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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

D3.1 Report on the draft ethical frameworks for FACILITATE

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Table of contents

Abbreviations

EHDS: European Health Data Space
EU: European Union
GDPR: General Data Protection Regulation
REC: research ethics committee

List of Tables

1. Summary

This report will describe the background and the methodology used to develop the draft ethical framework on the secondary use of clinical trial data and the ethical framework on the return of clinical trial data to patients. The purpose of the draft frameworks at this stage (October 2023) is to set out the key ethical principles that will guide both ethical frameworks and identify the key concepts and processes that will facilitate the implementation of both ethical frameworks in practice. At the next stage, work will commence on refinement of the ethical principles and provide detail on the processes to be followed to enable the ethical implementation of the principles, development of definitions of key terms with WP2, and alignment with the legal framework developed under WP2.

2. State of the art and general background to the ethical frameworks

Clinical trial data possesses substantial untapped value that is frequently underutilized beyond the confines of the trial, and not all clinical trial data typically find their way back to patients. To tackle these challenges, a paradigm shift in our approach before, during, and after clinical trials may be necessary. This transformation may entail addressing the legal and ethical barriers that impede both the return of data and the subsequent reuse of pseudonymized clinical trial data throughout and after the trial. To make meaningful progress in this field, we must depart from our current conventional practices, which often hinder the effective return and reuse of clinical trial data. Instead, our initial step should involve defining clear objectives and then exploring the most effective means to achieve them.

FACILITATE was established with the aim of building an actionable prototype process to sustain the return and reuse of pseudonymized clinical trial data. As part of this process, FACILITATE is developing a participant centric trusted legal and ethical ecosystem. In developing such an ecosystem, FACILITATE must operate within the law, notably the General Data Protection Regulation (GDPR). The law sets the minimum standards that must be met, but there are often gaps in the law as it struggles to keep pace with technology such as with Artificial Intelligence (AI) and Machine Learning (ML) innovations.

The GDPR and its application within Member States, particularly in the context of research, establish fundamental benchmarks for safeguarding personal data, including clinical trial data. However, to establish an ethical ecosystem centred around participants, FACILITATE must surpass these baseline standards. Instead, FACILITATE needs to identify a set of ethical principles that should guide its actions and, in collaboration with stakeholders, determine how these principles should be implemented in both the return of individual clinical trial data and the reuse of pseudonymized clinical trial data. Patients represent a crucial stakeholder group in this process, requiring involvement not only in shaping the frameworks but also in the clinical trial procedures themselves. Whereas sponsors increasingly consider participants in the clinical development of a new drug (from study protocol design, endpoint selection that reflects outcomes meaningful to patients, to recruitment and retention in clinical trials, CTR, ICH E6 (R3)) there is still an increasing need to structure patient participation to better and responsibly reflect their expectations and needs on the return and re-use of clinical trial data.

The ethical guidelines within FACILITATE, pertaining to both data return and secondary utilization, then, serve to outline the anticipated standards for the return of individual clinical trial data and the secondary use of clinical trial data for research. They offer guidance in areas where legal provisions may be lacking and steer us toward processes that prioritize participant centricity while acknowledging the diverse contexts in which clinical trials may occur. Finally, the standards set out in the ethical

frameworks, the subject of this deliverable, come from basic ethical principles, though the implementation may vary according to the context.

We anticipate a transformative shift in how to govern and give access to individual CT data and their use for secondary research. Therefore, when examining the ethical frameworks, it's crucial to bear in mind that FACILITATE did not emerge in isolation. Instead, it builds upon the foundation laid by preceding projects, ethical frameworks, regulations, and guidelines (as outlined in Table 1), empirical research, published conceptual analyses, industry initiatives toward patient-centred approaches, and efforts to establish procedures for returning individual clinical trial data to participants (such as the TransCelerate iPDR, jointly developed with patient groups, as referenced in the selected bibliography).

What sets FACILITATE apart is its pioneering participant-centric approach in the realm of returning individual clinical trial data and the secondary use of pseudonymized clinical trial data for research. This participant-centric orientation serves as our starting point for the processes to be developed within FACILITATE, including the ethical frameworks, and must prioritize granting participants as much agency as possible over decisions regarding the return of clinical trial data and their secondary use for research.

