RECOMMENDATION PAPER ON DECENTRALISED ELEMENTS IN CLINICAL TRIALS

Version 01, 13 December 2022

Draft agreed by DCT project team (experts from Clinical Trial Coordination Group, Clinical Trial Expert Group, EMA scientific committees, EMA working parties, and EMA staff)	December 2022
Draft agreed Clinical Trial Coordination Group	December 2022
Draft agreed by Clinical Trials Expert Group	December 2022
Draft agreed by GCP Inspector Working Group	December 2022
Adopted by ACT EU Steering Group	December 2022

For questions related to this document, please write to secretariat of CTCG: ctcg@hma.eu

Important notice: The views expressed in this recommendation paper on decentralised elements in clinical trials in the European Union/European Economic Area are not legally binding. Ultimately, only the European Court of Justice can give an authoritative interpretation of Community law. This document aims at informing on a harmonised perspective on the use of decentralised elements in clinical trials in the EU/EEA from the European Medicine Regulatory Network.

Recommendation paper on decentralised elements in clinical trials

TABLE OF CONTENT

ABBREVATION LIST

AE	**Adverse Event**
CRF	**Case Report Form**
CTCG	**Clinical Trial Coordination Group**
CTD	**Clinical Trial Directive**
CTEG	**Clinical Trial Expert Group**
CTR	**Clinical Trial Regulation**
EC	**European Commission**
EEA	**European Economic Area**
EMA	**European Medicines Agency**
EMRN	**European Medicines Regulatory Network**
ePRO	**Electronic Patient Reported Outcome**
EU	**European Union**
GCP	**Good Clinical Practice**
GDP	**Good Distribution Practice**
GMP	**Good Manufacturing Practice**
GDPR	**General Data Protection Regulation**
HMA	**Heads of Medicine Agencies**
ICH	**International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use**
IMP	**Investigational Medicinal Product**
IT	**Information Technology**
IVD	**In Vitro Diagnostic**
IVDR	**In Vitro Diagnostics Regulation**
IWG	**Inspector Working Group**
MDR	**Medical Device Regulation**
MS	**Member State**
SAE	**Serious Adverse Event**
SAWP	**Scientific Advice Working Party**
SNSA	**Simultaneous National Scientific Advice**

1. INTRODUCTION, SCOPE AND GENERAL CONSIDERATIONS

Clinical trials on Investigational Medicinal Products (IMPs) are increasingly using procedures conducted outside the traditional 'clinical trial site', a concept usually referred to as decentralisation. In addition, there is increasing use of digital tools within clinical trials. The COVID-19 pandemic highlighted the importance and usefulness of digital tools and decentralised procedures in a healthcare setting and in clinical trials. The guidance on the management of clinical trials during COVID-19 pandemic provided a set of recommendations that included adjustments to the informed consent process, the distribution of IMPs and in monitoring under specific circumstances. This guidance is specific to the COVID-19 health crisis in the European Union (EU)/European Economic Area (EEA) and is intended to be revoked when there is a consensus that the period of the COVID-19 outbreak in the EU/EEA has passed.

The above context and trend highlight the need to provide further recommendations on the introduction of decentralised elements in the conduct of clinical trials in the EU/EEA, regardless of any health crisis, and in consideration of the currently limited national guidances. The aim of this recommendation paper is to address this requirement. The intention is to facilitate the use of decentralised elements in clinical trials in the EU/EEA. However, the necessary level of trial participant's safety, protection of their rights and dignity should be ensured. In addition, the reliability of data for publication and submission for regulatory decision-making should be guaranteed.

It is acknowledged that certain decentralised elements in clinical trials have been adopted for some time and that not all of these elements are likely to have a significant impact on scientific validity, data integrity, benefit-risk ratio or the protection of trial participants' rights. If a decentralised element has been identified as a critical-to-quality factor as defined in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E8, a risk-proportionate approach should be followed and adapted to the risk of trial participants, trial integrity of the research carried out and to the risk related to reliability of trial results. This is in line with the Recommendations on risk proportionate approaches in clinical trials from the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014.

The recommendation paper will address the roles and responsibilities of the sponsor and investigator, electronic informed consent, IMP delivery, trial related procedures at home, data management and monitoring in a decentralised clinical trial setting. An overview of the current national provisions applicable in each Member State (MS)in relation to these topics is outlined in the appendix. It should be noted that the national provision appendix is for guidance purposes only as it is not feasible to give a complete overview of all scenarios for implementing decentralised elements in a clinical trial. 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. Sponsors are encouraged to seek scientific advice via the European Medicine Agency [EMA, scientific advice working party (SAWP)], or via national competent authorities [national or simultaneous national scientific advice (SNSA)] regarding the use of specific decentralised elements, especially on decentralised elements where experience and the evidence of their impact may be limited. Sponsors may also request a consolidated opinion via the Clinical Trial Coordination Group (CTCG) for regulatory issues of general impact not related to a specific trial.

This recommendation paper was created as part of the priority action 8 'Methodology guidances' of the ACT EU initiative of the European Commission (EC), the Heads of Medicines Agencies (HMA) and the EMA. It was drafted in a collaboration between the HMA Clinical Trial Coordination Group (CTCG), EC Clinical Trial Expert Group (CTEG) and the EMA GCP Inspectors Working Group (GCP-IWG). It includes broad perspectives from the European medicines regulatory network (EMRN) as well as perspectives by patient and health care professional representatives. Given the rapid advances in the field of decentralised clinical trials, the paper is expected to evolve when new insights and experiences are gained.

General considerations

Clinical trials with medicinal products have already adopted many decentralised elements such as electronic diaries, wearables, phone calls and online appointments. How decentralised elements are used in clinical trials depends on many factors including the type of clinical trial, the trial population, the disease being treated, the condition of the trial participant, the type of medicinal product, its characteristics and development stage. These elements should be considered individually and in combination when planning for and implementing the use of decentralised elements. In addition, the following general considerations should be taken into account:

- The rights, safety, dignity and well-being of the trial participants[1] should 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, the type of assessment, the characteristics of the investigational medicinal product(s), including its/their stage of development and thus the current knowledge about its/their efficacy and safety profile.

- Adherence to EU and national applicable laws, regulations and established standards and guidances for clinical trials (e.g. Clinical Trial Regulation: CTR EU no 536/2014, ICH E6, ICH E8, applicable Good Manufacturing Practice (GMP) provisions, applicable Good Distribution Practice (GDP) principles) and international ethical and scientific principles of medical research (e.g. Declaration of Helsinki) is required for all clinical trials regardless the use of decentralised elements. Particular emphasis should be placed on compliance with the General Data Protection Regulation (GDPR EU no 2016/679).

- Sponsors and investigators should engage potential trial participants, patients or patient organisations in a meaningful participatory process that involves them in an early and sustained manner in the design, development and implementation of the clinical trial. Early participant involvement in the design of the clinical trial is likely to increase scientific value. It may help develop trust in the trial, facilitate recruitment, and promote adherence. Patients also provide their perspective of living with a condition, which may contribute to the choice of decentralised elements, for example, the feasibility of appointments by videoconference instead of a physical visit, the use of digital tools, or the measurements of endpoints that are meaningful to patients and selection of the appropriate population.

- When developing a clinical trial with decentralised elements, investigators/healthcare professionals should be involved in the design, development, and implementation of the clinical trial. The expertise of the investigators/health care professionals may contribute to ensure clinically relevant objectives and endpoints, efficient safety monitoring and adequate medical care. They can also contribute to identify the consequences of having less personal contact or how to manage data collection and the quality and integrity of the (source) data.

- Any transfer of burden of trial related procedures to trial participants and/or investigators should be weighed against the potential benefits of using decentralised elements in the clinical trial. The sponsor may provide adequate support to trial participants and/or investigators to facilitate the appropriate conduct of their tasks.

- For transparency reasons, and to facilitate the assessment of the clinical trial by authorities and ethics committees, a summary of the decentralised elements planned in the clinical trial should be provided in the cover letter of the clinical trial application.

- If it is determined that decentralised elements are likely to have a significant impact on scientific validity, data integrity, benefit-risk ratio or impact on the protection of trial participants' rights, these should be considered in a specific and documented risk benefit assessment. This risk benefit assessment as well as any risk mitigation action taken should be

[1] Where patient/trial participant is mentioned in the paper, relatives and/or legal representatives of patient/trial participant are meant as well, whatever is applicable.

clearly described in the clinical trial protocol or other protocol related document as part of the clinical trial application to the MS. This is required for any element impacting the risk benefit assessment.

- In clinical trials with decentralised elements, parts of the clinical trial may be conducted outside the traditional patient care centers, with the involvement of service providers. General medical rules to protect patient's/trial participant's safety should be upheld in trials with decentralised elements especially when patients/trial participants are separated from traditional patient care centers. Among those is the assessment of individual patient's risk profile, including appropriate anamnestic information, physical examination and laboratory or imaging data by a responsible investigator with the required trial population specific medical background. Exceptions should be justified in the clinical trial application to ensure appropriate case-by-case review.

- The sponsor should provide in the clinical trial application a description of the funding of the clinical trial and any other (financial) arrangements between funder, investigator and service providers involved in the conduct of the clinical trial. Any conditions, such as economic interests and institutional affiliations, that might influence the impartiality of the investigator should be provided as well, as would be expected for any trial.

- Trials with decentralised elements should be designed to generate reliable and robust data. Regarding regulatory decisions supporting marketing authorisation, the data is required to meet the same expectations as those from trials with on-site procedures. Sponsors should carefully discuss expected challenges prospectively and clarify how they plan to address potential limitations introduced by decentralised elements in advance to ensure scientific quality of the clinical trial. The following are examples:
  - potential differences between the study population and target population which may trigger discussion on the generalisability of the results (e.g. due to potential exclusion of digitally illiterate persons or people who live in areas with limited internet connection).
  - imposed modifications in outcome assessments which may trigger a discussion on their validity (e.g, due to heterogeneous implementation of decentralised procedures across clinical trials sites or among trial participants).
  - the potential increase in missing data, overall or for specific endpoints. See also chapter 6 on data management.

