remotely and/or in person during the same act or on different days. The eIC is applicable to the initial consent and any future re-consenting. eIC is understood to include any type of consent applicable to a clinical trial (for example: child assent) and the signature of any other person in addition to the participant (for example: legal representative, impartial witness, etc.).

3.2 Considerations

In trials that use eIC, a hard-copy consent will be offered as an alternative to ensure the inclusion of all potential participants, thus preventing the digital divide bias.

The eIC must provide the same information as the one on paper, in accordance with Annex VIII of the AEMPS instructions document, in an electronic format that may include multimedia components which would allow different options for reading and interacting, in such a way that ensures that potential study participants are fully informed through the study medical staff despite the complexity of the information provided, with the purpose of ensuring their full understanding of all content.

In the context of decentralized studies and in combination with telemedicine, the eIC provides the possibility of fulfilling the obligation of informing participants in real time by ensuring that both parties can see and communicate with each other through video and audio and can verify their respective identities. This also allows the process to be done in

any geographic area without participants having to be in the region where the research site is located. This provides all participants with increased accessibility to clinical trials and greater diversity in the recruited population. It is important to note that eIC is not intended to replace the essential face-to-face conversation between the participant and the PI or SI. However, potential participants and the site will be offered the possibility of the consent process at the site if they so wish.

The eIC offers the possibility of remote signing (electronic or paper) when the participant (or his/her legal representative, father/mother in case of pediatric trials, etc.) cannot physically visit the research site.

The eIC accelerates the reporting of new trial information to participants since they do not need to wait for the next research site visit.

In keeping with the current Spanish legal framework, oral consent can be obtained as long as it is documented in the participant's medical record and subsequently ratified in writing or via eIC; i.e., the participant and the investigator sign the form.

3.3 Processes

Fulfilling GCP and the regulations

The main basis is that eIC and traditional IC processes must conform to the guidelines of Good Clinical Practice (Section 4.8 Informed Consent Form). Close communication between the investigator and the potential trial participant (being face-to-face in real time) is expected regardless of whether it is done in-person or, for example, as a video conference. Communication should take place in terms that the trial participant understands.

Formal aspects of the application for approval

1. The clinical trial protocol or annexed document must include the informed consent procedure (screening, eligibility assessment, and the actual informed consent process).

2. To ensure an adequate ethical review, the informed consent procedure must be described in the part II documentation submitted to the ERB.
3. Information about the platform used and data protection must also be included.

Technical aspects of the platform where eIC will be obtained

It allows for it to be stamped with the date and time (including time zone) in real time. There should be no question about when the signature occurred. The system must use timestamps which cannot be manipulated by system configuration for the audit trail on the action of signing and dating by the trial participant and the investigator or qualified person who led the informed consent interview.

This platform can provide information to the participant in the form of images, videos, etc., so that they receive broader and more understandable information than through the paper consent process.

Technical aspects of the e-signature

The method used to document consent must coincide with the national legislation; for example, on the acceptability of electronic signatures.

The eIC e-signature must have specific technical characteristics that ensure its integrity, identification, and transparency of the data, so it must be "qualified, advanced, and open-source". eIC is possible as long as it is obtained with a high-security-level signature in accordance with eIDAS Regulation No. 910/2014, Chapter 8), and provided that personal data confidentiality and security and the secure access to it are guaranteed. Only these types of signatures have the specifications, procedures, or controls whose purpose is to prevent misuse or undue alteration of identity.

The EMA *Guideline on computerized systems and electronic data in clinical trials* and chapter 3 of the document, Recommendations on using decentralized elements in clinical trials, should also be taken into account.

In addition, the eIC must fulfill the Guideline for Good Clinical Practice, Section 5.5.3 - Data Validation, and Section 1.65 - VALIDATION OF COMPUTERIZED SYSTEMS. In addition, it must adhere to the Personal Data Protection Act (Organic Law 3/2018, of December 5, on Personal Data Protection and the Guarantee of Digital Rights) as well as the General Data

Protection Regulation (EU) 2016/679.

Computer programs and IT systems that support e-signatures must be ICH-GCP-validated systems.

e-signatures must allow information and password (if applicable) retrieval at any time and by any site personnel authorized to access it, for which an appropriate procedure will be set up (for example, using the participant's email or telephone number).

Obtaining the IC remotely

The informed consent process must be documented such that trial participant reception of the information, the discussion between the person qualified to obtain the consent and the trial participant, and that the consent form was given according to the applicable GCP guidelines can be verified.

Regardless of the means used in the process and how the participant's informed consent is obtained (either electronically or traditionally on paper), the parties involved should be offered the option of remotely carrying out the process and obtaining the signature. For example, undertaking the informing process over the telephone or a videocall (telemedicine), emailing the ICF to the participant, participant's verbal acceptance, participant's remote signature on paper or via e-signature and then sending it to the research site by courier or digital means, participant's verbal consent with subsequent written corroboration, participant's remote signature of eIC at his/her home, etc., all under the premise that these actions will be adequately documented in the participant's medical record.

Data protection and storage aspects

Such technical issues as the following should be taken into account:

1. What signature data will be accessible to the monitor, in what format, and location (at the site, remotely, etc.).
2. The sponsor is responsible for validating the system used in accordance with data protection laws and those applicable to the use of electronic systems.
3. What tools will be used (devices, apps, websites, etc.) and whether they will be

provided by the sponsor or will the participant be expected to access them on their own devices. We recommend using technological choices that are commonly used by the population.

