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FACILITATE

FrAmework for ClInicaL trIal participants daTA reutilization for a fully Transparent and Ethical ecosystem

WP3 - Ethics, standardization and regulatory framework

D3.3 Ethical standards and guidelines No. 1

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Abbreviations

Accelerating Clinical Trials in the EU (ACT EU workplan)
Clinical Data Sharing (CDS)
Deliverable (D)
European Federation of Pharmaceutical Industries and Associations (EFPIA)
Good Clinical Practise (GCP)
Innovative Medicines Initiative / Innovative Health Initiative (IMI/IHI)
Informed Consent Form (ICF)
International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
Number (No.)
Research Ethics Committee (REC)
Return of Individual Participant data (RoIPD)
Secondary use (SU)
Work Package (WP)
World Medical Association (WMA)

1. Summary

This report will describe the background and the methodology used to develop the ethical standards and guidelines No. 1. The focus at this stage is on the development of initial recommendations for a legally and ethically valid process (framework), including requirements for informed consent, for return of individual participant data (RoIPD) in the European context. The purpose is to set out the foundational requirements for the FACILITATE consent on RoIPD, including the governance requirements. At the next stage, the deliverable ethical standards and guidelines No.2 will provide further detail on the proposed standards required for consent to RoIPD. This report also updates on the progress of the guideline for consent to secondary use (SU) and the bottlenecks and challenges thus far.

2. Background to the draft guideline

Considerable types of data are generated throughout a clinical trial that can be valuable to the patient both during and after the clinical trial. In particular, the sharing of this data can prevent redundant, burdensome, and potentially invasive medical tests. Data sharing can better inform patients healthcare decisions, and it also demonstrates respect and acknowledges the important role patients have in the clinical trial process. RoIPD entails making data easily accessible, available, and comprehensible to study participants. Nevertheless, returning data to study participants or patients after the clinical trial is generally not practiced, in part because to protect participant privacy, pharmaceutical companies do

not know the identity of their trial participants and thus do not have direct access to the participants.
The sharing of clinical trial data back to participants is a multifaceted issue stemming from intricate challenges in operational execution, compounded by inconsistencies in legal and ethical frameworks regarding patient safeguards. In response to these challenges, FACILITATE was established with the overarching goal of constructing a functional prototype process to sustain the return of individual participant data. Additionally, FACILITATE seeks to evaluate ethical and applied practices for the compliant reuse of pseudonymized clinical trial data. Central to this endeavor is the development of a proposed legal and ethical framework aimed at bolstering a trusted clinical research ecosystem that addresses critical imperatives such as public health, scientific innovation, and the unmet needs of all patients.
Through a multidisciplinary and collaborative strategy wherein stakeholders share knowledge, competencies, resources, and risks, public-private partnerships like FACILITATE have the potential to accelerate the Return of Individual Participant Data (RoIPD). However, the efficient return of individual participant data is hindered by an array of organizational, ethical, behavioural, and technical challenges, which ultimately diminishes this additional and important aspect of the utility of the data generated by clinical research studies.
To address these challenges, FACILITATE aims to provide guidance by convening experts from diverse realms of expertise to develop ethical codes of conduct and harmonize consent processes. Cross-cutting solutions and enablers include the principles of transparency, flexibility, and co-design, which are pivotal in fostering trust in the processes enabling RoIPD. Given the complex hierarchy of relationships involved in large sponsored clinical studies, agreements on data sharing become multi-layered, multi-partner documents, spanning from direct patient-clinician interactions to research institutions or healthcare organizations.

As discussed in the Report on the draft ethical frameworks for FACILITATE (D3.1), the GDPR and its application within Member States, particularly in the context of research, establishes fundamental benchmarks for safeguarding personal data, including clinical trial data. As part of a process (of which this the deliverable is the first), these draft ethical frameworks outline substantive and procedural principles, as well as an implementation framework to support RoIPD while exploring the options to similarly provide a framework to support Secondary Use (SU) of pseudonymized clinical trial data for research. The purpose of the guideline is to offer guidance in areas where legal provisions may be unclear or inconsistent, ensure that we work towards participant centric processes, and provide flexibility to account for the diverse contexts in which clinical trials occur, in order make RoIPD feasible and sustainable, and making a valuable contribution to respecting the needs of trial participants.

D3.1 concluded by pointing out that the next stage of the process would involve providing more detail to the concepts and processes that have been identified in D3.1. The importance of transparent and accountable processes, and the need for participant information and decision processes are highlighted. This Report describes the first approach to the development of a framework for decision making regarding the RoIPD and also outlines the

challenges in the completion of the guideline on SU of clinical trial data and reports the decision of WP3 to move the work on SU to a second stream, enabling a comprehensive reexamination of the issue in the context of the rapidly evolving data sharing landscape in the EU, including current measures set forth in the ACT EU Workplan.