  These considerations are of utmost importance especially in trials identified as pivotal in marketing authorisation applications. Sponsors are strongly encouraged to seek scientific advice for these trials. In addition, qualification advice is encouraged when new methods or endpoints are planned to be used.

- IT devices / technologies which are developed and utilised should be fit for the purpose of reliable data collection and handling in accordance with the protocol. The use of computerised systems and/or the creation/capture of electronic clinical data, should be compliant with the 'Guideline on computerised systems and electronic data in clinical trials' EMA/226170/2021[2].

- A contingency plan should be in place to minimise the impact of any risk, for example malfunction of a digital tool or disruption of a planned decentralised visit, for identified critical-to-quality decentralised elements.

- When medical devices, including in-vitro diagnostics (IVDs), are used in the clinical trial, their use should be compliant with the applicable medical device legislation, such as the Medical Device Regulation (MDR) EU no 2017/745, the In Vitro Diagnostic Directive 98/79/EC and/or the In Vitro Diagnostic Regulation (IVDR) EU no 2017/746.

The following chapters outline more specific considerations regarding the decentralisation of certain clinical trial aspects.

[2] At the time of publication of this recommendation paper, the EMA GCP-IWG Guideline on computerised systems and electronic data in clinical trials was being revised following the end of consultation on 17 December 2021: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-computerised-systems-electronic-data-clinical-trials_en.pdf

2. CLINICAL TRIAL OVERSIGHT: ROLES AND RESPONSIBILITIES

When parts of the clinical trial are conducted off-site, and when additional service providers such as home nurses or providers of technology become involved, it is essential that the specific roles and responsibilities of the sponsor, investigator, and any additional parties are clearly defined and understood prior to the start of the trial. In addition, when trial participants are visiting the clinical trial site less frequently, alternate methods of clinical monitoring of the trial participants' current health status and related data collection may need to be utilised. Data may be received from different routes, for example collected at home by the participants themselves, by visiting (external) healthcare professionals, or by digital tools. This poses a challenge to the oversight on the rights, safety, dignity and well-being of the trial participants as well as the reliability of trial results. As a general concept, introducing decentralised elements should be considered as an extension of the clinical trial site with the inclusion of the trial participants' home, resulting in an additional obligation of oversight for investigators and sponsors. It is therefore important that, when decentralised elements are implemented, it is ensured that the investigator and sponsor still can fulfil their legal obligations as laid down in the CTR or the CTD and ICH E6. In addition, with a potential increase in the number of parties involved in the clinical trial, adherence to the GDPR needs to be safeguarded.

The protocol should reflect that the sponsor and the investigator are in full control of their respective areas of responsibilities at all times, e.g. with respect to the data processing, the communication flow, and ultimately the rights, safety, dignity and well-being of the trial participants and reliability of the trial data. In this section considerations in relation to investigator and sponsor oversight are outlined.

Considerations on responsibilities

- Notwithstanding the potential involvement of additional service providers, the clinical trial specific tasks as described in the protocol are ultimately the responsibility of either the investigator or the sponsor, in accordance with ICH E6. Great care should be taken that the delegation of tasks to the different parties is well defined. The introduction of decentralised elements in a clinical trial may have a relevant impact in the trial conduct, therefore, it should be clearly documented which tasks are conducted when, by whom, and in which setting (e.g. at the clinical site, at the trial participant's home, etc.), and how the required oversight by the sponsor and/or supervision by the investigator is achieved. The general overview of the workflow of these different tasks and actions to be taken within the trial should be described in the protocol, and in more detail in a protocol related document.

- In case service providers have been delegated trial specific tasks, a corresponding rationale and the extent of their involvement should be described in a high level in the protocol, and in detail in a protocol related document. The investigator retains the ultimate responsibility for tasks involving trial related medical decisions (i.e. trial participant eligibility and enrolment, protocol specified medical procedures, changes in medication, etc.) and for the rights, safety, dignity and well-being of the trial participants. See also the appendix for current national provisions regarding the involvement of external health care providers.

- Any trial specific task that is delegated to a service provider should be specified in a written agreement between the responsible party for the task (according to ICH E6) and the service provider (see also the EMA GCP IWG Q&A B.2, and B.8). When the sponsor selects a service provider and the investigator is not involved in the contractual arrangement with this service provider, the contract between the sponsor and the investigator should clearly document the contractual arrangements with the service provider if it concerns tasks under investigator's responsibility. This allows the investigator to agree or not to the deployment of service providers for certain trial specific tasks related to the medical care of trial participants. As stated previously, in the general considerations of this paper, it is recommended that the investigator should be involved in an early stage when designing the decentralised elements in

the clinical trial. In this way it can be assessed early on what are the needs of the investigator with regard to the use of service providers for trial specific tasks that fall under the responsibility of the investigator.

- The sponsor should ensure that the contracted service provider is qualified and experienced in the tasks they conduct for the trial. This should be reflected in the contract between the sponsor and the investigator, in order that the investigator is aware of, and can agree or not with the qualification of the service provider when the delegated tasks lie within the investigator's responsibility. The investigator should have the possibility to ask for any additional information in order to perform due diligence and to require any change to the agreement or to the service when considered necessary, including the possibility to reject a certain service provider.
  It is the investigator's responsibility to ensure that the service provider is properly trained on the trial specific tasks they have to conduct, when these tasks concern the medical care of the trial participants or lie within the investigator's responsibility.

- To maintain the investigator's responsibility regarding the medical care and safety of the trial participant and to ensure that the sponsor has adequate oversight over the conduct of the clinical trial effective lines of communication should be established, documented and shared with all relevant parties, including trial participants, investigators, sponsor and any service providers. All parties involved should have access to the information required to fulfil their roles and responsibilities related to the conduct of the clinical trial at any time. In case of an emergency, an effective communication plan needs to be in place, so that all relevant parties can act without undue delay. The trial participant should be well informed and receive contact details for all necessary situations including who to contact for acute cases, but also for device failures, questions on home visits, etc.

Considerations on keeping oversight on incoming data

- Trial participants, investigators and service providers involved in the trial should receive training on how to use the digital tools employed in the trial, to ensure proper data collection, review, and transmission. In addition, the trial participants and service providers should receive training on what is considered an (serious) adverse event ((S)AE), who they should report this to, in what timeframe, and how to manage the (S)AE.

- When AEs are reported via several routes (digital tool, external healthcare professional, or trial participant) it is important that procedures are in place to identify potential duplicates.

- The use of digital tools (such as wearables) result in an increase in the amount of incoming data. This may challenge the capacity of the investigators to fulfil their responsibilities. Emerging data could be continuously at hand, and a clear procedure should be in place to determine how to handle this constant flow of information. The review frequency of the incoming data by the investigator should be based on the relevance of the data to the safety and well-being of the trial participant, and the relevance of the data for the efficacy.
  The review of safety data should be planned with a risk-based perspective, which may include the IMP safety profile, the indication, known potential risks, the use of notifications and alerts. The priority is to capture and assess SAEs in a timely manner, without creating an unacceptable burden for the investigator and/or the trial participant. The use of notifications and alerts is recommended to ensure timely assessment of SAE related data. In designing a trial with digital tools, the sponsor and investigator should anticipate what kind of safety alerts may occur and specify in the protocol how these alerts will be handled. If it is foreseen that a digital tool may generate critical safety data that needs immediate medical attention, a plan should be in place describing this. It should be outlined in the protocol how the investigator and/or the service provider should manage these situations, what actions should be taken and by whom. A

schematic overview of parties involved, information flow and respective duties is recommended. The trial participant should be informed what to expect and what actions they may need to follow in these situations. In addition, a participant targeted scheme of the duties and information flow with the parties involved might enhance understanding.

- The sponsor should ensure that digital tools are transmitting the required alerts as planned. The tool that generates alerts to the investigator should be validated. A risk mitigation plan should be in place for times that the tool may not work as intended.

- The trial participant should be fully informed in advance on how the information transmitted via digital tools, for example electronic Patient Reported Outcomes (ePROs), will be acted upon. It should be made clear to the trial participant that the investigator may not review such data in real time, and that if the trial participant experiences any specific safety concern they need to directly contact the investigator to report such an issue.

3. INFORMED CONSENT PROCESS

An important aspect of a clinical trial is that the potential trial participants give their voluntarily informed consent to participate. To give consent, the potential participant needs adequate information. Informed consent is not only of ethical and legal importance: good communication between the investigator and the trial participant is beneficial for mutual trust and may promote trial compliance. Therefore, when considering the appropriateness of conducting the informed consent process in a remote manner, to use digital information leaflets, and/or to use electronic methods for the signature of the informed consent form, several aspects have to be thoroughly assessed. These include the design of the clinical trial, the characteristics of the trial population, and the risks, burdens and potential benefit related to participating in the clinical trial.

The entire procedure for obtaining informed consent, i.e. the selection, the evaluation of the eligibility, and the actual informed consent process, should be described step-by-step in the clinical trial application to ensure appropriate ethical review. The rationale for not having a physical examination as part of this procedure should be given in the protocol or other protocol related document. The sponsor should also describe in the protocol the chosen method for obtaining informed consent.

Regardless if only a part of or the whole informed consent process is conducted remotely, the process should still be carried out in compliance with the principles laid down in the CTR or the CTD, ICH E6, the GDPR and national legislation.

The informed consent process should be documented in a manner that allows verification of the receipt of information by the trial participant, the discussion between the person qualified to obtain the consent and the trial participant, as well as giving of the consent.

Informed consent interview

ICH E6 requires that all potential trial participants are fully informed on the clinical trial and are given the opportunity to ask questions. In general, this should be a physical meeting between the investigator and the potential trial participant. However, in some cases it can be justified that this is done remotely. The more vulnerable the trial population, the more limited the current knowledge of the efficacy and safety profile of the IMP(s), the more complex the trial concept and the higher the risks associated with the trial-specific interventions, the more necessary is a physical meeting between trial participant and investigator for the purpose of informed consent. In case the potential trial participant is not visiting the clinical trial site, the following aspects should be considered and addressed in the clinical trial application:

- As part of the process of obtaining informed consent, it is considered essential that face-to-face communication takes place between the potential trial participant and the investigator, or a qualified person designated by the investigator. If this discussion is done in a digital/virtual meeting, it is recommended that this takes place in real time where the parties can both see and communicate with each other via audio and video. The remote face-to-face contact should allow for asking questions and the investigator should make every effort to check the identity of the participant if they are not already known by them, and conversely, the participant should have the right to ask for proof of the investigator's identity if they have not been in contact before. Deviation from (remote) face-to-face communication should be justified in the clinical trial application, together with a description of how the verification of the identity of the investigator and the trial participant will be performed in such cases, and how it will be determined that the trial participant has understood the information. See also the appendix for the current national provisions.