4. Interrelationship between the different systems (databases) used by the sponsor.
5. Evaluate potential firewall problems that could make it difficult to access the eIC system and provide alternatives.
6. Confidentiality between the trial participant and the investigator must be maintained, which involves using a secure method (for example, data encryption) without the sponsor being able to take part in or have access to the informed consent process.
7. Ensure that all confidentiality guarantees are met according to the applicable regulations (GDPR and LOPDGDD), regardless of the system used.
8. The channel of communication should allow for the explicit identification of the participant or his/her legal representative, if applicable.
9. Provide all necessary instructions and training to the participant and consider all possible choices in the system: signature of legal representative, impartial witness, signature of withdrawal of consent, assent of minors, etc.
10. Informed consent forms must be personally documented, dated, and signed by the research staff and the participants in the different possible forms (handwritten signature on paper, in-person e-signature on electronic media, remote e-signature, etc.) using systems that guarantee this identification.
11. The trial participant must be able to download and print the trial informed consent form and information sheet and must always have access to these documents during the course and after the end of the clinical trial. When the trial ends, there should be a method for alerting participants of their right to download the information they want from the system and/or other possible options to access it after their participation ends.
12. The electronic systems used must meet the general requirements of electronic systems in clinical trials. They must be validated for their purpose (example: using

track changes, user control, computer security methods, etc.). In turn, e-signing methods must conform to the applicable standards.

Monitoring and filing aspects

Documentation must be filed in accordance with the investigator's trial master file, and version control must be used. Likewise, the necessary file storage period after the trial ends, according to applicable legislation, must be guaranteed.

You should ensure a system that allows research site staff access to the signed informed consent forms and their copies once the site is closed out, according to the requirements in the applicable regulations and ICH Guideline.

Generally speaking, the sponsor should not have access to communication between the trial participant and the investigator, except to fulfill its monitoring and auditing obligations. This must be ensured by controlling user access to the information storage systems.

Remote monitoring in real time and contemporaneously (signed consent forms and source documents for obtaining IC). Thus, the type of information which can be reviewed by the monitor as well as the confidentiality measures to be followed, based on the legal requirements for established remote monitoring and the EMR models at each research site, must be defined.

Potential privacy risks

Sponsors should address the risk of possible disclosure of personally identifiable information related to eIC (see Annex I) from the computer platform or the electronic data repository.

Sponsors must ensure that all guarantees are in place to confirm the security of stored and in-transit data, thus preventing the access or intervention of malicious parties.

4 TELEMEDICINE

4.1 Definition

Telemedicine is the use of information and communication technology to provide remote medical care to a participant over any type of remote device. Another term used is the virtual visit. Of note, telemedicine can also be used in combination with other decentralized trial modules, such as at a nurse's visit at the participant's home.

4.2 Considerations

Telemedicine is a means for clinical trial participants not to have to visit the research site or to visit less frequently, as long as no examination or other intervention is required and they have access to mobile and/or video communications with their physician-investigator. Therefore, telemedicine is a decentralizing element that can bridge the gap between the clinical trial and the participants, make recruitment easier without generational or social discrimination, and increase retention by facilitating the reconciliation of family and work life.

Participants will also be able to report safety-related information and quality-of-life parameters in real time.

Despite its benefits, telemedicine also presents some challenges for all people involved, such as the digital divide, and it requires an investment of time by the participant, who has to learn how to use digital tools, and the investigator, who has to ensure that participants are sufficiently informed to properly use the technology. From the participants' point of view, their privacy and confidentiality must be ensured so as not to reveal information or data to any unwanted recipients and to prevent inadvertent access to telemedicine tools by people outside the trial. Thus, it should be noted that using platforms/applications that transmit data requires the submission of a data protection impact assessment.

Likewise, the technology and/or platforms used must always allow access to records for possible audits or inspections.

4.3 Processes

Below are the processes to keep in mind when planning a clinical trial that aims to incorporate telemedicine:

1. Assess clinical trial complexity.
2. Consider the **trial target population** and whether telemedicine can be an alternative for facilitating recruitment and providing greater participant comfort and accessibility. Also consider the extra burden that implementing this decentralized element may have on the participant/investigator/site.
3. Consider what **value** it provides and assess the **impact** on costs and operations. Evaluate the inclusion of a **definition of telemedicine in the protocol** or other related annex.
4. It is important to specify in the **protocol** or annex **which study visits/activities are applicable to implementing telemedicine** and when it is essential that participants attend the site in person. A **contingency plan** must also be prepared for cases where remote contact may fail and/or data collection devices/digital tools do not work as intended (possibility of offline access, direct telephone call to the research team, or site visit).
5. It is important that the protocol clearly describe how remotely identified **adverse events** (AEs) will be assessed and managed, as well as the care that will be provided to AEs requiring urgent or in-person care. It should also be underscored that when participants experience any safety problem, they will always have the possibility to contact the research team directly to report it.
6. Define in the **study data monitoring and management plan** the type of data to be collected via telemedicine and consider how the data will be entered in the case report form and monitored by the sponsor. Likewise, define where the telemedicine-collected data will be stored and who will have access to it.

7. Define the **responsibilities** of each party involved in its implementation. Sponsors are responsible for protecting data and secure routes or access for each party, and principal investigators are responsible for ensuring that a specific procedure can be done using telemedicine rather than requiring an in-person visit.

8. Participants in the trial must be informed, through **the patient information sheet**, of the possibility of using telemedicine at certain protocol visits and what this service consists of; they must consent to its use accordingly. It is also important to ensure that information reaches caregivers.

9. **Channel selection.** The channel/platform to be used must be defined and whether remote visits will be conducted over videocall or telephone call. Therefore, the sponsor will be responsible for offering the channel (app) to the participant to download on their own electronic device or it may be pre-installed on a device provided by the sponsor. Likewise, the sponsor must provide all the training material so that the investigator's team and the study participants can acquire the necessary knowledge to ensure the correct management of the channel/application. The research team will be responsible for ensuring that participants understand the instructions and can properly follow them. There should be no case in which participants are excluded because they do not have their own electronic device which can run the app proposed by the sponsor.

10. **Provider selection** for device delivery and application use. Providers have coverage for all countries; device/app configuration supports all languages; sites and users have tech support 24 hours a day, if possible. It should also be ensured that data privacy laws are followed at all times and that accessibility is guaranteed.

5 MOBILE HEALTHCARE (ASM)

5.1 Definition

A nurse or other qualified healthcare professional going to the participant's home or other previously agreed location to perform certain study procedures.

