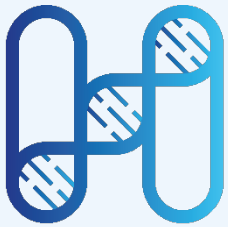

HEREDITARY

HetERogeneous sEmantic Data integratIon for the guT-bRain interplaY

Deliverable 2.19

UNITO clinical studies documentation

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No GA 101137074. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

Funded by
the European Union

EXECUTIVE SUMMARY

This deliverable provides comprehensive documentation on the regulatory, ethical, and legal approvals required for the clinical studies conducted by UNITO as part of the HEREDITARY project. It details the procedures followed to secure the necessary approvals, ensuring full compliance with relevant regulatory bodies, ethical standards, and data protection laws.

The document covers ethical approvals, regulatory compliance, and data access and transfer agreements associated with the clinical use cases led by UNITO under the HEREDITARY project. It also outlines the processes for obtaining informed consent for new data collection, ensuring that consent is freely given, specific, informed, and unambiguous. The enrolment procedures at UNITO are meticulously designed to meet these requirements.

Additionally, the deliverable addresses the potential for incidental findings during research. The HEREDITARY project has established an incidental findings policy that respects the privacy rights of participants while considering ethical obligations. Although the use of anonymized data minimizes the risk of linking incidental findings to individual participants, the policy provides clear guidelines on how to manage such findings if they occur.

Overall, this deliverable demonstrates HEREDITARY's commitment to ethical research practices and the protection of data subjects in the design of Use Cases 1 and 2. By aligning with GDPR, upholding rigorous ethical standards, and implementing comprehensive data protection measures, the project ensures that its research contributes to scientific knowledge while respecting the privacy and autonomy of participants.

DOCUMENT INFORMATION

Deliverable ID	D2.19
Deliverable Title	UNITO clinical studies documentation
Work Package	WP2
Lead Partner	UNITO
Due date	30.09.2024
Date of submission	20.09.2024
Type of deliverable	R
Dissemination level	PU

AUTHORS

Name	Organisation
Maurizio Grassano (Author)	UNITO
Umberto Manera (Author)	UNITO
Federico Casale (Author)	UNITO
Adriano Chio (Author)	UNITO
Gianmaria Silvello (Reviewer)	UNIPD

REVISION HISTORY

Version	Date	Author	Document history/approvals
1.0	29.08.2024	Maurizio Grassano	First draft
1.1	05.09.2024	Gianmaria Silvello	Revision of the first draft
2.0	16.09.2024	Maurizio Grassano	Second draft
2.1	19.09.2024	Anna Romanovych	Revision of the second draft and format edition
2.2	20.09.2024	Gianmaria Silvello	Second review of the deliverable and minor fixes

Contents

1 Introduction 7
2 Data to be included in the study 9
2.1 Summary of data to be used in Use Cases 1 and 2 10
3 Ethical conduct of the study 12
3.1 Ethical approvals 12
3.1.1 Ethical Approval Documentation 13
4 Data Transfer Agreements 15
4.1 Data Minimization and Pseudonymization 15
4.2 Data Transfers to Third Parties and International Transfers 16
5 Informed consent for new data 17
5.1 Procedure of enrollment 17
5.2 Informational Sheet and Informed consent 19
6 Incidental Findings Policy 20
7 Conclusion 21
REFERENCES 22
ANNEXES 23

List of Tables

Table 1. List of ethical approvals Comitato Etico Territoriale (CET) Interaziendale A.O.U. Città della Salute e della Scienza di Torino 13
Table 2. Criteria for Patient Enrollment in the Event of Additional Data Requirements for Use Cases 1 and 2. 18

1 Introduction

This deliverable provides the legal context and documentation for the neurodegenerative use cases within the HEREDITARY project, specifically Use Case 1 (Neurodegenerative Diseases Phenotyping and Prognosis Evaluation) and Use Case 2 (Next-Generation Diagnosing and Treatment Response for Neurodegenerative Diseases). These use cases are at the core of the HEREDITARY project, which aims to enhance the understanding and treatment of neurodegenerative diseases, particularly amyotrophic lateral sclerosis (ALS), through advanced data integration and analytics.

