Neuronet

IMI2 821513 – NEURONET

Efficiently Networking European Neurodegeneration Research

WP3 – Tools and Services

D3.4 - First version of guidance on standards and practices for protecting data privacy

Contents

Document history

Version	Date	Description
V1.1	12/02/2020	First draft
V1.2	20/02/2020	Comments
VX.X	24/02/2020	Draft
VX.X	dd/mm/yyyy	Final version

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
8. **SARD**: Sanofi-Aventis Recherche & Développement
9. **PUK**: Parkinson's Disease Society of the United Kingdom LBG

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

CSA: Coordination and Support Action

WP: Work Package

WG: Working Group

ELSI: Ethical, Legal and Social Implications

GDPR: General Data Protection Regulation

Publishable summary

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. Neuronet intends 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.

This deliverable reports on the development of guidance and advice on the protection of patient privacy, encompassing both legal and ethical aspects of this important topic. Specifically, this deliverable summarises the key data protection concepts for health research involving personal data, focusing particularly on the GDPR. An overview of ethical concepts for health research using personal data is also provided, with an exploration of informed consent for data sharing and reuse. Together, these tenets of data protection and ethics will form the basis for guideline development, which will be materialised in D3.9 "Final version of guidance and advice on standards and practices for protecting data privacy" (due in month 30). Finally, this deliverable outlines 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.

1 Introduction

Protecting data gathered in association with patient care is a core value in healthcare, linked to the fundamental human right to privacy enshrined in the United Nations Universal Declaration of Human Rights (1948). Moreover, respecting patient privacy is an expression of respect for patient autonomy, and a prerequisite for trust. This extends to individual patient-level data gathered in clinical research studies, such as interventional trials or observational studies, as well as in "real-world" health settings, such as in GP consultations or during regular hospital appointments.

Data that is gathered in clinical research studies and during the delivery of "real-world" care can include simple variables such as age, gender and BMI (body mass index) as well as more complex data such as blood test results, cognitive assessments, medical imaging and genetic data. In many neurodegenerative disease (ND) studies these are collected on a longitudinal basis, covering multiple points across the timespan of ND development. Clinical data on ND are therefore both costly to generate and enormously valuable.

Reflecting the value of these datasets, the last two decades have seen the development of global data sharing initiatives such as the International Neuroimaging Data-sharing Initiative (INDI)(1) and the Clinical Study Data Request (CSDR) platform(2). These and other initiatives aim to facilitate the secondary use of patient data in health research, maximising the financial, scientific and ethical return on investment. The benefits of sharing patient data for health research purposes include, among others, (a) the possibility for other scientists to validate the results of health research; (b) enabling researchers to build on the work of others more efficiently; (c) facilitating meta-analyses of aggregated patient data, increasing the impact of single studies; (d) decreasing the burden on research participants through the reuse of existing data.

However, patient datasets contain sensitive information which requires a high level of protection to ensure it is not unnecessarily disclosed. Failure to adequately protect patient data against loss or misuse can exposes data subjects to substantial ethical risks, breaching their right to confidentiality and privacy and potentially exposing them to social or personal harm. To ensure that patient privacy is adequately respected, data protection and ethics form an integral part of EU-funded health research. Indeed, Article 19 of Regulation (EU)1291/2013 (3), which established the Horizon 2020 Framework Programme for Research and Innovation, states: "particular attention shall be paid to (…) the right to privacy, the right to the protection of personal data, the right to the physical and mental integrity of a person, the right to non-discrimination and the need to ensure high levels of human health protection".

2 Background and context

Compliance with the ethical and data protection requirements that underly patient privacy is seen as pivotal to achieve real excellence in health research. 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. An initial survey of IMI project coordinators performed by Neuronet identified "guidance/best practice on data privacy and related regulations" and "guidance/best practice on ethics approvals and Informed Consent Forms" as priority areas in which IMI ND projects would like more support. This deliverable therefore reports on the development of guidance and advice on the protection of patient privacy, focusing primarily on data protection and ethics in health research.

In this deliverable, we summarise the key data protection concepts for health research involving personal data, particularly in relation to the GDPR (Section 3). We provide an overview of the key ethical concepts for health research using personal data, outlining criteria for informed consent in primary health research and for the secondary use of data (Section 4). Embedded in these sections are "discussion point" boxes, identifying areas and issues that may serve as topics for discussion in the Neuronet Patient Privacy and Ethics Working Group – or as areas where best practice exists in the IMI ND projects supported by Neuronet. Finally, we report on the results of an initial survey of ELSI deliverables and topics currently being addressed in the projects of the IMI ND portfolio (Section 5).

3 Data protection in health research

Data protection is both a central issue for research ethics and a fundamental human right. Indeed, the right to data protection is enshrined in the EU Charter of Fundamental Rights and the Treaty on the Functioning of the European Union, which give effect to individuals' right to privacy by providing them with control over the way information about them is collected and used. The vast majority of the 15 IMI ND projects currently supported by Neuronet involve the use of personal data, ranging from projects that re-use existing clinical datasets (such as ADAPTED and IM2PACT) to those that include research studies generating new clinical datasets (such as EPAD, AMYPAD and RADAR-AD). As such, data protection is a central concern for IMI ND projects and, by extension, for Neuronet as well.

