PROJECT
i-PROGNOSIS: Intelligent Parkinson early detection guiding novel supportive interventions

GRANT AGREEMENT No.
690494

D1.2 - First version of ethics and safety manual

CONTRACTUAL SUBMISSION DATE
July 2016

ACTUAL SUBMISSION DATE
July 2016

DELIVERABLE VERSION
7.0 (Final)

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 690494.

GRANT AGREEMENT No.	690494
PROJECT ACRONYM	i-PROGNOSIS
PROJECT FULL TITLE	Intelligent Parkinson early detection guiding novel supportive interventions
Type Of Action	Research & Innovation Action (RIA)
Topic	H2020-PHC-21-2015 - Advancing active and healthy ageing with ICT: Early risk detection and intervention
Start Of Project	1 February 2016
Duration	48 months
Project URL	www.i-prognosis.eu
EU Project Officer	Ramón Sanmartín Sola

DELIVERABLE TITLE	First version of ethics and safety manual
DELIVERABLE No.	D1.2
Deliverable Version	7.0
Deliverable Filename	i-PROGNOSIS-690494_D1.2.docx
Nature Of Deliverable	R (Report)
Dissemination Level	PU (Public)
Number Of Pages	69
Work Package	WP1 - Management
Partner Responsible	AUTH
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ABSTRACT

This deliverable presents a summarisation of international, European and national regulations and guidelines regarding ethical research issues, devices safety, and data management, with appropriate references. Moreover, a first plan for ethical and safety compliance, as well as identified concerns, are presented for the three data collection phases of the i-PROGNOSIS project, along with the general project

management of ethical issues and data control. The aim of this report is to constitute a reference manual regarding ethical, safety and data handling issues for the project consortium.

KEYWORDS

Certification; Compliance; Consent; Data management; Device safety; Directive; Europe; Guideline; International; National; Regulation; Research ethics; Standard

SIGNATURES

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LIST OF MAIN ABBREVIATIONS

AGA	Annotated model Grant Agreement
AUTH	Aristotle University of Thessaloniki
CRB	Centre for Research Ethics and Bioethics
CIOMS	Council of International Organizations of Medical Sciences
DESCA	Development of a simplified Consortium Agreement
DMP	Data Management Plan
EC	European Commission
eCF	electronic Consent Form
ECHR	European Convention on Human Rights
EDPS	European Data Protection Supervisor
eIC	electronic Informed Consent
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
FMH	Faculdade de Motricidade Humana
HRA	Health Research Authority
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISA	International Sociological Association
KCL	King's College London
KI	Karolinska Institutet
NA	New Approach
NHS	National Health System
REC	Research Ethics Committee
SME	Small and Medium-sized Enterprise
TUD	Technische Universität Dresden
UNESCO	United Nations Educational Scientific and Cultural Organization
WMA	World Medical Association

1 EXECUTIVE SUMMARY

During its life, the i-PROGNOSIS project will encapsulate multimodal data collection phases towards the development of early Parkinson's disease (PD) detection tests and novel supportive interventions. As the corner stone of these data collection phases are the individuals that will provide the data, special attention will be given on the compliance of the collection processes with ethical regulations and guidelines on research involving human beings, as well as on the safety of the sensor devices involved and the protection of personal and health data.

To this end, the present deliverable "D1.2 First version of ethics and safety manual" constitutes a reference guide for the i-PROGNOSIS investigators by reporting on the international, European and National ethical regulations, device safety standards and certifications, as well as accepted data management procedures. Moreover, this deliverable presents a first plan for the i-PROGNOSIS scheduled data collection to be compliant with the reported regulations and guidelines and evaluates potential concerns early in order to be mitigated effectively, through the proper management of ethical and data handling-related issues.

2 INTRODUCTION

2.1 RELEVANT PROJECT ASPECT

Within the i-PROGNOSIS project, three data collection periods are planned, i.e., the GData (generalised data) collection for the development of the first stage of PD detection (Task 6.2), the SData (specialised data) collection for the development of the second stage of PD detection (Task 6.3), and the interventions data collection for the development of the supportive interventions (Task 6.4). Each of these periods is preceded by a pilot data collection phase (Task 6.1) to test the functionality of the system and each one of them is accompanied by medical evaluation sessions to assess the efficacy of the developed technologies (Task 6.5).