In a clinical trial with decentralized elements, trial-related procedures can be done outside the research site where the clinical trial is being conducted, such as at the participant's home. A study staff member can do the procedures at the trial participant's home, as can a person hired for the trial and trained and delegated to perform them.

5.2 Considerations

Please bear in mind that there may be personal/social circumstances that make it difficult to adequately monitor the participant at home.

Trial-related procedures should only be done at the home or agreed-upon place as long as these do not entail additional risk to the trial participants, household members, or caregivers, or to data reliability, if the person responsible for the task is trained to perform it, and if the site or PI agrees to it.

Safety follow-up: There must be an SOP for reporting and managing adverse events reported by trial participants or any delegated person during home visits.

Medical decision-making tasks should remain the responsibility of a qualified physician.

Local nursing: If the site decides to use its own staff members to travel to the place agreed with the participant, the PI is responsible for making certain that they are adequately qualified and trained on their delegated tasks.

The staff must be covered by proper indemnity insurance that covers travel to the home or site agreed with the participant.

5.3 Processes

The following are the most relevant elements to consider for trial procedures or examinations performed outside the research site:

1. **ASM staff qualification:** The sponsor is responsible for hiring ASM service providers that provide appropriately experienced, qualified, and certified staff members for the tasks to be performed; the individuals should have accredited training in Good Clinical Practice, privacy, and data integrity, in accordance with current legislation, and be familiar with the study protocol and the documents associated with providing the service. All training must be completed and properly documented before the ASM can perform any study-related activities. It is also necessary for the ASM service provider to have indemnity insurance which covers its staff members.
2. **Study task training and delegation:** The ASM staff will contact the PI/site team to arrange a call/visit to meet with the team so that the PI can confirm whether or not they have the appropriate qualifications for the delegated task. The study delegation of duties log must clearly identify the tasks for which they have been delegated.
3. **Privacy and personal data confidentiality:** The research site will send the participants' personal information to the ASM provider; it must guarantee protection of the participants' privacy and data confidentiality during the transmission. The provider is responsible for maintaining participant privacy and data confidentiality during the study and for making certain that such data is securely destroyed when the study ends. The site/PI and the provider are responsible for ensuring that the privacy and confidentiality of the personal data obtained and maintained are respected in accordance with GCP, the clinical trial requirements, and personal data protection legislation. The sponsor will in no way whatsoever have access to such data.
4. **Source documentation:** All information collected by the ASM staff during a visit to the participant's home or place agreed with the participant must be adequately documented. This will be classified as a source document and, therefore, should be sent to the site according to the trial management procedures. The PI/site is

responsible for maintaining source data in accordance with the ICH Guideline.

5. **Protocol:** The activities the ASM service will perform at the home/agreed place and at the applicable visits must be described and justified. Trial participants should have the opportunity to meet with the research team in person if necessary or if they prefer, and participants and ASM staff should have a direct line to the research team if they need more support to perform a trial task.
6. **Patient information sheet:** Trial participants must be informed about the option of using a homecare service, about what a visit to their home or agreed place will consist of, and about how their data will be processed. They must also give their explicit consent to the service.
7. **Contract:** A contract must be entered into that adheres to the provisions of "Q&A: *Good Clinical Practice* (GCP), *Questions 10 and 11*", listing the tasks to be performed by each party involved and stating the responsibilities of the contracting parties. The sponsor or its appointed agent may hire the provider and pay for the contracted tasks if the site/principal investigator does not have the material/economic resources necessary to do so. The provider will have to take into account the Principal Investigator's instructions/guidelines since he/she is ultimately responsible for any subcontracted tasks and especially with respect to the qualification that must be met by the staff who will perform said subcontracted tasks.

6 DELIVERY OF STUDY DRUGS TO THE PARTICIPANT'S HOME

6.1 Definition

Decentralized element related to shipping the study drug/comparator/auxiliary or concomitant medication from the research site to the participant's home (or other location indicated by the participant).

6.2 Considerations

The use and implementation of this decentralized element makes conducting clinical trials more **flexible**, which is an advantage for both participants and the research team.

This decentralized element must be included in the trial protocol (or an annex), patient information sheet, and informed consent form. All parties involved, including the Pharmacy Department, must be informed that this decentralized element will be implemented and agree to the assigned tasks and/or training to be received for carrying out the clinical trial activities.

The site will inform the Pharmacy Department (especially during the initial pre-screening/screening phases of the site) of any term or condition that is related to the implementing this decentralized element and that may be directly related to the activities and/or responsibilities of the Pharmacy Department. We recommend that the site and the Pharmacy Department agree to determine the number of clinical trials/recruited patients that can be covered by the material and human resources available at that time. Important factors to consider are the complexity of medication management and the responsibilities that each person involved at the site and the sponsor will assume (e.g., hiring transportation/distribution services, etc.).

The trial can be better integrated into the daily routine of trial participants, thereby **reducing the time** and **mobility** required. As a result, more participants would have access to novel treatments regardless of their location, hence preserving their well-being

and quality of life. Likewise, it would contribute to preventing a decline in the clinical condition of many participants as this relates to traveling to the site.

When study drug (or auxiliary medication) dosing is planned at the trial participant's home, a risk assessment should be completed to determine whether this activity is appropriate. The sponsor will have to undertake the risk assessment (at the study level and at the time of implementing this item). The study doctor will also have to undertake an individual risk assessment for each participant who will make use of this element.

The risk assessment should at least include the following aspects: the knowledge and lack thereof of the drug and its safety profile, trial population, route of administration, if a post-dosing observation period is required, drug preparation and stability, storage conditions, need for emergency plans, and shipping logistics (distribution and delivery conditions; for example, risk of dispensing the study drugs to an unexpected participant). Likewise, the additional workload that this element may entail for the participants themselves will be assessed (the study doctor or delegated site staff, in coordination with the Pharmacy Department, must provide clear instructions on drug use and storage) as well as for the rest of the people involved in the process (investigators, nurses, pharmacy, etc.).

The entire process must be adequately documented in the study file.