From 1995, the Data Protection Directive (95/46/AC) regulated the processing of personal data (such as individual-level patient data) within the EU (4). In May 2016, however, this Directive was replaced by a new Regulation (EU) 2016/679 on the protection of personal data (5). This Regulation, termed the "General Data Protection Regulation" or GDPR, came into application on 25 May 2018, after a two-year transition period from the Data Protection Directive.

3.1 Key concepts of the GDPR

One of the three core objectives of the GDPR is to ensure the free movement of data throughout the EU, whilst also guaranteeing the right to personal data protection within and beyond the EU. It does so by laying down rules on the processing and free movement of personal data, based on six key principles (discussed in greater detail in section 3.2 below). Each of these principles apply to all personal data processing, including processing of personal data for research purposes.

In this section, the primary legal concepts enshrined in the GDPR will be defined, providing a basis for the subsequent section, which will address the GDPR requirements for personal data processing.

3.1.1 Personal data

The GDPR defines personal data as follows:

> *"'Personal data' means any information relating to an identified or identifiable natural person ('data subject')"*

Of particular relevance to Neuronet and neurodegenerative disease research, the GDPR recognises "*data concerning health*" and "*genetic data*" as **special categories of personal data**, meriting a higher degree of protection than less sensitive types of personal data (discussed in section 3.2.2 below). In Article 4 of the GDPR, data concerning health is defined as:

"personal data related to the physical or mental health of a natural person, including the provision of health care services, which reveal information about his or her health status;"

Discussion point: Are brain imaging scans personal data?
Beyond "identifiability", the GDPR does not give a specific interpretation of personal data; it does not explicitly mention brain scans (such as MRI & EEG), which are performed in many IMI ND projects. Studies have found anatomical and bioelectronic features of the brain that may be considered unique identifiers. *In the absence of other identifiers, should brain scans be considered personal data under the GDPR?*

In turn, genetic data is defined as:

"personal data relating to the inherited or acquired genetic characteristics of a natural person which give unique information about the physiology or health of that natural person and which result, in particular, from an analysis of a biological sample from the natural person in question."

3.1.2 Data processors and controllers

In Art.4(2), the GDPR defines personal data processing as:

"..any operation or set of operations which is performed on personal data, or on sets of personal data, whether or not by automated means, such as collection, recording, organisation, structuring, storage, adaptation or alteration retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restruction, erasure or destruction."

Individuals or organisations that are directly involved in processing personal data can be identified as data controllers or data processors.

A data controller is a person or organisation that has full authority to decide why and how personal data is to be processed, and that has the overall responsibility for the data (Art.24). For example, sponsors of clinical trials are often defined as data controllers, as they determine the study protocol that dictates what personal data is collected. As a number of projects in the IMI ND portfolio involve multi-site clinical research studies, it is important to note that controllership can be jointly held. This point has been clarified in the recent Guidelines from the European Data Protection Supervisor (EDPS), the consultative, independent European supervisory body that monitors compliance with the GDPR.

A data processor is a person or organisation that processes personal data on behalf of the data controller, unless specifically required to do so by Union or Member State law. Under the terms of the GDPR, the data processor can only process personal data if explicitly instructed to do so by the controller. As such, processor liability is more limited in scope compared to the controller's liability. For example, if a contract research organisation (CRO), while processing clinical study data on behalf of a sponsor, commits an infringement of the GDPR, the sponsor (and data controller) can be held liable for any damages that are incurred.

Discussion point: Controllership for multi-site clinical studies
The GDPR provides for sole or joint controllership of data processing operations. This has led to the development of two positions when it comes to controllership of multi-site clinical trials: one where Sponsors and Sites are joint controllers and another where Sponsors and Sites are separate controllers for different purposes of the data processing. *Is there a need for further clarification of how Sponsor and Sites should be defined for the purposes of processing personal data in clinical trials for ND?*

3.1.3 Anonymisation and pseudonymisation

Identifiability is an important consideration for health researchers, as fully anonymised personal data is not within the scope of the GDPR. Article 4 of the GDPR specifies what conditions must be met for a natural person to be identifiable:

> *"..an identifiable or natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person"*

However, the GDPR sets a high bar for anonymisation, which must be full and irreversible. As such, anonymisation requires not only deleting all directly identifying attributes (e.g. names, phone numbers, addresses) from the data set, but also the removal of data which in combination reveal unique characteristics.

Article 4 of the GDPR defines pseudonymisation as:

> *"the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person."*

In practice, pseudonymisation involves the replacement of identifying attributes by one or more artificial identifiers. For example, personal data from participants in a clinical research study could be pseudonymised by replacing their names with randomly-allocated numerical identifiers. It is important to note that pseudonymised data still falls within the remit of the GDPR, because it is possible to re-identify the data subject with the use of additional information. However, pseudonymisation is seen as an effective "technical and organisational measure" to ensure some of the rights of data subjects are met.

Discussion point: Appropriate methods for pseudonymisation
There is no single easy solution to pseudonymisation that works for all approaches in all possible scenarios. Effective pseudonymisation requires a high level of competence in order to reduce the threat of discrimination or re-identification, whilst also maintaining the degree of utility necessary for the processing of pseudonymised data. *Is there a need for guidelines on the pseudonymisation of special categories of personal data in IMI ND projects?*

3.2 GDPR requirements for the processing of personal data

The concept of "data protection by design and by default" has been woven into the fabric of the GDPR, and is enshrined in Articles 5 and 25 of the Regulation text. In practice, this means that data controllers and processors (e.g clinical trial sponsors, principal investigators, CROs and downstream data handlers) must integrate data protection measures into every aspect of their personal data processing activities, from the design stage onwards.

