IMI2 821513 – NEURONET

Efficiently Networking European Neurodegeneration Research

WP3 – Tools and Services

D3.9 - Final version of guidance on standards and practices for protecting data privacy

Lead contributor	Angela Bradshaw (3 – Alzheimer Europe)
Other contributors	Jean Georges (3 – Alzheimer Europe)

Document history

Version	Date	Description
V1.1	08/08/2022	First draft
V1.2	26/08/2022	Comments
V1.3	30/08/2022	Final version

Contents

Definitions and abbreviations

Partners of the NEURONET Consortium are referred to herein according to the following codes:

1. **SYNAPSE**: Synapse Research Management Partners SL
2. **NICE**: National Institute for Health and Care Excellence
3. **AE**: Alzheimer Europe
4. **JANSSEN**: Janssen Pharmaceutica NV
5. **LILLY**: Eli Lilly and Company Limited
6. **ROCHE**: F. Hoffman – La Roche AG
7. **TAKEDA**: Takeda Development Centre Europe LTD (*terminated partner*)
8. **SARD**: Sanofi-Aventis Recherche & Développement
9. **PUK**: Parkinson's Disease Society of the United Kingdom LBG
10. **TAKEDA AG**: Takeda Pharmaceuticals International AG

Grant Agreement: The agreement signed between the beneficiaries and the IMI JU for the undertaking of the NEURONET project.

Project: The sum of all activities carried out in the framework of the Grant Agreement.

Work plan: Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.

Consortium: The NEURONET Consortium, comprising the above-mentioned legal entities.

Consortium Agreement: Agreement concluded amongst NEURONET participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

IMI: Innovative Medicines Initiative

ND: Neurodegenerative Disorders

WP: Work Package

Abstract

Neuronet is a Coordination and Support Action (CSA) aiming to support and better integrate projects in the IMI Neurodegenerative Disorders (ND) portfolio. WP3 *Tools and Services* aims to develop tools and services to support the IMI ND projects in areas where unmet needs have been identified. One of these areas of unmet need is patient privacy, particularly following implementation of the General Data Protection Regulation (GDPR) in May 2018. WP3 aimed to compile and share learnings on patient privacy, to ensure best practice, reduce duplication of effort and create resources that will be of value to existing and future IMI ND projects.

In the present deliverable, *D3.9 Final version of guidance on standards and practices for protecting data privacy*, we performed a content analysis of reports from IMI ND projects, including guidance documents on informed consent, data management plans, research study documentation, and other reports relating to patient privacy. This content analysis identified cross-cutting themes in how projects address patient privacy and informed consent. All projects had a strong awareness of the need to ensure privacy and confidentiality, with key responsibility often assigned to clinical sites and principal investigators. Reidentification and capacity to consent were frequently identified as ethical concerns for projects, with project reports describing the methods and measures used to ensure respect of confidentiality and autonomy.

Based on our content analysis, we also developed recommendations and identified examples of good practice that could be of value to other IMI and IHI projects. Clearly identifying roles and responsibilities for entities and individuals involved in data collection, use, management and sharing, supported by risk and data protection impact assessments, can mitigate privacy risks whilst enabling smoother data flows. It is similarly important to identify and anticipate secondary uses of data from the earliest stages of project design, so that data governance and consent processes can be adapted accordingly, including adoption of measures to address fluctuating capacity. Finally, involving all stakeholders, including people with neurodegenerative diseases and their caregivers, in the design and development of research projects can help identify potential patient privacy risks and create ethical solutions that meet the needs of patients, participants and other key stakeholders.

1 Introduction

Compliance with the legal and ethical requirements that underly patient privacy is pivotal for public-private partnership (PPP) research projects that involve the collection, use, sharing or re-use of patient data. Loss or misuse of patient data exposes patients to substantial ethical risks, breaching their right to confidentiality and privacy, and potentially exposing them to social or personal harms. However, patient privacy concerns have also been perceived as a barrier to primary health research and, in particular, research that involves secondary use of patient data.

As an Innovative Medicines Initiative (IMI)-funded coordination and support action, Neuronet was designed to support and enhance collaboration between the diverse projects in the IMI neurodegeneration portfolio, which span the full spectrum of biomedical research from fundamental, laboratory-based science to projects involving clinical trials and real-world data. An initial survey of IMI project coordinators performed by Neuronet identified data privacy, ethics approvals and Informed Consent Forms among other priority areas in which IMI ND projects would like more support, particularly following implementation of the General Data Protection Regulation (GDPR) by the EU in May 2018.

To address these areas of unmet need, WP3 *Tools and Services* aimed to develop tools, services and guidance, intending to compile and share learnings to support good practice, reduce duplication of effort and create resources that will be of value to existing and future neurodegenerative disease (ND) projects. In addition, Neuronet launched four Working Groups in 2019, creating structures for peer to peer support and exchange on the following topics: data sharing, ethics & patient privacy, sustainability and regulatory/HTA interactions. As such, the WGs have made an important contribution to Neuronet's goal of compiling and leveraging the expert knowledge that is presently scattered across the different neurodegeneration projects in the Innovative Medicines Initiative (IMI) portfolio.

The first WP3 deliverable on patient privacy (*D3.4: First version of guidance on standards and practices for protecting data privacy*) was published in March 2020. This deliverable summarised the key ethical and legal concepts for health research involving personal data, focusing particularly on the GDPR and informed consent for data sharing and reuse. The deliverable also outlined the results of a preliminary exercise to map the ELSI (Ethical, Legal and Social Implications) deliverables and topics currently being addressed in the projects of the IMI ND portfolio.

The present deliverable, *D3.9 Final version of guidance on standards and practices for protecting data privacy*, builds on D3.4, performing a content analysis of reports from IMI ND projects on their informed consent and data management policies. The results of the content analysis are presented, detailing how each project addresses the issue of patient privacy. Based on this analysis, we identify cross-cutting practices used by projects to ensure patient privacy, and provide recommendations and examples from specific projects on how patient privacy requirements can be met in practice.

2 Background and context

Compliance with ethical principles and data protection legislation is a fundamental requirement for all research activities funded by the IMI. Article 34 of the IMI Model Grant Agreement (MGA) identifies nine core ethical principles that funding beneficiaries must abide by, including "*ensuring honesty and transparency towards research subjects and notably getting free and informed consent (as well as assent whenever relevant)*", and "*ensuring privacy and*

confidentiality" (IMI2 Annotated MGA, pp291). In addition, a detailed ethics review is incorporated into the application process for IMI funding, and all IMI applicants must perform an "ethics self-assessment" that describes ethical issues that have been identified, whilst also stating how they are going to be addressed.

Meanwhile, Article 39 of the MGA deals with the processing of personal data, stating that *"the beneficiaries must process personal data under the Grant Agreement in accordance with EU and national laws on data protection (in particular, the General Data Protection Regulation EU 2016/679)."* Art.39 of the MGA also explains that personal data processing in respect of the GDPR also forms part of the ethical obligations for projects.