3. Methodology

Following the completion of the draft ethical frameworks on RoIPD and SU of clinical trial data (D3.1), it was clear that assessment on consent processes and requirements was essential. To support the development of this work, a small working group (guideline working group) was formed out of members of work package (WP) 3, comprised of members of academia, patient representatives, and EFPIA partners. The guideline working group met every 2 weeks and reported back to WP3 on the development of the guidelines. The guidelines on consent for RoIPD were discussed first and separately from the guideline for consent to SU.

To start this process, a document was circulated to members of the guideline working group asking them to insert their comments on specific points and questions.

A. **For RoIPD feedback was asked for the following points:**

Timing of consent

- At what point should participants be informed about the RoIPD?
- At what point should they express their preferences on RoIPD?
- Should participants be approached at another time later in the clinical trial about their RoIPD preferences?
- Any other comment on timing?

Who should obtain the consent

- What person should engage with the participant to obtain their consent on RoIPD?
- Any other comments on person?

B. **To inform the development of SU, feedback on the following was requested:**

Timing of consent

- At what time should participants be informed about the possibility of their data being used for SU?
- Should consent to SU be a separate form and should consent to SU be done at a different time to consent to the clinical trial?
- If so, at what point?
- Any other comment on timing?

Who should obtain the consent

- What person should engage with the participant to obtain their consent on SU?
- Should this be separate from the person who obtains the consent to participation in clinical trial?
- Any other comment on the person?

Specificity of consent

- How specific should the consent to SU be (provide examples)?
- Should a participant be able to opt-out? How long should they be provided with the opportunity to opt-out? Can this timing be study specific or should it be set?
- Should a participant be able to opt-in? How long should they be provided with the opportunity to opt-in? Can this timing be study specific or should it be set?
- If no response to an opt-out or opt-in is provided, can their data be used?

Oversight of SU

- Who should be responsible for assessing applications for secondary use?
- Describe the types of individuals/expertise required for an assessment.
- Should the decision makers be independent? What do you mean by this?

After each meeting, the guideline was revised and updated based on the agreement of key points. In January 2024, the working group on consent was no longer needed and it was replaced with weekly WP3 meetings. The guideline on consent for RoIPD was completed in February 2024 and will be discussed below, as it was decided that this would be a draft guideline focused on consent for RoIPD.

While the importance of secondary use (SU) of clinical data for research is widely recognized, it is accompanied by a myriad of challenges. Addressing specific hurdles through recommendations may prove ineffective if related barriers are not comprehensively addressed or if underlying systemic issues remain unresolved. As such, we have established an ad hoc inter-work package workgroup to conduct an in-depth analysis of common issues and dimensions concerning data sharing and the effective reuse of pseudonymized data. This analysis will be conducted from the perspectives of experts with experience in the SU of clinical trial data for research separate from the framework on RoIPD presented here.

4. The guidelines on consent

4.1 Guideline on RoIPD

The draft guideline on consent for RoIPD (Appendix 1) provides the ethical guideline and governance guidance on returning individual clinical trial data to patients. The ethical guidance on RoIPD provides information on the notification to patients on the right to have their data returned, the requirements in the informed consent form (ICF), details on informed decisions making and specifically the timing of the discussion on consent to data return, and the option to decline data return. The governance guideline on RoIPD offers detailed

requirements concerning data generation and RoIPD clarity, flexibility in RoIPD preferences, possible separation of consent forms for clinical trials involving RoIPD, the necessity of qualified personnel for consent processes, and the integration of the RoIPD process into the clinical trial protocol.
Further details on each of the provisions are required and thus at this stage the guideline is a **draft guideline (first version)** on consent for RoIPD. This guideline will be completed at the next stage of the process.

Some Workgroup members with significant clinical trials experience raised operational feasibility concerns regarding mandating the introduction of staged Informed Consent process for the Return of Individual Patient Data (RoIPD). They propose emphasizing to clinical trial sponsors the critical need to establish a clear RoIPD strategy and operational process early on and communicate this clearly to participants to ensure that any needed participant consent regarding RoIPD was informed. This should be documented into a RoIPD operational guideline or integrated within the study protocol or clinical development plan, as appropriate. This documentation would clearly communicate the types of study data to be returned to participants, the timelines for this return, and the methods by which it will be carried out. This approach aims to streamline the process, reducing complexity by avoiding additional documentation and ensuring participants are fully informed from the outset.