One of the main goals of the ongoing Task 1.4 - *Ethical and Safety Management* is to evaluate the ethical feasibility and safety of the proposed PD detection and interventions applications and the respective data collection phases, based on the reviewed ethical, safety and data protection requirements applying in the respective host countries of the data collection studies. Moreover, in Task 1.4, appropriate and compliant procedures regarding the data collection phases will be established. The products of Task 1.4 will be two deliverables, i.e., a first version of the ethics and safety manual (present report) on month 6 of the project and prior to the beginning of all data collection phases and a final version of it on month 36, when all data collection phases will be unfolding.

2.2 PURPOSE OF DOCUMENT

The present deliverable D1.2 - *First version of ethics and safety manual* constitutes a reference guide for the i-PROGNOSIS investigators by reporting on the international,

European and national ethical regulations, devices safety standards and certifications, as well as proper data management procedures. Furthermore, this deliverable presents an early plan for the i-PROGNOSIS data collection to be ethically compliant, identifies potential concerns regarding aspects of the data collection phases and evaluates their significance, in order to mitigate them as early as possible in the project. At the end, the established i-PROGNOSIS management procedures and roles regarding ethical issues and data handling are presented. As the report is public, it can also serve as a reference guide for researchers conducting similar to i-PROGNOSIS data collection studies.

Ethical, safety and data management procedures reported here are subject to change based on the applications development and review of data collection protocols by the concerned ethics committees. Their final versions will be presented in D1.5 - *Final version of ethics and safety manual* (month 36).

2.3 DOCUMENT STRUCTURE

The present report is structured as follows: Section 3 presents the ethical regulations and guidelines categorised in three levels, i.e., International, European, and National level. This section also elaborates on the issue of the electronic informed consent, a new means of seeking informed consent for research studies. Section 4 reports on regulations and directives regarding medical devices safety and highlights the main standards and certifications for such devices. Section 5 is about the data protection, access, exchange and usage regulations and requirements. Based on the previous sections, Section 6 presents the actions to be taken for the i-PROGNOSIS three data collection phases to be compliant in terms of research ethics and device safety, as well as the data management procedures conforming to the appropriate requirements that will condition all of the three phases. Issues of concern are also defined and evaluated and a general procedure for managing adverse events is also described. Section 7 concludes the deliverable by presenting the management framework of ethical issues in the i-PROGNOSIS project. Finally, Appendix I includes a generic consent form that will be adapted to the needs of the SData and interventions data collection phases, whereas Appendix II provides a tentative check-list of ethical issues to be used by i-PROGNOSIS investigators during participants' enrolment in data collection phases.

3 ETHICAL REGULATIONS & GUIDELINES

3.1 INTERNATIONAL ETHICAL GUIDELINES

This section summarises international ethical regulations and guidelines applicable for medically-oriented research involving human subjects.

3.1.1 Declaration of Helsinki

The Declaration of Helsinki (World Medical Association, 2013) constitutes a statement on ethical guidelines regarding medical research that involves human subjects,

developed by the Word Medical Association (WMA). The key points of the Declaration of Helsinki (World Medical Association, 2013) are summarised below:

General principles

DH1. The health and well-being of patients involved in a medical research must be the first consideration of the researchers and it should be safeguarded by all means. To this end, medical research should be subjected to ethical standards to protect the subjects' health and rights.
DH2. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic, and therapeutic interventions.
DH3. Researchers must consider country-specific ethical, legal and regulatory norms as well as applicable international standards. To this end, researchers with appropriate ethics and scientific education must have a leading role in research studies involving human subjects.
DH4. Patients must not participate in research studies if the researchers have good reason to believe that their participation may have adverse effects on their health status. In such a case, harmed subjects must be compensated and treated appropriately.