- The sponsor should ensure that trial participants and investigators are given the option to have the informed consent interview on site if this is preferred by the trial participant or the investigator. However, in duly justified cases only the remote option may be offered.

- Individual participant related factors affecting the use of decentralised elements of the clinical trial should be evaluated by the investigator during the informed consent interview.

- The reliability and confidentiality of the method used should be ensured. As a general principle, the communication channel used for the informed consent interview should be encrypted to protect the confidential information that will be discussed.

Digital information leaflet

- The use of different kinds of media may enhance the trial participant's comprehension of the trial. However, when considering the use of electronic methods, the sponsor should also be aware that its use may unintentionally discriminate against participants who cannot or prefer not to use such technology. Alternative methods for the electronic provision of information should be available. There may be exceptions where the sponsor only provides a digital information leaflet. In such circumstances, this should be described in the protocol and justified in the clinical trial application.

- The sponsor is responsible to verify whether a clinical trial site and/or the data protection officer of that site agrees to the use and storage of electronic methods for the consent process.

- It should be ensured that the information provided to the trial participant is in a form that can be stored and retrieved by the trial participant.

Informed consent signature

- There are various ways of obtaining a signed informed consent form by remote means. This includes for example a paper consent form sent to the participant signed with a 'wet ink signature' and sent back by post, or a digital consent form signed with an electronic signature, i.e. completely digital.
  Regardless of the format of the informed consent, the method should allow reconstruction of the process, including the validity of the signatures. The sponsor should ensure that the systems used have proportionate security levels and that safeguards regarding confidentiality are in place. In general, the electronic signature functionality should be in accordance with the requirements described in the Guideline on computerised systems and electronic data in clinical trials[3].
  In addition, the method used to record informed consent should follow national requirements with regards to acceptability of electronic signatures (see appendix for current national provisions).

- When using electronic methods, the trial participants should be able to download an electronic copy of the signed and dated informed consent form, or to receive a print-out of the electronic copy. If an electronic copy, it should be protected against modification; any modification should invalidate the signatures.

- Existing procedures related to re-consent should be adapted to the use of electronically signed consent forms.

- Procedures should be in place to handle follow-up steps after the consent has been withdrawn electronically, including partial withdrawal and complete withdrawal, due to the impact on patient participation and data collection. These procedures should include timely notification to the investigator and a communication plan with all other stakeholders. By any means, withdrawals should also be possible outside of the system, and this should be recorded by the investigator.

[3] At the time of publication of this recommendation paper, the EMA GCP-IWG Guideline on computerised systems and electronic data in clinical trials was being revised following the end of consultation on 17 December 2021: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/draft-guideline-computerised-systems-electronic-data-clinical-trials_en.pdf

4. DELIVERY OF INVESTIGATIONAL MEDICINAL PRODUCTS AND ADMINISTRATION AT HOME

Where it is intended for the IMP[4] to be delivered and/or administered at the trial participant's home, a risk assessment should be completed to determine if such an approach is appropriate. The risk assessment should at a minimum take into account the following aspects: the knowledge and uncertainty of the IMP and its safety profile, the route of administration, the trial population, whether an observation period is required, the need for emergency plans, the preparation of the final IMP for administration, its stability, the storage conditions, and the robustness of IMP delivery logistics (the risk of an inadvertently IMP delivery to a non-intended recipient).

The CTR aims to harmonise the rules of the conduct of clinical trials in the member states, while setting high standards of quality and safety of IMPs to ensure the protection of public health. Therefore, the import of IMPs into the EU requires an authorisation (CTR article 61), and the applicable principles of GDP should be considered in the logistics of IMPs. Shipping and the contractual agreements regarding IMP shipment between sponsor and investigator site or pharmacy are covered by the 'Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice'. IMP delivery to the trial participant is not, however, within the scope of that guideline.

In this section considerations are given concerning the delivery of the IMP and the administration at the trial participant's home.

Considerations on IMP delivery direct to trial participants

- If the IMP is not dispensed to the trial participant by the investigator or delegated healthcare professional at the site, it is recommended that the vendors responsible for delivery to the participant are authorised to distribute or dispense medicinal products as much as possible. Any non-authorised vendor used in the logistics should be qualified and supervised by the authorisation holder, in accordance with the principles of GDP. There must be a written contract which clearly establishes the duties of each party. It is recommended that the number of separate transportation steps are minimised.

- The investigator remains responsible for the decision of treatment which should be documented (for example prescription or Interactive Response Technology system) prior to any delivery of IMP to the trial participant's home. Delivery to the participant's home could mean another suitable address the participant prefers to receive the IMP at, provided that:
  - regulatory requirements are complied with;
  - risks of exposure to conditions that could impact quality and integrity of the product are minimised;
  - the applicable principles of the guidelines on GDP of medicinal products for human use are taken into consideration.

  When the given address is abroad, it should be verified whether the national legislation of that country allows the IMP to be delivered there (see appendix on national provisions). The given address should also be the place where the IMP is stored and administered, to avoid additional transport by the trial participant themselves.

- There are several options for delivery of the IMP to the trial participant's home, depending on what is permitted by national requirements. This can include delivery from the pharmacy of the investigator site, from a delegated pharmacy, or from a depot. The sponsor has the overall responsibility for the process and the contracts or agreements, which should reflect the principal investigator's responsibilities pursuant to ICH E6. Please refer to the appendix for the acceptable options in the member states regarding the delivery of the IMP to the trial participant's home. The arrangements for delivery of the IMP to the trial participant should be described in the clinical trial protocol or the Investigational Medicinal Product Dossier.

[4] The recommendations for IMP delivery and administration at home also apply to auxiliary medicinal products (AxMP).

- The sponsor should ensure that the personal data of the trial participants required for the delivery of the IMP is used in accordance with the GDPR on a need-to-know basis. For example, it should be ensured that personal data is solely accessible to those involved in the delivery of the IMP and will not be stored for other purposes than the delivery of the IMP. Access to the personal data should be restricted as soon as the final delivery is completed. Information should be made available only for the purpose of monitoring, auditing, inspections, and to trial participants for the exercise of their GDPR rights.

- Trial participants should be made aware during the informed consent process that their contact details will be used for delivery purposes if the IMP is to be delivered to the trial participant's home. Details regarding the use of contact information should be outlined in the participant information.

- When delivering the IMP, it should only be handed over to the trial participant (or a representative, if applicable), or the present health care professional involved in the clinical trial. Sponsor procedures should be in place covering delivery and receipt of the IMP. With regard to receipt of IMP, the procedure should detail the steps and responsibilities in relation to confirmation of IMP identity (e.g. batch number) to ensure that what has been dispatched has actually been delivered. In some cases, the trial participant (or a representative) may not be available to accept and sign the receipt of the IMP. In this case, the IMP should be brought back by the service provider to the original location (investigator's site, (central) pharmacy, or depot).

- As an alternative to delivering the IMP to the trial participant's home, the IMP could be dispensed by local pharmacies (based on a prescription issued by the investigator), provided that the labelling requirements in the CTR or CTD are fulfilled, and if national requirements allow (see appendix). In particular, sponsors are reminded to consult Article 61(5) of CTR regarding labelling requirements. The local pharmacy should be aware that the prescription of the IMP is in the context of a clinical trial, and if necessary, be trained to dispense the IMP.

Considerations on IMP storage and administration at the trial participant's home

- The sponsor and the investigator should consider during the planning stage of the clinical trial how the appropriate storage conditions of the IMP can be met, and whether the IMP is suitable for administration at home. The inclusion/exclusion criteria should include provisions related to the adequacy of the trial participant's home for storage of the IMP, such as temperature control and restricted access where necessary. Sponsors may consider providing trial participants additional equipment necessary for IMP storage. This should be described in the protocol or other protocol related document (e.g. pharmacy manual), including the documentation provided to participants. The investigator should give instructions to the trial participants on the use and storage of the IMP. The instructions should be realistic, feasible and the additional burden for the trial participant should be part of the aforementioned risk assessment.

- The investigator and the sponsor should consider whether administration at home can be done by the trial participants themselves or if a trained, experienced and qualified healthcare professional is required for administration. In the case of complex administrations, special preparation or handling requirements, or when required by the safety profile of the IMP (e.g. unknown or potential serious adverse events in connection to the administration), health care professionals should always be involved.

- Generally, if an IMP is required to be administered by a healthcare professional, shipping directly to the trial participant may not be appropriate. In the event it is required for IMP to be shipped directly to the trial participant separately, clear instructions for storage of the IMP prior to healthcare professional visit should be given, as well as a clear explanation that the IMP is not to be administrated before the visit of the healthcare professional nor before the investigator's decision.

- If it is anticipated that the trial participants will prepare and administer the IMP as outlined in the protocol, they should be instructed in advance about these aspects. Where appropriate, there should be instructions provided regarding these steps as well as dosing, in addition to what is already present on the IMP label or package leaflet. These instructions should be adapted to the needs of the individual trial participants. The use of electronic step-by-step instructions which are easily and promptly accessible (such as QR code scanning), could be considered. Depending on the safety profile of the IMP, the investigator should contact the trial participants after the first delivery of the IMP to ensure proper handling of the IMP. The sponsor may consider providing additional equipment necessary for the safe administration, use and destruction of the IMP to the trial participants, in which case this should be described in the protocol or other protocol related document (e.g. pharmacy manual), including the documentation provided to the participants.

- The investigator should follow-up, at regular intervals, with participants to ensure the IMP is taken appropriately and according to the IMP instructions.