To date, the IMI has launched 24 projects on neurodegenerative disease, involving over 250 private and public sector organisations from 25 different countries, and providing over EUR386 million in funding. The vast majority of these projects involve the use of personal data from patients or research participants, ranging from projects that re-use existing datasets (such as PD-MitoQUANT and ADAPTED) to those that include research studies generating new clinical data (such as EPAD, AMYPAD and RADAR-AD). Compliance with ethical and legal requirements for patient privacy is therefore a central concern for IMI ND projects and, by extension, for Neuronet as well. D3.4 and D3.9 are designed to understand how IMI ND projects are meeting these requirements, and provide guidance to support them in addressing any challenges they may encounter.

3 Legal and ethical frameworks for patient privacy

In D3.4, we described the key data protection concepts for IMI ND projects, detailing some of the core ethical considerations for health research, and outlining criteria for informed consent. Here, we provide a brief summary of these concepts, to illustrate the patient privacy requirements and considerations that projects must navigate, to ensure compliance with legal and ethical frameworks for clinical research.

3.1 Legal frameworks: data protection legislation

The "General Data Protection Regulation" or GDPR, came into application on 25 May 2018, after a two-year transition period from adoption of the GDPR, which was preceded by the Data Protection Directive. The GDPR regulates the use and re-use (known as processing) of all personal data in the EU, with personal data defined as "any information relating to an identified or identifiable natural person". "Data concerning health" and "genetic data" are viewed as special categories of personal data, meriting a higher degree of protection. The GDPR states that

In D3.4, and through discussions with the Ethics and Patient Privacy Working Group, a number of challenges relating to the GDPR were identified, including:

- *How to identify and manage GDPR roles for multi-site clinical research studies (e.g. controllership)*
- *Appropriate methods for pseudonymisation and anonymisation and addressing challenges of reidentification*
- *Choosing a practical lawful basis for data processing to avoid unnecessary limitations on the secondary use of data (e.g. legitimate interests vs consent)*
- *Dealing with regulatory divergence between different EU member states due to derogations under the GDPR*

data should be accurate and kept in an identifiable form for no longer than is necessary; that data should be processed lawfully, fairly and transparently; that data should be collected for specific, limited and legitimate purposes; and that data should be processed in a way that ensures appropriate security of the data.

To meet these GDPR requirements, data controllers (individuals or legal entities with overall responsibility for data) and processors (individuals or legal entities that process data on behalf of controllers) must integrate data protection measures into every aspect of their personal data processing activities, from the design stage onwards. This includes the application of technical and organisational measures where relevant, such as the pseudonymisation of data to remove identifiers.

3.2 Ethical frameworks: Informed Consent

Conducting ethical health research implies the application of fundamental ethical principles to the research project in question. Informed consent is an ethical and legal requirement for research that involves human participants, and is enshrined in numerous international conventions and documents, including the European Convention on Human Rights. Informed consent is designed to ensure that, firstly, individuals control whether or not they participate in clinical research and, secondly, that they can choose to do so when the research is consistent with their values, interests and preferences. It meets the core ethical requirement of respect for autonomy, by enabling individuals to exercise their rights to self-government and self-determination.

In D3.4, and through discussions with the Ethics and Patient Privacy Working Group, a number of challenges relating to informed consent were identified, including:

- *How to adapt informed consent forms and study documentation to meet the needs of individuals from different backgrounds and with different types of cognitive impairments?*
- *Ethics of recontacting and reconsenting participants and/or study partners/caregivers for secondary use of samples or data*
- *What are the most appropriate and ethical options to determine the wishes (and enable continued participation) of people who may lose capacity during a clinical research study?*

The first question on the ethics checklist for IMI funding recipients relates to whether informed consent has been obtained; applicants are asked to provide copies of informed consent forms and supporting patient information sheets/leaflets. In addition, they must provide details on the informed consent procedures and, where vulnerable individuals or groups are involved, they must "demonstrate appropriate efforts to ensure fully informed understanding of the implications of participation". This references the concept of capacity, which describes a person's ability to make a decision.

In practice, informed consent is materialised using two documents: firstly, a patient information sheet (PIS), and secondly, an informed consent form (ICF). The EU Clinical Trials Regulation identifies key pieces of information that must be given to research participants to enable them to make an informed decision on participation, including the objectives, benefits, risks of the clinical research study; the participants' rights; and the expected conditions and duration of the

study. Many PIS also contain information about data protection, particularly where consent is the legal basis for data processing under the GDPR.

4 Patient privacy work in IMI ND projects

As discussed in the introduction to this deliverable, WP3 of Neuronet aims to create guidance tools on four key priority areas, including patient privacy and ethics, by compiling state-of-the-art knowledge and existing practices across IMI ND projects, mapping informed consent and data protection policies and consulting with experts in the Neuronet Working Group.

As well as providing an overview of the key data protection and ethical concepts for health research, D3.4 reported on the first step in this mapping process, assessing the scope of the data protection and ethics work in IMI ND projects. A keyword search of the deliverables listed in the Descriptions of Action from all IMI ND projects supported by Neuronet (apart from PD-MIND, PD-MitoQUANT and IMPRiND, which did not make their DoAs available) was performed, using the following search terms: “ethics”, “ethical”, “privacy”, “data protection”, “POPD”, “ELSI”, “legal”. D3.4 was published just after the launch of Mobilise-D and IDEA-FAST, and before PRISM2 and EPND were funded, so the list below has been updated to include these projects[1]. At the time of writing, only the DoA of EPND was available for analysis, so where IDEA-FAST, Mobilise-D and PRISM2 appear in the list below, this reflects the deliverables listed on project websites or CORDIS.

KEY DELIVERABLE THEMES	PROJECT(S)
Data Protection: authorisations, data protection authority opinions, data protection frameworks	AETIONOMY, PRISM, IDEA-FAST, Mobilise-D, EPND, RADAR-CNS, ROADMAP
Reports from Legal and Ethical Advisory Boards	AETIONOMY, PRISM, RADAR-AD, AMYPAD
Ethical codes of practice & ethical requirements	AETIONOMY, EMIF, EPND, ROADMAP
Forms and approvals for clinical Research Ethics Committees (REC)	AETIONOMY, ADAPTED, IDEA-FAST, IM2PACT, Mobilise-D, PHAGO, PRISM, RADAR-AD
Informed consent forms and templates	AETIONOMY, IDEA-FAST, PRISM, RADAR-CNS
Disclosure of results to participants	AMYPAD, EPAD, RADAR-AD
Understanding stakeholder views – e.g priority outcomes for people affected by NDs, feedback on research protocols, ICF and PIS, advice on issues related to recruitment and retention	AMYPAD, EPND, Mobilise-D, RADAR-CNS, RADAR-AD, ROADMAP
Ethics for animal research	EQIPD, IM2PACT, PHAGO
"ELSI issues"	EPND, EMIF, EPAD, MOPEAD, RADAR-AD, ROADMAP

Our analysis showed that data protection and ethical approvals, forms and authorisations are a priority area for the majority of the IMI ND projects, in line with the results of the initial survey of IMI ND project leaders that identified “Guidance on data privacy and Ethics approvals” as an

[1] It should be noted that evaluation of the contents of these deliverables was not within the scope of this initial, preliminary survey, but was performed as part of the present report. Moreover, the focused terms of the keyword search may have inadvertently missed ethics and data protection work in Neuronet-supported projects that is being reported in deliverables which don’t contain the keywords.

area in which further support would be helpful. Reflecting discussions in the Neuronet Working Group on Ethics and Patient Privacy, "disclosure of results to participants" is a topic that is of particular interest to projects involving people with presymptomatic, preclinical or early Alzheimer's disease, including AMYPAD, EPAD and RADAR-AD. Similarly, a common theme for many projects is the involvement of stakeholders and the views of people affected by NDs, highlighting a growing appreciation of the value of public involvement work for ND research.