To reinforce the concept of data protection by design and by default, the GDPR lays out six founding principles for processing personal data. Underlying these principles are the six legal bases (or scenarios) for data processing; unless organisations can demonstrate that the proposed data processing activity fits within one or more of these scenarios, that activity can be deemed unlawful. Finally - and of particular relevance to Neuronet - the so-called "Research

Exemption" (laid out in Article 89 of the GDPR) aims to facilitate research by enabling some of the rights of the data subject to be derogated. The GDPR principles, legal bases for data processing and research exemption will be presented and briefly discussed in this section of the deliverable.

3.2.1 Principles of personal data processing

Article 5 of the GDPR lists 6 key principles relating to the processing of personal data. These principles state that personal data should be:

a. Processed lawfully, fairly and in a transparent manner;
b. Collected for specified, explicit and legitimate purposes (the "purpose limitation principle");
c. Adequate, relevant and limited to what is necessary in relation to the purposes of data processing (the "data minimisation principle");
d. Accurate and, where necessary, kept up-to-date;
e. Kept in an identifiable form for no longer than is absolutely necessary for the purposes of data processing (the "storage limitation principle");
f. Processed in a manner that ensures the security of the personal data, using appropriate technical and organisational measures.

Each of these principles apply to **all** personal data processing operations without exception, including processing of personal data for research purposes.

3.2.2 Lawful bases for personal data processing

The first principle of the GDPR (see 3.2.1 above) requires that all data processing operations be lawful, fair and transparent. In Article 6, the GDPR describes the 6 lawful bases for data processing, one or more of which must be satistfied:

a. The data subject has given consent to the processing of his/her personal data for one or more specific purposes ("consent");
b. Data processing is necessary for the performance of a contract to which the data subject is party ("contract");
c. Data processing is necessary for compliance with a legal obligation to which the controller is subject ("legal obligation");
d. Data processing is necessary in order to protect the vital interests of the data subject or of another natural person ("vital interests");
e. Data processing is necessary for the performance of a task carried out in the public interest or in exercise of official authority ("public interest");
f. Data processing is necessary for the purposes of the legitimate interests pursued by the controller, except where such interests are overridden by the interests or fundmental rights and freedoms of the data subject ("legitimate interest").

As noted in Section 3.1.1 above, data concerning health and genetic data (such as the clinical research data generated by IMI ND projects) are classed as "special categories of data", meriting a higher degree of protection than less sensitive types of personal data. In order to lawfully process special category data, you must identify both a lawful basis under Article 6 of the GDPR (as above) **and** a separate condition for processing under Article 9, as listed below:

a. The data subject has given explicit consent to the processing of these data for specified purposes;

b. Processing is necessary for the purposes of carrying out the obligations and exercising specific rights of the controller or of the data subject in the field of employment and social security and social protection law;
c. Processing is necessary to protect the vital interests of the data subject or of another national person where the data subject is physically or legally incapable of giving consent;
d. Processing is carried out in the course of its legitimate activities with appropriate safeguards by a foundation, association or other not-for-profit body;
e. Processing relates to personal data which are made manifestly public by the data subject;
f. Processing is necessary for the establishment, exercise or defense of legal claims;
g. Processing is necessary for reasons of substantial public interest;
h. Processing is necessary for the purposes of preventive or occupational medicine, for the assessment of the working capacity of the employee, medical diagnosis, the provision of health or social care;
i. Processing is necessary for reasons of public interest in the area of public health;
j. Processing is necessary for archiving purposes in the public interest, scientific or historic research purposes or statistical purposes in accordance with Article 89(1).

Many of the IMI ND projects supported by Neuronet involve the secondary use of special categories of personal data, which may have been collected for a different purpose to that proposed by the project. This can cause issues in terms of compliance with the GDPR, particularly where the lawful basis for collecting the data was consent and no consent for secondary use has been obtained. It should be noted here that GDPR consent to data processing is not the same as consent to participate in research, and that the interpretation and definition of valid consent differs between the fields of data protection ("GDPR consent to data processing") and research ethics ("medicolegal consent to participation in research"). For example, while informed consent is an absolute medicolegal requirement for interventional research involving human participants, there is more flexibility under the GDPR, for which consent is only one of the six potential lawful bases for data processing.

Recontacting and reconsenting research participants for new data processing operations (such as sharing or reusing data for a different purpose to that originally stated) can be problematic, particularly when a long time has elapsed since data collection or when the ability of participants to provide "freely-given, specific, informed and unambiguous" consent has become impaired. Moreover, relying on consent as a lawful basis for data processing can cause issues when a research participant withdraws consent, as their data will then need to be expunged from all databases, repositories and data storage locations.

Discussion point: Chosing a lawful basis for data processing
The choice of lawful basis for processing of special categories of data (e.g data concerning health and genetic data) can place limitations on the reuse or sharing of this data. This may be particularly problematic in large IMI ND consortium projects that involve multi-site clinical studies and multiple controllers. *Do IMI ND projects require extra guidance on the most practicable and appropriate lawful basis for data processing? Should these discussions involve people with ND?*

Consequently, many academic institutions now recommend that their researchers use Art.6(e)("*task carried out in the public interest*") as the most appropriate and practicable lawful basis for personal data processing. Conversely, for non-public authorities such as charities,

commercial companies or NGOs, Art.6(f) ("*legitimate interest*") is often touted as being the most practical lawful basis. Where special categories of personal data are being processed in research studies – e.g health or genetic data – condition (j) in Art.9 GDPR (see above) can be an appropriate basis for data processing. In this way, the GDPR provides researchers with a means to circumvent the need to obtain specific, explicit consent to particular data processing operations – but only if "appropriate safeguards" are in place to ensure the rights and freedoms of the data subject. This condition is enshrined in Article 89 of the GDPR, which sets out the derogations and safeguards that relate to data processing for scientific research.