- Procedures should be in place for IMP accountability and treatment compliance of trial participants. These tasks fall under the investigator's responsibility according to ICH E6.

- Procedures should be in place for IMP return from the trial participant's home, and destruction of the unused IMPs, in compliance with the protocol and local safety requirements. The procedure should also cover recalls during the conduct of the trial, and the steps taken to avoid that the IMP remains at the trial participant's home beyond the envisaged treatment period.

5. TRIAL RELATED PROCEDURES AT HOME

In a clinical trial with decentralised elements, trial related procedures may take place outside of the clinical trial site, such as in the trial participant's home[5]. These procedures could be performed by the trial participant, the investigator staff visiting the trial participant at home, or a person contracted for the trial and delegated to perform them. For these procedures or examinations performed at home, considerations include, but may not be limited to the following:

- The investigator should ascertain whether the trial participant's home situation and premises are suitable to have trial related procedures performed at home. It should be considered that there may be 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. The trial participant should be informed during informed consent process about trial procedures planned to take place 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 and the person performing the task is qualified and/or trained to perform the task. For example, if biological samples are collected at home, it should be considered whether persons taking the sample are qualified and allowed by legislation to take the sample. In addition, adequate handling and storage conditions for the samples throughout the entire process should be assured.
- In the event of trial participants performing trial related tasks it should be ensured that appropriate training is provided to them, and any additional trial participant burden duly considered, including tasks related to digital data collection.
- The sponsor and/or investigator should ensure that appropriate guidance and training is provided to the delegated person(s) to conduct the tasks at home correctly.
- The insurance or indemnity or a guarantee or a similar arrangement foreseen by CTR or the CTD should be in place to cover any damage resulting from trial related procedures performed at home.
- The investigator should monitor compliance of the trial participant considering the lack of/decrease in the number of face-to-face visits/meetings between the trial participant and the investigator and/or delegated staff.
- The trial participants should be given the opportunity to visit the investigator in person if needed/preferred and they should be able to have a direct contact line if further support to perform a trial related task/collect data is needed.
- 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 (see also chapter 2 about considerations on maintaining oversight on incoming safety data).
- The sponsor should provide alternatives if a trial participant is unable or not willing to use her/his/their own private device (mobile phone, tablet, etc.) to capture trial data.

[5] A trial participant's home can be more than one home, e.g. children with parents that are separated.

6. DATA COLLECTION AND MANAGEMENT INCLUDING DEFINING AND HANDLING SOURCE DATA

Decentralised clinical trials are characterized by an extensive shift of data collection from the investigator/investigator site to the trial participants and/or their caregiver and/or service providers (e.g. home nurses). Direct data capture by electronic systems (e.g. electronic Case Report Forms (CRFs), ePROs, wearables etc.) may occur, for instance, at the clinical trial site or off-site locations.

According to ICH E6, the data recorded during the clinical trial should be credible, reliable and verifiable. In addition, the data protection requirements according to the GDPR should be adhered to (see also chapter 1, general considerations).

Utilising multiple systems and parties adds complexity and requires an adequate oversight and implementation of adequate measures by the sponsor. To this end, the sponsor should:

- Ensure that all parties involved in the clinical trial have an overview of the data flow; a data flow diagram with additional explanations in the protocol is highly recommended.
- Ensure that the used data acquisition tools are configured and validated in accordance with their intended use.
- Determine the type and scope of the trial participants' personal data to be collected and ensure adequate protection in compliance with the GDPR of such personal data in any step of the process.
- Ensure that when source data captured by a data acquisition tool is transferred to another location and subsequently irreversibly deleted from the data acquisition tool, both the data and the metadata are transferred (see ICH E6 1.63 Certified Copy).
- Implement measures such as encryption to minimise the risk of unauthorised access, when transferring the data from a data acquisition tool to a server.
- Ensure access to trial data is controlled by defined user rights and methods of access for all relevant parties involved. Unauthorised access should be prevented using appropriate security measurers e.g. firewalls.
- Ensure control of and continuous and complete access by the investigator to both source data generated either on-site or off-site as well as source data reported to the sponsor (e.g. central lab data).

The risk of erroneous data entry for data measured and entered directly by trial participants, especially on primary, key-secondary or safety endpoints should be minimised by appropriate measures.

Additional advice on elements specific to digital data capture systems can be found in the 'Qualification opinion on eSource Direct Data Capture (DDC) (EMA/CHMP/SAWP/483349/2019)' from the EMA Scientific Advice Working Party (SAWP) and the 'Notice to sponsors on validation and qualification of computerised systems used in clinical trials (EMA/INS/GCP/467532/2019)'. In addition, reference is made to the EMA GCP matters Q&A B3 'How and where should source data be defined' as well as to the EMA GCP matters Q&A B5 'What are the expectations of the investigator's copy of the CRF when using a web based application'.

7. TRIAL MONITORING

Trial monitoring is part of the quality control processes in clinical trials.

- As detailed in ICH E6, the monitoring strategy should be based on the specifics of a clinical trial. These specifics may include, as applicable, decentralised processes and tools described in the previous sections. For example, if according to the trial protocol, safety and/or efficacy data are collected via ePRO or wearables, or if key processes (e.g. those related to primary endpoints) are performed outside the investigator site (e.g. at central reading facilities, central laboratories), the specific risks associated with these decentralised processes, tools, locations, and individuals involved should be taken into account in the monitoring strategy.

- Monitoring procedures can be divided into centralised and site monitoring, and generally a combination of them both is appropriate. Site monitoring is usually performed on-site. Depending on its purpose and suitability it may be performed off-site (remotely).

- When establishing remote access for the purpose of monitoring, the principles of necessity and proportionality should always be adhered to. The monitoring strategy chosen should not unduly burden the site.

- If remote access to source data and documents is foreseen, additional measures with respect to confidentiality of data access and security of the systems should be in place. Further guidance on this is being drafted by the GCP IWG. See appendix with current national provision overview per MS whether remote access to medical records by the monitor or auditor is allowed.

APPENDIX: NATIONAL PROVISIONS OVERVIEW

This overview of national provisions does not purport to be an interpretation of law and/or regulations and is for guidance purposes only.

The answers to the questions stated in the national provision overview are giving by the individual Member States and relates to the context and general recommendation as provided in the recommendation paper. References for the relevant sections within the recommendation paper are given in the question header.

Please note that footnotes from each Member State are given in the tables following the national provision overview. The footnotes provide legislation reference, background or conditions for a 'No' or a 'Yes'.

The national provision overview will be updated as new data emerge.

Please see relevant footnotes for responses marked with an asterisk. A footnote may be raised even though no response is given.	AT	BE	BG	CY	CZ	DE BfArM	DE PEI	DK	EE	EL	ES	FI	FR	HR	HU	IE	IS	IT	LI	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK
The delivery of IMPs from sponsor/site, in relation to RP section 4.																															
Q1: Is it possible to deliver IMPs directly to trial participants from their associated trial site?	No *	No *			Yes *	Yes *		Yes	Yes	*	Yes *	Yes	*	No *	Yes	Yes		Yes		Yes *			Yes *	Yes *	Yes	Yes	Yes *	Yes	Yes *	No *	Yes
Q2: Is it possible to deliver IMPs directly to trial participants from the pharmacy associated with the trial site?	No *	No *			Yes *	Yes *		Yes	No *	*	Yes *	Yes *	*	No *	Yes			Yes		No *			Yes *	Yes *	Yes	Yes	Yes *	No *	Yes *	*	Yes
Q3: Is it possible to deliver IMPs directly to trial participants from any delegated pharmacy?	No *	No *			Yes *	Yes		Yes *	No *	No *	No *	No *	Yes	No *	Yes			*		No *			No	Yes *	Yes	No *	Yes *	No *	Yes *	No *	Yes
Q4: Is it possible to deliver IMPs directly to trial participants from the IMP manufacturer with a MIA license?	No	No *			No *	No		*	No *	No *	No *	No *	No *	No *	Yes	No *		*		No *			No	No	No *	No *	Yes *	No	No	No *	No
Q5: Is it possible to deliver IMPs directly to trial participants from the trial sponsor (sponsors intermediaries/depots)? If yes, footnote states if a licence is required for the depot to carry out this task and how to obtain this licence.	No	No *			No *	No		*	No *	No *	No *	No *	No	No *	No			*		No			No	No	No *	No *	No *	Yes *	No	*	No
The shipment of IMPs from sponsor/site across boarders within the EU, in relation to RP section 4.																															
Q6: Is it possible to deliver IMPs directly to trial participants from e.g. distribution/manufacturing/pharmacy licence holders located in other EU MSs if legally allowed to carry out this task in the country of origin?	No *	No *			No *	No *		Yes	No *	No *	No *	No *	No *	No *	Yes			*		No *			No	No *	No *	No *	No *	Yes	No *	No *	No
Q7: Is it possible to deliver IMPs directly to investigators from e.g. distribution/manufacturing/pharmacy licence holders located in other EU MSs if legally allowed to carry out this task in the country of origin?	Yes *	Yes *			Yes	Yes *		Yes	Yes	Yes *	No *	No *	Yes *	No *	Yes	Yes		*		Yes			Yes	No *	No *	No *	Yes *	Yes	No *	No *	Yes
Labelling of IMP, in relation to RP section 4.																															
Q8: Is it possible for any delegated pharmacy to label IMP or is this restricted to the pharmacy associated with the trial site?	No	No *			Yes *	*		Yes	*		Yes *	No *	No *	No *	Yes			Yes		Yes *			No	*	No *	No *	No	No	Yes *	*	Yes