4.1 Content analysis of patient privacy deliverables from IMI ND projects

For the present deliverable, we performed a content analysis of publicly available deliverables from IMI ND projects on topics specifically relating to patient privacy and informed consent, including many of the deliverables identified in the table above[2]. In total, we identified and were able to access 13 deliverables from 8 projects for the content analysis. These deliverables are listed in the table below, linking to online sources in the section text where available.

PROJECT	DELIVERABLE TITLE	DOCUMENT TYPE	DOCUMENT SOURCE
AMYPAD	D6.2 Ethics policy and guidance document	Report; confidential	Request to AMYPAD partner
EMIF	D10.5 Final version of the EMIF Code of Practice	Report: confidential	Request to EMIF partner
EPAD	D8.1 Initial ethics policy review and information governance framework	Report; public	EPAD website
EPAD	D8.5 Final report on ethical, legal and social implications and recommendations	Report; public	EPAD website
IDEA-FAST	D8.1 Model informed consent for the Feasibility Study	Report; public	IDEA-FAST website
IDEA-FAST	D8.2 Model informed consent for the Clinical Validation Study	Report; public	IDEA-FAST website
MOBILISE-D	D1.4 Data management plan v2	Report; public	Mobilise-D website
PD-MITOQUANT	D3.4 Data management and sharing plan (DMSP)	Open Research Data Pilot; public	PD-Mitoquant website
RADAR-CNS	D6.1 Report on mental capacity and consent issues. Template for informed consent for all disease areas in RADAR-CNS	Report; public	RADAR-CNS website
RADAR-CNS	D1.8 Mid-term ethics report	Report; public	RADAR-CNS website
RADAR-CNS	D5.1 Protocol development and achievement of local ethics approval	Report; public	RADAR-CNS website
RADAR-AD	D1.9 First update of data management plan	Report; public	RADAR-AD website
RADAR-AD	D1.5 Research protocol	Report; public	RADAR-AD website

[2] A limitation of our analysis is that it is limited to the contents of deliverable reports from projects, with no cross-referencing to patient-facing and other confirmatory materials, which were not accessible at the time of writing. As such, the findings of this deliverable may not fully reflect the practical implementation of measures to ensure patient privacy and informed consent during the respective projects.

4.1.1 AMYPAD

The AMYPAD project, which is led by VU University Medical Center in Amsterdam and GE Healthcare, aims to determine the value of beta-amyloid imaging as a diagnostic and therapeutic biomarker for Alzheimer's disease. AMYPAD was launched in autumn 2016, and will finish in September 2022. AMYPAD is a clinical research project, recruiting participants to two studies: the Diagnostic and Patient Management Study/DPMS and Prognostic and Natural History Study/PNHS.

The DPMS is following-up a memory clinic population suspected of possible Alzheimer's disease (AD), focussing on those with subjective cognitive decline (SCD), mild cognitive impairment (MCI) and dementia where Alzheimer's disease is in the differential diagnosis, to determine the usefulness of β-amyloid imaging with regards to diagnostic confidence, decision trees, change in diagnosis, and alterations between planned and actual patient management plans. In total, 844 participants were recruited from 8 different memory clinics in 7 different EU countries, receiving one or two PET scans and clinical assessments. Conversely, the PNHS aims to evaluate the value of quantitative PET amyloid imaging measures for predicting progression within an AD risk probability spectrum based on quantitative PET amyloid imaging measures, with or without other biomarkers. Unlike the DPMS, this study draws on the EPAD project and cohort network. In total, 1,321 participants were recruited from 10 parent cohorts based in 7 different countries, receiving a baseline PET scan and a follow-up scan. Historical cohort data was also shared for the PNHS, increasing the total number of scans to over 2,700.

With a strong clinical component, and involving the use and reuse of retrospective cohort datasets, as well as the collection of prospective data and samples, AMYPAD raises a number of important legal and ethical issues, which overlap to a certain extent with those raised by its sister project, EPAD (see below). To address these issues, work package 6 of the project developed specific guidance and recommendations for each study, published in D6.2 "Ethics policy and guidance document". This document is not publicly-available, but was accessible to AMYPAD partners including the authors of the present Neuronet deliverable. According to this deliverable, the areas of research ethics addressed for the PNHS in D6.2 include 1) the integration of informed consent for the PNHS into the EPAD project; 2) return of results and disclosure of AD risk; 3) management of incidental findings; 4) experience of participation in the PNHS; 5) data sharing and governance, and 6) continuity between EPAD and the PNHS.

Recommendations in the deliverable relating to patient privacy and consent aimed to achieve convergence and harmonisation between the EPAD-LCS and PNHS study, to enable smooth data flows and informed engagement of participants in both studies, whilst respecting their rights. For example, recommendations included the following suggestions:

- *Integrate the informed consent for this study into the staged consent model of EPAD, providing relevant, indispensable and material information at appropriate stages of a participant's involvement, and asking for informed consent whenever important decisions need to be made*
- *Make consent to individual data sharing between the PNHS and EPAD a necessary condition to PNHS participation*
- *Cover data sharing between EPAD and PNHS in the EPAD informed consent process*

- *Align procedures for access requests and monitoring with the procedures with EPAD, ensuring that data are ready and available to be shared at the earliest possible opportunity.*

In addition, the PNHS recommendations also included provisions to ensure meaningful, informed consent separate to the EPAD-LCS:

- *Consent for participation in the PNHS cannot be inferred from consent for participation in the EPAD LCS, and should be asked separately.*
- *PNHS participants' capacity to consent must be monitored and registered during the course of the PNHS in accordance will local governance requirements, conducting more formal assessment of capacity using an external healthcare professional when there is reason to doubt capacity.*

Within the deliverable, separate ethics guidance was provided for the DPMS, as this study was embedded in the clinical setting of memory clinics, and not organised as an independent, longitudinal cohort study. As such, DPMS participants had already sought medical counsel for memory or other cognitive complaints, and may have had a diagnosis of MCI, SCD or dementia. Recommendations relating to patient privacy and consent in the deliverable were primarily focused on ensuring that participation in the DPMS was integrated into the continuum of care for patients attending the memory clinics, and providing suitable and accessible materials for education and communication to participants who may have existing cognitive issues. Recommendations also included provisions to enable participation in the DPMS for those with existing cognitive problems. For example:

- *Providing for proxy informed consent, ensuring that the proxy consenter takes into account the participant's wishes, values and beliefs, and advance directive (if it exists).*
- *Respecting the right of a participant to withdraw at any time from the DPMS irrespective of capacity to consent; allowing for the proxy consenter to withdraw consent on behalf of the participant*
- *Enabling the involvement of study partners, who can support the participant and potentially act as a proxy consenter; providing suitable materials and information for both participant, study partner and proxy consenter*

Giving effect to these recommendations, the deliverable outlined specific consent clauses for the PNHS and DPMS relating to patient privacy, including:

- *Agreeing to the use of data for the goals outlined in the patient information sheet*
- *Agreeing to sharing of data between EPAD and AMYPAD*
- *Agreeing that research data can be made available provided that identifying information is not used*
- *Agreeing to storage of research data for 15 years following completion of the study*

Optional informed consent clauses relating to patient privacy included:

- *Agreeing to be re-contacted about research with the same or other objectives*
- *Agreeing to be re-contacted about future research on the basis of data collected during the AMYPAD studies*

In both sets of recommendations (for the PNHS and DPMS), the national leads and principal investigators (PIs) were named as responsible for ensuring that all relevant local and/or national legal and regulatory requirements are met, including ensuring that procedures related to data storage, sharing and access must conform to all relevant national and European legislation.

4.1.2 EMIF

The European Medical Information Framework (EMIF) project was launched under IMI1, in January 2013, and ran for 5 ½ years until June 2018. Broadly focused on improving access to health data, EMIF was sub-divided into three sub-projects: EMIF-Plat (platform), EMIF-Met (metabolic) and EMIF-AD (Alzheimer's disease). Unlike the other projects described in this deliverable, EMIF was broadly categorised as a "platform project", with a primary focus on developing infrastructures and tools to enable research, with "case studies" in the areas of metabolic diseases and Alzheimer's to test and refine these project assets. As well as an overall project co-ordinator and leader (University of Oxford and Janssen Pharmaceutica NV), each sub-project had an academic and EFPIA lead; VuMC (Amsterdam) and UBC Pharma in the case of EMIF-AD.

EMIF-PLAT created a platform, catalogue and other tools to enable researchers to find, evaluate, use and re-use health data from different sources in Europe. EMIF-AD, on the other hand, involved several clinical cohort studies, including the EMIF-AD Multimodal Biomarker Study, which collected longitudinal biosamples and data from over 1,200 participants based in different countries, and at different stages of AD development. To facilitate access to these resources and enable recruitment from individual cohort studies, EMIF-PLAT created the EMIF Catalogue, a web portal designed as an interface between data custodians/cohorts and researchers. In addition, EMIF-AD and EMIF-PLAT developed an AD database on tranSMART to store and share harmonised individual level data from over 12 cohorts, including omics data generated as part of the EMIF-AD multimodal biomarker study.

Many EMIF deliverables were not available publicly. However upon request to the authors, we were kindly granted access to D10.5: "Final version of the EMIF Code of Practice". The EMIF Code of Practice (ECoP) was been developed in order to support compliance with legislation and policies on data protection and confidentiality, and to promote best practices in the conduct of clinical research using health data. It is an extensive and well-researched document that identifies mandatory data processing principles for using the EMIF platform, as well as codes of practice for the EMIF catalogue, EMIF data queries, and data sharing from the EMIF research studies.

The first sections deal with data processing in the EMIF platform. Section 2.2. of the ECoP is focused on protecting personal data, recognising the importance of patient privacy and stating that "*personal data or samples that identify individuals may only be used for a Full Research Study under the terms of informed consent and any accompanying ethical approvals*." A number of sections of the EMIF ECoP, including 2.2., explicitly state the dangers of reidentification, and identify specific measures to avoid this. For example, section 2.3. states "*Anonymised data should be treated as if it still carries a small residual risk of re-identification, and therefore still be subject to robust information security practices.*" Section 2.4. suggests that pseudonyms (or identifiers) for de-identified datasets not be consistently reused for multiple data releases to the same data user, as this risks unintended disclosure of identifying patterns. Section 2.5 also states "*It is not recommended that data custodians apply the same pseudonyms when releasing*

datasets to different research users. If the same identifiers were to be used, research users could collaborate to pool their data and increase the risk of identifying patterns."

De-identification, anonymisation and pseudonymisation also feature prominently in the ECoP sections on the EMIF catalogue, data queries and data sharing. Of particular interest and relevance for patient privacy and consent, recommendations for data custodians wishing to share their data and/or samples include the following criteria for reviewing data sharing requests:

- *Whether the purpose of the proposed research is consistent with the custodian's ethical approval and any applicable participant consent;*
- *Whether a risk assessment identifies an unacceptable risk to the confidentiality of the participants' identities or if disclosing inferences might be made.*

Similarly, recommendations are made to ensure that research users accessing shared data do so in a way that protects patient privacy and respects the terms of informed consent, for example:
"If a dataset deliberately contains identifiable data…research users must respect the privacy of those individuals and ensure that information gained about individuals is strictly contained to the systems, documents and persons authorised to be directly involved in the research, and at no point disclosed to any other parties."

Data users are identified as liable with regards to compliance with data protection and clinical research regulations, and are also asked to ensure that staff using EMIF data are trained in "data protection and information security practices".

4.1.3 EPAD

The European Prevention of Alzheimer's Dementia (EPAD) project was led by the University of Edinburgh and Janssen Pharmaceutica NV, spanning a period of almost 6 years between 2015 and 2021. EPAD aimed to speed up the drug discovery and development process, by creating a pan-European register of people across the risk spectrum for dementia and performing a longitudinal cohort study (LCS) involving participants at risk of dementia. Similar to its sister project AMYPAD, EPAD had a strong clinical component and involved the use of retrospective data as well as a prospective, longitudinal cohort study (LCS), which recruited participants from over 30 parent cohorts, located across the EU.

A key EPAD achievement was the establishment and follow-up of the LCS. The LCS screened over 2,000 participants and collected a wide range of clinical, cognitive, imaging and biomarker data, with several follow-up visits over a period of almost 3 years (a full list of the EPAD study outcomes can be found on the EPAD website: https://ep-ad.org/open-access-data/data/). EPAD also collected thousands of samples from participants, creating the EPAD Bioresource (hosted at the University of Edinburgh) with defined access procedures managed by the EPAD sample access committee (SAC). EPAD had and maintains a firm commitment to data sharing, with LCS data now accessible through the AD Workbench of the Alzheimer's Disease Data Initiative.

An evaluation of the publicly-available deliverables of EPAD identified one deliverable with particular relevance to patient privacy. To support the development of study governance, protocols and ethical review applications, EPAD published D8.1 "Initial ethics policy review and information governance framework" in 2016. This document is publicly-available through the

EPAD website (https://ep-ad.org/about/publications/). Similar to the AMYPAD deliverable described above, this report provided recommendations on how to address challenges in specific areas, including 1) Informed consent through the EPAD journey; 2) return of results and disclosure of AD risk; 3) management of incidental findings; 4) experience of participation in EPAD; 5) data sharing and governance, and 6) continuity between the LCS and the EPAD Proof of Concept Study (PoC).