The HEREDITARY project addresses the limitations of current symptom-based classifications of neurodegenerative diseases, which often fail to capture their biological heterogeneity. By integrating multimodal data—including genetic, clinical, biomarker, and imaging data—the project seeks to refine patient classification and prediction, uncover novel biomarkers, and explore etiological mechanisms. This approach necessitates processing sensitive personal data on a large scale, utilizing a privacy-preserving federated learning infrastructure.

- **Use Case 1: Neurodegenerative diseases phenotyping and prognosis evaluation.** This use case focuses on understanding ALS by identifying endophenotypes through the integration of multimodal data. It aims to detect genomic variants and biological pathways associated with clinical features and patient survival.

- **Use Case 2: Next-generation diagnosing and treatment response for neurodegenerative diseases.** This use case aims to develop a biologically informed, biomarker-driven classification system for neurodegenerative diseases, enabling precision medicine approaches.

Given the sensitive nature of the data involved and the scale of the project, it is crucial to establish a robust legal and ethical framework to ensure compliance with applicable regulations and to protect the rights of data subjects. This document outlines the key legal considerations, primarily focusing on the General Data Protection Regulation (GDPR)[1] and relevant EU and national legislation, that govern the processing of personal data in scientific research within the context of these neurodegenerative use cases.

Use Cases 1 and 2 will be conducted mainly using data from two Italian clinical centers (UNITO and UNIPD); therefore, this deliverable particularly focuses on adherence to Italian and European legislation regarding data privacy and security. Specifically, Article 2-quater of the Italian Privacy Code[2] and Article 21, paragraph 5 of Legislative Decree No. 101 of August 10, 2018[3], underscore the importance of adhering to the GDPR, particularly in contexts involving sensitive personal data.

[1] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJ 2016 L 119/1.

[2] d.lgs 196/2003, “Privacy Code”, Article 2-quater, “Ethical rules”

[3] d.lgs 101/2018, “Provisions for the adaptation of national legislation to the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016,

In this context, "personal data" refers to "any information relating to an identified or identifiable natural person ('data subject')." A natural person is considered identifiable if they can be identified, directly or indirectly, by reference to an identifier such as a name, identification number, location data, online identifier, or one or more factors specific to their physical, physiological, genetic, mental, economic, cultural, or social identity.

The use of personal data for scientific research in the medical, biomedical, and epidemiological fields is permitted, provided that the data subject's consent is obtained. However, consent is not required when, for specific reasons, informing the data subjects is impossible or involves a disproportionate effort, or when it would make it impossible or seriously impair the achievement of the research purposes (Article 110 of the Italian Privacy Code[4]). The provisions detail the circumstances under which it is impossible to obtain consent, linking them to specific ethical and organizational reasons, and require these reasons to be duly justified in the research project[5] . In such cases, the data controller must adopt appropriate measures to protect the rights, freedoms, and legitimate interests of the data subjects. The research program must receive a favorable opinion from the competent territorial Ethics Committee and be submitted for prior consultation with the Privacy Authority[6] in accordance with the Italian law (4) and the GDPR[7].

The principle of data minimization is crucial, stipulating that data must be "adequate, relevant, and limited to what is necessary in relation to the purposes for which they are processed" (Article 5, paragraph 1, letter c of the GDPR)[8]. In accordance with this principle, the processing of personal data for scientific research in the medical, biomedical, or epidemiological fields may include health-related data, and, only where indispensable for the research purposes, may it also include data relating to sexual life or sexual orientation, as well as racial and ethnic origin[9].

Personal data must also be processed in compliance with the principle of transparency (Article 5, paragraph 1, letter a of the GDPR(8), meaning that the data subjects must be provided with clear and understandable information, as specified in Article 13 of the GDPR for data collected directly from them[10], or Article 14 for data collected from third parties[11].