Risks, burdens and benefits

DH5. Most interventions involve risks. As a result, medical research must only be conducted when the importance of the objectives outweighs the underlying risks. Researchers must *a priori* define the risks arising from the research and take mitigation measures.
DH6. If there is conclusive proof that the risks outweigh the potential benefits, at any point during the study, the researchers must assess whether to continue, modify or immediately stop the study.

Scientific requirements and research protocols

DH7. Medical research involving human subjects must conform to generally accepted scientific principles.
DH8. The design and performance of each research study must be described and justified in a research protocol. The protocol must include all the relevant information and a statement of the ethical considerations involved and how the principles of the Declaration of Helsinki have been addressed.

Research ethics committees

DH9. The research protocols must be submitted to the concerned research ethics committee for modifications and approval. The committee must be transparent in its functioning and review the research protocol by taking into consideration the laws and regulations of the country or countries in which the research is performed and all the relevant international ethical norms and standards.
DH10. The research ethics committee must have the right to monitor the ongoing research study based on information provided by the researchers. No changes

must be made to the research protocol without knowledge and approval by the committee. Researchers must submit a final report containing a summary of the study and its outcomes to the committee.

Privacy and confidentiality

DH11. All the necessary precautions must be taken to ensure the privacy of the research subjects and the confidentiality of their personal information.

Informed consent

DH12. Participation of individuals capable of giving informed consent must be voluntary. Individuals capable of giving informed consent must be provided with all the relevant information about the study prior to participating, as well as be informed on their rights to refuse to participate and to withdraw their consent without consequence.
DH13. Provided that the potential subject has assimilated the information, the researcher must seek for the subject's freely-given informed consent in writing or through another documented and witnessed way. The researcher seeking for the subject's consent must not be related to the subject.
DH14. Medical research subjects must be given the option of being informed on the general outcomes of the study.
DH15. For individuals incapable of giving informed consent, the consent must sought by the legally authorised representative. The researcher must also seek for the assent of the individual, if the individual can give it, and respect a potential dissent. These individuals must be considered for participating in a study only when certain conditions apply, i.e., the research intends to promote the health of the individual's group, the research cannot be performed with other individuals, and the risks and burdens of the study are minimised.
DH16. Researchers can proceed to include an individual incapable of giving informed consent and without a legally authorised representative, if there is detailed justification on the reasons why in the research protocol and that protocol has been approved by the concerned research ethics committee. Nevertheless, if circumstances change, the consent must be sought as soon as possible during the study.

Use of placebo

DH17. New interventions must be evaluated against best proven interventions, except when no proven intervention exists or when the use of additional interventions may affect the efficacy or safety of the new intervention based on compelling and sound methodological reasons or when patients may be subject to additional risks and irreversible harm.

Post-trial provisions

DH18. Sponsors of research studies, researchers, and host country governments must reassure that participant have access to potentially benefiting interventions post-trial. The latter must be disclosed to the participants during the informed consent process.

Research registration and publication and dissemination of results

DH19. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

DH20. All involved parties in the publication and dissemination of results are ethically obliged with regard to the publication and dissemination of results. Outcomes of a research study, positive, negative or inconclusive, must be published or made publicly available. Reports on research not in accordance with the principles of the Declaration of Helsinki must not be accepted for publication.

Unproven interventions in clinical practice

DH21. Unproven interventions may be used by a physician when it offers hope of saving life, re-establishing health or alleviating suffering. Informed consent given either by the individual or the authorised representative must precede the use. The unproven intervention should subsequently become the object of research targeting the evaluation of its safety and efficacy.

The numbering above is used for reference purposes within this document and does not necessarily reflect the numbering of principles in the Declaration of Helsinki. For the detailed guidelines, the reader is referred to the Declaration of Helsinki full publication (World Medical Association, 2013) that is also available online[1].