2.1 What has been done

Informed consent stands as an enduring legal and ethical imperative that must be adhered to in research endeavours, including clinical trials. It empowers research participants to exercise their autonomous choice regarding the utilization of their body and health data.[1,2] The current landscape of informed consent is in a state of ongoing evolution. Criticisms revolve around the lengthy and complicated nature of informed consent forms.[3] Moreover, legal constraints often hamper effectively informing participants and render them too intricate to genuinely raise awareness among participants about their involvement in research.[4] Finding the right balance to effectively inform participants for return of data and secondary use of data for research will be addressed through ethical guidelines developed under the FACILITATE project.

In the context of today's data-driven world, where data can be readily reused and shared for diverse purposes, there are concerns that the traditional informed consent process may no longer be suitable.[3,5,6] These critiques have given rise to the notion that informed consent may no longer be well-suited, especially for data driven research. There's a growing recognition that we may need to adjust the mechanisms governing data sharing in research. While it's true that the current informed consent processes employed by sponsors may not align perfectly with the needs of contemporary data-driven research, informed consent continues to stand as a fundamental ethical imperative in clinical research. In addition to serving as consent for participation in a clinical trial, informed consent also represents a mechanism through which an individual can express their preferences regarding the use of their data. A participant-centric approach cannot be realized without taking into account the individual's voice, making informed consent an indispensable component. Therefore, it's clear that achieving the objectives of FACILITATE necessitates informed consent as a central feature.

Research shows that participants have varying preferences regarding the reuse and sharing of their data, depending on the research purpose and data user, and the fact that these preferences can evolve over time.[7,8] Similarly, individualized preferences exist regarding the return of results, and these preferences may change as well. Therefore, while retaining the informed consent process, it should be reimagined to accommodate personalized decisions and possess the flexibility to adapt over time. FACILITATE's processes and ethical frameworks should thus facilitate the return and secondary use of clinical trial data while accounting for evolving individual preferences.

Alternative models to traditional informed consent have emerged. One such model is broad consent, where participants agree to various research uses of their samples and data, with independent oversight. However, broad consent may not be legally acceptable for research in certain Member States and has been criticized for being overly expansive, potentially lacking the essence of informed consent. It is also a static process, failing to consider evolving participant preferences.[9–13]
In response to these criticisms, tiered consent has been proposed. It offers participants multiple consent options, including a broad consent choice.[14,15,16,17,18] Although tiered consent [19,20] provides more flexibility, it remains static, reflecting participant views at a specific moment and disregarding potential changes in preferences over time. Both models, however, are not fit for the purpose of FACILITATE.

2.2 Where we want to go

When considering the informed consent process for FACILITATE, it necessitates a consent approach that enables data sharing and data return while also being adaptable to accommodate changes in participant preferences over time.[21] Transparency regarding data use is paramount, requiring an information process that is updated as meaningful knowledge for participants becomes available. Interactive consent models have been proposed to engage participants in determining their consent preferences at a given moment, with a process that allows for adjustments in preferences over time. Such consent mechanisms utilize information technology (IT) to facilitate continuous communication and information dissemination to participants. This process enables participants not only to modify the information they receive and their consent choices but also to potentially engage in research that wasn't initially anticipated at the time of consent.[22,23–25] This may include data return to participants. Technical solutions for consent have already found application in the context of clinical trials, with electronic informed consent becoming more prevalent, especially since the COVID-19 pandemic. Participants are becoming increasingly engaged with IT platforms as a component of the consent process in clinical trials.[5,26,27] Electronic consent could be further developed as it has the potential for further enhancement by offering participants the choice to remain informed about data usage and adjust their consent preferences.

FACILITATE is developing its processes at a time of continuous and important regulatory change. In particular, the draft European Health Data Space (EHDS), if passed, will change the governance of the secondary use of electronic health data, that includes clinical trial data. WP3 in conjunction with WP2 are actively monitoring the developing proposals and will incorporate regulatory changes, when necessary, in subsequent deliverables.

FACILITATE is learning from the practical experiences of the other consent models presented previously to gain insights into how we can build a new consent process, a process we are calling “FACILITATE Consent”. The purpose of the FACILITATE Consent process is to take a participant centric approach to the return of individual clinical trial data to patients and enable the secondary use of pseudonymised clinical trial data for research. FACILITATE is building a participant centric prototype process that will support the FACILITATE consent. To align with the expectations of participants[17], it will need to be a process that provides participants with information that is updated as new, meaningful knowledge emerges. It should also allow participants to modify their preferences and incorporate mechanisms for oversight.