According to the principle of storage limitation, data should be "kept in a form which permits identification of data subjects for no longer than is necessary for the purposes

concerning the protection of natural persons with regard to the processing of personal data, as well as the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)", Article 21, Paragraph 5

[4] d.lgs 196/2003, "Privacy Code", Article 110, "Medical, biomedical, and epidemiological research"

[5] d.lgs 101/2018, Section 5.3

[6] Regulation (EU) 2016/679 of the European Parliament, Article 36 "Prior consultation"

[7] Regulation (EU) 2016/679 of the European Parliament, Article 89 "Safeguards and derogations relating to processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes"

[8] Regulation (EU) 2016/679 of the European Parliament, Article 36 "Principles relating to processing of personal data"

[9] d.lgs 101/2018, Section 5.4

[10] Regulation (EU) 2016/679 of the European Parliament, Article 13 "Information to be provided where personal data are collected from the data subject"

[11] Regulation (EU) 2016/679 of the European Parliament, Article 14 "Information to be provided where personal data have not been obtained from the data subject"

for which the data are processed." Personal data may be stored for longer periods if they are processed solely for archiving purposes in the public interest, scientific or historical research purposes, or statistical purposes, subject to the implementation of appropriate technical and organizational measures required by this Regulation to safeguard the rights and freedoms of the data subjects (Article 5, paragraph 1, letter of the GDPR (8).

Among the principles applicable to processing established in Article 5 of the GDPR, the principle of accountability is particularly significant. It requires that "the data controller must comply with and be able to demonstrate compliance with the principles and obligations set out in the Regulation" (Articles 5, paragraph 2 (8), and Article 24 of the GDPR[12]). This principle is closely linked to another duty imposed on the data controller: to ensure that data protection rights and regulations are safeguarded and implemented from the design stage and by default (privacy by design and by default, Article 25 of the GDPR[13]).

In line with the obligation of data protection by design, data controllers must take an active role in applying these principles, aiming to achieve a real protective effect. Article 25 of the GDPR (13) obliges data controllers to ensure that data protection is integrated into processing from the design stage and by default throughout the entire lifecycle of the processing activity. The data controller must adopt appropriate technical and organizational measures designed to effectively implement data protection principles and integrate the necessary safeguards into the processing to comply with data protection regulations and protect the rights and freedoms of the data subjects.

In the following chapters, we will provide a detailed examination of how the neurodegenerative use cases within the HEREDITARY project are designed and implemented to meet the ethical and legal requirements outlined in this chapter. We will explore the specific measures taken to ensure compliance with GDPR. Furthermore, we will illustrate how these use cases adhere to the ethical standards necessary for the responsible processing of sensitive personal data, ensuring the protection of the rights and freedoms of the data subjects involved in these crucial research activities.

2 Data to be included in the study

As outlined in the description of Neurodegenerative Use Cases 1 and 2 (see Deliverable 2.16[14]), the HEREDITARY project will utilize:

- legacy data, sourced from previous EU-funded projects (such as BRAINTEASER[15]) and collected by the ALS Centers of UNITO and UNIPD, all of which have received prior approval from local ethics committees;
- new data collected from individual patients enrolled during the project.

[12] Regulation (EU) 2016/679 of the European Parliament, Article 24 “Responsibility of the controller”
[13] Regulation (EU) 2016/679 of the European Parliament, Article 25 “Data protection by design and by default”
[14] “HEREDITARY Deliverable 2.16, “Design of Neurodegenerative Use Cases”, available at https://hereditary-project.eu/deliverables/
[15] https://brainteaser.health/

All data will be handled using the most appropriate methods to ensure privacy and security, such as anonymization.

2.1 Summary of data to be used in Use Cases 1 and 2

The study population will include all patients with ALS who have been followed-up at the ALS Center of UNITO.

Inclusion Criteria

The following criteria must be met in order to be included in the study:

- The patient and/or legally acceptable representative must have given written informed consent (IC) and assent to the collection and use of data for scientific purposes, if indicated per patient's age and institutional guidelines, and any authorizations required by local law.
- Patient's medical records or registry data are available for data extraction.

Exclusion Criteria

Medical data or registry data from patient records that do not minimally contain the following are not eligible for participation:

- Age at onset of first sign(s) or symptom(s) of ALS.
- Site of the first ALS-related symptom or sign.
- Age at time of clinical diagnosis of ALS.