Please see relevant footnotes for responses marked with an asterisk. A footnote may be raised even though no response is given.	AT	BE	BG	CY	CZ	DE BfArM	DE PEI	DK	EE	EL	ES	FI	FR	HR	HU	IE	IS	IT	LI	LT	LU	LV	MT	NL	NO	PL	PT	RO	SE	SI	SK
The shipment and hand-out of IMPs from pharmacies. This is currently not included in the recommendation paper but may be relevant in next version of the RP.																															
Q9: Is it possible to deliver or dispense authorised IMPs directly to trial participants from pharmacies not associated with the clinical trial sites? This include authorised investigational medicinal products not used according to their SmPC.	Yes *	No *			No *	Yes		Yes *	No *	No *	No *	No *	No *	No *	Yes			*		No *			No	Yes *	Yes *	No *	No *	No *	Yes *	*	Yes *
Q10: Is it possible to deliver or dispense non-authorised IMPs directly to trial participants from pharmacies not associated with the clinical trial sites?	No	No *			No *	Yes		No *	No *	No *	No *	No *	No *	No *	Yes			*		No *			No	Yes *	Yes *	No *	No *	No *	Yes *	*	Yes *
The eConsent process, in relation to RP section 3.																															
Q11: Is a physical face to face meeting between the trial participant and the PI or a member of the research team always mandatory during the consent procedure (even if the rest is conducted remotely)?	No	No			No *	Yes *		No *	*	*	No *	No	No *	No *	Yes *	No		No *		No			No	No *	No	No	Yes *	No	No	*	No
Q12: Is it possible to use electronic signatures instead of wet ink? If yes, please specify in the footnotes which eIDAS category is expected for the electronic signature.	Yes *	Yes *			Yes *	Yes *		Yes *	Yes *	*	Yes *	Yes *	Yes *	Yes *	Yes *	Yes		Yes *		Yes *			Yes	Yes *	Yes *	*	Yes *	Yes *	Yes *	*	Yes *
Trial participant oversight and home visits, in relation to RP section 2 and 5.																															
Q13: Is it possible for the PI to delegate tasks under their responsibility to a qualified (for the delegated task) external healthcare provider?	Yes	Yes *			Yes *	Yes *		Yes	Yes *	Yes *	Yes *	Yes	Yes *	Yes	Yes *	Yes		Yes		Yes *			Yes	Yes *	Yes *	*	Yes *	Yes *	Yes *	Yes	Yes
Q14: Certain tasks/procedures carried out at home may require supervision of the investigator (a physician). Is it allowed for the physician to supervise remotely?	Yes	Yes *			No *	Yes *		Yes	*	*	*	Yes	*	Yes *	Yes *	*		Yes		Yes			Yes	Yes *	Yes	*	Yes *	No *	Yes *	*	No
Trial Monitoring using remote access to source data, in relation to RP paper section 7																															
Q15: Is remote access to the medical records allowed by the monitor or auditor?	Yes *	No *			No *	Yes *		Yes *	*	No	*	Yes	Yes *	No *	Yes *	Yes *		Yes *		Yes *			Yes	Yes *	*	*	*	No	No	No *	No

Footnotes to the DCT Provision Overview by Member States

	AT
Q1	§57, §59(1), (9) AMG (Austrian Medicines Act)
Q2	§57 AMG (Austrian Medicines Act), exception: Authorised or registered, non-prescription medicinal products could be delivered directly to patients as per §59(10) AMG (Austrian Medicines Act).
Q3	§57 AMG (Austrian Medicines Act), exception: Authorised or registered, non-prescription medicinal products could be delivered directly to patients as per §59(10) AMG (Austrian Medicines Act).
Q4	-
Q5	-
Q6	§57 AMG (Austrian Medicines Act), exception: Authorised or registered, non-prescription medicinal products could be delivered directly to patients as per §59(10) AMG (Austrian Medicines Act).
Q7	§57, §59(1), (9) AMG (Austrian Medicines Act)
Q8	-
Q9	(For non-prescription medicinal products only), packaging and labelling must not be changed, IMP must be from trial stock
Q10	-
Q11	-
Q12	The use of advanced and qualified electronic signatures is accepted. Integrity and authenticity of the signature must be undisputable.
Q13	-
Q14	-
Q15	Allowed for original electronic medical records only. The electronic medical record system must be validated for that purpose.

	BE
Q1	Not allowed, unless specified in the CTA why a waiver should be authorized, referring to the Q&A n°10: https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp
Q2	Same approach as in Q1 and according to the RD of 21 January 2009, a pharmacy in Belgium must deliver each medication in person to a patient, with the exception in art. 29 of medication free of prescription.
Q3	According to the RD of 21 January 2009, a pharmacy in Belgium must deliver each medication in person to a patient, with the exception in art. 29 of medication free of prescription.
Q4	According to the RD of 21 January 2009, a pharmacy in Belgium must deliver each medication in person to a patient, with the exception in art. 29 of medication free of prescription. An investigator can also provide the trial participant in person with an amount of medication (IMP).
Q5	Same as Q4
Q6	Same as Q4
Q7	According to art. 43 of the RD 9/10/2017
Q8	Labelling is a manufacturing operation. Labelling is only possible if the site/pharmacy has a GMP licence.
Q9	Only a delegated pharmacy (delegated by the PI) can deliver or dispense IMPs.
Q10	Only a delegated pharmacy (delegated by the PI) can deliver or dispense IMPs.
Q11	-
Q12	According to the national guidance on e-ICF, for remote signing, only an advanced or a qualified electronic signature as defined in the eIDAS regulation (Ref. 3) should be used as they uniquely identify the individual signing. Only a qualified electronic signature has the equivalent legal effect of a handwritten signature (eIDAS, art 25. §2.). Signatures via e-ID (Ref. 4) or itsme® (Ref. 5) are qualified electronic signatures. The advanced signature should comply with the defined requirements as described in the article 26 of the eIDAS Regulation that give guarantees of the identification of the individual signing. More information is available on the website of the FPS Economy (Ref. 6). References are available in https://consultativebodies.health.belgium.be/en/e-ICF%20guidance%20Belgium_30-09-2020
Q13	Provided that the delegated tasks fall under the qualification of the study personnel according to the Belgian legislation.
Q14	Provided that the delegated tasks fall under the qualification of the study personnel according to the Belgian legislation.
Q15	Remote source data verification is as such not allowed. This is only possible in specific cases, approved during the CTA process under the following conditions: - An agreement has been setup describing rSDV which is approved by all parties (institution, principal investigator and the sponsor or the CRO assigned). - The rSDV can be organized by the investigator's site and is therefore technically feasible without compromising the confidentiality of the Electronic Medical Records data.

No footnotes for: BG

No footnotes for: CY

	CZ
Q1	It is possible, but it will be assessed on a case by case basis with respect to the character of the particular IMP and its pharmaceutical form (tablets, infusion etc.) It would not be possible in case of IMPs that need to be diluted or reconstituted before administration, because these operations have to be carried out by healthcare professionals appointed by the healthcare service provider (Section 79 (10) of Act no. 378/2007 Coll., on Medicinal Products). The sponsor must then proceed in accordance with national guideline VYR-44, available on SUKL's website.
Q2	It is possible if the pharmacy is closely connected with the trial site. It is possible then to deliver IMPs directly to trial participants from the pharmacy based on investigator´s request. But it will be assessed on a case by case basis with respect to the character of the particular IMP and its pharmaceutical form (tablets, infusion etc.) It would not be possible in case of IMPs that need to be diluted or reconstituted before administration, because these operations have to be carried out by healthcare professionals appointed by the healthcare service provider (Section 79 (10) of Act no. 378/2007 Coll., on Medicinal Products). The sponsor must then proceed in accordance with national guideline VYR-44, available on SUKLS's website.
Q3	It is possible if the pharmacy is connected with the trial site per contract. It is possible then to deliver IMPs directly to trial participants from the pharmacy based on investigator´s request. But it will be assessed on a case by case basis with respect to the character of the particular IMP and its pharmaceutical form (tablets, infusion etc.) It would not be possible in case of IMPs that need to be diluted or reconstituted before administration, because these operations have to be carried out by healthcare professionals appointed by the healthcare service provider (Section 79 (10) of Act no. 378/2007 Coll., on Medicinal Products). The sponsor must then proceed in accordance with national guideline VYR-44, available on SUKLS's website.
Q4	In general, the trial site pharmacy or PI is responsible for IMP handling. (Section 75 (5) and section 77 Act no. 378/2007 Coll., on Medicinal Products). Also, in line with the GCP the sponsor must not know trial participant's identification.
Q5	In general, the trial site pharmacy or PI is responsible for IMP handling. (Section 75 (5) and section 77 Act no. 378/2007 Coll., on Medicinal Products) Also, in line with the GCP the sponsor must not know trial participant's identification.
Q6	In general, the trial site pharmacy or PI is responsible for IMP handling. (Section 75 (5) and section 77 Act no. 378/2007 Coll., on Medicinal Products)
Q7	-
Q8	Delegated pharmacy can label IMP, but it must be treated contractually in case that delegated pharmacy and trial site are not the same legal entities.
Q9	In general, the trial site pharmacy or PI is responsible for IMP handling. (Section 75 (5) and section 77 Act no. 378/2007 Coll., on Medicinal Products)
Q10	In general, the trial site pharmacy or PI is responsible for IMP handling. (Section 75 (5) and section 77 Act no. 378/2007 Coll., on Medicinal Products)
Q11	But in accordance with Act no. 378/2007 Coll., on Medicinal Products, an investigator must always be a physician and only the investigator is responsible for dialogue with the participant during the consent procedure.
Q12	In our view, it is possible to use a qualified electronic signature in accordance with Regulation (EU) no. 910/2014 of the European Parliament and of the Council of 23 July 2014 on Electronic Identification and Trust Services for Electronic Transactions in the Internal Market and Repealing Directive 1999/93/EC (the „eIDAS regulation"). However, given that the acceptability of electronic signatures concerns all EU member states and the approach should be harmonised, we recommend to confirm with the European Commission should there be any differing views.
Q13	Home care is possible in the CZ, but with certain limits – please see more information on the website here https://www.sukl.eu/medicines/home-care?lang=2
Q14	Due to safety of patients. Supervision of a physician is necessary due to situations where potential action from a physician would be required in case of any urgent emergency (risk procedure etc.) In such case remote supervision can put the participant in danger (connection loss, misunderstanding in communications etc.)
Q15	As the medical records are currently available in the paper form at the trial sites, the remote access is not allowed. With the ongoing digitization of healthcare systems at the trial sites, the remote access to the medical data will be reviewed case by case.

