ID-DarkMatter-NCD deliverable report

D7.3 Ethics and Governance framework

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Review

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Technical review			Thomas Vogl
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17 11.25	4	all	Amended Final Version including updates on the external Ethics Advisor, ethical aspects of the use of animal models including oversight mechanisms and	Mikael Muegge	FINAL

			approval processes, as well as management of incidental findings. Also includes a more structured, prescriptive framework, such as checklists for sample shipments as well as decision trees for common ethical questions.		

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Description of deliverable incl. background, and related previous deliverables

Introduction

The present *Ethics and Governance Framework* provides an overview of the ethical and governance principles underpinning the project's research activities. This document consolidates and builds upon the discussions and outcomes of the Ethics and Governance Committee (EGC) meetings see deliverable 7.2 (Ethics Report (From the inaugural meeting of the EGC – ethics guidance council), as well as the comprehensive set of ethical approvals previously secured (detailed in Annex A).

As the project does not introduce new cohorts or collect additional biological samples beyond those already included in prior approvals, no new ethical approvals have been deemed necessary at this stage. All research activities continue to rely on samples and data from pre-enrolled cohorts, which were originally collected under strict ethical oversight at their respective institutions. Consequently, no substantial amendments or revisions to existing ethical frameworks have been required.

This document also reflects on the generalizability and applicability of the current framework across the consortium. While many ethical principles apply universally, institutional differences in handling previously collected cohorts require some partner-specific approaches to compliance. These distinctions, as well as common guiding principles, are outlined to ensure continued alignment with applicable ethical standards, data protection regulations, and governance requirements. This deliverable, under WP7, aims to provide a framework on how ethical issues are handled in the ID-DarkMatter-NCD project.

Background/setting and premises

In ID-DarkMatter-NCD, samples from several human disease cohorts will be analysed, as well as experiments with mouse models for the respective diseases carried out. However, in this project we are not assembling any new cohorts, but we are relying on existing biobanking efforts, with the vast majority of samples having been collected outside of clinical trials. Therefore, we aim to retrospectively analyse and deeply phenotype samples of 6 different immune related non-communicable diseases (IR-NCDs) as well as healthy controls, previously bio banked by our consortium partners.

Hence, the purpose of the general ethics module in ID-DarkMatter-NCD (including D7.2 and 7.3) is rather to monitor the use of these samples and not the conduction of novel studies or the collection

of samples. Therefore, the key aim of this ethics framework is to align with the ethics governance council (EGC), which is to monitor that the work conducted is covered by existing ethical approvals (and to provide assessment in case new studies should be commenced against expectation).

We had already filed the ethical approvals for all experiments as part of the clinical annex of the original proposal, as well as including them in D7.2 and this document as Annex A. These approved cohorts include the population scale cohort at UMCG [LL-Pop], IBD samples from UMCG (1000IBD), disease of rheumatic disease patients from LUMC (LUMC-RA), IBD samples from UKSH (UKSH-IBD), RA/SLE/MS samples from VHIR (VHIR-IMID), MS samples from UNIBAS (UNIBAS-MS), the only exception being three clinical trials run independently by SU/APHP (SU/APHP-FMT - NCT02097797, NCT04997733, NCT03483246).).

Related previous deliverables

The general setting of our cohorts (particularly that no new patients are enrolled in this project and rather bio banked samples being used) had already been outlined in the initial proposal. In the D7.2 we had reported on the inaugural ECG core team meeting. The purpose of that meeting had been to outline the setting of ID-DarkMatter-NCD and the planned work, to those unfamiliar to the project. Report D7.2 served as a useful reference and white paper for project members to look up the ethics strategy (as well as a resource for new EGC members in case some existing members should leave the respective institutions). Indeed, Alberto Fresolone (who was part of the ECG core team) has accepted a new role elsewhere and we are here updating the ECG team composition (Table 1 below)

Table 1: ECG core team (*) and members. # denotes a new member compared to the last report (D7.2), as Alberto Fresolone has left the respective partner institution.

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Role and Status of the External Ethics Advisor

To strengthen ethical oversight and ensure independent review within the project, an External Ethics Advisor (EEA) has been formally appointed in accordance with the Grant Agreement. The role is currently held by Prof. Johannes Griss (Medical University of Vienna), whose background as a medical doctor and researcher specializing in clinical biobanking and multi-omics data analysis provides the expertise required to advise the consortium on complex ethical and data-related matters.