Our FACILITATE Consent process represents an evolution of existing models, incorporating the most effective elements to align with our objectives. Furthermore, recognizing the unique ethical considerations surrounding data return and the secondary use of clinical trial data, we have opted for separate ethical frameworks. These frameworks are anchored in ethical principles and offer a practical roadmap for their implementation. Despite their separate nature, both frameworks are

integrated possibly into a single prototype process, ensuring a comprehensive approach to both the return of individual CT data and the secondary use of pseudonymized CT data for research.

3. Methodology

The ethical frameworks build upon existing legal and ethical frameworks, previous and ongoing research projects, empirical research, and existing literature on both secondary use of clinical trial data and return of clinical trial data to patients. WP3 has adopted the methodology of reflective equilibrium that follows the path of reflection[28,29], discussion and revision to reach a conclusion that is acceptable to WP3 and follows the participant centric approach of FACILITATE.[15,16] This methodology reflects the co-creation approach that is a central to the work of FACILITATE. Ongoing consultation is therefore a key feature of the developing ethical frameworks, with regular consultative discussions within WP3, within FACILITATE, and more recently, external stakeholders.

As a first step in this process, WP3 leaders looked to the results of research consortia, including RD Connect, Prefer, Cybergovernance, and EHDT. Particular attention has been given to the recent results of the Cybergovernance project that provided results from discrete choice experiments from 12 European countries with 5015 participants who completed the survey.[17] The results clearly demonstrate that participants want to be informed about the use of their data, want independent external ethics oversight, and prefer having control over the use of their data. WP3 also conducted an extensive literature review to ensure its work is informed by empirical work, conceptual analysis, and policy developments in the return of clinical trial data and secondary use of data.

3.1 Identification of ethical principles

WP3 conducted a review to identify key legal and ethical frameworks on the return of clinical trial data and the secondary use of data. These frameworks were discussed at WP3 meetings, with further frameworks suggested by WP3 members. These legal and ethical frameworks on the return of clinical trial data (appendix 1) and secondary use of clinical trial data (appendix 2) were analysed with the following ethical principles identified:

Return of clinical trial data	**Secondary use of clinical trial data**
Respect for persons and community	Respect for persons and community
Beneficence	Beneficence
Privacy	Equitable access
Utility	Data stewardship
Empowerment	Privacy
Public interest	Trustworthiness
Transparency	Transparency
Accountability	Accountability
	Engagement
	Consistency

	Legitimacy

Table 1: Initial principles identified to guide the ethical frameworks

These principles and the explanation of these principles in the context of FACILITATE were discussed at bi-weekly WP3 meetings, further developed, and refined. Over the following consultations (see below) with the wider FACILITATE consortium, other principles were proposed. These proposals were discussed, with additions and changes made throughout the process.

3.2 Implementing framework

The next stage saw discussion on implementing these principles into practice to develop an ethical process for the return of clinical trial data and the secondary use of clinical trial data. The processes to implement these ethical principles were identified in part through a literature review that looked at empirical research that reported on patient views and other stakeholders as well as the empirical work conducted by WP3. This is to ensure that our ethical frameworks are rooted in public preferences. For the return of clinical trial data, the discussions to date have focused on when to return what data, by whom, what data can be returned directly to a participant, and patient control. For the secondary use of clinical trial data for research, discussions have focused on the role and form of consent, when research ethics committee (REC) approval is needed, criteria to determine access for secondary use, the need for independent oversight (that can be an independent process that may sit within an internal body), and patient control.

The implementing frameworks were first discussed at several bi-weekly WP3 meetings. The proposed framework on secondary use of clinical trial data was circulated to WP2, WP3, and WP6 for discussion, comment, and feedback in September 2022. An online meeting with WP2, WP3, and WP6 was held on 5 October 2022 to discuss the outcomes of this feedback and to find agreement on key issues. Similarly, the ethical framework on the return of clinical trial data was circulated to WP2, WP3, and WP6 in November with a follow-up meeting held on 2 December 2022 to discuss the outcomes of this feedback and find agreement on the key issues.

At the FACILITATE in-person meeting in Modena in November 2022, an informal meeting was held with members of WP3 to discuss certain sections of the ethical frameworks. At that meeting it was decided that an in-person meeting would be necessary to discuss in depth key aspects of the ethical frameworks. This was proposed and agreed at the meeting later that day.