	DE (BfArM)
Q1	Not subject to CT legislation
Q2	Certain restrictions for e.g. hospital pharmacies may apply.
Q3	-
Q4	In principle: Not allowed. According to Section 47 (1) sentence 1 number 2 letter g German Medicinal Product Act pharmaceutical entrepreneurs and wholesalers may only supply pharmacy only medicinal products only then directly and only to hospitals and doctors if the medicinal products are labelled "Intended for clinical trials", provided they are supplied free of charge. Exceptions: According to an exemption valid until 31. December 2023, the NCA may, by way of derogation from Section 47 (1) sentence 1 number 2 letter g AMG, permit pharmaceutical entrepreneurs (also: sponsors) and wholesalers to make medicinal products labelled for clinical trials available free of charge to participants in a clinical trial if, after an assessment to be carried out by the sponsor on a case-by-case basis, the safety of the persons participating in the clinical trial and the validity of the data collected in the clinical trial are guaranteed and the pseudonymisation of the data is ensured by appropriate measures that the trial participants have the right to contact the sponsor.
Q5	
Q6	See explanation to Q4
Q7	Section 47 (1) sentence 1 number 2 letter g and section 73 (2) number 2 German Medicinal Product Act.
Q8	It is crucial, that the manufacturer or the pharmacy has a manufacturing license
Q9	
Q10	
Q11	Face to face meeting not subject to German Medicinal Product Act. According to Model Professional Code for Physicians of the German Medical Association exclusive counselling or treatment via communication media is permitted in individual cases if this is justifiable from a medical point of view and the required medical care is observed, in particular by the way in which the findings are ascertained, counselling, treatment and documentation are carried out and the patient is also informed about the special features of exclusive counselling and treatment via communication media.
Q12	Only possible, when qualified electronical signature (eIDAS)
Q13	Possible in principle, but medical activities must be carried out by a physician
Q14	„In principle, yes, subject to the qualification requirements under national law for the medical personnel to whom a task is assigned; a number of medical tasks may according to national law only be performed by physicians (with a medical license to „In principle, yes, subject to the qualification requirements under national law for the medical personnel to whom a task is assigned; a number of medical tasks may according to national law only be performed by physicians (with a medical license to practice medicine
Q15	In principle, yes, provided that the investigators can and does comply with their obligation to maintain the confidentiality of his patients' health records; therefore, the responsibility for answering this question is with the respective investigator

No footnotes for: DE (PEI)

	DK
Q1	-
Q2	-
Q3	Yes, for hospital pharmacies.
Q4	A framework is being developed and will be provided in national guidance.
Q5	A framework is being developed and will be provided in national guidance.
Q6	-
Q7	-
Q8	-
Q9	If dispensed and then delivered according to normal prescription practice and taken by pharmacy standard stock of medicinal products.
Q10	-
Q11	The physical face-to-face meeting is the primary expectation, but video-based communication can be accepted in certain situations, as per decision of the ethical committee.
Q12	Currently both NemID (OCES standard) and MitID (eIDAS-compliant) is accepted.
Q13	-
Q14	-
Q15	Please consult the DKMA DCT guidance for specific requirements if utilised for rSDV.

	EE
Q1	-
Q2	Not allowed for hospital pharmacies
Q3	The conditions and procedure for the issue of prescriptions for medicinal products and for the dispensation of medicinal products by pharmacies and the format of the prescription
Q4	Medicinal Products Act
Q5	Medicinal Products Act
Q6	Medicinal Products Act
Q7	-
Q8	Re-labelling is restricted to associated pharmacy
Q9	The conditions and procedure for the issue of prescriptions for medicinal products and for the dispensation of medicinal products by pharmacies and the format of the prescription
Q10	The conditions and procedure for the issue of prescriptions for medicinal products and for the dispensation of medicinal products by pharmacies and the format of the prescription
Q11	ECs decision
Q12	Qualified electronic signatures acceptable in Estonia: • National ID-card • Mobile-ID • Smart ID
Q13	-
Q14	Case by case
Q15	Remote SDV not allowed

	EL
Q1	Direct shipment to the patient is not addressed in CT legislation. In general, the trial site Head of hospital pharmacy or PI is responsible for IMP handling. Ministerial Decree O.J. 4131/2016, Art 6.
Q2	Direct shipment to the patient is not addressed in CT legislation. In general, the trial site Head of hospital pharmacy or PI is responsible for IMP handling. Ministerial Decree O.J. 4131/2016, Art 6.
Q3	In general, the trial site Head of hospital pharmacy or PI is responsible for IMP handling. Ministerial Decree O.J. 4131/2016, Art 6.
Q4	In general, the trial site Head of hospital pharmacy or PI is responsible for IMP handling. Ministerial Decree O.J. 4131/2016, Art 6.
Q5	In general, the trial site Head of hospital pharmacy or PI is responsible for IMP handling. Ministerial Decree O.J. 4131/2016, Art 6.
Q6	In general, the trial site Head of hospital pharmacy or PI is responsible for IMP handling. Ministerial Decree O.J. 4131/2016, Art 6.
Q7	Yes, however IMPs are shipped to the trial site (not to specific investigators).
Q8	-
Q9	In general, the trial site Head of hospital pharmacy or PI is responsible for IMP handling. Ministerial Decree O.J. 4131/2016, Art 6.
Q10	In general, the trial site Head of hospital pharmacy or PI is responsible for IMP handling. Ministerial Decree O.J. 4131/2016, Art 6.
Q11	Although not specifically addressed in CT legislation, a face-to-face meeting is implied. Ministerial Decree O.J. 4131/2016, Art. 9. In addition, the National Ethics Committee interpretation is that a face-to-face meeting is required for the provision of Informed Consent.
Q12	In general, electronic signatures are acceptable in Greece. However, CT specific legislation does not address the issue. The National Ethics Committee requires wet ink signatures.
Q13	Ministerial Decree O.J. 4131/2016, Art. 3
Q14	Not specifically addressed in current CT legislation
Q15	-

	ES
Q1	Real Legislative Decree 1/2015 article 3.6 c) and Royal Decree 1090/2015 article 39 ñ) (however this activity should be managed by the Pharmacy Department [unless the site has no Pharmacy]).
Q2	Real Legislative Decree 1/2015 article 3.6 c) and Royal Decree 1090/2015 article 39 ñ)
Q3	Real Legislative Decree 1/2015 article 3.6 c) and Royal Decree 1090/2015 article 39 ñ). It is covered by Autonomous Communities legislation (e.g. Law 19/1998 the organization of pharmaceutical services in Madrid)
Q4	Real Legislative Decree 1/2015 article 3.6 c) and Royal Decree 1090/2015 article 39 ñ)
Q5	Real Legislative Decree 1/2015 article 3.6 c) and Royal Decree 1090/2015 article 39 ñ)
Q6	Real Legislative Decree 1/2015 article 3.6 c) and Royal Decree 1090/2015 article 39 ñ). It is covered by Autonomous Communities legislation (e.g. Law 19/1998 the organization of pharmaceutical services in Madrid)
Q7	Real Legislative Decree 1/2015 article 3.6 c) and Royal Decree 1090/2015 article 39 ñ). Except if the trial site has no Pharmacy Department.
Q8	Regulation 536/2014 article 61.5 a). If the delegated pharmacy is taking part in the same clinical trial in the same Member State.
Q9	Real Legislative Decree 1/2015 article 3.6 c) and Royal Decree 1090/2015 article 39 ñ)
Q10	Real Legislative Decree 1/2015 article 3.6 c) and Royal Decree 1090/2015 article 39 ñ)
Q11	Physical face to face is not specifically established by any national provisions.
Q12	If high level of eIDAS and if the confidentiality of the personal data, data security and secure access to the data is ensured
Q13	If an adequate investigator oversight and proper contractual arrangements between sponsor, trial site and investigator is ensured. Data protection aspects should also be considered.
Q14	Certain tasks/procedures should be defined in order to provide proper assessment. General Data Protection Regulation (GDPR) should be addressed in this regard.
Q15	There are no specific national provisions; GDPR covers this aspect in the entire EU and should be considered.

	FI
Q1	-
Q2	In special and justified circumstances only
Q3	Medicinal Act §15 b. Fimea Administrative Regulation 2/2016
Q4	Medicinal Act §15 b. Medicinal Act §31
Q5	Medicinal Act §15 b
Q6	Medicinal Act §17. Medicinal Act §15a
Q7	Medicinal Act §17
Q8	Medicinal Act §15a
Q9	Fimea Administrative Regulation 2/2016
Q10	Fimea Administrative Regulation 2/2016
Q11	-
Q12	Legal requirement according to legislation on patient records. Also, electric identification via suomi.fi-identification (allows eIDAS identification).
Q13	-
Q14	-
Q15	-

	FR
Q1	The shipment to patient home by PUI (hospital pharmacy) are allowed by 'retrocession' (article L. 5126-6 CSP). For experimental drugs in the context of a CT and in absence of any legal specification, ANSM and Ethics Committees may accept it.
Q2	The shipment to patient home by PUI is allowed by 'retrocession' (article L. 5126-6 CSP). For experimental drugs in the context of a CT and in absence of any legal specification, ANSM and Ethics Committees may accept it.
Q3	-
Q4	In accordance with art R 5124-2 and -3 of CSP
Q5	-
Q6	As per French legislation.
Q7	Yes, but under conditions for the shipping to the investigators as per article L 5126-7 of CSP. PUIs are allowed to provide investigators of the same CT or professionals with similar activities outside of France (article R 5124-4 of CSP), with experimental drugs. In the same way dispensers of experimental drugs who are based outside of France, may be allowed to provide French investigators of the same CT with experimental drugs. However, these deliveries should be in conformity with articles L5121-108 and L5124-13 of CSP and customs code (importation authorization if clinical trial is not already authorized). Under these conditions the ANSM may agree. The labelling should be in French language.
Q8	The community pharmacy is not allowed to label experimental drugs. The labelling of experimental drugs should be performed either by a pharmaceutical entity with a GMP manufacturing authorization, or by a PUI pharmacy with authorization of preparing products needed for clinical trials (article R.5126-9 CSP).
Q9	Not possible for a PUI pharmacy in a hospital that is not involved in the given clinical trial (article L. 5126-1 CSP). Possible for a community pharmacy under conditions of article D. 5125-45-1 of CSP - if specified in the protocol, the ANSM may agree.
Q10	Not possible (article L. 5126-1 and D. 5125-45-1 of CSP)
Q11	Not mandatory
Q12	Based on the following legal references: - Article L1122-1-1 alinéa 1st of CSP & article 1367 of Civil code. - The European regulation (UE) number 910/2014 of European Parlement and of Counsil of 23 juillet 2014 concerning the electronic identification does distinguish three types of electronic signatures: the simple electronic signature, the advanced signature (article 26 of regulation) and qualified signature. The e-consent is legal (via these 3 categories of signature) but not yet used in France under this scope.
Q13	Provided that the delegation is appropriately planned in the study protocol and validated by competent authorities. This possibility allows to involve the private physicians who work outside the hospitals in clinical studies.
Q14	As of today, it is not forbidden in the regulation. As a consequence, it is allowed for a given trial provided that there is no opposition from ANSM or from the Ethics Committees.
Q15	Fulfilling the recommendations of the CNIL (French DPA) about regulation and sensitive data protection. cf. provisional recommendations during the Covid crisis (https://www.cnil.fr/fr/recommandations-provisoires-controle-qualite-essais-cliniques-crise-sanitaire)"