Recommendations relating to patient privacy and consent were adapted to the structure and process of participation in EPAD, which was envisaged as a staged process from the EPAD register, to the EPAD LCS, and on to the EPAD PoC. A key recommendation was to create a **staged consent model**, with informed consent envisaged as a continuous process that asks for consent whenever important decisions are made, presenting the required information and materials to participants at these decision points. In particular:

- *In order to prevent the 'fish trap phenomenon' (where participants feel they have to proceed onwards through the different EPAD stages), EPAD should always and explicitly present information about the entire EPAD journey to (potential) EPAD participants*.

Similar recommendations regarding capacity to consent and the involvement of study partners were made for EPAD and AMYPAD (involving study partners to support participants; requirement to monitor capacity, and formally assess such in the case of reasonable doubt). On data governance and storage, similar to AMYPAD there was a recommendation that all procedures must conform to relevant national and European legislation, and that conformity with these laws and regulations was the responsibility of EPAD national leads and principal investigators. Specifically, on ensuring compliance with data protection laws (which, at the time, did not include the GDPR), D8.1 states:

"It should also be clear to what extent to which individuals and data are identifiable – particularly on the basis of EPAD genetic and imaging data – and whether there are limits to anonymity or confidentiality of data. Establishing a framework for sharing EPAD data also involves ensuring that research complies with applicable privacy and data protection regulations at every stage of data sharing. EPAD should be in a position to provide assurances to citizens that confidentiality and privacy are appropriately protected when data are collected, stored, processed, and exchanged. Furthermore, given that neither anonymization nor compliance with consent are likely to offer sufficient privacy protections there should be clear pathway of accountability."

Giving effect to these recommendations, the deliverable outlined specific consent clauses for the PNHS and DPMS relating to patient privacy, including:

- *Agreeing to the use of data for the goals outlined in the patient information sheet*
- *Agreeing to the use of data/samples to test new biomarkers, that weren't mentioned in the information sheets, during EPAD, without further/separate consent being requested from me*
- *Agreeing to storage of research data for 15 years following completion of the study*

Optional informed consent clauses relating to patient privacy included:

- *Agreeing to be re-contacted about research with the same or other objectives*
- *Agreeing to data collected about (participant) being returned to the PI of the original parent cohort*

In the years following finalisation and publication of D8.1, EPAD investigators further refined and expanded on the recommendations, publishing an additional deliverable (D8.5) entitled "Final report on ethical, legal and social implications and recommendations" in 2020 (the document can be downloaded via the EPAD website: https://ep-ad.org/about/publications/).

Primarily focused on the return of results, incidental findings, and participation in the EPAD Participant Panel, the deliverable also included updated recommendations on information that should be provided to participants during the staged, informed consent process. Although not relating directly to patient privacy, these recommendations provide a useful overview of how information can be provided in many different formats, from different sources (e.g in-person, video, leaflet) to ensure meaningful and truly informed consent for people across the risk spectrum for dementia.

4.1.4 IDEA-FAST

The IDEA-FAST project (Identifying Digital Endpoints to Assess Fatigue, Sleep and Activities in daily living in neurodegenerative disorders and Immune-mediated inflammatory diseases) was launched in November 2019, with a 5 ½ year duration. Led by the University of Newcastle (UK), University of Kiel (Germany), Janssen Pharmaceutica NV and Takeda, IDEA-FAST aims to identify digital endpoints for fatigue and sleep disturbances that will provide a more sensitive, reliable measure of the severity and impact of these symptoms in a real-life setting. The project is focusing on a number of immune-mediated inflammatory diseases, as well as two neurodegenerative diseases: Parkinson's disease and Huntington's disease. With a strong clinical component, and involving the development of a digital data management platform, patient privacy is an important concern for IDEA-FAST.

IDEA-FAST is undertaking two clinical studies: a Feasibility Study (FS), and a Clinical Observation Study (COS). According to publicly-available information on these studies, the FS started recruitment in July 2020, and aims to gather feedback from participants on preferences between different digital endpoints and corresponding devices and sensors. The COS will launch this year and will be a 1-year longitudinal study focused on validating the preferred endpoints and devices, aiming to recruit almost 1,000 participants from several sites across Europe.

An evaluation of the publicly-available deliverables of IDEA-FAST identified two deliverables of particular relevance to patient privacy. As part of their activities in WP8 (Data protection, ethics and legal challenges), IDEA-FAST partners have generated model informed consent forms for both FS and COS studies, which are publicly available on the (D8.1 and D8.2) on the project website (https://idea-fast.eu/results-and-publications/). The forms were adapted from the model informed consent form generated by the DO>IT subproject of the Big Data for Better Outcomes IMI project (freely available via the IMI catalogue of project tools: https://www.imi.europa.eu/projects-results/catalogue-project-tools). Both deliverables highlight the fact that the IDEA-FAST studies cover several disease areas, and different participating centers in various EU countries, hence providing a model informed consent form which centers and PIs can adapt for their specific studies.

The two deliverables contain several references to the GDPR and patient privacy:

- The model patient information sheets (PIS) for each study include a specific point entitled "What happens to my data and biosamples gathered in the study?" which explains how the data will be stored and how confidentiality will be respected:

- *"Each participant will get a unique code-number and your name and contact details will not be visible in the central collection of the data. Only members of your treatment team will have access to your contact details."*
- *"The central collection is of course well secured according to the latest standards. There are strict access rules and only researchers of the IDEA-FAST team will have access to those data which are necessary for their specific analyses."*

- The PIS also explains that withdrawal from the study does not equate to cessation of data processing:
  - *"You can stop your participation at any time. Stopping however is not the same as a withdrawal of consent for processing personal data. Data that have been collected can still be used."*
- The PIS also includes a section on additional research (or re-use of data), stating the following:
  - *"We expect that the data will be of great interest for other research into the disease which you are suffering from or related areas such as sleep, fatigue or quality of life research into chronic diseases. We therefore ask for your separate consent for the additional use of your data for such additional research, other than the present study. You are in no way obliged to consent to additional research if you want to participate in the present study."*
  - *"The additional research might take place after the standard retention period of the coded data of 25 years. If you consent to additional research, you can also indicate whether the data may be kept longer than 25 years."*

In addition, the deliverables both include GDPR statements, which explain 1) which data and biosamples are collected; 2) what they are needed for; 3) who the data controller is; 4) who can access the data; 5) the legal basis for data processing; 6) the length of storage and retention; and 7) the subject's data protection rights.

For both FS and COS, the identified legal basis for data processing is consent:

"When consenting to participate in the study, you also consent to data processing which is necessary for the aims of the study."

For the FS, Imperial College London is identified as the data controller for the study, as their secure servers will host the coded data. Conversely, for the COS it is Kiel University who is acting as the data controller, "*as they developed the study*"; the device-makers are also identified as data controllers, however an additional organisational measure is in place here as "*any data the device makers may have will be erased as soon as the data collection has ended, which means as soon as you have completed the study*."

The data and biosample retention period for both studies is identified as 25 years, and participants may withdraw consent, from which point onwards the collected data will not be used "for any further analyses" although data will be retained to validate results and ensure research integrity.