3.2.3 Derogations under the GDPR: the research exemption

Art.89 GDPR is also known as the "Research Exemption" as it enables the processing of health or genetic data for scientific research purposes if there are appropriate technical and organisational safeguarding measures in place (Art.89(1)). In addition, Art.89(2) permits member states to derogate from certain rights of the data subject (access, rectification, restriction and the right to object), but only to the extent that these rights would seriously impair scientific research.

Discussion point: Member state derogations
Article 89 GDPR provides for member state derogations from the data subject rights referred to in Art.15, 16, 18 and 21, If appropriate safeguards are in place. The scope for derogation and the lack of specific information on appropriate safeguards may be problematic for multinational clinical studies. *Have IMI ND projects experienced issues due to member state derogations?*

In practice, this has led to a degree of regulatory divergence between different member states when it comes to the safeguards that must be applied when processing special categories of data for research purposes. For example, Spain has mandated a technical and functional separation between the investigation team and the person(s) who pseudonymise the data. Conversely, Italy will accept an approval from the relevant research ethics authority when it is impossible or hard to recontact the data subject to obtain consent for data processing.

4 Ethics in health research

When it comes to patient privacy, data protection and ethics are inextricably linked. In essence, the GDPR gives effect to the fundamental human right to data privacy, applying a rights-based approach to data protection. Indeed, Article 4 GDPR states:

> *"The processing of personal data should be designed to serve mankind. The right to the protection of personal data is not an absolute right; it must be considered in relation to its function in society and be balanced against other fundamental rights, in accordance with the principle of proportionality. This Regulation respects all fundamental rights and observes the freedoms and principles recognised in the Charter and as enshrined in the Treaties."*

However, not all ethical principles are codified in EU law, which entails a need for researchers to consider legal and ethical issues as both joint and separate entities. This fact is acknowledged in Recital 33 of the GDPR, which states that "data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with **recognised ethical standards** for scientific research".

For all activities funded by the EU, ethics is an integral part of research. From the project pre-proposal stage through to the dissemination of results, ethical compliance is seen as pivotal to achieve real research excellence. As such, 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. Specifically, researchers *"must ensure respect for people and for human dignity and fair distribution of the benefits and burden of research, and must protect the values, rights and interests of the research participants."* (6).

In this section, we will provide an overview of the key ethical concepts for health research using personal data, outlining criteria for informed consent in primary health research and for the secondary use of data.

4.1 Ethical requirements for health research

Conducting ethical health research implies the application of fundamental ethical principles to the research project in question. At this point, it should be noted that the IMI ND portfolio incorporates many projects that involve preclinical research in animals, cells and tissues. However preclinical research entails distinct ethical risks and considerations, currently outwith the scope of the Working Group on Patient Privacy and Ethics. Consequently, this deliverable is primarily focused on health research that actively involves human participants.

The ethics of health research involving human participants requires a context-sensitive approach and a balanced risk assessment about likely harm to the individual (or his/her community) on the one hand, versus the right to perform research for societal benefit on the other hand. In his highly-cited 2000 paper, Ezekiel Emanuel and colleagues (7) identified 7 fundamental requirements for ethical clinical research, which incorporate all of the Medical Ethics principles first described by Beauchamp and Childress in 1979: respect for autonomy, non-maleficience, beneficience, and justice (8). Emanuel's ethical requirements are listed in the table below:

ETHICAL REQUIREMENT	EXPLANATION
SOCIAL OR SCIENTIFIC VALUE	To justify their use of resources, health research studies should aim to improve health & wellbeing, or increase knowledge; providing society with accurate answers to questions that were worth asking
SCIENTIFIC VALIDITY	To justify their use of resources, health research studies should involve robust techniques and be methodologically rigorous
FAIR SUBJECT SELECTION	Subject selection should be guided by the scientific goals of the study; subjects who bear the risk of participation in research should be able to enjoy the benefits; subjects or groups of subjects should not be excluded from participating without a good scientific reason.
FAVOURABLE RISK-BENEFIT RATIO	Risks to individual subjects should be minimised and benefits should be enhanced (risks should be proportionate to benefits)
INDEPENDENT REVIEW	Research should be reviewed by an independent panel with no conflicts of interest, to ensure social accountability, ethical trial design and a favourable risk-benefit ratio
INFORMED CONSENT	Individuals must be provided with the information required to decide whether they enrol in clinical research, including purpose, procedures, risks, benefits and alternatives - thereby ensuring respect for autonomy and personhood
RESPECT FOR SUBJECTS	Subject autonomy and welfare should be respected by allowing them to withdraw from research, protecting their privacy, informing them of risks or benefits (and results of research), and maintaining their welfare

"Respect for Communities" could arguably be added to this list, given the importance of promoting and respecting the values and interests of different communities, as well as protecting them from harm (9).