	HR
Q1	The IMP must be managed by trial site pharmacy or PI.
Q2	According to the Medicinal Product Act only wholesale distributors can distribute medicinal products and the IMP is dispensed to the participant by the trial site pharmacy or PI.
Q3	According to the Medicinal Product Act only wholesale distributors can distribute medicinal products and the IMP is dispensed to the participant by the trial site pharmacy or PI.
Q4	According to the Medicinal Product Act only wholesale distributors can distribute medicinal products and the IMP is dispensed to the participant by the trial site pharmacy or PI.
Q5	According to the Medicinal Product Act only wholesale distributors can distribute medicinal products and the IMP is dispensed to the participant by the trial site pharmacy or PI.
Q6	According to the Medicinal Product Act only wholesale distributors can distribute medicinal products and the IMP is dispensed to the participant by the trial site pharmacy or PI.
Q7	According to the Medicinal Product Act only wholesale distributors can distribute medicinal products and the IMP is dispensed to the participant by the trial site pharmacy or PI.
Q8	According to the Medicinal Product Act only wholesale distributors with a manufacturing authorisation are allowed to perform labelling of IMPs.
Q9	According to the Medicinal Product Act only wholesale distributors can distribute medicinal products and the IMP is dispensed to the participant by the trial site pharmacy or PI.
Q10	According to the Medicinal Product Act only wholesale distributors can distribute medicinal products and the IMP is dispensed to the participant by the trial site pharmacy or PI.
Q11	Although not specifically addressed in CT legislation, a face-to-face meeting is implied.
Q12	Although not specifically addressed in CT legislation, the use of qualified electronic signatures is accepted.
Q13	-
Q14	It depends on the task/procedure.
Q15	If on-site SDV is not possible, remote SDV is allowed if EU (EC, EMA, HMA) GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC is respected. Remote SDV must be submitted as substantial protocol amendment to CEC/RA and must be precisely specified in the protocol as to how it will be carried out. Permission to perform remote monitoring should be previously carefully considered with clinical trial site and prior permission and agreement must be reached between the site and the sponsor/CRO.

	HU
Q1	-
Q2	-
Q3	-
Q4	-
Q5	-
Q6	-
Q7	-
Q8	-
Q9	-
Q10	-
Q11	35/2005. (VIII. 26.) Health Ministry Decree
Q12	e-IDAS Art. 6., 7. , 26. , 27. , 36. , 37.
Q13	Consent of the trial participant to the home visits does not reduce in any aspect the responsibilities of the PI.
Q14	Consent of the trial participant to the home visits does not reduce in any aspect the responsibilities of the PI.
Q15	In case of emergency remote SDV should be allowed if EMA „GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC (most recent version)" is respected with special attention to paragraph 11. d) and Annex 1. In general, the prerequisite of RSDV may not be less stringent.

	IE
Q1	
Q2	
Q3	
Q4	An MIA in itself does not provide for direct distribution to clinical trial participants
Q5	
Q6	
Q7	
Q8	
Q9	
Q10	
Q11	
Q12	
Q13	
Q14	Dependant on task
Q15	There are no provisions in national legislation which prohibit remote access to medical records. However, such access can only be permitted by the institution / persons responsible for control of the data, in consideration of application data protection requirements.

No footnotes for: IS

	IT
Q1	-
Q2	-
Q3	Not according to the current provisions for CT according to Directive; national provisions for CT according to CTR are to be made available shortly
Q4	Not according to the current provisions for CT according to Directive; national provisions for CT according to CTR are to be made available shortly
Q5	Not according to the current provisions for CT according to Directive; national provisions for CT according to CTR are to be made available shortly
Q6	Not according to the current provisions for CT according to Directive; national provisions for CT according to CTR are to be made available shortly
Q7	Not according to the current provisions for CT according to Directive; national provisions for CT according to CTR are to be made available shortly
Q8	-
Q9	Not according to the current provisions for CT according to Directive; national provisions for CT according to CTR are to be made available shortly
Q10	Not according to the current provisions for CT according to Directive; national provisions for CT according to CTR are to be made available shortly
Q11	(CTR art.29 does not foresee a face to face interview, no additional national provision exists on this aspect)
Q12	PADES electronic signature on pdf files is surely accepted; other formats (e.g. CADES) to be confirmed
Q13	-
Q14	-
Q15	In compliance with the GDPR

No footnotes for: LI

	LT
Q1	National legislation does not foresee the delivery of IMP directly to trial participants. Nevertheless, the IMP delivery from trial site to trial participant could be allowed on case by case basis, when justified and clearly described in the clinical trial application.
Q2	Law of pharmacy https://www.e-tar.lt/portal/lt/legalActEditions/TAR.FF33B3BF23DD
Q3	Law of pharmacy https://www.e-tar.lt/portal/lt/legalActEditions/TAR.FF33B3BF23DD
Q4	Law of pharmacy https://www.e-tar.lt/portal/lt/legalActEditions/TAR.FF33B3BF23DD
Q5	-
Q6	Law of pharmacy https://www.e-tar.lt/portal/lt/legalActEditions/TAR.FF33B3BF23DD
Q7	-
Q8	Re-packing and re-labelling can be performed in the hospital pharmacy, associated with the clinical trial site: The Order of the Minister of Health of the Republic of Lithuania No V-571 regarding the procedure of re-packing and re-labelling of IMPs at the clinical trial sites
Q9	Law of pharmacy https://www.e-tar.lt/portal/lt/legalActEditions/TAR.FF33B3BF23DD
Q10	Law of pharmacy https://www.e-tar.lt/portal/lt/legalActEditions/TAR.FF33B3BF23DD
Q11	-
Q12	Qualified electronic signature should be used.
Q13	Delegation of specific functions is possible, contract needed with the relevant and licensed Health care institutions.
Q14	-
Q15	Yes, if electronic medical records are used and access to medical records of particular patient is feasible.

No footnotes for: LU

No footnotes for: LV

	MT
Q1	Activity has to be approved so a request should be made to the Medicines Authority
Q2	Activity has to be approved so a request should be made to the Medicines Authority
Q3	-
Q4	-
Q5	-
Q6	-
Q7	-
Q8	-
Q9	-
Q10	-
Q11	-
Q12	-
Q13	-
Q14	-
Q15	-

	NL
Q1	Only in specific circumstances, see Medicines Act (Geneesmiddelenwet), 61.2.
Q2	Medicines Act (Geneesmiddelenwet), article 61.2.
Q3	Medicines Act (Geneesmiddelenwet), article 61.2.
Q4	Medicines Act (Geneesmiddelenwet), article 34.2 and 61.2.
Q5	-
Q6	Medicines Act (Geneesmiddelenwet), article 61.2, 61.5 and 61.6.
Q7	Medicines Act (Geneesmiddelenwet), article 34.2 and 61.2.
Q8	Medicines Act (Geneesmiddelenwet) article 18.1 and 18.7.
Q9	Under the conditions mentioned in Medicines Act (Geneesmiddelenwet) articles 18.1, 34.2 and 61.2.
Q10	-
Q11	However, see requirements in article 6 of the Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen), especially 6.5, 6.6 and 6.7.
Q12	Article 6.2 of the Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen). Guidance on electronic signature (in Dutch): https://www.ccmo.nl/onderzoekers/publicaties/publicaties/2022/08/31/handreiking-elektronische-toestemmingsverlening
Q13	Taking into account the requirements mentioned in the Healthcare Professionals Act (Wet op de beroepen in de individuele gezondheidszorg).
Q14	Taking into account the requirements mentioned in the Healthcare Professionals Act (Wet op de beroepen in de individuele gezondheidszorg).
Q15	Taking into account the requirements mentioned in the General Data Protection Regulation (GDPR).

	NO
Q1	-
Q2	-
Q3	-
Q4	Forskrift om tilvirkning og import av legemidler § 3-2/Forskrift om grossistvirksomhet § 13
Q5	Forskrift om tillvirkning og import av legemidler § 3-2 /Forskrift om grossistvirksomhet § 13
Q6	Forskrift om tillvirkning og import av legemidler § 3-2/forskrift om grossistvirksomhet § 13
Q7	Forskrift om tillvirkning og import av legemidler § 3-2/forskrift om grossistvirksomhet § 13
Q8	Pharmacies with a “pharmacy manufacturing license” are allowed to re-label IMP. Only pharmacies with an ordinary MIA can label IMP.
Q9	Provided agreement with the sponsor (Apotekforskriften § 27 g)
Q10	Provided agreement with the sponsor (Apotekforskriften § 27 g)
Q11	-
Q12	Qualified electronic like for instance BankID is acceptable.
Q13	Provided contractual arrangement
Q14	-
Q15	No national legislations regulating such activities. However, compliance with GDPR is a prerequisite as well as adherence to local procedures.