List of data to be included in the study

Clinical Data

- ALS Sign/Symptom Onset
- Pre-ALS Diagnosis Progression
- Confirmed ALS Diagnosis
- Demographics
  - Sex
  - Country
- Medical and Treatment History
- Family History
- Is patient a fraternal or identical twin
- Age at ALS Onset
- Site of the first ALS-related symptom or sign
- Time from signs/symptoms onset to ALS Diagnosis
- Investigations:
- Upper/lower motor neuron involvement
- Atypical features
- Cognition:
- Progression Post-ALS Diagnosis
  - Disease Severity and Function Impairment:
  - ALSFRS(-R):
- Lung Function:
  - Spirometry

    - SVC
    - FVC % predicted and liters
- Ventilatory Support
    - Non-invasive Ventilatory Support
    - Invasive Ventilatory Support
- Late Stage Features:
    - Percutaneous Endoscopic Gastrostomy
- Death

Genetic Data

- Whole genome sequencing data
- Genome Wide Association Study data

Neuroimaging Data

- Brain Magnetic Resonance (MR) images
- 18-FDG PET images

3 Ethical conduct of the study

To ensure the quality and integrity of research, all Clinical Use Cases lead by UNITO will be conducted under the Guidelines for Good Pharmacoepidemiology Practices (GPPs)[16] issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki[17] and its amendments, and any applicable national regulations and guidelines.

3.1 Ethical approvals

The HEREDITARY project plans to use data that have been retrospectively collected for ALS cases. A recent amendment to the Italian Privacy Code[18] has set forth safeguards to be adopted for the processing of personal data for medical, biomedical, and epidemiological research purposes, particularly concerning deceased or non-contactable patients. With this modification, it is no longer required to submit the research project and the related impact assessment for prior consultation when it is impossible to inform the individuals concerned, or if doing so would involve disproportionate effort or severely jeopardize the study's results. Instead, compliance with the specific safeguards established by the Privacy Authority is sufficient.

The Authority has established that in such cases, data controllers—beyond obtaining the favorable opinion of the competent territorial Ethics Committee on the research project—must justify and document the ethical or organizational reasons for not being able to obtain patient consent. They must also conduct and publish the impact assessment, notifying the Privacy Authority accordingly. Organizational impossibilities may include situations where contacting the individuals would involve disproportionate effort due to the particularly large sample size or, after all reasonable efforts to contact them (including verification of survival status, consultation of clinical documentation, use of provided contact numbers, and acquisition of publicly accessible contact details), the patients are found to be deceased or unreachable at the time of enrollment in the study.

The Neurodegenerative Use Cases 1 and 2 within the HEREDITARY project plan to analyze multimodal anonymized data from patients affected by ALS. Below is a brief justification for why a waiver of specific informed consent is warranted within the scope of HEREDITARY:

- ALS is a rare disease, and its natural history, particularly concerning the variability of disease progression, remains largely uncharacterized. There is a significant unmet need in this disease, as there are no available treatments that modify the disease. Consequently, there is a lack of real-world data describing the longitudinal evolution and the mechanisms responsible for the clinical

[16] Public Policy Committee, International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf. 2016 Jan;25(1):2-10. doi: 10.1002/pds.3891. Epub 2015 Nov 5. PMID: 26537534.
[17] World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191-4. doi: 10.1001/jama.2013.281053. PMID: 24141714.
[18] d.lgs 196/2003, “Privacy Code” artt. 2-quater e 106 - “Code of Conduct for processing for statistical or scientific research purposes” - Published in Gazzetta Ufficiale No. 130 of June 5, 2024

characteristics of ALS, as well as the patterns and variability of disease progression.

- ALS is associated with a high mortality rate, with a median survival of approximately four years from the onset of symptoms. In most cases, death occurs within five years of disease onset. Consequently, if the study were to include only living (incident) cases, it would exclude most ALS cases. The urgent need to understand disease progression and natural history necessitates analytical approaches, such as those planned for HEREDITARY, which become significantly more effective with a larger sample size. Insufficient sample size is a major limitation that can hinder the application of advanced statistical tools and machine learning, potentially leading to inconsistent results or erroneous conclusions. Therefore, restricting the analysis to living patients from whom informed consent can be obtained would severely limit the scope and potential of the HEREDITARY project.
- No data directly identifying the patient (e.g., name, initials, institutional identification numbers, medical record number, full date of birth, full date of exams or evaluations, etc.) will be collected or transferred.
- Patients who meet the inclusion criteria will be selected by the center and will be protected using a code, which is a unique identification number specifically assigned to the patient. The coding list with the ID number to reidentify the patient or link the data to the patient will remain at the center and will not be communicated outside the center. Patient ID records will be destroyed at the end of the study to ensure data anonymization, if required by local data protection laws.