This element is expected to improve participant **satisfaction**, promote **retention**, increase treatment adherence (and consequently a potential clinical benefit), and create an experience more focused on the participant's needs.

In addition, **the impact on sites is minimized** due to the reduced number of in-person visits for healthcare personnel and the participant.

This development helps promote equality in access to health services because participants, regardless of mobility and physical distance from research sites, can participate in clinical trials without this being an obstacle. This will likely **be useful to recruitment** and ultimately make novel medications available to participants in a shorter time.

The possibility of using this decentralized element should be clearly stated **in the protocol or related documents**, and optional visits will be specified within the protocol

diagram.

Using decentralized processes must always ensure that the principal investigator of the trial and the sponsor can comply with their legal obligations established in sections 4 and 5 of the ICH-GCP Guideline.

All aspects and considerations applicable to Spain must be taken into account, including those in the EMA document: ***Recommendation Paper on Decentralized Elements in Clinical Trials/Appendix: National Provisions Overview, V02, dd March 13, 2023, for Spain*, and according to the AEMPS instructions.**

6.3 Processes

The research site team (or delegated and trained staff; e.g., pharmacy, nursing, etc.) will ensure that participants receive the drug treatment according to the corresponding clinical trial protocol and pharmacy manual. The participant will be provided with the necessary information about the dispensed drug, route of administration, storage, possible adverse reactions, and drug interactions, etc. In addition, treatment adherence will be encouraged and followed.

Medication delivery to the participant:

Delivering the drug to the participant should always be done from the research site or its delegated pharmacy and never directly from the sponsor or its delegates' facilities.

Informed Consent Form

Trial participants must be informed of this option and agree that, under certain circumstances, their personal data may be provided to a shipping/distribution company in order to ship the study drugs to their home. All necessary measures will be taken to ensure that personal data is protected against unauthorized or accidental disclosure. The company hired by the sponsor (or by the research site) will keep their personal information confidential, and no personally identifiable information will be shared with the sponsor. The sponsor and the research site will respect Organic Law of 3/2018, of December 5, and other current data protection laws, such as Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016, on Data Protection (GDPR).

All personal data protection information should be included in the informed consent form. This information also applies to personal data processing related to this decentralized element.

Selecting a shipping/distribution company

The sponsor will hire the shipping/distribution company specifically for this service. The contract will include a data protection clause in which both parties (sponsor and courier) pledge to respect data protection laws and confirm that necessary security measures will be implemented to prevent the shipping/distribution company from transferring any personal data from the participant to the sponsor. In addition, it must be stated that the shipping/distribution company will process the participant's personal data according to applicable data protection laws.

This shipping/distribution service can also be provided, hired, and managed directly by the participating site under the same terms as those mentioned above. In these cases, the sponsor will be required to assist in order to ensure that the study drug is correctly handled and packaged.

In addition, according to GCP guidelines, investigators are responsible for the drug, so it is necessary to obtain their agreement and that of the pharmacy department for implementing this decentralized element in the study in question.

Collecting/processing participants' personally identifiable data (name, address, and contact details)

Providing the site with a courier-specific form has been proposed. The research staff will complete it with the participant's personal data and then send it to the courier at the time the drug will be shipped. This form also includes the email address of the person at the site to whom the temperature log should be sent after being downloaded (*see temperature management during shipment*).

If the form cannot be completed on paper, the data must be provided to the shipping/distribution service and/or stored securely according to data protection laws. The following methods may be used: sending encrypted emails or password-protected zip files, telephone, or secure platform, among others.

Temperature management during shipment

You should able to prove that study drug storage conditions have been met throughout the supply chain. The courier will be instructed that after it delivers the drug to the participant and has downloaded the temperature log, it will have to send the log to the site contact person listed on the form. Once the temperature log has been reviewed, the site will contact the participant, who has been instructed to wait for the site to communicate its approval over the phone, before the drug can be taken/administered.

Ultimately, drug storage during the shipment and communication with the participant must be ensured for the correct receipt and administration of the drug.

Confirmation of reception

The following checks must be performed from the site: package status and its contents, confirm number of containers, batch numbers, and temperature maintenance during shipment. All this information must be correctly documented.

The medication must be delivered personally to the participant or his/her legal representative; otherwise, the drug will have to be returned to the hospital site of origin. The participant who receives the drug at home must record and report its receipt and plan for the possibility of having to return unused medication and/or empty containers based on the express clinical trial requirements.

Participants can return the unused medication at their upcoming site visits or by the courier used to ship the study drug. In both scenarios, participant proof of reception will be part of the investigator's file.

Study drug storage and dosing

You must guarantee that the study drug is stored and protected in accordance with the protocol requirements (or other guidelines adapted from the study). You must ensure that participants have clear instructions on drug storage and protection in terms of temperature and/or other drug-specific conditions.

Firstly, this decentralized element should be used in cases of participant self-administered drugs, and provided that it is permitted under current legislation. On the contrary, if special administration by a healthcare professional is required, then you must have the home nursing service activities described in section 5 (mobile healthcare)

available.

Drug accountability and treatment adherence

The Principal Investigator should continue monitoring the correct use of the drug by participants, including adherence and compliance during remote study visits. The site's pharmacy department can assist with these activities as agreed by each participating site.

The sponsor must provide the appropriate means to perform a periodic drug compliance check and set up the processes for adequate documentation of drug accountability in the applicable systems.

We stress here that all forms used during the process will not be shared with any representative of the sponsor.

7 SATELLITE/COLLABORATING SITES

7.1 Definition

In certain clinical trials, the situation may arise in which some of the participating sites have branch offices or associated sites in different locations that collaborate on participant pre-screening and recruitment activities and/or that conduct follow-up/treatment visits and/or trial-specific procedures. These types of sites are called satellite/collaborating sites (hereinafter, SS) and will be linked to a main health site of the trial.