The External Ethics Advisor serves as an independent supervisory body complementary to the Ethics Governance Council (EGC). His key responsibilities include:

- Providing impartial advice on emerging ethical questions, particularly regarding data protection, consent scope, and secondary use of clinical data.
- Reviewing procedures for human sample and data transfers between partners to ensure full compliance with GDPR and local ethical approvals.
- Advising on the ethical implications of the use of animal models and the management of incidental findings, in close coordination with the EGC and institutional ethics boards.
- Participating in EGC meetings as an observer when invited, ensuring transparent alignment between internal and external ethics governance mechanisms.

Prof. Griss has accepted this appointment following consultation with the coordinator, as confirmed in the letter of invitation and acceptance. His advisory role ensures that the consortium maintains an independent and expert perspective on all ethical issues arising during project execution.

This framework document highlights and summarized some aspects in greater depth (as well as raising points of differences between partner institutions) and providing re-assessments demonstrating that no key aspects have changes compared to the planned activities for the ethics framework.

Framework based on ECG meetings and partner discussions

The ethical framework for ID-DarkMatter-NCD has largely remained the same as initially proposed and discussed in ECG meetings. The inaugural ECG meeting had taken place on June 6th, 2024, via a Webex online call. In that meeting, the EGC went over the structure of the project (briefly outlined in the introduction of this report), as well as approvals available (Annex A).

Since then, the key points, sample set/human cohort have not changed, these remain as:

- ID-DM-NCD has access to >10,000s of samples (cases of the 6-IR-NCDs & controls)
- relevant age/sex matched subgroups will be selected (>1,000 per disease)
- thereby we will correct for confounding factors (as we have shown that especially age/sex can bias immune repertoire analyses [Vogl et al., 2021, Nature Medicine]).

Based on these considerations, we had defined key aims and tasks to ensure that all national and international regulatory and ethical requirements are fulfilled will be performed in cooperation with all partners. Contact with all project partners is crucial for communication of critical information from project management as well as ethics to partners and vice versa.

One issues previously raised had been power calculation. This aspect relates to whether our cohorts are large enough to yield statistically significant results (if not this would render the work useless). As the cohorts' sizes have rather increased, previous considerations still hold up: Given that machine learning (ML) models will be leveraged to classify cases from controls, response to treatment, progression etc. (see the main proposal, B forms section 1.2.1.4), these approaches differ from classical power calculation (as we will run cross-validation in each dataset). Hence, the minimal number of samples needed is hard to estimate (as this would also depend on the strength of the signal). However, we have already worked with ML and human cohorts, with cohorts of 40 cases vs. controls (Vogl et al., 2022, Science Advances), that yielded insightful results. Hence, by working here with cohorts of ~1,000 cases/controls, it should even be possible to detect weak signals.

Related to the generalizability of this framework, some aspects hold universally true: At all partner institutions, we would need to apply for new ethical approvals, if we were to assemble for new cohorts. However, as we are working only with samples of previously enrolled cohorts, this issue is not relevant.

Yet, differences exist in how ethical approvals of these previously collected cohorts are handled between the different partner institutions: For example, if blood samples from the Spanish partner VHIR are measured in Austria (MUW), no additional ethical approval is required at MUW. The original approval from Spain suffices (as long as the respective type of analysis is covered). On the other hand, analysing samples collected elsewhere at Karolinska Institutet (KI) in Sweden, requires application for ethical approval at KI. Hence, the two institutions MUW and KI represent rather the two most extreme cases, making it difficult to formulate a single, comprehensive guideline. Therefore, a key realization of this framework is that partner specific guidelines need to be followed, and requirements fulfilled.

Ethical Governance of Animal Models and Incidental Findings

In line with Deliverable D7.2, this framework has been expanded to explicitly include ethical oversight mechanisms concerning (i) the use of animal models and (ii) the management of incidental findings.

Use of Animal Models:

All in vivo experiments in ID-DarkMatter-NCD are conducted exclusively under existing national and institutional ethics approvals, following the requirements of EU Directive 2010/63/EU on the protection of animals used for scientific purposes. Each partner performing animal work (e.g., MUW, UNIBAS, VHIR) has confirmed valid approvals from their respective Animal Welfare and Ethics Committees. Oversight is maintained by:

- Adherence to the 3Rs principle (Replacement, Reduction, Refinement).
- Transparent documentation of experimental protocols and welfare measures.
- Monitoring and reporting of any amendments or renewals through the EGC ethics tracking log.