3.1.1 Ethical Approval Documentation

All data collected within the HEREDITARY project have received the necessary ethical approvals for research purposes, in compliance with GDPR and relevant ethical standards. Ethical oversight for this project has been provided by local ethics committees, ensuring that all procedures for data collection, processing, and sharing comply with established guidelines and regulations. Specifically, data processed in HEREDITARY were collected under the following projects approved by UNITO ethics committee.

Table 1. List of ethical approvals Comitato Etico Territoriale (CET) Interaziendale A.O.U. Città della Salute e della Scienza di Torino

Project	Protocol Number	Date of approval	Data
BRAINTEASER	0079511	26/07/2021	Clinical data Genomic data
EUROMOTOR	0036344	18/05/2011	Clinical data Genomic data
INITIALS	0038876	12/04/2018	Clinical data Genomic data
PERMEALS	0038490	24/03/2022	Clinical data Neuroimaging data
INSPIRED	0011669	02/02/2017	Clinical data

Project	Protocol Number	Date of approval	Data
			Neuroimaging data
EXTRALS	0064510	05/12/2012	Clinical data Neuroimaging data

These approvals (Annexes 1-7) confirm that all data collection processes meet the ethical requirements for protecting the rights and well-being of the data subjects involved.

Furthermore, to promote transparency and advance scientific research, anonymized genetic and clinical data collected through previous EU-funded projects have been made openly accessible upon request[19][20]. These datasets are available on designated platforms, providing researchers and stakeholders with the opportunity to utilize the data while ensuring compliance with data protection regulations. The open-access data repositories include the BRAINTEASER repository, available after request at https://zenodo.org/records/8083181.

[19] dbGaP Study Accession: phs000101.v5.p1
[20] https://www.projectmine.com/research/data-sharing/

4 Data Transfer Agreements

The Use Cases 1 and 2 within the HEREDITARY project involve the collection, processing, and transfer of sensitive clinical data across multiple partners. To ensure these activities are conducted in full compliance with the GDPR, the project has established comprehensive Data Transfer Agreements (DTAs). These agreements provide a structured framework for the secure and lawful handling of data, safeguarding the rights of data subjects and ensuring adherence to the highest standards of data protection.

The DTAs underpinning the Neurodegenerative Use Cases 1 and 2 of HEREDITARY are meticulously designed to align with the strict requirements of the GDPR. Specifically, they ensure that all data processing activities are grounded on a lawful basis as mandated by GDPR Articles 6 and 9. The processing of health-related data is justified under the legal grounds of public interest in scientific research. Furthermore, the agreements stipulate that data processing is conducted transparently and fairly, with the explicit or legally supported consent of the data subjects.

The DTAs ensure that all partners in the HEREDITARY project respect and facilitate the exercise of data subjects' rights. Data subjects are granted full access to their data and retain the rights to rectification, erasure, restriction of processing, data portability, and objection. The DTAs outline clear procedures for how these rights can be exercised and how partners must respond to requests from data subjects, ensuring compliance within legally defined timelines.

The DTAs clearly define the roles of Data Controllers and Data Processors in accordance with GDPR guidelines (12) [21]. Each partner's responsibilities are explicitly stated, ensuring clarity in data management practices. Data Controllers are responsible for determining the purposes and means of processing personal data, while Data Processors handle data on behalf of the controllers, adhering strictly to the instructions provided. The agreements also mandate the appointment of Data Protection Officers (DPOs) for each partner, whose duties include monitoring compliance with the GDPR and overseeing data protection strategies.