3.1.2 CIOMS Guidelines for Biomedical Research

The Council of International Organizations of Medical Sciences (CIOMS) has produced a series of international ethical guidelines for biomedical research involving human subjects with the collaboration of the World Health Organization (WHO). The key points of the third in the series (Council for International Organizations of Medical Sciences, 2002) that are also related to the i-PROGNOSIS project are provided below:

General ethical principles

Three general ethical principles are defined: i) respect for persons' autonomy and protection of persons with impaired autonomy (*Respect for persons*); ii) maximisation of benefit and minimisation of harm (*Beneficence*); iii) treat each person in accordance with what is morally right and proper (*Justice*).

Guidelines

G1. The research involving human beings must be ethically justified and scientifically validated.

G2. Proposals to conduct research involving human beings must be submitted for review by one or more scientific and ethical review committees (related to DH9 of the previous section).

[1] Declaration of Helsinki (WMA, 2013)
http://jama.jamanetwork.com/article.aspx?articleid=1760318

G3. The external sponsor and the individual researchers must submit the research protocol for review by a local or national ethics committee in the country of the sponsor.

G4. The researcher must obtain informed consent of the prospective participant in the study or her/his authorised representative (related to DH13 of the previous section). Waiver of informed consent is regarded uncommon and it must be approved by an ethical committee (related to DH16 of the previous section).

G5. The researcher must provide the prospective participants with detailed information about the study and her/his rights - the complete list of the parts of the information can be found in p. 39 of the guidelines of the Council for International Organizations of Medical Sciences, 2002 (related to DH12 of the previous section)

G6. Researchers and sponsors have a duty to: refrain from unjustified deception, influence or intimidation; seek consent after ascertaining that the individual has assimilated the information; obtain a signed form as evidence of informed consent or justify the lack of, which must be further approved by the concerned ethics committee; renew the consent form if changes are made to the study or at predetermined intervals of a long-term study even if there are no changes.

G7. Subjects participating in a research study may be reimbursed, be paid or receive medical services for free (related to DH18 of the previous section). The latter must be approved by the ethical committee.

G8. For all biomedical research involving human subjects, the researcher must ensure that potential benefits and risks are reasonably balanced and risks are minimised (related to DH5 and DH6 of the previous section).

G9. When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons.

G10. When conducting research in populations and communities with limited resources, the sponsor and the researcher must ensure to highest possible extent that the research is responsive to the needs of the population or community and any product developed will be made reasonably available for the benefit of the population or the community.

G11. Subjects in the controls group of a research study must receive an established effective intervention as a general rule. Ethical acceptable exceptions may apply (related to DH17 of the previous section).

G12. Groups or communities to be invited to be subjects of research should be selected in such a way that the burdens and benefits of the research will be equitably distributed. The exclusion of groups or communities that might benefit from study participation must be justified.

G13. Special justification is required for inviting vulnerable individuals to serve as research subjects and, if they are selected, the means of protecting their rights and welfare must be strictly applied.

G14. Guideline 14 refers to research involving children and it is irrelevant to the i-PORGNOSIS project.

G15. The researchers must reassure that certain conditions apply prior to undertaking research involving individuals incapable of giving informed consent. The list of conditions can be found in p. 70 of the guidelines of the Council for International Organizations of Medical Sciences, 2002 and relate to DH15 and DH16 of the previous section.

G16. Ethics committees, researchers or sponsors must not exclude women of reproductive age from biomedical research. The potential risks on her pregnancy and her foetus, must be discussed with the woman, in case she becomes pregnant during the research study.

G17. Researchers and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the foetus and their subsequent offspring, as well as to their fertility.

G18. The researcher must establish secure safeguards of the confidentiality of subjects' research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality (related to DH11 of previous section).

G19. Researchers should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would equitably compensate them for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependants are entitled to compensation. Subjects must not be asked to waive the right to compensation.

G20. In externally sponsored collaborative research, sponsors and researchers are ethically obliged to strengthen the capacity for ethical and scientific review and biomedical research in host countries that lack such capacity.

G21. External sponsors are ethically obligated to provide health-care services that are essential for the safe conduct of the study, as treatment for subjects that suffered injuries during the study, or as part of the commitment of the sponsor to make a beneficial product from the study, reasonably available to the population or community concerned.

For the detailed guidelines the reader is referred to the full publication of the International Guidelines on Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences, 2002) that is also available online[2].