4.2 Guideline on SU

The draft guideline on SU of clinical trial data contains ethical guidelines and guidelines for the management of SU of clinical trial data. The ethical guidance on SU provides information about notification at the time of enrolment that study participants will be invited to consent to the use of their clinical trial data for future research purposes, consent to SU of clinical trial data, informed decision making for SU and flexibility in consent preferences. The governance guidance intended for SU provides detail on the proposed separation of the consent to SU with consent to the clinical trial, the need for a qualified person for consent discussion and the inclusion of the process for obtaining consent to SU to be included in the clinical trial protocol.

Discussions on recommendations regarding SU have highlighted differing viewpoints and considerations regarding consent for the secondary use of clinical trial data, particularly regarding the following aspects:

1. **Lack of Consensus on SU Definition:** There is a notable absence of a universally agreed-upon understanding or consensus regarding the scope of secondary use among stakeholders.
2. **Opt-In versus Opt-Out:** Some stakeholders advocate for patients to actively opt-in into research participation, while others suggest an opt-out approach, where patients are automatically included unless they choose otherwise.

3. **Granularity of Consent:** Stakeholders have varying perspectives on the level of detail required for consent options, with some emphasizing the importance of granular consent and others preferring a broader framework.
4. **Static versus Interactive Consent:** There are differing opinions on the consent model, with some stakeholders favoring an interactive approach that allows patients to modify their consent preferences over time, while others prefer a more static approach.
5. **Timing of Consent:** Some stakeholders suggest consenting to SU separately from the initial consent to the clinical trial, while others advocate for simultaneous consent for SU and the clinical trial.
6. **Separation of Consent Forms:** There is discussion about whether a distinct informed consent form (ICF) specifically addressing SU should be separate from the ICF for the clinical trial to ensure clarity and transparency.

These discussions are occurring within the broader context of ongoing dialogues surrounding the proposed European Health Data Space (EHDS). Given the dynamic nature of these discussions and the complexities involved, partners within the consortium have encountered challenges in reaching consensus on a single direction moving forward. Therefore, this report will outline the progress made thus far. Moving forward, the next phase of the project will delve deeper into the rationale behind various decisions and identify areas where consensus can be achieved.

Appendix 1: Framework on consent: return of data (RoIPD)

Introduction

The Declaration of Helsinki[1] (64 WMA General Assembly, Fortaleza, Brazil, October 2013) establishes ethical guidelines for conducting medical research with human participants. It emphasizes the need to safeguard the dignity, autonomy, privacy, and confidentiality of participants, along with the requirement to obtain informed consent when using identifiable human biological materials and data. Although the Declaration primarily targets physicians, these principles are fundamental to the protection of all human medical research participants, whether patients or healthy volunteers, and should be upheld by all individuals and teams involved in such research. Together with the Declaration of Taipei[2] (revised by the 67 WMA General Assembly, Taipei, Taiwan, October 2016) they aim to ensure ongoing protection through informed consent. Furthermore, the principles of autonomy, privacy, and confidentiality grant individuals the authority to manage how their individual research data are utilized.

Ethical recommendations for Returning Individual Clinical Trial Data to Participants

1. **Sponsors of clinical trials:** The responsibility of planning and discussing the plan of the Return of Individual Participant Data (RoIPD) lies with the Sponsor, who should engage investigators and patients whenever possible. Subsequently, the RoIPD process should be facilitated through the Investigators, as they are informed about the Sponsor's plans and can accordingly inform participants about the process and timing of data return.
2. The **Investigator or the participants physician** has an important role to play in helping a participant and/or their family interpret their returned data and understanding any medical significance of these data. Participants should be encouraged to discuss their data with a healthcare professional before making any healthcare decisions based on these data.
3. **Right to Data Return (RoIPD) Notification**: It is increasingly acknowledged that there is an ethical obligation to return individual clinical trial data to participants. At the start of their participation in a clinical trial, participants are to be informed that they will have their individual clinical trial data returned to them on request.
4. **Informed Consent Form (ICF) Requirement**: In accordance with ICH GCP, Sponsors must ensure that the participant fully understands and specifically consents, as appropriate, to the conditions and process for RoIPD. Sponsors are encouraged to consider a co-creation process involving participants from the onset of the protocol development or earlier. This would confer agency to the participant and help ensure

[1] https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
[2] https://www.wma.net/what-we-do/medical-ethics/declaration-of-taipei/

that the concerns and needs of the participant are considered and taken into account in the design of the consent and RoIDP processes. Such an approach ensures transparency regarding RoIPD.

5. **Informed Decision Making**: Timing for Consent and Data Return Discussion: Participants will be told at the time of consent to the trial that they will be asked to consent to RoIPD only when they feel fully informed about the process. When signing the consent at the onset, it should be made clear to the participant that consent can be revoked or changed at any time throughout the trial or after the trial.
6. **Option to Decline Data Return**: Ensure that participants understand that while they have the right to access their individual clinical trial data, this procedure also provides them with the opportunity to indicate if they prefer not to have some or any data returned. This choice will not impact their legal rights under data protection law and could be changed over time.