Of the ethical requirements listed above, Informed Consent has probably received the most attention in the literature; it will be addressed in Section 4.3 below. When considering clinical research involving people with progressive neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), three further ethical challenges come to the fore: 1) fairness and equity in research participation, particularly for vulnerable groups; 2) justifying the risk-benefit ratio, particularly in clinical research that includes people in the preclinical stages of disease; 3) disclosing risk marker status to research participants, particularly in relation to progressive, neurodegenerative diseases with a lack of disease-modifying treatment options.

4.1.1 Fairness and equity

Fairness and equity are closely linked to the principle of justice described by Beauchamp and Childress. In the health research setting, this principle extends to participation in clinical research. Specifically, individuals or groups should not be excluded from participating in clinical research studies based on vulnerability, gender, ethnicity or other factors unrelated to the scientific goal of the clinical research study – just as these groups should not be marginalised from health benefits due to their vulnerable/ethnic/socioeconomic(or other) status. Indeed, health research guidelines such as the Australian National Statement on Ethical Conduct in Health Research include specific statements on people with a cognitive impairment, intellectual disability or mental illness (10):

> "*people with a cognitive impairment, intellectual disability, or mental illness are entitled to participate in research, which need not be limited to their particular impairment, disability, or illness*" (Chapter 4.5).

From an ethical perspective, it is important that groups such as these have equitable access to participation; this reflects their value to society, going beyond the stereotypes and misconceptions that are frequently part of the process of stigmatisation of these groups of individuals. However, there is also a scientific prerogative to equitable participation: to ensure the validity and applicability of clinical trials, it is important that participants recruited to research studies be reasonably representative of the population that will be later treated by the drug – including vulnerable, multimorbid populations, of different ages and genders and from diverse backgrounds. Otherwise, there is a risk that older people may be denied the right and opportunity to have access to treatments and interventions that are beneficial (and not harmful) to them. This is reflected in the European Medicines Agency's 1994 guidance note on studies for geriatric populations (CPMP/ICH/379/95), which states the following (11):

Discussion point:Tools & measures for equitable participation
Clinical research studies for neurodegenerative diseases can be ethically challenged by issues with recruiting participants with different degrees of cognitive impairment, or from different socioeconomic backgrounds. *What are key barriers and facilitators for engaging individuals and communities from different backgrounds in ND research?*

> *"Drugs should be studied in all age groups, including the elderly, for which they will have significant utility".*

To ensure equitable access to research participation, researchers are encouraged to systematically identify then dismantle barriers to participation, for example by embedding measures to enhance inclusion (e.g recruiting interpreters – although this can raise other ethical

and methodological issues), and ensuring that tools employed in health research studies are suitable for use by a broad range of groups (e.g using neuropsychological tests that are less affected by cultural or socioeconomic factors). Researchers should also avoid dismissing groups as "hard to reach", which risks placing the blame on the potential participants rather than structural factors, attitudes and assumptions that can lead to discrimination.

4.1.2 Risks and benefits

In its 2016 International Ethical Guidelines for Health-related Research, the CIOMS (Council for International Organisations of Medical Sciences) states (12):

> *"The researcher, sponsor and research ethics committee must ensure that risks to participants are minimised and appropriately balanced in relation to the prospect of potential individual benefit and the social and scientific value of the research."*

The term 'risk' encompasses physical, mental and emotional harms as well as concerns such as incurred costs and practical inconvenience – which could also be termed "burdens" of research participation. Estimating risk is complicated by differing estimations and differing viewpoints; for example, a participant with cognitive impairment may find a research intervention to be emotionally distressing, unlike the researcher who designed the intervention. Conversely, an overestimation of harm by researchers may lead to the possible benefits of research participation being undervalued. In his chapter in Heather Wilkinson's 2001 book on the perspectives of people with dementia, James McKillop (who was diagnosed with multi-infarct dementia at the age of 59) describes his positive experience of research participation (13):

> *"I met kindred spirits, gained confidence to face the public and speak out…. My experiences (and those of others) will surely shape the future and others will benefit."*

Lucy Norman, who is living with Parkinson's Disease and is a patient ambassador for Parkinson's UK, had similar positive experiences of research participation (14):

> *"It's very exciting and gives you a massive sense of achievement, as well as allowing you to build new friendships. For me, it's another level of support, from a team of clinicians and researchers who are fascinated by my experiences and my condition. "*

A further consideration for risk-benefit calculations in health research is the disease stage that is being studied. For example, longitudinal studies of neurodegenerative diseases such as AD may last for several years, with participants being enrolled at very early, presymptomatic stages of the disease process. From a practical perspective, this entails exposing participants to (occasionally invasive) interventions for a prolonged period of time, placing greater procedural burdens on individuals. This can complicate ethical discussions on the risks and benefits of participating in research, as these will vary over time.

Discussion point: Risk/benefit estimates in longitudinal studies
For longitudinal cohort studies or interventional studies of long duration, risk/benefit estimates can be complicated by disease variation across the lifespan. *Are there measures that can be taken to facilitate accurate risk/benefit estimation in longitudinal studies that enroll participants in preclinical stages of ND?*

4.1.3 Respect for persons: disclosing risk

Several projects in the IMI ND portfolio revolve around the identification and detailed study of risk factors for disease. For example, ADAPTED is studying how different variants of APOE (a genetic risk factor for AD) play a role in the progression of mild cognitive impairment (MCI) to dementia in AD, while AMYPAD is studying the value of PET-amyloid brain imaging in diagnosing AD. The ethical issues that arise from the disclosure of risk exist in a continuum with the risk and benefit calculations for the inclusion of presymptomatic participants in longitudinal clinical studies. In his 2015 Neurology article, Scott Kim and coauthors highlight a further ethical challenge that goes beyond the testing of risky interventions in people who may never develop AD: the potential for psychological harm due to disclosure of risk status, particularly for diseases with few or no effective treatment options (15).