Following the online meetings with WP2, WP3, and WP6 both frameworks were revised and circulated to all partners in the consortia for review, comment, and feedback in February 2023. Partners discussed the frameworks internally within their own organization and feedback was provided from each partner in advance of the in-person meeting in Bolzano (IT) on 15 & 16 March 2023. The frameworks were also circulated to the DAG and DAG+ for feedback, and this feedback was provided in advance of the in-person meeting.

While this discussion was ongoing internally within partners' organisation, in February 2023, 3 members of WP3 (Johanna Blom, Deborah Mascalzoni, Ciara Staunton) had an external stakeholder engagement meeting at Stellenbosch Medical School, Tygerberg Hospital, Cape Town, South Africa. It was decided to host a workshop at this campus for a number of reasons: the representatives were in South Africa as part of a panel on return of results at the International Congress of Human Genetics;

South Africa has a robust research ethics framework in place; South Africa has a data protection regulation (Protection of Personal Information Act 2013) that is similar to the General Data Protection Regulation (GDPR); South Africa is the site of numerous clinical trials, particularly in HIV and TB; and South Africa is collaborating with international research and thus cognizant of the issues related to data sharing.

In total there were 22 participants in attendance with expertise in bioethics, law, clinical trials, policy, research ethics, research integrity, bioinformatics, data management. JB, DM, and CS opened the meeting by outlining FACILITATE, its aims, objectives, ambition, and process of working. Next, the qualitative research to date and the results of the literature review were discussed with the participants. Finally, the participants were informed about the ethical frameworks, the principles guiding the frameworks and the preliminary outline of the implementing framework.

Overall, the participants were positive of the project and its aims. They felt that if it is done correctly, it could be a valuable and useful system. The participants had several recommendations on consent, transparency, governance, and communication with research participants. They also raised the issue of how these frameworks would apply to non-EU partners. These issues were raised and discussed at the next WP3 meeting.

Finally on 15 & 16 March, an in-person meeting was held amongst some partners (those who could attend) in Bolzano (IT). In advance of this meeting, the feedback of all partners was shared amongst the consortium so all could see the comments and concerns of others within the consortium. At that meeting it was decided to focus on agreement of the key concepts and processes that should be included in the implementing framework and further detail will be provided in the next stage of discussion. At this meeting the draft of the implementing framework was agreed by the attendees and then circulated to WP3 for discussion and agreement.

The current agreed draft text of the ethical framework on return of clinical trial data is in appendix 3 and the draft text of the ethical framework on reuse of clinical trial data is included in appendix 4.

4. Next steps

The next stage in the development of the ethical frameworks will focus on providing detail to the concepts and processes that have been identified in the ethical frameworks. There will be closer alignment with WP2, in particular to agree on common definitions and ensure that the regulation produced by WP2 complements the ethical framework.

A series of external engagement on the current draft of the ethical frameworks have been planned. WP3 will meet separately with patients, regulators, and clinicians.

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Appendix 1: Instruments analysed for return of data

CIOMS	International Ethical Guidelines for Health-related Research Involving Humans
MRCT	Return of Individual Results to Participants Recommendations Document
American College of Medical Genetics and Genomics	Recommendations for reporting of secondary findings in clinical exome and genome sequencing
World Medical Association	Declaration of Helsinki
World Medical Association	Declaration of Taipei
UNESCO	Universal Declaration on Human Rights and the Human Genome
UNESCO	International Declaration on Human Genetic Data
ICH	Guideline for genomic sampling and management of data
Council of Europe	Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research
Council of Europe	Recommendation (2006)4 of the Committee of Ministers to member states on research on biological materials of human origin
Council of Europe	Oviedo Convention
European Commission	General Data Protection Regulation
European Commission	Clinical Trials Regulation
European Commission	Draft Regulation for a European Health Data Space
National Academy of Sciences	Returning Individual-Specific Research Results to Participants: Guidance for a New Research Paradigm
Global Alliance for Health	2021 Policy on Clinically Actionable Genomic Research Results
OECD	Recommendation on Health Data Governance