4.1.5 Mobilise-D

The Mobilise-D project (Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement) was launched in April 2019, with a 5 year duration. Similar to IDEA-FAST, Mobilise-D is led by the University of Newcastle (UK; Prof. Lynn Rochester); Roche is the leader on the EFPIA side. The project also involves the University of Kiel (Germany), with strong collaborations in place with IDEA-FAST. While IDEA-FAST is focused on fatigue and sleep disturbances, Mobilise-D is focused on gait and movement, aiming to develop a comprehensive system to analyse peoples' gait through digital technologies. Mobilise-D is also focusing on several diseases (COPD, congestive heart failure, hip fracture recovery) including two neurodegenerative diseases: multiple sclerosis and Parkinson's disase.

Mobilise-D is undertaking two clinical studies: a Technical Validation Study (TVS), and a Clinical Validation Study (CVS). The TVS is a multisite validation study (UK, Israel, Germany) evaluating physical activity in controlled, simulated and real life settings, testing the device-algorithm pair to be used in the further studies of the overall work of the Mobilise-D consortium. The CVS is a longitudinal, observational cohort study, aiming to enroll 2400 participants with 600 from each disease area, across 16 different sites. The study consists of a baseline visit, with four follow-up visits every 6 months. Similar to the TVS, Newcastle University is the sponsor for the CVS. Mobilise-D aims to make the data from these studies available to the wider community, subject to ethical and legal requirements, anticipating that these data will be shared through a secure platform (following an application and authorisation procedure).

Analysis of the publicly-available deliverables of Mobilise-D identified one deliverable with particular relevance to patient privacy: D1.4 "Mobilise-D Data Management Plan, v2". This deliverable provides the second version of the Mobilise-D Data Management Plan (DMP) outlining the current understanding of how the research data collected or generated will be handled during and after the Mobilise-D project. Mobilise-D was launched after the GDPR came into application, and as such the DMP deliverable specifically references this regulation, stating that:

Mobilise-D researchers commit to the highest standards of data security and protection in order to preserve the personal rights and interests of study participants, adhering to the provisions set out in the GDPR, Directive 2006/24/EC (retention of data generated or processed in connection with electronic communications) and Directive 2002/58/EC (Directive on privacy and electronic communications), as well as the 1995 Data Protection Directive.

With specific reference to data protection, the deliverable explains specific measures to secure data privacy, including the provision of information on data processing in consent forms and patient information sheets, and the following measures (reproduced verbatim):

- *Anonymisation and pseudonymisation: All personal data obtained in Mobilise-D will be available to partners within the consortium only after anonymisation. Keys to re-identification will be held confidentially within the respective research units. In situations where re-identification of study participants becomes necessary, for example for the collection of additional data, this will be possible only through the research unit and in cases where informed consent for such cases has been given.*
    - *All Mobilise-D data are anonymised or pseudonymised before sharing. It is forbidden to match or attempt to match individual records to any other data.*

- *Consent: Data are processed only for the purposes outlined in the patient information and informed consent forms. Use for other purposes will require explicit patient approval. Also, data are not transferred to any places outside the consortium without patient consent. The deliverable also lays out the data protection terms to be identified in the patient information sheet and consent forms, explaining that data collectors collecting personal data will inform the study participants on the following parameters:*
  - *the identity of the data controller*
  - *the voluntariness of the collection of data*
  - *the purposes of the processing*
  - *the nature of the processed data, including its type (identifiable, coded, anonymised) the handling of the data*
  - *the existence of the right of access to, and the right to rectify the data concerning themselves*
  - *the sharing of data across research groups*
  - *that consent may be withdrawn and how this is done*
- *Non-commercial use of personal data: None of the personal data will be used for commercial purposes, but the knowledge derived from the research using the personal data may be brought forward to such use as appropriate, and this process will be regulated by the Grant Agreement and the Consortium Agreement, in accordance with any generally valid legislation and regulations.*
- *Management of personal data transfers: If necessary, for work defined within the proposed application, data can be provided without restriction within the European Economic Area (EEA). Mobilise-D data can also be transferred to a country or territory outside the EEA if the applicant and their collaborators provide an adequate level of protection of personal data and operate under the data protection scheme in place in their country. If requested by Mobilise-D, a copy of this data protection registration should be provided.*
- *Data security: Secure data access, such as passwords, firewalls, etc., must be in place to ensure that the data are kept secure. Data may not be stored on servers or cloud storage where terms and conditions of use may enable a 3rd party access or ownership of data.*
- *Data retention: After the project duration mentioned in the proposal, data should not be used anymore and must be deleted. The applicant must complete a document where they state the data have been deleted.*

Of note, and similar to many of the IMI ND projects that involve clinical research, both data protection and ethical research measures are identified as the responsibility of clinical sites, with the deliverable stating that local ethical and data protection rules must be respected.

4.1.6 PD-MitoQUANT

PD-MitoQUANT was a translational research project funded by the IMI for a period of 3 ½ years between 2019 and 2022. Led by Jochen Prehn of the Royal College of Surgeons in Ireland, with involvement of Takeda, Lundbeck and UCB on the EFPIA side, PD-MitoQUANT aimed to understand mitochondrial dysfunction in Parkinson's disease, primarily using laboratory-based and in silico methods, with some use of clinical data and samples provided by participants from other research studies.

According to D3.4 "Data management and sharing plan" (DMSP), published in July 2020 as part of the project's participation in the Open Research Data pilot (available online: https://www.pdmitoquant.eu/project-in-progress/public-deliverables/), a small proportion of the data generated by PD-MitoQUANT came from sequencing studies of human biological material. In addition, PD-MitoQUANT also analysed clinical data from patients who donated tissue samples and cell material, through a collaboration with Parkinson's UK and a French clinical partner. All these data are classified as sensitive personal data about health, and as such processing operations fall under the remit of the GDPR.

With respect to patient privacy and confidentiality, the PD-MitoQUANT DMSP clearly states that all personal data processing operations must be in compliance with the GDPR, explaining the technical and organisational measures used to ensure data are appropriately pseudonymised:

"In all cases where human clinical data is used, the key for decoding will stay with the participating institution-hospital/biobank and will not be made available outside the hospital/institution, i.e. this information will not be shared with the consortium members. This coding includes not only the removal of personal identifiers and information, but also of clinical information that could potentially be used to identify a single individual or to expose transmissible disease susceptibilities."

In addition, the DMSP identifies the lawful bases for data processing and sensitive data processing as consent in both cases, also explaining that broad consent is provided for working with human materials, sharing data and collaboration with commercial partners:

- ***Article 6.1(a):*** *The data subject has given consent to the processing of his or her personal data for one or more specific purposes;*
- ***Article 9.2(a):*** *the data subject has given explicit consent to the processing of those personal data for one or more specified purposes, except where Union or Member State law provide that the prohibition referred to in paragraph 1 may not be lifted by the data subject*

4.1.7 RADAR-CNS

The RADAR-CNS project (Remote Assessment of Disease and Relapse in Central Nervous System disorders) was launched in April 2016, lasting for 6 years, until April 2022. Similar to IDEA-FAST and Mobilise-D, RADAR-CNS was focused on remote assessments and digital biomarkers for disease. RADAR-CNS aimed to develop new ways of monitoring major depressive disorder, epilepsy and multiple sclerosis, using wearable devices and smartphone technology. The project was jointly led by King's College London and Janssen Pharmaceutica NV, and involved a number of clinical studies for the different disease areas, focused on patient preferences, feasibility, and clinical validation. For example, in epilepsy, 7 different wearable devices were evaluated (e.g. smart watches, ring device, headband) for monitoring seizures, recruiting almost 250 participants across two sites. In major depressive disorder, 623 participants were recruited from 3 different sites, with outcome assessments every 3 months and remote monitoring through fitbit and smartphone. In total, 1450 participants were recruited to the RADAR-CNS studies. RADAR-CNS also developed an open-source mHealth platform to collect, store, manage and share data from the digital devices used the RADAR-CNS studies, called RADAR-Base.