Management of Incidental Findings:

A harmonized procedure for identifying and handling incidental findings has been adopted across the consortium, based on the project's new **Standard Operating Procedure (SOP) on Handling Incidental Findings in Scientific Research**.

This SOP defines:

- The steps for anticipating, assessing, and confirming incidental findings for clinical relevance.
- Cross-partner communication and documentation protocols in compliance with GDPR**.**
- The roles of principal investigators, treating physicians, and ethics committees in determining disclosure pathways.

The EGC and the External Ethics Advisor jointly ensure that both human- and animal-related research activities comply with ethical and legal standards and that all partner institutions maintain equivalent levels of ethical diligence

Related to the composition of the EGC core team (Table 1) we are still advocating representation from multiple work packages (not all partners are needed, as some institutions are not working with patient samples). Initially (D7.2) we had decided on scientifically independent members from UMCG, UKSH/CAU and UNIBAS to the EGC (entries 5 to 7 in Table 1), as these represent the largest clinical cohorts. The core team consists of members of the coordinating party and management team, namely Prof. Dr. Jürgen Zezula who is co-chair of the ethical committee of the MUW (but not scientifically involved or affiliated with ID-DarkMatter-NCD), the project coordinator Thomas Vogl, as well as Georg Melzer-Venturi and Mikael Muegge of the project management partner EUT-RS.

Operational Tools and Frameworks

To enhance usability and harmonization across partners, this revised framework introduces a more prescriptive and practical structure, moving beyond descriptive background information. The following tools and instruments are being implemented to facilitate ethical compliance and operational transparency across the consortium:

1. **Ethics and Governance Checklists:**
    - Pre-analysis checklist confirming valid approvals, consent scope, and data-transfer compliance.
    - Sample shipment checklist ensuring material transfer agreements (MTAs) and temperature-controlled logistics are in place.
    - Pre-publication checklist verifying anonymization, authorship ethics, and acknowledgment of approvals.

2. **Decision Trees for Common Ethical Scenarios:**
    - Clear stepwise workflows for questions such as:
        - “Does new ethical approval need to be sought?”
        - “Can data be transferred across borders under current consent?”

- "Who should be informed if an incidental finding is identified?"

- These decision trees will be maintained in the internal project repository and periodically updated by the EGC.

3. **Data Sharing Process Table:**

The following table provides a concise overview of the processes and responsible entities for data sharing among partners:

Data Type	Originating Partner	Recipient Partner(s)	Approval / MTA Required	Transfer Mechanism	Oversight / Verification
Clinical and demographic data	MUW, UMCG, UKSH	VHIR, UNIBAS	Yes – institutional DTA	Secure encrypted upload to project repository	EGC & DPO review
Omics and molecular data	MUW, UNIBAS	KI, VHIR	No (if anonymized)	Controlled-access repository	EGC supervision
Imaging data	UKSH	MUW	Yes – DTA	Secure data exchange via institutional server	Institutional Ethics Committee
Animal model data	MUW, VHIR, UNIBAS	All partners (aggregated results only)	Not applicable	Internal repository (restricted)	External Ethics Advisor

This structured approach transforms the framework into an operational tool, enabling all partners to follow clear, standardized steps when addressing ethical, data protection, and sample governance issues.

Conclusions

This updated Ethics and Governance Framework reconfirms that the ID-DarkMatter-NCD project continues to operate fully within the scope of its extensive existing ethical approvals and builds on the outcomes of the Ethics and Governance Committee (EGC) meetings. As no new cohorts have been added and no new participant recruitment is planned, no amendments to the existing approvals are required. While ethical principles are applied consistently across all partner institutions, differences in administrative handling of previously collected cohorts reflect local institutional requirements and are fully respected within this framework.

The appointment of Prof. Johannes Griss as External Ethics Advisor strengthens independent oversight and ensures alignment with international best practices. The integration of the Standard Operating Procedure (SOP) on Handling Incidental Findings, the inclusion of animal research governance, and the introduction of checklists, decision trees, and a data-sharing process table transform this deliverable from a descriptive document into a practical and prescriptive reference framework for all partners.

Together, these measures reinforce the consortium's commitment to transparent, harmonized, and accountable research practices, ensuring that ID-DarkMatter-NCD operates in full compliance with EU and institutional ethical standards. This framework thus provides a robust, living governance model guiding both current and future biomedical research within the consortium.

Disclaimer

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