Appendix 2: Instruments analysed for secondary use of data

Council of Europe	Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research
Council of Europe	Recommendation (2006)4 of the Committee of Ministers to member states on research on biological materials of human origin
Council of Europe	Oviedo Convention
Council of Europe	Convention 108 +
European Commission	General Data Protection Regulation
European Commission	Clinical Trials Regulation
European Commission	Draft Regulation for a European Health Data Space
European Commission	Data Governance Act
CIOMS	International Ethical Guidelines for Health-related Research Involving Humans
World Medical Association	Declaration of Helsinki
World Medical Association	Declaration of Taipei
RD-Connect	International Charter of principles for sharing bio-specimens and data
OECD	Recommendation on Health Data Governance
OECD	Recommendation of the Council on Enhancing Access to and Sharing of Data
European Medicines Agency	European Medicines Agency policy on publication of clinical data for medicinal products for human use
Medical Research Council (UK)	Good practice principles for sharing individual participant data from publicly funded clinical trials
Global Alliance	Framework for responsible sharing of genomic and health-related data
TransCelerate	A Privacy Framework for Clinical Data Reuse: Secondary Data Use in the Pharmaceutical Industry
EFPIA	Safeguards framework for secondary use of clinical trial data for scientific research
European Data Protection Supervisor	Preliminary opinion on scientific research

Appendix 3: Draft ethical framework on return of clinical trial data

Disclaimer: this document is a draft version and will be revised, updated, and more detail provided as the project evolves.

A3.1 Background

Sizable amounts of data are generated during a clinical trial that can be of benefit to the study participant. Data that are relevant to a study participant may also arise after the clinical trial. Communicating individual data to study participants can avoid the duplication of potentially invasive and expensive medical examinations, benefiting the study participant and society. Individual data generated during the clinical trial may support better informed healthcare decisions, and therefore communication of these data to the study participants in a timely manner can impact their health.

Returning individual clinical trial data to study participants respects their role in clinical trials and their autonomy. It also empowers them to make informed healthcare decisions. Currently, returning individual clinical trial data to study participants does not routinely occur after the clinical trial, in part due to impediments of pharmaceutical companies contacting study participants after the clinical trial, lack of technology to ensure the return in accepted conditions, and aggregated results of the clinical trials disclosure as per regulations on public sites. Furthermore, the return of individual clinical trial data is legally and ethically complex, with different challenges depending on the typology of the data.

Despite these challenges, study participants have a right to access their personal data under the General Data Protection Regulation (GDPR). It is therefore critical that processes are put in place to overcome these complexities. The FACILITATE project seeks to develop a participant-centric approach to the systematic return of individual clinical trial data. It envisages a bottom-up, participant-centric process to the return of individual clinical trial data empowering study participants to have more control over their healthcare decision-making while balancing other interests, including the scientific integrity of the trials. In so doing, this process should help private and public researchers provide clarity on how to navigate the ethical complexities in returning individual clinical trial data to participants.

This ethical framework sets out the ethical principles and processes to facilitate a participant-centric approach in the return of individual clinical trial data. It is intended to help industry, academia, and all partners in clinical trials, navigate the complex landscape in returning clinical trial data to patients.

A3.2 Aims of the framework

This framework seeks to ensure that the return of individual clinical trial data to study participants during and after the clinical trial is ethically managed. This framework:

- Identifies the pertinent principles to guide the individual return of clinical trial data to patients.
- Identifies and mitigates risks to participants and their families in the return of clinical trial data.
- Provides a transparent and accountable patient-centric process for ethical return of results during and after the clinical trial.

A3.3 Application of the framework

This framework applies to the return of clinical trial data to participants during and/or after a clinical trial that falls under the EU Clinical Trials Regulation.

A3.4 Definitions

To be agreed with WP2 in a later stage

A3.5 Principles to guide the return of clinical trial data to study participants

This ethical framework is guided by the Substantive Principles outlined below, which facilitate the ethical return of clinical trial data to study participants. The Procedural Principles are to be met in the process of the return of clinical trial data to participants. No one principle supersedes another, rather a balance must be struck among them.

The implementing framework describes how these principles are applied in practice and how this balance is achieved.