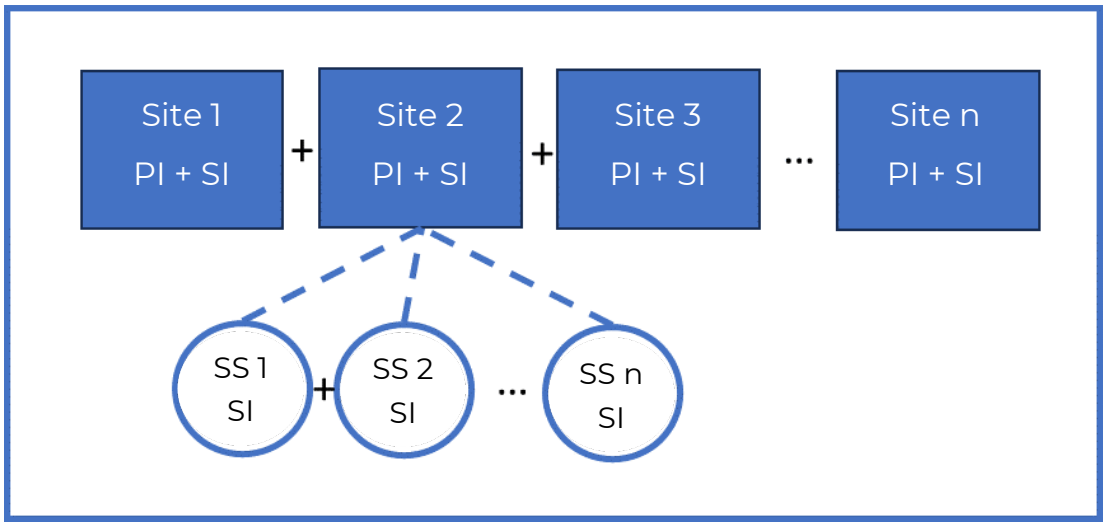

Figure 1. Organizational chart for multicenter clinical trials with satellite/collaborating sites. PI: Principal Investigator, SI: Sub-investigator, SS: Satellite site.

7.2 Considerations

It is essential that the roles, specific responsibilities, and delegations of the sponsor, investigator, and SS are clearly defined and understood by all parties prior to the start.

The sponsor is responsible reaching an agreement with the PI on the decentralized activities that will be carried out at the SS, according to the protocol contents. Likewise, you must make certain that participants are informed of the possible decentralized procedures in the patient information sheet and informed consent form for the study (PIS-ICF).

The sponsor must ensure that the trial logistics can be implemented in the SS, as well as the availability of a budget for this, when applicable. The sponsor is furthermore responsible for confirming the it is feasible for the pre-selected SS to carry out the decentralized activity applicable to the clinical study; i.e., confirming whether or not the sites have the necessary structure, sufficient human resources, and qualified and adequately trained personnel for said activity. The sponsor must ensure that the team and the delegated staff are adequately trained on the protocol (provided that the activity to be performed is specific to the protocol) and on GCP. All of this must be documented, following the practices determined by the sponsor in this regard.

The PI is ultimately responsible for tasks involving trial-related medical decisions (e.g., eligibility and inclusion of trial participants, protocol-specified medical procedures, changes in medication, etc.) and for the rights, safety, dignity, and well-being of trial participants. The PI is responsible for delegating and overseeing all study-related tasks and those persons performing them at the SS. The PI must ensure that SS personnel are adequately qualified for the tasks to be performed and that they have been appropriately trained on the ones he/she has delegated to them.

It is necessary to establish effective, documented, and shared lines of communication with all relevant parties, including trial participants, investigators, the provider, and the SS. All parties involved must have access at all times to the information necessary to perform their clinical trial-related duties and responsibilities. There must be an effective communication plan for emergencies so that all relevant parties can act in a timely manner. Whenever possible, we recommend preparing written guidelines or procedures that define the communication process to be followed.

7.3 Processes

Agreement and policy

The trial agreement must clearly state the tasks delegated to the SS and the financial compensation it will receive for them. It should also describe how the PI will supervise the healthcare professionals that will perform trial-related tasks under his/her responsibility.

Likewise, the sponsor must ensure that the trial policy covers everything that has a direct

causal relationship with the study, regardless of the site where the activity takes place.

Protocol and PIS-ICF

The protocol or other related documents must justify the inclusion of decentralized activities and provide a detailed description of them and of the visits at which they will be done. If it is determined that SS collaboration is likely to have a significant impact on the scientific validity, data integrity, risk-benefit ratio, or participant rights, then performing a risk-benefit assessment will be necessary. This assessment, as well as any risk mitigation measures taken, should be clearly described in the clinical trial protocol or any other related documents.

The study patient information sheet must include this information and describe the follow-up/treatment visits and/or trial-specific procedures, and any pre-screening activities done at the SS, all in compliance with current data protection laws. Study participants must receive the contact details of the research team, either at the PI's site or the SS, for any situation that may arise; this should include the contact person if they have an adverse event.

The possibility of obtaining the PIS-ICF at an SS could be considered provided that the collaborating investigator at said site is trained and delegated to do so.

Source documents and investigator file

At all times, source documents must be identified and available to the different parties involved (sponsor representatives, competent authorities, research team) at all research sites, whether main or satellite. You must fulfill the legal obligation of keeping these source documents on file, according to current legislation. Moreover, you must comply with the GDPR, the LOPDGDD, and ICH E6 guideline: "data obtained in the trial must be credible, reliable, and verifiable." If SSs are used, the documentation on file at the different SSs will be pooled at study close-out and stored at the PI's site.

Should data be collected at participant visits, obtaining it must be flexible, either through the PI's site only and/or through the SS, with access to the eCRF given in both cases.

It is essential that principal investigators of the trial have access to participant data from the SS so they can fulfill their responsibility for overseeing the trial. The information available in the eCRF, ePRO questionnaires, handheld devices, and any participant data

collection system must be available to the trial PI.

