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WHITE PAPER

THE EMA RECOMMENDATION PAPER ON DECENTRALIZED ELEMENTS IN CLINICAL TRIALS: AN OVERVIEW

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On December 13th, 2022, the European Medicines Agency (EMA) published a recommendation paper on the use of decentralized methods in clinical trials for regulatory submission[1]. This is intended to provide recommendations beyond the extent of the temporary guidance introduced to address the emergency response to the COVID-19 pandemic[2]. It provides valuable insights into regulatory thinking and the differences in regulatory interpretation across the EU/EEA member states, which will help to inform study design and trial technology implementation.

The recommendations focus primarily on the following decentralized elements:

- Informed consent process
- Medication provision directly to the patient at home
- Trial-related procedures at home (e.g., conducted independently by the patient, or by a nurse during a home visit)

Below, we summarize some of the key themes.

THEME 1. PATIENTS AND INVESTIGATORS ARE KEY STUDY DESIGN PARTNERS

The recommendations stress the importance of enabling patients or patient organizations to provide the perspective of those living with the condition to help determine the choice and feasibility of including different decentralized elements.

In addition, the paper identifies that investigator input in the study design stage may help to ensure that clinically relevant objectives and endpoints are maintained in the event of decentralization, and that the reduction in personal contact between site and patient is considered and mitigated as necessary.

THEME 2. MAINTAINING RELIABLE AND ROBUST DATA

In numerous places, the theme of maintaining reliable and robust data emerges. The EMA stresses that data collected using decentralized methods should meet the same expectations as those from trials with on-site procedures. This needs careful planning and implementation to ensure that decentralization does not adversely affect the scientific quality of the clinical trial. Specifically, they cite three considerations to ensure reliable data and inferences:

a. Whether modifications of outcome assessments to enable decentralized application might affect the precision, accuracy, and reliability of data

b. Whether recruiting patients with sufficient digital literacy might affect the generalizability of the study results to the target patient population

c. The potential for an increase in missing data, affecting the robustness of inferences

This leads us to an important principle – the thoughtful application of decentralized methods as they apply to the implementation of outcome assessments. For example, while it's technically possible to migrate in-clinic, face-to-face assessments to remote administration over telemedicine, it's vital that this is done in a way that maintains the measurement accuracy and consistency of the original measure. This is where the marriage of scientific and psychometric expertise, along with technology provision, becomes a vital combination.

In terms of digital literacy, there are several considerations. First, while the bring-your-own-device (BYOD) approach is attractive in terms of lowering the training barrier by using devices the patient is already familiar with, it is important to ensure that participation is not restricted to patients who own compatible hardware to access the study applications. In such cases, patients should be offered a provisioned solution for use during the trial. More generally, however, we should consider whether the inclusion of more remotely conducted assessments and procedures will require patients to have greater technology literacy, and whether this has the potential to bias the study sample and lead to less diversity. In these cases, feasibility research in the target population should provide valuable insights to inform study and solution design.

Increasing the number of remote assessments that are conducted independently by the patient has the potential to cause greater levels of missing data. Again, this can be explored by feasibility research where needed. Good solution design should always include compliance encouragement and monitoring mechanisms such as reminders and alarms for the patient, as well as non-compliance notifications and compliance reports for the sponsor and the site.

THEME 3. APPROPRIATE DELEGATION OF INVESTIGATOR AND SPONSOR RESPONSIBILITIES

The EMA states that decentralized elements should be considered an extension of the clinical site so when these are implemented, the specific roles and responsibilities of the sponsor, investigator, and any additional parties (e.g., service and technology providers) must be clearly defined and understood prior to the start of the trial. When decentralized elements are implemented, the investigator and sponsor must still fulfill their legal obligations per the EU Clinical Trial Regulation (EU-CTR) or Clinical Trial Directive (CTD), and ICH E6. This requires a priori documentation of 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.

Contractual agreements

With decentralization, the sponsor may contract a service provider to conduct an element that falls under the responsibility of the investigator according to good clinical practice (GCP). In this case, the EMA recommends that the contract between the sponsor and investigator should clearly outline these tasks, enabling the investigator to agree or disagree with this provision by accepting or declining the contract. The sponsor remains responsible for ensuring that the contracted service provider is qualified and experienced in the tasks they are required to conduct, and this information should be available to the investigator for their decision making.

Training of service providers

When a service provider is contracted to undertake a task that falls under the investigator's responsibility, it remains the responsibility of the investigator to ensure that the service provider is properly trained on the conduct of these tasks. Enabling this in a practical manner might involve furnishing investigators with documentation that details the qualification of the service providers, so they are able to inspect the adequacy of study-specific training provided by the sponsor/CRO.

Patient and data oversight

Decentralization can be associated with a greater number of clinical data sources, increasing data oversight challenges for investigators. The EMA recommends that the review frequency of each data source 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 assessment of treatment efficacy.