Discussion point: Risk disclosure with altered cognition
For certain IMI ND projects, discussions around disclosure of risk status may be complicated by the cognitive status of research participants. *How should discussions on risk be adapted to ensure the rights and opinions of cognitively-impaired individuals are respected?*

This ethical challenge is particularly pertinent due to the increasing use of genomic and biomarker technologies in clinical studies; in time, these technologies may also become established in primary and secondary care. In 2013, the Alzheimer's Disease Neuroimaging Initiative (a global initiative which gathers extensive medical and imaging data from participants across the spectrum of cognition) surveyed investigators or research staff on their attitudes towards the disclosure of risk status (16). Ethical arguments surrounding the disclosure of risk for participants with normal cognition invoked the principle of respect for autonomy. Conversely, some respondents argued that participants' "right to know" should be respected, and that researchers should avoid the paternalistic withholding of risk marker status. In support of this argument, the 2014 "Value of Knowing" survey carried out by Alzheimer Europe found that over 60% of respondents (2687 representatively-sampled adults from 4 EU countries and the US) would be very/somewhat likely to get a test that could predict whether they were likely to develop AD in the future (17).

4.2 Informed Consent

Informed consent is an ethical and legal requirement for research that involves human participants, and is enshrined in numerous international conventions and documents. In the current Clinical Trials Directive (2001/20/EC) - which will be superceded when the new Clinical Trials Regulation EC(536/2014) enters into application - informed consent is defined as follows (18):

> *..a decision, which must be written, dated and signed, to take part in a clinical trial; taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent."*

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. The first question on the ethics issue checklist for H2020 applicants (19) 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.

4.2.1 Informed consent, capacity and cognition

One of the main determinants of capacity is cognition. Any condition that affects a person's cognitive abilities may therefore impair (or alter) that person's decision-making capacity. This is an important consideration for IMI ND projects that study conditions such as Alzheimer's or Parkinson's disease, which are both associated with cognitive impairment. However, assuming a lack of capacity solely because of an ND diagnosis would be discriminatory.

In his 2008 conceptual framework for capacity assessment in cognitively-impaired individuals, Jason Karlawish outlines four key decision-making abilities that underly the concept of capacity: understanding, appreciation, choice and reasoning. In clinical practice, specific tools and questionnaires are used to determine whether individuals have the capacity to consent, assessing these four decision-making abilities. For example, the MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR) helps trained researchers to understand whether potential participants can adequately understand, appreciate, reason and express their choices. In his 2008 article, Jason Karlawish showed that people with mild AD generally retain sufficient capacity for informed consent, in particular those with preserved awareness of their diagnosis, symptoms and prognosis (20). A similar 2013 study involving participants with PD showed that people with impaired cognition also had impairments in their decisional capacity, measured using the MacCAT-CR and two cognitive assessment scales, the Montreal Cognitive Assessment (MoCA) scale and the mini-mental state examination (MMSE)(21). As conditions such as AD and PD are progressive, it is important for NDD researchers to be aware that decline in capacity may occur during the timeframe of a clinical study, so that they can make provisions that will empower participants to remain involved, to withdraw if they wish to and to exercise their autonomy. It should also be noted that people with NDD may require certain accommodations to empower them to provide informed consent, such as adapting the environment or removing stressors.

Discussion point: informed consent and capacity

Instruments for collecting informed consent may not always be appropriate or well-adapted to different groups (for example minority groups with specific cultural requirements) resulting in their exclusion from research. *Should these instruments be validated in consultation with people from these groups?*

Measures such as advance research directives or proxy decision making can extend a person's autonomy into the future, beyond the point at which they lose the capacity for informed consent. For example, a 2011 JAMA Psychiatry study showed that a substantial proportion of people with AD who did not have the capacity to consent to clinical studies had preserved capacity to appoint a research proxy (22). However, there may be divergences in opinion or a lack of transparency between participants and their research proxies, which can have a negative impact on the person's right to autonomy and self-determination. Advance research directives are legal documents that provide a more direct

Discussion point: advance directives and research proxies

For longitudinal research studies, there is a risk that participants may lose capacity during the course of the study. *What are the most appropriate and ethical options for continued participation of these individuals? In addition, how should assent and dissent for research be defined, for persons lacking consent capacity?*

means for people with diminishing capacity to ensure their voices are heard during decision-making processes in clinical research studies. Advance directives can be used to appoint a proxy, although it may be advantageous for research participants to have both an advance directive and a proxy who has the power to make decisions not covered in the directive. Some of the ethical arguments supporting the use of advance directives for persons with cognitive impairments and/or dementia are summarised in the 2009 Alzheimer Europe Position Paper on the Use of Advance Directives (23) and addressed in the Alzheimer Europe's 2019 report entitled "Overcoming ethical challenges affecting the involvement of people with dementia in research: recognising diversity and promoting inclusive research" (24).