A3.6 Substantive principles

Rights and respect for individuals and wider society	Individuals have the right to make autonomous and informed decisions. This includes what, if any, clinical trial data should be returned to them. The return of clinical trial data must respect the right of study participants to be informed, their right to access or not their data, and respect a participant's preferences on the return of clinical trial data. The return of data should not be contingent on the participant's completion of the clinical trial.
Beneficence	The return of clinical trial data must be guided by a consideration of the best interests of the study participant.
Non-maleficence	Clinical trial data shall be returned to participants in a manner that maximizes any benefits and minimizes any risks to participants.
Privacy and confidentiality	The return of clinical trial data must respect the individual subject's privacy and the confidentiality of their data. Any limitation of that right must be necessary, limited, proportionate, accountable, and transparent with protections in place to continue to safeguard the subject's privacy and confidentiality.
Utility	The return of clinical trial data must be of value of the study participant (this should be subjective rather than objective e.g., actionable).
Empowerment	Study participants should be empowered to make informed decisions about their healthcare. The individual clinical trial data returned and the process for returning it, including who returns the clinical trial data, should enable this empowerment.
Public value	The primary goal of clinical research is production of generalizable knowledge for the patients who will benefit of the scientific knowledge. Clinical trials are critically important in improving the public's health.

	Any return of clinical data, and the timing of that return, must be balanced against the scientific integrity of the clinical trial.
Data custodianship	To return high quality and reliable data to a participant, it is essential to have control over the process that generates the results themselves. Traceability of the processes that generated the results can ensure the accuracy and pertinence of the data that is returned to the right clinical trial participant.
Justice	Returning clinical trial data must be done in a manner that is lawful, fair and just.

A3.7 Procedural values

Transparency	The process to be followed in the return of clinical trial data must be clear and explained to the study participants at the time of the informed consent. It must be clear to study participants the type of data that will be returned and when. The process to be followed if a participant changes their preferences must be clear and communicated to the participant.
Accountability	It must be clear who is responsible for ensuring that clinical trial data is returned to participants.

A3.8 Implementing an ethical process on the return of individual clinical trial data

A3.8.1 Transparent and accountable processes

The roles and responsibilities of key individuals in the decision-making process shall be identified.

There shall be clear, transparent, and ongoing information to participants throughout the entire process on the return of clinical trial data.

A3.8.2 Participant information and decision process

During the clinical trial informed consent process, participants shall be informed that the purpose of the clinical trial is to identify generalizable results based on statistical inference and not individual care.

It must be planned in the protocol whether they may or may not receive individual data during the trial, depending on the type and set-up of the trial (blinded or not etc.) Participants shall also be clearly informed that during and after the clinical trial, data may emerge that may be relevant for their health and the modalities foreseen for potential recontact in those cases.

Participants shall be informed on how to access their individual data of all medical tests if they consent to it.

Participants shall be informed that data may arise that can impact decisions on their healthcare during the clinical trial. Data that can lead to decisions that are lifesaving, urgent, or actionable must be

returned to the participant during the clinical trial. This applies even if the return of individual data can result in the unintentional unblinding of the individual and risks the integrity of the overall trial.

Participants shall be informed that data that are not urgent but actionable may arise. They shall be informed about these data, unless for reasons that may include preserving the integrity of the clinical trial. All data shall be returned to participants after the clinical trial. Sensitive data shall be returned in the appropriate manner.

Study participants shall be informed who is responsible and how the data will be returned to them (e.g., in the form of a letter, through a portal, by their health care practitioner, study team member, etc.).

Study participants shall be informed that they shall receive the general study results at the end of the clinical trial. This can be in several different methods that can include an invited meeting, a webinar, or information printed on a website. What is important is that all patients are made aware of where and how the general study results will be returned, that the information is clear and understandable, and that patients have the opportunity to ask questions.

A3.8.3 Participation information and decision tool

Individual data after the clinical trial shall be communicated to participants through a participant tool through which the participant and their physician(s) can access their data.

Participants shall be informed that it is their responsibility to ensure that their contact details are kept up to date on this tool. They shall be informed that failure to do so can impact their ability to receive ongoing information.

Appendix 4: Draft ethical framework on secondary use of data

Disclaimer: this document is a draft version and will be revised, updated, and more detail provided as the project evolves.

A4.1 Background

Clinical trials collect, use, and produce sizable quantities of health and other related data. These data are potentially a valuable resource that can be used for future research beyond the original clinical trial. The secondary use of data gathered through clinical trials can help ensure that the maximum value to human health is extracted from these data and potentially avoid unnecessary exposure to clinical trials. At the same time, the secondary use of clinical trial data can impact individual rights and interests, including the right to autonomy, data protection, privacy, and non-discrimination and they should be used with respects to participant rights and interest to build and consolidate participants trust.