Governance recommendations for (RoIPD) in Clinical Trials

1. **Clarity on Data Generation and RoIPD:** At the point of obtaining consent for RoIPD, participants must be clearly informed that all activities within the study will generate data and that they retain the right to decide if they wish to receive this data as it becomes available and explained in the study ICF.
2. **Flexibility in RoIPD Preferences:** Communicate to participants that they have the freedom to modify their RoIPD preferences at any stage of the trial, including instructions on how to update these preferences.
3. **Separation of Consent Forms:** It is recommended that the Informed Consent Form (ICF) dedicated to RoIPD should be distinct from the ICF for clinical trial participation.
4. **Qualified Personnel for Consent Process:** The individual responsible for discussing RoIPD with participants and obtaining the ICF must be knowledgeable enough to address potential questions, fully understand the clinical trial's scope, and possess the necessary communication skills for this sensitive engagement.
5. **Protocol and Ethics Committee Approval:** It is strongly advised that the procedure for securing RoIPD consent must be approved by and explicitly included in the clinical trial protocol and receive approval from the Research Ethics Committee (REC). Furthermore, any modifications to the RoIPD process need REC endorsement, as required by ICH GCP

Appendix 2: Draft guideline on consent: secondary use (SU)

Considerations on consent: secondary use of data

Introduction

The draft guideline is written adhering to the latest versions of The Declaration of Helsinki[1] (64 WMA General Assembly, Fortaleza, Brazil, October 2013) and The Declaration of Taipei[2] on Ethical Considerations Regarding Health Databases and Biobanks which offers guidelines for safeguarding individuals who contribute their health information and/or biological samples for future research or other applications. This document builds upon the protections established by the Declaration of Helsinki[1], expanding them to include digital settings and uses like administrative or commercial activities. A key emphasis of the Declaration of Taipei[2] is to ensure ongoing protection through informed consent. Given the inherent uncertainty about how data or samples might be used in the future, the Declaration introduces a multi-stage process as an alternative to traditional informed consent. This involves setting up a specific governance structure and requiring review by an ethics committee. With ongoing discussions about regulations for health and medical databases, incorporating the principles set out in the Declaration is strongly recommended.
Importantly, FACILITATE acknowledges that it is not the sole authority on this matter, and there are several other EU IMI/IHI projects developing ethical and legal frameworks for Clinical Data Sharing (CDS) and reuse. Therefore, it is essential to achieve an IMI/IHI-wide agreement and conduct a comprehensive portfolio assessment of all projects to ensure alignment and consistency.

While there is currently a lack of consensus among WP3 members regarding the content of this section, it is acknowledged that it will be addressed and revised by an ad hoc inter-work package workgroup.
Among the challenges encountered on various points related to the recommendations for informed consent and the governance related to SU are the following:

Guidelines for Informed Consent on Secondary Use of Clinical Trial Data

1. **Notification at Enrolment**: Participants are to be informed upon their enrolment in a clinical trial that their data may be utilized for research beyond the scope of the trial.
2. **Consent for Secondary Use**: Participants should be informed that they will be asked to sign an informed consent form (ICF) for the secondary use of their clinical trial data. Consent will be asked for once participants feel adequately informed and have had the opportunity to reflect and ask any questions they may have.
3. **Informed Decision Making for Secondary Use**: Ensure that participants understand they will provide consent for the secondary use of their data when they are ready,

having been given adequate information, reflection time, and opportunities to ask questions.

4. **Flexibility in Consent Preferences**: Participant will be informed that they have the right to modify their consent preferences regarding the secondary use of their data at any point in the future.

Governance Guidelines for the Secondary Use of Clinical Trial Data

1. **Separation of Consent Forms**: The ICF for the secondary use of clinical trial data must be distinct from the ICF for initial clinical trial participation and the ICF for the return of data.
2. **Qualified Personnel for Consent Discussion**: The individual tasked with discussing the secondary use of data and obtaining the ICF should be well-informed, capable of addressing participant questions, understand the clinical trial in detail, and possess the communication skills necessary for an effective discussion.
3. **Protocol Inclusion and Ethics Approval**: The procedure for obtaining consent for the secondary use of clinical trial data must be detailed in the trial's protocol and receive approval from the Research Ethics Committee (REC). Additionally, any amendments to the consent process for secondary use require REC approval.

Because of the challenges encountered related to the points under guidelines for informed consent as well as governance related to SU e special workgroup has been developed that has the mandate to explore in-depth the nature of these challenges and in light of this develop possible solutions.