4.2.2 Categories of information for Informed Consent Forms (ICF)

The conditions for informed consent are outlined in Article 29 of the Clinical Trials Regulation (CTR), which states:

> *"Informed consent shall be written, dated and signed by the person performing the interview…and by the subject or, where the subject is not able to give informed consent, his or her legally-designated representative."*

In practice, informed consent is materialised using two documents: firstly, a patient information sheet (PIS), and secondly, an informed consent form (ICF). Although the CTR doesn't provide a specific template for ICF, it does identify key pieces of information that must be given to research participants to enable them to make an informed decision on participation. This information is usually provided in the PIS that accompanies the ICF, and must contain details on:

Discussion point: models of informed consent

An ethical risk identified for the EPAD project was the potential for participants to enter a "fish trap", where individuals find it hard to retreat from participation once they start along the route of involvement in a multifaceted, multi-stage study. *Which models of consent are best suited to ensure that participants are informed about the totality of multi-stage studies?*

1. The nature, objectives, benefits, implications, risks and inconveniences of the research
2. The subject's rights, in particular the right to refuse or withdraw from participation without any resulting detriment or having to provide justification
3. The expected conditions and duration of the clinical research study, as well as the follow-up measures if the study is discontinued
4. The EU clinical study registration number and information about the availability of results

Many PIS also contain information about data protection, particularly where consent is the legal basis for data processing under the GDPR (see Section 3.2.2 above). To comply with the GDPR, this information has to include the contact details of the data controller and data protection officer (DPO), information on what personal data will be collected, how and for what purpose, information on who will have access to the personal data and how the participant's data protection rights (e.g the right to correct or remove data) will be met. Importantly, ICF and PIS can also include provisions for the re-use of personal data for secondary research, which can have a big impact on whether or not data can be shared (see section 4.2.2 below).

Practical considerations for informed consent forms

Qualitative studies show that ICFs have become longer and more complicated over time, in an attempt to comply with increasingly stringent regulatory requirements on the one hand, and on the other hand, to ensure that ICFs reflect the fact that informed consent is an ongoing, dynamic process. However, this may have the undesired side-effect of making consent documentation harder to understand, decreasing the ability of potential participants to exercise autonomous decision-making. In particular, persons with NDD-associated cognitive impairment may find excessive information overwhelming, with important and relevant information getting lost amongst the technical and scientific details of research studies. A recent multi-country study of over 2000 research participants found that the most important categories of information are those dealing with the risks and benefits of the study (25). Informed decision-making could be supported by simplifying ICFs to bring these categories of information to the fore, using visual or memory aids, or using interactive approaches that engage family members or carers in the consent process. Patient and public involvement (PPI) during the drafting process for ICFs and PIS can also help tailor the content and layout of these documents to the target research participant audience, further enhancing the consent process.

Discussion point: enhancing inclusion with adapted ICFs
To respect the principles of fairness and equity, it is important that different participant groups have equitable opportunities to take part in research. *How can decision-making be appropriately supported in different communities – for example in less individualistic communities where decisions tend to be made by families?*

Informed consent templates

A number of recent initiatives have created ICF templates, aiming to streamline and simplify the ICF development process. For example, the IMI-funded DO->IT coordination and support action (CSA) supported four disease-specific big data projects under the "Big Data for Better Outcomes" banner, including ROADMAP. DO->IT generated a harmonised ICF template for clinical research, aiming to cover all information required by the GDPR and including provisions for secondary data use beyond the scope of the original research project (26). RD-CONNECT, a project funded under the FP7 framework programme that aimed to facilitate rare disease research, created a generic ICF template for longitudinal genomics studies (27). Finally, the Global Alliance for Genomics and Health (GA4GH) has created generic data sharing prospective consent documentation, aimed at enabling the secondary use of data (28). These openly-available templates will contribute to Working Group discussions within Neuronet on the development of a template ICF for ND research.

4.2.3 Informed Consent for data sharing and reuse

Recent qualitative studies have highlighted the willingness of research participants to share data. A 2018 survey of clinical trial participants found that fewer than 8% of the 771 respondents felt the potential negative consequences of data sharing outweighed the benefits (29). The desire to help others as much as possible was a dominant theme in the survey, with several respondents urging greater cooperation and less competition among researchers. An earlier focus group study of participants in the ACT aging and dementia cohort identified scientific advancement, research efficacy and health improvements as important outcomes from data sharing (30). Importantly, most participants didn't see data sharing as a reason NOT to participate in a study, with some saying that it would actually encourage them to sign up.

From both legal and ethical perspectives, informed consent forms and information sheets should address the possibility of future archiving (in data repositories, for example) and/or sharing of research data generated in clinical studies. However, it is not always possible to

provide specific details on all future uses of research data, as required using the single-study model of consent. This has led to the development of new and adapted consent models that aim to overcome this issue, whilst retaining a high level of protection against ethical risks.

"Broad" consent is one such model, providing researchers with the scope to use data (and biosamples) for a range of research studies without having to obtain new consent, subject to ethics oversight. From a legal perspective, Recital 33 of the GDPR is supportive of broad consent, stating:

> *"It is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection. Therefore, data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognised ethical standards for scientific research."*

Broad consent processes are therefore particularly suited to research studies that envisage data sharing and reuse, with the proviso that ongoing oversight is provided by a research ethics committee, for example. The Global Alliance for Genomics and Health (GA4GH) has developed a framework for responsible sharing of genomic and health data, complemented by consent recommendations for research and international data sharing involving persons with dementia (31). In these recommendations, GA4GH and coauthors indicate that broad consent (combined with ethical oversight) is a viable way to support autonomous decision-making whilst also facilitating scientific research for the common good.