To safeguard the integrity and confidentiality of the data, the DTAs require the implementation of robust technical and organizational measures. These measures are tailored to mitigate risks associated with data processing, ensuring a high level of security against unauthorized access, accidental loss, or unlawful processing. In the event of a data breach, the agreements outline immediate notification procedures to both the relevant supervisory authorities and the affected data subjects, as required by GDPR Articles 33 [22] and 34 [23].

4.1 Data Minimization and Pseudonymization

In accordance with GDPR principles, the DTAs emphasize data minimization, ensuring that only the data necessary for HEREDITARY's objectives are processed. Additionally,

[21] Regulation (EU) 2016/679 of the European Parliament, Article 28 "Processor"
[22] Regulation (EU) 2016/679 of the European Parliament, Article 33 "Notification of a personal data breach to the supervisory authority"
[23] Regulation (EU) 2016/679 of the European Parliament, Article 34 "Communication of a personal data breach to the data subject"

to further protect data subjects' privacy, the agreements mandate the pseudonymization of clinical data before it is transferred between partners. This process involves replacing personal identifiers with coded information, thereby reducing the risk of unauthorized identification while still allowing for meaningful research.

4.2 Data Transfers to Third Parties and International Transfers

The DTAs impose strict controls on the transfer of data to third parties, ensuring that such transfers are only conducted with the explicit consent of the data provider and in compliance with GDPR provisions. While no data transfers outside the EU are currently planned, the agreements stipulate that if such transfers become necessary, they must adhere to GDPR's rules on international data transfers. This includes ensuring that the receiving countries provide an adequate level of data protection or that appropriate safeguards, such as standard contractual clauses, are in place.

The model of the data transfer agreement, including details of the parties involved, terms, and conditions, is provided as Annex 7.

5 Informed consent for new data

The acquisition of consent will comply with the requirements set out in the GDPR. According to GDPR[24], to be valid, consent must be:

a. *Freely Given*: The data subject must not be forced or deceived into providing consent.
b. *Specific*: Each consent must be for a single, well-defined purpose, allowing the data subject to agree or disagree with the specific processing operation. The purpose of processing must be specified before or at the time of data collection.
c. *Informed*: Data subjects must be provided with all necessary information regarding the processing of their personal data, enabling them to give informed consent.
d. *Unambiguous*: The individual's intention to allow the processing of their data must be clear and without doubt. As per GDPR, consent can be given by a statement or a clear affirmative action, allowing for "implied consent" under certain conditions, provided the actions are unambiguously clear and demonstrable.

5.1 Procedure of enrollment

The Neurology Unit 1 (City of Health and Science) at UNITO, involved in HEREDITARY, is a referral (tertiary) center for ALS, Multiple Sclerosis (MS), frontotemporal dementia (FTD), and other neurodegenerative disorders in the region. These centers have specialized multidisciplinary teams providing optimized diagnostic and management services for patients with neurodegenerative diseases.

Patients attending these centers are either diagnosed there or referred for advice and subsequent follow-up by non-specialized neurological departments in the area. All ALS patients and patients with neurodegenerative diseases (including MS and FTD) followed by Neurology Unit 1 are eligible for enrollment in HEREDITARY. The enrollment (inclusion/exclusion) criteria are detailed in Table 2. Patients meeting the criteria will be invited to participate in the study.

Investigators at the clinical sites will be responsible for obtaining written informed consent (IC) or assent from the patient or a legally acceptable representative. A legally acceptable representative is an individual or entity authorized under applicable law to consent on behalf of a patient for participation in the study.

Informed consent will be obtained after providing an adequate explanation of the study's purpose, aims, methods, and the patient's rights and responsibilities, and before any protocol-specific data collection begins.

If requested by the patient, a designated person may be present during the enrollment procedure and participate in the discussion. After a detailed explanation of the study's aims and procedures, provided in language and terms intelligible to the participants, the information sheet will be read with the patients. Patients will have ample time to ask any questions they deem necessary, and comprehensive answers will be provided. The patient or legally acceptable representative must be given sufficient time to consider

[24] Regulation (EU) 2016/679 of the European Parliament, Article 7 "Conditions for Consent"

participation in the study. If, after this process, the patient decides to participate, they will sign and date the informed consent form.