3.1.3 Universal Declaration on Bioethics and Human Rights

The Universal Declaration on Bioethics and Human Rights (UNESCO, 2005) constitutes a compilation of ethical guidelines regarding medicine, life sciences and technologies as applied to human beings. It was produced by the United Nations

[2] International ethical guidelines for biomedical research involving human subjects (CIOMS, 2002) http://www.cioms.ch/publications/layout_guide2002.pdf

Educational Scientific and Cultural Organization (UNESCO) in the context of its Bioethics Program. The main points of the declaration are summarised below:

UN1. Human rights are to be fully respected and the interest and welfare of individuals are priorities over the sole interest of science or society.
UN2. Benefits regarding individuals participating in research must be maximised and harm must be minimised (related to DH5, DH6, and G8 of the previous sections).
UN3. The autonomy of individuals should be respected. For persons incapable of exercising autonomy, special measures should be taken.
UN4. Voluntary informed consent must be acquired by the concerned individuals prior to the conduct of interventions or research studies (related to DH13 and G4 of the previous sections). For research carried out on a group of people or a community, additional agreement of the legal representatives of the group or the community must be sought.
UN5. Individuals incapable of given informed consent must be included in research studies in accordance of the best interest of the concerned individual and in accordance to the domestic law. Research carried out on such individuals, provided that here is no research alternative, must have direct benefit for them or, otherwise, create minimal risk or burden (related to G9 of the previous section).
UN6. Research studies must respect human vulnerability and personal integrity.
UN7. The privacy of the individuals concerned and their personal information must be respected to greatest possible extent and in accordance to the international human rights law (related to DH11 of previous section).
UN8. Individuals concerned must be treated justly and equitably. No group of individuals must be discriminated against others or stigmatised. Cultural diversity and pluralism should be given due regard, unless, such considerations infringe upon human rights.
UN9. Solidarity among human beings and international cooperation towards such end should be encouraged. Research and advances in technology should aim to promote health and social development - the complete list of axes are included in Article 14 of the declaration (UNESCO, 2005).
UN10. Benefits resulting from any scientific research and its applications should be shared with society as a whole and within the international community (related to DH18 of previous section) - the complete list on the nature of such benefits is included in Article 15 of the declaration (UNESCO, 2005).
UN11. The impact of life sciences on future generations, including on their genetic constitution, should be given due regard.
UN12. Research conducted must pay due respect to environmental issues, the biosphere and biodiversity.
UN13. Professionalism, integrity and transparency must govern decision-making and addressing of bioethics issues and persons or professionals concerned should be engaged in such debates.
UN14. Independent, multidisciplinary and pluralist ethics committees should review research studies, scientific and technological developments and foster public awareness of bioethics (related to DH9 and G2 of previous sections).

UN15. Transnational research pursued in a State(s) and funded by another State(s) must comply with the bioethics requirements of both the host State and the State of the funding source.

The complete list of articles of the declaration can be found in the full publication of the declaration (UNESCO, 2005) which is available online[3].

The compilations of guidelines presented in the previous sections constitute the most prominent reference documents regarding ethical guidelines that are acceptable worldwide. In the following sections, Europe-specific and national regulations are presented.

3.2 EUROPEAN REGULATIONS & DIRECTIVES

3.2.1 Research Ethics

There are mainly three horizontal texts that govern ethics at EU level:

EU1. *The Charter of Fundamental Rights of the European Union*[4] which recognises a range of personal, civil, political, economic and social rights. The Lisbon Treaty incorporates the Charter into the Treaty on the European Union, giving the charter an equal legal effect, and states that all European legislation needs to conform to the principles of the Charter. Consequently, this also applies to the European research policy. Key articles of the Charter are:
- ❖ Article 3 – Right to the integrity of the person;
- ❖ Article 7 – Respect for private and family life;
- ❖ Article 8 – Protection of Personal Data;
- ❖ Article 13 – Freedom of the Arts and Sciences.

EU2. *The European Convention on Human Rights (ECHR),* which is an international treaty to protect human rights and fundamental freedoms in Europe. The EU is legally bound to the ECHR[5].