A survey of publicly-available deliverables from RADAR-CNS identified three deliverables relating to patient privacy and consent: D6.1 "Report on mental capacity and consent issues. Template for informed consent for all disease areas in RADAR-CNS"; D1.8 "Mid-term ethics report"; and D5.1 "Protocols development and achievement of local ethic approval". All these deliverables are available through the Neuronet knowledge base (https://kb.imi-neuronet.org/).

D6.1 described how RADAR-CNS will address mental capacity, explaining that participants in RADAR-CNS studies may be vulnerable to fluctuating (or loss of) capacity due to their cognitive and/or mental disorders. Unlike in AMYPAD, RADAR-CNS did not make any provisions for study partners' consenting on behalf of participants, so a lack of capacity to provide informed consent was an effective exclusion criteria for the RADAR-CNS studies.

D6.1 also includes a template consent form, to be used as a basis for all study sites. There are a number of clauses relating to data protection and privacy in the form, including (reproduced verbatim):

- ***I agree to my anonymised data being entered into a study database.*** *I understand how the information will be collected and stored, that participating in this research is voluntary, that my personal data will not be shared with anyone outside the research team or my clinical team, and that I am free to withdraw at any time without giving a reason and without my medical treatment or legal rights being affected.*
- ***I agree to my anonymised data being shared with commercial third parties and made available for further analyses****, including for comparison to data collected with other similar studies at [enter site name**]. I understand that this will not involve sharing of any personal information from which I could be identified.*
- ***I give permission for a researcher to look at my medical records****, in order to collect additional information on my medical history, and to contact my doctor for clarification. I understand that this and all other information about me will be kept confidential*
- *SUBJECT TO CHANGE, DEPENDING ON WEARABLE DEVICE CHOICE.** **I understand that data from XXXX is also stored on the XXXX database****, and I have read and agree to the terms and conditions and privacy policy of the XXXX company.*

The patient information sheet was not included as part of the deliverable, however we note the use of the word "anonymised" in the template informed consent form and in the study protocols, which are published in D5.1 "Protocol development and achievement of local ethic approval". D5.1 also outlines the technical and organisational measures undertaken to ensure patient privacy and confidentiality:

"Participant privacy and confidentiality will be respected throughout the course of the study. Data will be encrypted and transferred via internet and Bluetooth connections to secure servers managed by the university (King's College London). Each participant will be assigned a sequential identification number, used to collect, store, and report participant information. Identifiable information will be stored within a password protected eCRF, disjoint from the RADAR-CNS platform, accessible only to members of the immediate research team. The identification number will be common across the eCRF and RADAR-CNS platform. All patients will be identified through an identification number, the personal data (name and surname will be recorded in a separate paper folder within our hospital)." (pp33)

Unlike D6.1 and 5.1, which were more focused on methods, tools and protocols, D1.8 consists of a report from the RADAR-CNS independent ethics advisor, Tim Newton from King's College

London. In this brief report, he reviews documentation and interviews study managers for the workpackages, reporting on his review of ethics approvals, scope of recruitment, perceived benefits and harms of participation, and threats to the integrity of the research. There is a brief section that relates specifically to consent, which is primary focused on reviewing how RADAR-CNS ensured that meaningful informed consent was given and that capacity was addressed properly, and concludes that:

"Overall appropriate steps were taken to ensure initial and ongoing capacity for consent, relative to the risks of the particular work package and research element. For WP4, the in-hospital group were extensively screened to ensure capacity, and there was only a short period of involvement in the research (between 3 and 10 days). There was one instance of withdrawal, involving an individual with a prolonged period of postictal confusion." (pp5).

4.1.8 RADAR-AD

The RADAR-AD project (Remote Assessment of Disease and Relapse – Alzheimer's Disease) is the sister project to RADAR-CNS, similarly using the RADAR-Base platform to collect, manage, store and share digital biomarker data. RADAR-AD was launched in January 2019 and will finish in June 2023, jointly led by King's College London and Janssen Pharmaceutica NV. The aim of RADAR-AD is to develop a digital platform that draws on smartphone, wearable and home-based digital technologies to track subtle changes in the cognitive and functional abilities of people with Alzheimer's disease. RADAR-AD is performing clinical studies that aim to assess different remote monitoring technologies and how the data that are generated using these technologies reflect the activities of daily living in people at different stages of Alzheimer's disease (from preclinical to mild/moderate stages). There are 10 participating centers in the RADAR-AD studies, based in 8 EU countries and the UK. Further details on the main clinical study can be found in the RADAR-AD study protocol (https://www.radar-ad.org/sites/radarad/files/2021-02/Research%20protocol.pdf).

A survey of publicly-available deliverables from RADAR-AD identified two deliverables relating to patient privacy and consent: D1.9 "First update of data management plan" (this had been preceded by a draft version); and D5.1 "Research protocol". These deliverables can be accessed via the RADAR-AD website (https://www.radar-ad.org/our-research/project-deliverables).

Similar to the AMYPAD clinical observational study, participants may be recruited from memory clinics and/or ongoing observational studies, and may have varying degrees of cognitive impairment. In D5.1, sections 8.2 and 8.3 (pp42) outline the ethical considerations for the RADAR-AD clinical study, stating that "*the minimal MMSE score for participation is 17, which means that no incapacitated subjects are allowed to participate in the study*." Based on D5.1, there appear to be no specific provisions that could enable a research partner to act as a proxy for consent in the case of loss of, or lack of capacity. The informed consent procedure is described as follows:

"If eligible the candidate will be informed orally and in writing (i.e. an information letter) about the study and asked to participate. The aim of the study and the procedure will be explained to the participant. Participants are informed that they can withdraw from the study at any point of the study without any consequences. It is made clear that withdrawal from the study will not affect further treatment or legal rights. The participant will have a sufficient amount of time (i.e.

at least 7 days) before making a decision about involvement in the study. Subsequently, the participant is asked to sign an informed consent form according to the national guidelines."