Since involving an SS adds complexity to the trial, the sponsor will make sure that measures are adopted that contribute to PI oversight. These measures are intended to:

- Ensure that all parties involved understand the data flow in the trial, including a diagram of the data flow in the protocol or in documents attached to the protocol (manual or similar).
- Make certain that data collection tools/systems are correctly configured and validated for use.
- Determine the type of participant personal data and ensure adequate protection, in accordance with current data protection laws.
- Make sure that when data is transferred from the system to another location, or when data is removed from it, that it also disappears from the transferred system.
- Minimize the risk of unauthorized access, such as using data encryption.
- Ensure controlled access to data, even using a firewall for this.

Serious adverse event/adverse event reporting.

Using the SS model should not increase participant safety risk. Therefore, there must be procedures to guarantee that "adverse events" (AEs) reported by the participant to the SS investigators are properly notified. The collected safety data must take into account the IMP safety profile, indication, known potential risks, and use of notifications and alerts.

The priority for any SS and the main site should be to collect and to evaluate SAEs immediately. We recommend preparing a risk mitigation plan in case the AE reporting system fails to work as expected.

Regarding trial safety information notification, the sponsor must include safety alerts in the protocol and how investigators will handle them, including an immediate medical care plan, if necessary. Participants should be informed of the actions to be taken in these situations, and we recommend incorporating a specific approach to facilitate their understanding of this.

Participants should clearly understand that any specific safety problem they experience

must be reported directly to the research team.

The sponsor will ensure that all personnel delegated to AE/SAE reporting at the SS and the main site have been previously trained and delegated; these actions need to be adequately documented as well.

Monitoring

The monitoring strategy should be based on the specific characteristics of the clinical trial. For this strategy, the specific risks associated with the collaboration of these sites, tools/systems, locations, and involved staff must be considered.

Monitoring procedures can be centralized (remote) or onsite (in person) or a generally accepted combination of both. Both possibilities can be assessed at both the main site and the SS.

The principles of necessity and proportionality must always be respected for remote monitoring, and no site should be assigned an excessive burden.

If remote access to source data and documents is planned, additional data access confidentiality and system security measures should be adopted at all study sites. This should be accomplished through a nationally implemented process approved by the AEMPS and the AEPD: Informational letter on remote source data access from the General Sub-directorate - General Data Protection Register *.https://www.aepd.es/es/documento/monitorizacion-remota-verificacion-datos-fuente.pdf*

Study drug dosing

Should study drug dosing be the SS-performed decentralized activity, the sponsor will ensure the availability of the study drug at the main site and the SS, if applicable. This must be included in the contract or agreement, specifying the responsibilities of the investigator and the sponsor.

In addition, all SS personnel handling the drug must be trained by the sponsor or its representative (or the main site research team if this concerns an SS), before the delegation of tasks by the principal investigator takes place.

The sponsor must guarantee that its drug dispensing, receiving, and storing procedures

at the PI's site and/or at the applicable SS coincide with the protocol instructions. If dispensing will be done at an SS, access to the applicable dispensing systems must be guaranteed.

It must be feasible to handle, track, account for, and calculate compliance with the drug at the SS, and these actions must be adequately documented.

Network site model

As a special situation, we would like to discuss a model of network sites (hereinafter, NS). For this option, healthcare sites, even in different locations or branches, are linked together so that the same tasks can be carried out in any of them.

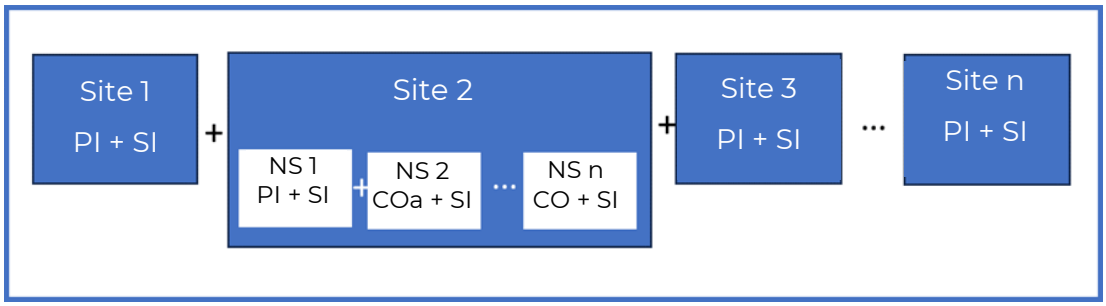

Figure 2. Organizational chart for multicenter clinical trials with network sites. PI: principal investigator, SI: sub-investigator, NS: network site, CO: co-investigator.

All specifications mentioned in the previous sections about SS apply to NS, the only exception being the model's organization based on different network branch offices or locations. To make this model more efficient, we recommend a single pharmacy department having responsibility over receiving the drug and its subsequent distribution to the other network sites participating in the study.

8 BIBLIOGRAPHY

- E6(R2) Guideline for Good Clinical Practice
- RECOMMENDATION PAPER ON DECENTRALIZED ELEMENTS IN CLINICAL TRIALS (EMA)
- Regulation (EU) No. 536/2014 of the European Parliament and of the Council of April 16, 2014, on clinical trials of medicinal products for human use, repealing Directive 2001/20/EC
- CTIS Guidance - SPAIN
- Decentralized Clinical Trials for Drugs, Biological Products, and Devices (FDA)
- Guideline on computerized systems and electronic data in clinical trials (EMA)
- Use of Electronic Informed Consent Questions and Answers Guidance for Institutional Review Boards, Investigators, and Sponsors (FDA)
- Royal Decree 1090/2015, of December 4, that governs clinical drug trials, drug research ethics committees, and the Spanish Clinical Study Register.
- AEMPS document, Instructions for Conducting Clinical Trials in Spain
- Informational letter on remote source data access from the General Sub-directorate - General Data Protection Register
- The Danish Medicines Agency's guidance on the implementation of decentralized elements in clinical trials with medicinal products
- Decentralised clinical trials (DCTs) with medicinal products in Switzerland
- Electronic Informed Consent Guidelines Switzerland
- European Regulation eIDAS (electronic identification, authentication, and trust services) dated 2014

9 ANNEX I - eIC CHECKLIST

This document has been prepared with the purpose of providing guidance on the requirements that Health Authorities and clinical trial sponsors can use to generate and/or evaluate the technical aspects of different tools aimed at ensuring the validity of a participant's consent to participate in a clinical trial using eIC.