5 Data protection and Ethics 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 best practice across IMI ND projects. Neuronet will also perform a mapping exercise of data access, informed consent and data protection policies of the IMI ND project portfolio, consulting with experts in the Neuronet Working Groups to develop templates and guidance documents based on these practices and policies. As well as providing an overview of the key data protection and ethical concepts for health research, this deliverable reports on the first step in this mapping process, providing an overview of the data protection and ethics work in IMI ND projects.

The IMI ND projects supported by Neuronet cover the full spectrum of research, from fundamental laboratory research on cells to applied, clinical research involving human research participants. Of note, clinical research or reuse of clinical datasets is a feature of all Neuronet-supported IMI ND projects apart from EQIPD, which has a specific focus on preclinical models of disease (still subject to particular legal and ethical requirements). For example, the PHAGO project is performing *in vitro* studies of TREM2 and CD33 (receptors that are thought to determine the function and behaviour of microglia) using induced pluripotent stem cells, but will also perform PET imaging on a small cohort of research participants who carry disease-causing mutations in TREM2 and CD33. In comparison, the AMYPAD project is entirely focused on clinical research, carrying out beta-amyloid PET scans on a large cohort of participants in the very early stages of AD – while the AETIONOMY project re-used and integrated -omics datasets from existing cohorts of research participants with AD or PD.

Results of preliminary mapping exercise

A keyword search of the deliverable titles 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 DoA available) was performed, using the following search terms: “ethics”, “ethical”, “privacy”, “data protection”, “POPD”, “ELSI”, “legal”. It should be noted that evaluation of the contents of these deliverables was not within the scope of this initial, preliminary survey. 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. To address this potential oversight, the extended mapping exercise will also incorporate discussions with the leaders of work packages that deal with patient privacy issues.

Unsurprisingly, our keyword search revealed that all projects have generated – or will generate – deliverables that deal with data protection and ethics, which highlights the importance of privacy considerations to IMI ND projects. For reasons of confidentiality, the lists of deliverables that were generated from the keyword searches cannot be made available here. Instead, we have mapped the key themes that are being addressed in the IMI ND project deliverables, listed in the table below:

KEY DELIVERABLE THEMES	PROJECT(S)
Data Protection: authorisations, data protection authority opinions, data protection frameworks	AETIONOMY, PRISM, RADAR-CNS, ROADMAP
Reports from Legal and Ethical Advisory Boards	AETIONOMY, PRISM, RADAR-AD, AMYPAD
Ethical codes of practice & ethical requirements	AETIONOMY, EMIF, ROADMAP
Forms and approvals for clinical Research Ethics Committees (REC)	AETIONOMY, ADAPTED, IM2PACT, PHAGO, PRISM, RADAR-AD
Informed consent forms and templates	AETIONOMY, 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, RADAR-CNS, RADAR-AD, ROADMAP
Ethics for animal research	EQIPD, IM2PACT, PHAGO
"ELSI issues"	EMIF, EPAD, MOPEAD, RADAR-AD, ROADMAP

Based on this preliminary thematic analysis, it appears 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 area in which further support would be helpful. Interestingly, “disclosure of results to participants” is a topic that is being addressed in ethics workpackages of the AMYPAD, EPAD and RADAR-AD projects, exploring some of the issues summarised in section 4.1.3 above. Finally, four projects have deliverables that are focused on the views of people affected by NDs, highlighting a growing appreciation of the value of PPI to research projects that involve human participants.

6 Conclusion

The advent of the Big Data era at the start of the 21st century, accompanied by technological advances in computing and informatics, has led to a sea change in neurodegenerative disease research. The benefits of Big Data are undeniable: high volumes of data can be turned into actionable knowledge for researchers, drug developers and clinicians, with the potential to transform healthcare systems and yield substantial improvements for patients and citizens.

However, these benefits do not come without risk. Patient datasets contain sensitive information that require a high level of protection, to ensure that data subjects are not exposed to ethical risks such as breach of confidentiality or social harm. Re-identification of individuals in the Big Data era is of particular concern; for example, each person's DNA sequence is unique and a DNA sample can arguably never be truly anonymised. Consequently, the last decade has seen the development of a more stringent regulatory environment for health research, materialised in the GDPR and CTR. Alongside, ethical frameworks have been extended and refined, taking into account some of the ethical concerns around Big Data. This dynamic legal and ethical environment can be a challenging one for research projects to navigate - particularly in projects such as those funded by the IMI, where data often needs to cross public-private boundaries, travelling through the EU and beyond.

One of Neuronet's goals is to help IMI ND projects navigate the ethical and data protection challenges that inevitably arise in health research projects that involve human participants. This deliverable charts the first step along that course. Here, we have provided an overview of the key data protection concepts for health research, identifying areas that could benefit from further discussion. These include controllership for multi-site clinical research studies, appropriate and/or harmonised measures for pseudonymisation and the choice of lawful basis for data processing. Alongside, we have summarised some of the key ethical requirements for health research, identifying areas for discussion on equitable participation, risk disclosure and consent for data sharing. Finally, we have reported on an initial survey of ELSI deliverables in IMI ND projects, which showed that almost all of the projects supported by Neuronet are working on data protection and ethical approvals, forms and authorisations, identifying a further area for discussion by our Patient Privacy and Ethics Working Group.

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