	PL
Q1	-
Q2	-
Q3	Public pharmacies do not IMPs. 68.1 pharmaceutical law (u.p.f). Retail trade in medicinal products is carried out in generally accessible pharmacies, subject to the provisions of para. 2, art. 70 sec. 1 I art. 71 sec. 1. When Art. 86 par. 2a upf pharmaceutical services referred to in art. 4 sec. 3 points 5 and 7 of the Act of 10 December 2020 on the pharmaceutical profession and professional tasks referred to in art. 4 sec. 4 points 1, 2, 5-7, 15 and 16 of this Act, may be provided only in a hospital pharmacy, company pharmacy or hospital pharmacy separated from these pharmacies" (Article 4 paragraph 4 point 2 of the Act - "Examination in auxiliary tests including research conducted in the hospital as a member of the research team." Thus, community pharmacies cannot provide IMP for research.
Q4	No. Annex 13 of the Regulation GMP defines the obligations of the manufacturer of investigational medicinal products, including the points below are as follows: point 44. The distribution of investigational medicinal products is carried out in accordance with the instructions given by or on behalf of the sponsor in the distribution order. 46. Detailed inventory records of shipments of investigational product sent by the manufacturer or supplier shall be maintained. In particular, it includes data identifying recipients. Currently, the PF Act, art. 42 par. 2 point 2 defines to which entities the manufacturer/importer may distribute medicinal products, there is no direct recipient - study participant listed there.
Q5	-
Q6	No, in relation to generally available pharmacies - they cannot participate in clinical trials, they can only trade medicinal products - Art. 68 sec. 1 u.p.f.
Q7	No, in relation to generally available pharmacies - they cannot participate in clinical trials, they can only trade medicinal products - Art. 68 sec. 1 u.p.f.
Q8	Not. Any delegated pharmacy may not label the IMP, this is limited to the pharmacy associated with the study site. Article 38b upf
Q9	Pharmaceutical services referred to in Art. 4 sec. 3 points 5 and 7 of the Act of 10 December 2020 on the profession of a pharmacist, and the professional tasks referred to in art. 4 sec. 4 points 1, 2, 5-7, 15 and 16 of this Act, may be provided only in a hospital pharmacy, company pharmacy or a hospital pharmacy department established instead of these pharmacies" (Article 4 paragraph 4 point 2 of the u.o.z.f - "participation in research clinical trials, including trials conducted in a hospital as a member of the research team". Thus, generally accessible pharmacies cannot provide IMPs to trial participants. This is the task of a hospital pharmacy, an in-house pharmacy, a medical entity where a clinical trial is conducted
Q10	as above
Q11	Act on the Profession of Physicians and Dentists: Participant or his legal representative before expressing consent referred to in art. 25, receives oral and written information presented in an understandable way. The transfer of information is recorded in the documentation
Q12	Qualified electronic signature is acceptable
Q13	Not forbidden
Q14	Not forbidden
Q15	Not forbidden

	PT
Q1	as long as shipping conditions are kept under control
Q2	as long as shipping conditions are kept under control
Q3	to be assessed on a case-by-case basis; IMP circuit should be clearly and in detail described in the CT protocol
Q4	to be assessed on a case-by-case basis; IMP circuit should be clearly and in detail described in the CT protocol
Q5	Article 32nd, Law 21/2014, from the 16th of April, current version
Q6	Article 32nd, Law 21/2014, from the 16th of April, current version
Q7	to be assessed on a case-by-case basis; IMP circuit should be clearly and in detail described in the CT protocol
Q8	-
Q9	Article 32nd, Law 21/2014, from the 16th of April, current version; the pharmacies must be included on the IMP circuit described in detail in the CT protocol
Q10	Article 32nd, Law 21/2014, from the 16th of April, current version
Q11	Dialogue is mandatory
Q12	On a case-by-case basis; wet ink use should also be possible, along with e-signatures; according to the EC website, reuse of CEF eID sample implementation software is described as being implemented in Portugal; please refer to Autenticacao.gov.pt
Q13	Healthcare provider must be in direct dependency of the IP
Q14	Should be clearly specified in the CT protocol
Q15	Should be approached under the EU GDPR

	RO
Q1	-
Q2	In Romania, authorizes activities for pharmacies are explicitly mentioned in the Pharmacy Law nr 266/2008 which permit shipping activities only for OTC medicines
Q3	In Romania, authorizes activities for pharmacies are explicitly mentioned in the Pharmacy Law nr 266/2008 which permit shipping activities only for OTC medicines
Q4	-
Q5	Based on authorisation issued by ANMDMR
Q6	-
Q7	-
Q8	-
Q9	In Romania, authorizes activities for pharmacies are explicitly mentioned in the Pharmacy Law nr 266/2008 which permit shipping activities only for OTC medicines
Q10	In Romania, authorizes activities for pharmacies are explicitly mentioned in the Pharmacy Law nr 266/2008 which permit shipping activities only for OTC medicines
Q11	-
Q12	Advanced electronic signature/ Qualified electronic signatures
Q13	Only if it is an accredited medical service provider
Q14	Not yet. National provisions are under development
Q15	-

	SE
Q1	If relevant national legislation (for example "Lag (2009:366) om handel med läkemedel") is followed.
Q2	If relevant national legislation (for example "Lag (2009:366) om handel med läkemedel") is followed. Any pharmacy that is handling IMPs for a clinical trial site should have a CT specific delegation (either from site or sponsor/CRO) and established routines for handling IMP.
Q3	If relevant national legislation (for example "Lag (2009:366) om handel med läkemedel") is followed. Any pharmacy that is handling IMPs for a clinical trial site should have a CT specific delegation (either from site or sponsor/CRO) and established routines for handling IMP.
Q4	-
Q5	-
Q6	Current interpretation of "Lag (2009:366) om handel med läkemedel"
Q7	Current interpretation of "Lag (2009:366) om handel med läkemedel"
Q8	Labelling of IMPs in pharmacies is restricted to e.g. auxiliary labelling of authorised IMPs, if performed in accordance with relevant national pharmacy legislation. Please refer also to national legislation HSLF-FS 2021:109. Any pharmacy that is handling IMPs for a clinical trial site should have a CT specific delegation (either from site or sponsor/CRO) and established routines for handling IMP.
Q9	If relevant national legislation (for example "Lag (2009:366) om handel med läkemedel") is followed. Any pharmacy that is handling IMPs for a clinical trial site should have a CT specific delegation (either from site or sponsor/CRO) and established routines for handling IMP.
Q10	If relevant national legislation (for example "Lag (2009:366) om handel med läkemedel") is followed. Any pharmacy that is handling IMPs for a clinical trial site should have a CT specific delegation (either from site or sponsor/CRO) and established routines for handling IMP.
Q11	-
Q12	The system used (level of category) is the responsibility of the sponsor.
Q13	If relevant national healthcare legislation and hospital practices allows for it.
Q14	If relevant national healthcare legislation and hospital practices allows for it.
Q15	-

	SI
Q1	In case the trial site is a Hospital, the IMP must be managed by Hospital pharmacy Art 62, Par 3 and Par 7 of Pharmacy Practice Act
Q2	Always under supervision of the investigator of the trial site
Q3	In case the trial site is a Hospital, the IMP must be managed by Hospital pharmacy article 67 point 7 (1)
Q4	In case the trial site is a Hospital, the IMP must be managed by Hospital pharmacy article 67 point 7 (1)
Q5	Only in exceptional situation (IMP shortage due to for example COVID-19 lock-down and should be on the basis of a risk assessment with patient safety as utmost priority and only after agreement with the investigator and on the basis of the investigator's prescription.
Q6	In case the trial site is a Hospital, the IMP must be managed by Hospital pharmacy article 67 point 7 (1) Only after agreement with the investigator and on the basis of the investigator's prescription.
Q7	In case the trial site is a Hospital, the IMP must be managed by Hospital pharmacy article 67 point 7 (1) Only after agreement with the investigator and on the basis of the investigator's prescription.
Q8	Delegated pharmacy must comply with special requirements in accordance with Article 13 Par 2.
Q9	It is not appropriate if IMP is blinded. Under oversight of investigator of trial site. The trial drug must be marketed and used within the approved indication (according to the SmPC).
Q10	It is not appropriate if IMP is blinded. Under oversight of investigator of trial site. The trial drug must be marketed and used within the approved indication (according to the SmPC).
Q11	In accordance to ICH GCP The investigator, or a person designated by the investigator, should fully inform the participant or the participant's legally acceptable representative, of all pertinent aspects of the trial & and should answer all participant questions. The communication of this information should be documented.
Q12	Currently, there is no established practice.
Q13	-
Q14	depending on the procedure/task
Q15	If on-site SDV is not possible for a longer period of time due to for example lock-down due to pandemic, remote rSDV must be submitted as substantial protocol amendment to EC/RA and must be precisely specified in the protocol as to how it will be carried out, so that the rights of the participants will be protected and will not unnecessarily burden the staff at the trial site who must agree to such a method of data verification. Monitors should sign a written confidentiality agreement committing to securely destroy any copy of redacted documents, whether paper or electronic, as soon as they have been used for source data verification and committing not to make any copy (or recording in the case of video access) of any non-pseudonymised document.

References from SI:
(1) Pharmacy Practice Act (Official Gazette of the RS, no. 85/16, 77/17, 73/19 and 186/21)
(2) Regulation on the implementation of the Regulation (EU) on clinical trials of medicinal products for human use (Official Gazette of the Republic of Slovenia, No. 132/22)

	SK
Q1	
Q2	
Q3	
Q4	
Q5	
Q6	
Q7	
Q8	
Q9	Pharmacist must be delegated by PI.
Q10	Pharmacist must be delegated by PI.
Q11	
Q12	Qualified electronic signature for investigator and participant is required according to the Act No. 272/2016 on credible services for electronic transaction for domestic trade. According to the EU regulation, the new forms of eIDAS are AsiC-E, AsiC-S and are acceptable.
Q13	
Q14	
Q15	

Document History – Appendix: National Provisions Overview

Date	Version	Change	Changed by
13-Dec-2022	01	New document	EMRN DCT project group
13-Mar-2023	02	Data and footnotes from PT included, Q2 updated for EE with footnote	EMRN DCT project group