The informed consent form should be signed and dated by both the patient or legally acceptable representative and the person who conducted the informed consent discussion. If the patient is unable to sign due to severe motor impairment (e.g., paresis of hands), a person designated by the patient may sign on their behalf. This will be noted in the informed consent, and a copy of the personal ID of the signing person will be attached to the consent form. The original signed informed consent form should be retained by the investigators at the clinical sites and in all other locations as required by institutional policy, with a copy provided to the patient or legally acceptable representative.

During the discussion preceding enrollment, patients will be informed that:

a. They can withdraw from the study at any time, without having the obligation to state the reason for their decision.
b. They can still participate to the study even if they do not give their consent to the genetic analysis.
c. If the patients will decide not to be enrolled in the study or if they will withdraw from the study, they will still be followed up by the clinical centre according to the current clinical guidelines and their updates, without undermining for the quality of the care they will receive.
d. The enrolment in the study will not modify the treatment of the patients, including the chance to be enrolled in pharmacological or non-pharmacological trials possibly initiated during their participation in the HEREDITARY project.

Table 2. Criteria for Patient Enrollment in the Event of Additional Data Requirements for Use Cases 1 and 2.

Patients' enrollment criteria for Amyotrophic Lateral Sclerosis (ALS)	
Diagnostic criteria	• subjects with a diagnosis of ALS according to Gold Cost criteria (Shefner et al., 2020).
Inclusion criteria	• Both genders • Age ≥18 years • Capable of giving an informed consent
Exclusion criteria	• Clinical signs of severe dementia on basis of clinical judgement or neuropsychological testing • Instable or severe psychiatric disorders • Pregnancy

Patients' enrollment criteria for Multiple Sclerosis (MS)	
Diagnostic criteria	• subjects with a diagnosis of MS according to 2017 revised McDonald criteria (Thompson et al, 2018)
Inclusion criteria	• Both genders • Age ≥18 years • Capable of giving an informed consent

Patients' enrollment criteria for Multiple Sclerosis (MS)	
Exclusion criteria	• Clinical signs of severe dementia on basis of clinical judgement or neuropsychological testing • Instable or severe psychiatric disorders • Pregnancy

Patients' enrollment criteria for Frontotemporal Dementia (FTD)	
Diagnostic criteria	• subjects with a diagnosis of FTD according to the revised diagnostic criteria (Rascovsky et al, 2011)
Inclusion criteria	• Both genders • Age ≥18 years • Capable of giving an informed consent
Exclusion criteria	• Clinical signs of severe dementia on basis of clinical judgement or neuropsychological testing • Instable or severe psychiatric disorders • Pregnancy

5.2 Informational Sheet and Informed consent

To comply with the requirements detailed above, a written Informed Consent (IC) document will be prepared in the language(s) of the target patient population, specifically in Italian, based on the English version attached as an appendix. The Informed Consent document has been produced in accordance with Directive 2001/20/EC, Clinical Trials Regulation (EU) No 536/2014[25], as well as national regulations and the principles of the Declaration of Helsinki (17).

The Information Sheet and Informed Consent, translated into Italian and approved by the Ethical Committee, will be attached as annexes. All written information and other materials provided to patients and investigative staff will use vocabulary and language that are clearly understood by patients.

[25] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials in medicinal products for human use and repealing Directive 2001/20/EC. Off. J. 2014;L 158(27.05.2014):1.

6 Incidental Findings Policy

When conducting research involving human participants, it is crucial to anticipate the potential discovery of incidental findings and establish a procedure in advance for handling such situations. This preparation includes obtaining consent from participants and clarifying how any incidental findings will be managed (e.g., confidentiality, communication to research participants). Even when using anonymized data, where clinical validation of incidental findings is not possible, it remains important to outline the theoretical approach to dealing with these findings.

Incidental findings are unexpected results that arise during research but are unrelated to the study's primary objectives. It is essential to consider whether participants have the right to know or not to know about such findings and whether revealing these findings could lead to actions affecting them. Although the anonymized data used in the HEREDITARY project will not permit the clinical validation of incidental findings, researchers should still be aware of the ethical, legal, and practical challenges these findings present.