The *primary use* of data in clinical trials is regulated by several EU and local Regulations, mainly the EU Clinical Trials Regulation (CTR) and, from a data protection point of view by the EU General Data Protection Regulation (GDPR) and any applicable local data protection law. The process on the *secondary use* of clinical trial data for research is less clear. The CTR does anticipate the secondary use of clinical trial data for scientific research. It states that the sponsor may ask the subject for their consent for the use of their data for scientific purposes outside of the clinical trial protocol, that this consent may be withdrawn at any time, and that the secondary use of the clinical trial data for scientific research purposes must be in line with the applicable laws on data protection. The CTR also states that the secondary use of the data for scientific research be made subject to reviews that can include ethical reviews before the commencement of the research. Outside of these requirements, the CTR does not provide guidance on how to manage the secondary use of clinical trial data for scientific research, requiring those seeking to access clinical trial data for secondary purposes to navigate the differing legal rules and requirements on the secondary use of clinical trial data, including the General Data Protection Regulation (GDPR). In some countries, legal frameworks related to research on data (secondary use of health data already collected) exist and need to be contemplated within an ethical framework.

Study participants' trust in the secondary use of their data is critical. An important component in building this trust is the application of ethical principles to the secondary use of clinical trial data. Some of these ethical principles will be in addition to the requirements set out in law. Thus, adherence to legal requirements alone may be insufficient in ensuring participant trust in the secondary use of their clinical trial data, but rather both ethical principles and legal requirements should be met.

The FACILITATE project seeks to develop a participant centric approach to the secondary use of pseudonymized clinical trial data for scientific research. This ethical framework sets out the ethical principles and processes fostering a participant-centric approach to the secondary use of pseudonymised clinical trial data.

A4.2 Aims of the framework

This document provides a participant-centric ethical framework to ensure that study participants are empowered, and their rights and interests are protected when clinical trial data are used for scientific research that is in the public interest. This framework is to be adopted and contextualized to specific contexts to ensure that ethical checks and balances are in place in the secondary use of pseudonymised clinical trial data for scientific research. It is to complement the legal framework

developed as part of FACILITATE on the secondary use of pseudonymised clinical trial data for scientific research. Specifically, this ethical framework aims to:

- Identify the relevant ethical principles to guide the secondary use of clinical trial data for pseudonymised scientific research.
- Safeguard clinical trial subjects' interests while enabling the ethical secondary use of pseudonymised clinical trial data for scientific research.
- Complement existing national and international legal and ethical frameworks.

A4.3 Application of this framework

This framework applies to the secondary use of pseudonymized clinical trial data for scientific research. This framework does not apply to anonymous data.
This framework does not apply to reuse / reanalysis of biological samples.

A4.4 Intended audience

This ethical framework applies to all involved in the secondary use of pseudonymised clinical trial data for scientific research (both public and private), including researchers, and those involved in decision making and oversight of secondary use of clinical trial data.

A4.5 Definitions

To be agreed with WP2 in a later stage of the project

A4.6 Guiding principles

This ethical framework is guided by the following principles that should be applied in the secondary use of pseudonymised clinical trial data.

The substantive principles are ethical principles to determine whether data can be used for secondary use. The procedural principles are ethical principles to support the decision-making processes to be followed for the secondary use of clinical trial data. No one principle supersedes another but rather are to be balanced with the others.

The implementing framework provides guidance on how these principles are to be applied in practice.

A4.6.1 Substantive principles

Rights and respect for individuals	The secondary use of clinical trial data must respect the rights of participants. This includes, but is not limited to, their rights to non-discrimination, right to autonomy, and right to integrity.
Privacy and confidentiality	The secondary use of data for scientific research must respect the individual subject's privacy and the confidentiality of their data. Any limitation of that right must be necessary, limited, proportionate, accountable, and transparent with protections in place to continue to safeguard the subject's privacy and confidentiality.

Data custodianship	Data collected and produced during a clinical trial are a valuable resource that can be re-used for scientific research. The sustainable secondary use of the clinical trial data is contingent on the data being secure, accessible, with clear procedures in place to provide access to the data for ethically sound and scientifically robust research.
Non-maleficence	Clinical trial data shall only be used for secondary scientific research purposes if the purpose of the research is to benefit human health and any risks to the participants and their communities are minimized.
Trustworthiness	The re-use of the clinical trial data must be done in a manner that respects the individuals and their community in order to build trust.