This document provides general guidance, in the form of a checklist, applicable to clinical trials on the use of eIC to convey information related to this research study to potential participants. Answers to the questions in the guide should be affirmative, unless there are particular situations that must be justified in the “comments” section, which the Ethics Committee will assess.

This document discusses the specific aspects of the systems/technologies for digitally obtaining participant consent according to the essential aspects of GCP guidelines that must be met regardless of the IC process used.

It is intended to be a dynamic document that will be updated periodically and which is open to adding new content as technology advances and regulatory requirements are amended.

Section 1: General aspects				
No.	**Aspects to bear in mind**	**Reference** (Regulation, guideline, etc.)	**Select whether it complies (if NO, please explain or provide alternate plan)**	**Justification/Alternative plan** (refer to the system, clarification of content, etc.)
1.1	Documentation in the protocol (or annex) regarding: The entire informed consent procedure; i.e., screening, eligibility assessment, and the actual informed consent process should be described step-by-step in the clinical trial application to ensure adequate ethical review. The sponsor must also describe in the protocol or annex the chosen informed consent process as well as its justification (type of participant, disease, etc.).	EMA: Recommendation paper on decentralized elements in clinical trials Version 01, Dec. 13, 2022	Yes ☐ / No ☐	
1.2	There must be a procedure/system to guarantee that the eIC process is appropriate and inclusive. For example, for participants with impaired motor skills, who are not device savvy, participant age, language, level of electronic understanding, etc.		Yes ☐ / No ☐	

Section 1: General aspects				
No.	**Aspects to bear in mind**	**Reference** (Regulation, guideline, etc.)	**Select whether it complies (if NO, please explain or provide alternate plan)**	**Justification/Alternative plan** (refer to the system, clarification of content, etc.)
1.3	There must be alternative methods (e.g., paper version) to provide information and the informed consent form for people who are unable or unwilling to use electronic methods.	Guideline on computerized systems and electronic data in clinical trials EMA/INS/GCP/112288/2023 Section A5.3	Yes ☐ / No ☐	
1.4	At the end of the eIC process, you must make certain the participant receives a signed and dated copy of the information sheet and consent form, whether as a hard copy or electronic version. The copy must be available directly. Participants must have access to all versions of all consent forms they have signed.	Guideline on computerized systems and electronic data in clinical trials EMA/INS/GCP/112288/2023 Section A5.3.6	Yes ☐ / No ☐	
1.5	The original copy (hard copy or electronic) of the signed consent form must be filed such that the Principal Investigator has access to it.		Yes ☐ / No ☐	

Section 1: General aspects				
No.	**Aspects to bear in mind**	**Reference** (Regulation, guideline, etc.)	**Select whether it complies (if NO, please explain or provide alternate plan)**	**Justification/Alternative plan** (refer to the system, clarification of content, etc.)
1.6	The proposed eIC template* should be described (e.g., that the patient information sheet can be an electronic copy, while the ICF can be a hard copy, etc.). Hybrid model: It is permitted to combine hard and electronic copies indiscriminately in any of the actions related to the information and/or informed consent process. There is a hard-copy template of the patient information sheet to be offered or used. ** Regardless of the submitted eICF template, hard-copy consent forms should always be offered as an alternative to ensure the inclusion of all potential participants.*		Yes ☐ / No ☐ Yes ☐ / No ☐	

Section 1: General aspects				
No.	**Aspects to bear in mind**	**Reference** (Regulation, guideline, etc.)	**Select whether it complies (if NO, please explain or provide alternate plan)**	**Justification/Alternative plan** (refer to the system, clarification of content, etc.)
1.7	The type of consenting process or act must be stated: in-person and/or remote in real time.	EMA: Recommendation paper on decentralized elements in clinical trials. Version 01, Dec. 13, 2022. Appendix: National Provisions Overview, V02, dd March 13, 2023 (Spanish requirement)	In-person ☐ Remote ☐ Combination ☐	
1.8	Participant withdrawal of consent: There must be follow-up procedures for participants who have withdrawn [consent] electronically, including partial withdrawal and complete withdrawal, due to the impact on participant participation and data collection. These procedures should include timely notification of the investigator and a communication plan with all other parties involved. Withdrawing consent must be possible both inside and outside the system, and the investigator must record that action.	EMA: Recommendation paper on decentralized elements in clinical trials. Version 01, Dec. 13, 2022	Yes ☐ / No ☐ Regardless of format	

Section 1: General aspects				
No.	**Aspects to bear in mind**	**Reference** (Regulation, guideline, etc.)	**Select whether it complies (if NO, please explain or provide alternate plan)**	**Justification/Alternative plan** (refer to the system, clarification of content, etc.)
1.9	There must be a system to make certain that participants have the opportunity to ask questions and to receive answers before signing the hard-copy consent form for participating in the study even if the eIC process was done remotely. This interview process can be remotely conducted in real time or at the site in person at the request of the Investigator or participant.	Guideline on computerized systems and electronic data in clinical trials EMA/INS/GCP/112288/2023 Section A5.3 EMA: Recommendation paper on decentralized elements in clinical trials. Version 01, Dec. 13, 2022	Yes ☐ / No ☐	

Section 2: Technical aspects of e-signatures				
No.	**Aspects to bear in mind**	**Reference** (Regulation, guideline, etc.)	**Select whether it complies (if NO, please explain or provide alternate plan)**	**Justification/Alternative plan** (refer to the system, clarification of content, etc.)
2.1	When test data is handled electronically and/or for remote electronic test data systems, the sponsor must comply with ICH-GCP 5.5.3.	ICH-GCP 5.5.3	Yes ☐ / No ☐	
2.2	Computer programs/systems must be validated in accordance with ICH GCP. 1.65 VALIDATION OF COMPUTERIZED SYSTEMS for integrity, accuracy, reliability, constant performance, and intended use.	ICH GCP 1.65 VALIDATION OF COMPUTERIZED SYSTEMS	Yes ☐ / No ☐	
2.3	eIC signature must be an ADVANCED signature* (see Advanced Signature requirements)	European Regulation 910/2014 Article 8	Yes ☐ / No ☐	