The concept of incidental findings originates from medical and genetic research. Anticipatable incidental findings are those that might be associated with a specific test or procedure, even if their occurrence is rare. In contrast, some incidental findings are unforeseeable based on current scientific knowledge. While researchers in the HEREDITARY project cannot prepare specific protocols for unforeseeable findings, they should consider the theoretical implications and ethical responses should such findings arise.

The primary ethical concern for researchers is whether there is an obligation to share any incidental information with participants. Given the use of anonymized data in HEREDITARY, this obligation is less likely to apply; however, the duty of beneficence still requires that researchers consider participant well-being, aiming to maximize benefits and minimize harm wherever possible.

HEREDITARY's policy, given the use of anonymized data, is that researchers are not required to identify or validate incidental findings, as the anonymization process prevents tracing any such findings back to individual participants. However, if any potential incidental finding is discovered during the research process, the researcher should inform the Project Coordinator. The Project Coordinator, in consultation with relevant ethics and data protection authorities, will decide on the appropriate course of action, considering both the ethical framework and the privacy rights of participants. All decisions will be documented, kept confidential, and securely stored by the Project Coordinator.

7 Conclusion

This deliverable outlines the comprehensive approach taken by the HEREDITARY consortium to ensure that all data processing activities related to Use Cases 1 and 2 comply with the stringent legal and ethical standards set by the GDPR and relevant EU and national legislation. We have provided a detailed analysis of how the Neurodegenerative Use Cases 1 and 2 adhere to these ethical and legal requirements, highlighting the measures implemented to ensure responsible data processing and the protection of data subjects' rights throughout the research process.

We have detailed the specific ethical approvals obtained, the data minimization strategies employed, and the rigorous data protection measures implemented to safeguard the rights and freedoms of data subjects. The Data Transfer Agreements (DTAs) will govern the collection, processing, and sharing of sensitive clinical data, ensuring transparency, accountability, and adherence to all applicable data protection laws. By aligning with GDPR principles—including the lawful basis for processing, transparency, data minimization, and secure data handling practices—the HEREDITARY project is committed to maintaining the highest ethical standards in research.

The project's ethical framework, as applied to Use Cases 1 and 2, including policies on incidental findings and informed consent, further underscores the integrity and responsibility that underpin all research activities within HEREDITARY.

REFERENCES

Key	Reference
Rascovsky et al, 2011	Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., van Swieten, J. C., Seelaar, H., Dopper, E. G., Onyike, C. U., Hillis, A. E., Josephs, K. A., Boeve, B. F., Kertesz, A., Seeley, W. W., Rankin, K. P., Johnson, J. K., Gorno-Tempini, M. L., Rosen, H., Prioleau-Latham, C. E., … Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain : a journal of neurology, 134(Pt 9), 2456–2477. https://doi.org/10.1093/brain/awr179
Shefner et al, 2020	Shefner, J. M., Al-Chalabi, A., Baker, M. R., Cui, L. Y., de Carvalho, M., Eisen, A., Grosskreutz, J., Hardiman, O., Henderson, R., Matamala, J. M., Mitsumoto, H., Paulus, W., Simon, N., Swash, M., Talbot, K., Turner, M. R., Ugawa, Y., van den Berg, L. H., Verdugo, R., Vucic, S., … Kiernan, M. C. (2020). A proposal for new diagnostic criteria for ALS. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 131(8), 1975–1978. https://doi.org/10.1016/j.clinph.2020.04.005
Thompson et al, 2018	Thompson, A. J., Banwell, B. L., Barkhof, F., Carroll, W. M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M. S., Fujihara, K., Galetta, S. L., Hartung, H. P., Kappos, L., Lublin, F. D., Marrie, R. A., Miller, A. E., Miller, D. H., Montalban, X., Mowry, E. M., … Cohen, J. A. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet. Neurology, 17(2), 162–173. https://doi.org/10.1016/S1474-4422(17)30470-2

ANNEXES

Number	Name
1	Ethical Approval of the BRAINTEASER project
2	Ethical Approval of the EUROMOTOR project
3	Ethical Approval of the INITIALS project
4	Ethical Approval of the PERMEALS project
5	Ethical Approval of the INSPIRED project
6	Ethical Approval of the EXTRALS project
7	Model of the Data Transfer Agreement (DTA)