A.4.6.2 Procedural principles

Transparency	The process to decide on access for the secondary use of clinical trial data must be transparent, in line with publicly available policies on how the process to be followed in the secondary use of clinical trial data, and with the informed consent. This will help promote trustworthiness.
Accountability	It shall be clear what are the processes to be followed, who is responsible for ensuring that the processes on secondary use of clinical trial data are followed.
Empowerment	Participants should have a role in deciding on the secondary use of their data and their consent reflected in the process on secondary use.
Legitimacy	The secondary use of clinical trial data for scientific research must be compliant with all applicable laws, regulations, and guidance on research, research ethics, data protection, and any other relevant laws.

Appendix 5: Implementing an ethical process in the secondary use of clinical trial data for scientific research

A5.1 Transparent and accountable processes

The roles and responsibilities of key individuals in the decision-making process shall be identified. There shall be clear, transparent information to participants throughout the entire process of the secondary use of clinical trial data.

In addition to the individual information to participants, general information on the results of the secondary use of clinical trial data shall be shared with the public when pertinent and available.

A5.2 Participant information and decision process

Participants shall be approached during the trial, preferably not close to the consent to the clinical trial about the use of their clinical trial data for secondary research. Participants shall receive information regarding potential risks, including those related to privacy, along with the precautionary measures in place to minimize and mitigate these risks. They will also be made aware of the benefits associated with the use of their pseudonymized clinical trial data for secondary research purposes, as well as of broader societal benefits and the facilitation of data reuse in research.

At the time of consent for reuse, participants shall be presented with the typologies of research to which their pseudonymised clinical trial data may be used for secondary research. This is an opt in consent: this means that patients should express freely how they want to be recontacted and informed. Participants shall be informed that if they agree to the use of their pseudonymised clinical trial data in the secondary use, for the categories of research for which they have not been able to be provided with all relevant information ("pre-identified research areas"), they will be notified before the beginning of new research, enabling them to opt in/opt out as desired. Participants shall be informed about a designated time frame during which they can make their decision regarding the utilization of their pseudonymized clinical trial data for a specific research study. They will also have the choice to opt-in for each study involving the secondary use of their pseudonymized clinical trial data.

In addition to being contacted to opt-out, participants shall be informed that they can receive information that is updated as meaningful knowledge becomes available regarding the use of their pseudonymised clinical trial data in the secondary use of research. Participants shall be provided with the option of deciding how this information is communicated to them (e.g., a notification every time their clinical trial data is used, a yearly notification, no notification etc.). Participants can update their notification preferences at any time.

Participants shall be informed that they can change their preferences at any time and withdraw from the use of their pseudonymised clinical trial data in the secondary use of research. They shall be informed about how they can withdraw their consent. Participants shall be informed that their withdrawal applies to the future secondary use of clinical trial data only. Study participants shall be informed about limits on any withdrawal.

Different media and communication channels should be used where necessary to enable participants to understand this information. Participants' understanding of their participation in the secondary use of their clinical trial data shall be assessed.

A5.3 Participation information and decision tool

Notification to participants and the change of preferences in the secondary use of clinical trial data will be facilitated through a secure participant information and decision tool.

Participants shall be informed that it is their responsibility to ensure that their contact details are kept up to date on this tool. They shall be informed that failure to do so can impact their ability to opt-out.

A5.4 Independent oversight process

The secondary use of pseudonymised clinical trial data shall be assessed by an independent process of oversight that could reside within an internal or external body.[1] This independent process shall have the necessary expertise to manage an access request, that includes individuals that can represent patient perspectives and the other important stakeholders.
This independent body shall be responsible for overseeing the ethical use of secondary use of pseudonymised clinical trial data in research. It shall establish clear review criteria in the ethical use of secondary use of pseudonymised clinical trial data in research. This independent body shall decide whether the research falls within the participants selected decision. This independent body shall decide whether it is necessary to contact a participant if the secondary use of pseudonymised clinical trial data falls outside the preferences of the participant.

A5.5 Safeguards

Access to the secondary use of pseudonymised clinical trial data shall not be provided unless there are sufficient safeguards in place to guarantee the rights and interests of the affected parties, including participants and sponsors.

A5.6 Independent oversight of adherence

A process shall be put in place to ensure there is independent oversight of adherence to this framework.

[1] Discussions and decision-making processes have not yet been completed. Decisions are expected for D3.2.

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