D5.1 also details how data and documents will be handled and stored, alluding briefly to the pseudonymisation method that will be used ("all clinical and personal data will be provided with a code that cannot be related to an individual."). Details on the technical and organisational measures to ensure patient privacy are also provided:

"Anonymised data will be encrypted and transferred via internet and Bluetooth connections to secure servers managed by each local site. Each participant will be assigned a sequential identification number, used to collect, store, and report participant information. Identifiable information will be stored within a password protected eCRF, disjoint from the RADAR-AD platform, accessible only to members of the immediate research team. The identification number will be common across the eCRF and RADAR-AD platform. Data collected via the wrist-worn wearable devices (i.e. Axivity AX3, FitBit Charge 3) is first transmitted to respective company data warehouse from which data be accessed, encrypted and uploaded to a secure server maintained by the sponsor organisation, and will be not identifiable by patient name. Data collected via the smartphone will be encrypted and uploaded to secure servers by Wi-Fi or mobile data connection. Data will be temporarily cached on the smartphone until an appropriate connection is available and will then automatically be deleted from the phone memory. The research team will keep legible and accurate documents to ensure thorough documentation of study conduct." (pp44)

Although the lawful basis for data processing is not stated in the protocol, and the patient information sheets and informed consent forms were not available for analysis, D5.1 states "patients will be informed and asked to consent to sharing of information", which could indicate that consent is used as the lawful basis under the GDPR.

Elsewhere, the RADAR-AD data management plan (D1.9) contains short sections on data privacy and security, and "ethical aspects". The section on privacy and security primarily focuses on the latter, providing detailed technical information on the systems architecture and functionalities to ensure data are protected. The short ethical aspects section includes the following reference to data protection:

"In all cases, participants' data are collected and processed according to the European General Data Protection Regulation (GDPR) and any applicable national privacy regulation. The way of storing and utilizing the participants' data collected via RMTs respect the regulation (EU) No 1291/2013 of the European Parliament and of the Council of 11 December 2013 and the new Medical Device Regulation(EU 2017/745)." (pp16)

5 Summary and recommendations

In the present deliverable, *D3.9 Final version of guidance on standards and practices for protecting data privacy*, we have performed a content analysis of reports from IMI ND projects on their informed consent and data management policies. The content analysis provides an insight into the patient privacy- and consent-related concerns of projects, and how they address them; for example, EPAD developed a staged consent model that provided participants with required information and materials at key decision points when they progress between study stages, whilst also ensuring they understand the full scope of the EPAD studies. Reidentification was viewed as an important challenge by many projects, and as such data management plans from projects like Mobilise-D, PD-MitoQUANT and RADAR-AD explain how data are coded and what technical tools/methods are used to minimise reidentification risk.

Based on our content analyses of IMI ND project deliverables we have identified cross-cutting themes relating patient privacy and informed consent:

- *Projects are highly aware of the need to ensure privacy and confidentiality for research participants, with a strong focus on these topics in all the data management plans and ethical documentation that was analysed.*

- *In projects undertaking multi-site clinical research studies, clinical sites, principal investigators and data protection officers are often responsible for ensuring compliance with legal and ethical requirements for patient privacy.*
- *Reidentification of participants was identified as one of the key ethical risks for projects, particularly when sharing data and/or samples for secondary use.*
- *Capacity is an important concern for IMI ND projects recruiting participants for clinical studies*
- *Analysis of consent form templates and study documentation indicates that consent is frequently used as the lawful basis for data processing under the GDPR.*
- *However, projects provide varying amounts of information and details on data protection measures in consent forms and information sheets.*
- *Projects apply broadly similar strategies to reduce the risk of reidentification and ensure data security, such as pseudonymisation using identifier codes, encryption and password protection, etc*

Our content analyses also revealed some of the measures and methods used by projects to ensure patient privacy and informed consent. Below, we outline recommendations on good practices for patient privacy and informed consent, providing practical examples from IMI ND projects.

- At the project design stage, identify where risk assessments and data protection impact assessments (DPIAs) will be useful and necessary, through consultation with clinical sites, data protection experts and staff responsible for data management.
    - *In EPND, a DPIA in year 1 of the project is being used to identify and mitigate potential privacy risks linked to the different anticipated data flows, developed collaboratively by a team that includes clinical research leaders, technical platform developers and data protection specialists. The DPIA will be a living document that will be updated throughout the project.*
- Clearly identify the roles and responsibilities for entities/individuals involved in data collection, use, management, storage, re-use and sharing, and share this information

with research participants where relevant; ensure there are clear pathways for accountability.

  - *The IDEA-FAST consent form and patient information documents include a separate GDPR statement, clearly and succinctly explaining which data and samples are collected, what they are used for and by whom (including the identity of the data controller & processors), and the participants' rights as data subject.*

- For projects undertaking multi-site or multi-stage studies, adapt and align procedures for consent, management of access requests, and monitoring, to enable participation, and facilitate smooth pathways for data sharing
  - *EPAD included specific clauses in its consent forms for the Proof of Concept trial, in which participants could agree to specific data flows (e.g. "agree to data collected in this study to be returned to the LCS"). In addition, the project developed a staged consent model, providing relevant information at different stages and in different formats (eg. Leaflets, videos, converstions with researchers).*
- Consider all potential data flows in the short and long term when developing study documentation, ethical approvals and data protection clauses; plan for data sharing and secondary use of data/samples in data governance and consent processes
  - *EMIF developed a comprehensive Code of Practice identifying mandatory data processing principles for using the EMIF platform, as well as codes of practice for the EMIF catalogue, EMIF data queries, and data sharing from the EMIF research studies. This document provides extensive, accessible and straightforward guidance for different use cases and categories of user.*
- Plan ahead for situations where there may be a loss of or fluctuating capacity, embedding capacity assessments when relevant and adapting study protocols and consent methods to facilitate continued participation where desired
  - *AMYPAD monitored participant capacity to consent during the course of their PNHS study, with provisions to conducting more formal assessment of capacity using an external healthcare professional where necessary. AMYPAD also enabled the involvement of study partners for research participants, allowing these individuals to provide proxy informed consent in agreement with the participant's wishes, values and beliefs.*
- Involve people with lived experience of neurodegenerative disease in all stages of clinical research studies; in particular, develop study protocols, patient information sheets and consent forms/methods in consultation with patients/carers
  - *RADAR-AD created a patient advisory board, composed of people with dementia supported by friends, family members or caregivers. The patient advisory board provided feedback and input to patient information sheets and consent forms, and their perspectives on practical aspects of study implementation, improving RADAR-AD research.*

6 Acknowledgements

We are extremely grateful to AMYPAD and EMIF partners who provided access to their ethics policies and code of practice deliverables. We would also like to acknowledge the valuable contribution of the Neuronet Working Group on Patient Privacy and Ethics to this deliverable, which reflects discussions during Working Group meetings. Finally, we would like to acknowledge the contributing projects of the IMI neurodegeneration portfolio, whose deliverables form the backbone of this report.

The members of the Working Group who contributed to discussions on patient privacy and consent are:

Merce Boada, Fundacio ACE, Spain
Pilar Canabate, Fundacio ACE, Spain
Dianne Gove, Alzheimer Europe, Luxembourg
Nathan Lea, Cancer Research UK; European Institute for Innovation through Health Data
Federica Lucivero, University of Oxford, UK
Richard Milne, University of Cambridge, UK
Diana O'Rourke, NICE, UK
Edo Richard, Radboud UMC, the Netherlands