Section 2: Technical aspects of e-signatures				
No.	**Aspects to bear in mind**	**Reference** (Regulation, guideline, etc.)	**Select whether it complies (if NO, please explain or provide alternate plan)**	**Justification/Alternative plan** (refer to the system, clarification of content, etc.)
2.4	eIC signature must be an OPEN* signature (see Advanced Signature requirements)	European Regulation 910/2014 Article 8. Guideline on computerized systems and electronic data in clinical trials EMA/INS/GCP/112288/2023 Section 4.8	Yes ☐ / No ☐	
2.5	eIC signature must be a QUALIFIED signature* (see Advanced Signature requirements)	European Regulation 910/2014 Article 8. Guideline on computerized systems and electronic data in clinical trials EMA/INS/GCP/112288/2023 Section 4.8	Yes ☐ / No ☐	

Section 2: Technical aspects of e-signatures				
No.	**Aspects to bear in mind**	**Reference** (Regulation, guideline, etc.)	**Select whether it complies (if NO, please explain or provide alternate plan)**	**Justification/Alternative plan** (refer to the system, clarification of content, etc.)
2.6	The system should allow information and password retrieval at any time.	European Regulation 910/2014 Article 8. Guideline on computerized systems and electronic data in clinical trials EMA/INS/GCP/112288/2023 Section 4.8	Yes ☐ / No ☐	
2.7	The signature must not be rejectable (i.e., there can be no denying that something was signed after affixing the signature).	European Regulation 910/2014 Article 8. Guideline on computerized systems and electronic data in clinical trials EMA/INS/GCP/112288/2023 Section 4.8	Yes ☐ / No ☐	

Section 2: Technical aspects of e-signatures				
No.	**Aspects to bear in mind**	**Reference** (Regulation, guideline, etc.)	**Select whether it complies (if NO, please explain or provide alternate plan)**	**Justification/Alternative plan** (refer to the system, clarification of content, etc.)
2.8	Link must be unbreakable (between registration and signature).	European Regulation 910/2014 Article 8. Guideline on computerized systems and electronic data in clinical trials EMA/INS/GCP/112288/2023 Section 4.8	Yes ☐ / No ☐	
2.9	There must be a timestamp or audit trail that records not only the time of signature, but also the time zone in which the signature was affixed), thereby preventing it from being manipulated (for example, changing the time zone).	European Regulation 910/2014 Article 8. Guideline on computerized systems and electronic data in clinical trials EMA/INS/GCP/112288/2023 Section 4.8	Yes ☐ / No ☐	

Section 2: Technical aspects of e-signatures				
No.	**Aspects to bear in mind**	**Reference** (Regulation, guideline, etc.)	**Select whether it complies (if NO, please explain or provide alternate plan)**	**Justification/Alternative plan** (refer to the system, clarification of content, etc.)
2.10	The electronic copy of the eIC must be protected from changes.	EMA: Recommendation paper on decentralized elements in clinical trials Version 01, Dec. 13, 2022	Yes ☐ / No ☐	

* **Advanced, open, and qualified e-signature requirements**.

1. **ADVANCED SIGNATURE:** An advanced electronic signature will meet the following requirements:

   a) Be linked to the signatory in a unique way.

   b) Authentication: signatories can be identified by implementing identity verification systems to prevent impersonation, to ensure security, and to protect their privacy.

   c) If the e-signature is from a web interface, a user and password are necessary to prevent impersonation. Login must include an authentication process as a registered participant (e.g., sending a code to the user's phone).

   d) Created using e-signature creation data that signatories can use with a high level of trust and under their exclusive control.

   e) Be linked to the data signed by the person so that any subsequent modification thereof is detectable (audit trail).

2. **OPEN SIGNATURE**

In open systems, verification of signatory identity is based on identification data endorsed by a third party (typically electronic certificates, FNMT [*Fábrica Nacional de Moneda y Timbre* (National Mint and Stamp Factory)]). While evaluating the type of system, you need to consider that Regulation 910/2014 (article 2, point 2.2) would not apply to closed systems, so the guarantees offered by compliance with the regulation may not apply. Therefore, we would have to choose an open system.

3. **QUALIFIED SIGNATURE**

A qualified e-signature is an advanced e-signature that is created using a qualified e-signature creation device and is based on a qualified e-signature certificate;

e-signature QUALIFICATION (requirements for a qualified e-signature certificate) will need to be confirmed. Qualified e-signature certificates will contain:

a) A statement, at least in a format suitable for automatic processing, that the certificate has been issued as a qualified e-signature certificate;

b) A set of data that unequivocally represents the qualified provider of trusted services that issues the qualified certificates, including at least the Member State in which said provider is established, and - for legal entities: the name and, where applicable, the registration number as recorded in the official records, - for natural persons, the name of the person;

c) Minimally, the name of the signatory or a pseudonym; if a pseudonym is used, it will be clearly indicated;

d) e-signature validation data corresponding to the e-signature creation data;

e) The data relating to the start and end of the certificate's effective period;

f) The certificate identity code, which must be unique to the qualified trusted service provider;

g) The advanced e-signature or advanced e-seal of the issuing service provider;

h) The place where the certificate supporting the advanced e-signature or advanced e-seal referred to in letter g) is available free of charge;

i) The location of services that can be used to check the validity status of the qualified certificate;

j) When e-signature creation data related to e-signature validation data is on a qualified e-signature creation device, an appropriate indication of this, at least in a form suitable for automatic processing.

10 AUTHORS

These guidelines were prepared by a working group consisting of representatives from the:

- Spanish Agency for Medicines and Medical Devices
- Pharmaceutical industry
- Patient Organization Platform
- Ethics Committees
- Clinical research teams
- Spanish Society of Hospital Pharmacy