In cases where decentralized methods generate critical safety data that need immediate medical attention, there should be a description in the protocol about how the investigator and/or the service provider should manage these situations, what actions should be taken, and by whom. Where digital tools generate alerts or notifications related to safety events, they should be validated to show that they are generating the required alerts as planned.

A further interesting point the EMA raises is how to ensure patients understand that data they submit remotely through technology solutions such as ePRO may not be reviewed in real time. Patients should be instructed to make direct contact with the investigator/site in the event of any safety concern.

THEME 4. THE IMPORTANCE OF MAINTAINING CRITICAL ELEMENTS IN THE INFORMED CONSENT PROCESS

In the case of informed consent when it is conducted partially or completely remotely, the EMA stresses the importance of maintaining compliance with the principles within current regulations (EU-CTR/CTD, ICH E6, GDPR, and national legislation associated with individual EU/EEA member states). When using electronic consent (eConsent) solutions, the importance of the informed consent interview is emphasized to allow potential participants to ask questions before deciding whether to participate. When this interview is conducted remotely, the EMA recommends:

a. Face-to-face communication using video technology, for example

b. Where the patient is not already known to the investigator, the investigator should use the video meeting to confirm their identity, while the patient can also ask for proof of the investigator's identity

c. An on-site informed consent interview should generally be available as an option should the patient/investigator prefer this, although solely remote options can be justified in certain cases

Participants should always be able to download and retain a tamper-proof copy of their consent form and the study information.

THEME 5. GUIDING PRINCIPLES FOR GOOD DIRECT-TO-PATIENT MEDICATION PROVISION

Direct-to-patient (DtP) medication provision can be an essential component if the aim of decentralization is to reduce the number of on-site visits, so it is encouraging to see this element detailed in the EMA recommendations. Specifically, the EMA states:

a. The investigational medicinal product (IMP) should be suitable for a home delivery model with, for example, consideration of its storage and administration requirements.

b. The investigator remains responsible for the decision of treatment, and this decision should be documented (e.g., by prescription or through an RTSM solution).

c. Vendors responsible for providing the drug to patients are "authorized to distribute or dispense as much as possible," and non-authorized vendors must be qualified and supervised by the authorization holder.

d. When IMP is delivered, it should only be handed over to the trial participant (or their representative, where applicable). If they are not available to sign for it, the IMP should be returned.

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

f. Procedures should be in place for return of IMP from the patient's home to enable full accountability records and destruction.

g. The sponsor should ensure the privacy and protection of patients' name and address details so that they are only disclosed where needed for the purposes of delivery logistics and are not accessible after final delivery is completed.

These recommendations provide guidance for processes and technologies used in DtP medication provision solutions. It is important that RTSM solutions can accommodate the nuances of DtP medication provision, including encrypted storage of patient address details, integration with order management solutions operated by authorized specialist logistics vendors, full data protection and privacy of confidential patient data, and compliance with regulations such as GDPR.

THEME 6. FLEXIBILITY IN SOLUTION CONFIGURATION

The recommendation document appendix overviewing individual member state provisions importantly identifies differences in regulatory opinion across member states. This illustrates the importance of a flexible solution to accommodate differences in member state regulations, particularly for eConsent and DtP medication provision.

Specifically concerning DtP medication provision, member states have different opinions regarding the different logistical options: e.g., site-to-patient, pharmacy-to-patient, and depot-to-patient. RTSM solutions need to have the flexibility to fully manage all scenarios on behalf of the investigator, as required by the specific country regulations or site requirements. Further, supply chain structures will need to be designed to avoid certain pitfalls – for example, most member states do not currently approve direct-to-patient medication shipments from a depot within another EU/EEA member state.

CONCLUSIONS

Overall, this is a helpful recommendation paper containing fine detail on key aspects of the application of decentralized methods. It underlines the importance of maintaining investigator responsibility in delegated tasks, and the role the investigator plays in decentralized elements that are considered an extension of the site.

Importantly, while decentralized clinical trial (DCT) providers rarely consider DtP medication provision, the regulator provides helpful recommendations around good practices and the role that RTSM solutions and logistics providers can play.

The addendum to the recommendation paper provides a valuable corollary. While the paper is intended to facilitate the use of decentralized elements in clinical trials conducted in the EU/EEA, it remains at the discretion of the individual member states to determine whether the use of certain decentralized elements is acceptable in a specific clinical trial. The importance of flexibility in technology implementation is essential to enable application across member states imposing different restrictions or requirements around technology configuration and work processes.

Every clinical trial is required to ensure that accurate and reliable data are collected, independent of the settings in which data are gathered. Therefore, thoughtful application of decentralized methods, along with scientific rigor and attention to outcome measure properties, remain essential as we migrate assessments from in-clinic to remote. This requires vendors to exhibit an essential blend of scientific expertise alongside robust technology, operations, and logistics provision.

REFERENCES

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