EU3. *The European Directive 2001/20/EC*[6]*,* which sets out regulative and administrative provisions with regard to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

3.2.2 Ethics & Data Protection at EU level

At EU level, the key instruments are the Data Protection Regulation and Directive which have recently been revised in order to better take into account the digitalisation of the society (see also Section 5.1 for more details). The new

[3] Universal Declaration on Bioethics and Human Rights (UNESCO, 2005) http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html

[4] The Charter of Fundamental Rights of the European Union http://www.europarl.europa.eu/charter/pdf/text_en.pdf

[5] The European Convention on Human Rights http://www.coe.int/t/dghl/standardsetting/hrpolicy/accession/default_EN.asp

[6] EU Directive 2001/20/EC http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF

instruments have been published in the EU Official Journal on 4 May 2016. In particular:

EU4. *Regulation (EU) 2016/679*[7] of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC[8] (General Data Protection Regulation). The Regulation will enter into force on 24 May 2016 and it shall apply from 25 May 2018.

EU5. *Directive (EU) 2016/680*[9] of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data by competent authorities for the purposes of the prevention, investigation, detection or prosecution of criminal offences or the execution of criminal penalties, and on the free movement of such data, and repealing Council Framework Decision 2008/977/JHA. The Directive enters into force on 5 May 2016 and EU Member States have to transpose it into their national law by 6 May 2018.

The European Commission (EC) has made available a wide range of tools[10] to inform about the added value of the new instruments and the main changes. According to the EC, the scope of the new instruments is[11]:

"The Regulation updates and modernises the principles enshrined in the 1995 Data Protection Directive to guarantee privacy rights. It focuses on: reinforcing individuals' rights, strengthening the EU internal market, ensuring stronger enforcement of the rules, streamlining international transfers of personal data and setting global data protection standards.

The changes will give people more control over their personal data and make it easier to access it. They are designed to make sure that people's personal information is protected – no matter where it is sent, processed or stored – even outside the EU, as may often be the case on the internet."

Moreover, the key points highlighted by the EC for citizens and business - small and medium-sized enterprises (SMEs) are:

Citizens

- A right "to be forgotten"

[7] EU Regulation 2016/679 http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.119.01.0001.01.ENG&toc=OJ:L:2016:119:TOC
[8] EU Directive 95/46/EC http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML
[9] EU Directive 2016/680 http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32016L0680
[10] EC on the new instruments regarding data protection http://ec.europa.eu/justice/data-protection/reform/index_en.htm
[11] Questions and Answers - Data protection reform http://europa.eu/rapid/press-release_MEMO-15-6385_en.htm

- Easier access to one's data: Individuals will have more information on how their data is processed and this information should be available in a clear and understandable way. A right to data portability will make it easier for individuals to transmit personal data between service providers.
- The right to know when one's data have been hacked: Companies and organisations must notify the national supervisory authority of data breaches which put individuals at risk and communicate to the data subject all high risk breaches as soon as possible so that users can take appropriate measures.
- Data protection by design and by default
- Stronger enforcement of the rules: data protection authorities will be able to fine companies who do not comply with EU rules up to 4% of their global annual turnover.

Business and SMEs:

- One continent, one law: a single, pan-European law for data protection, replacing the current inconsistent patchwork of national laws. Companies will deal with one law, not 28.
- One-stop-shop: a 'one-stop-shop' for businesses: companies will only have to deal with one single supervisory authority, not 28, making it simpler and cheaper for companies to do business in the EU.
- The same rules for all companies – regardless of where they are established
- Technological neutrality.
- SMEs do not need to appoint a data protection officer unless their core activities require regular and systematic monitoring of the data subjects on a large scale or if they process special categories of personal data, such as that revealing racial or ethnic origin or religious beliefs.
- SMEs do not to keep records of processing activities, unless the processing they carry out is not occasional or likely to result in a risk for the rights and freedoms of data subject.
- SMEs will not be under an obligation to report all data breaches to individuals, unless the breaches represent a high risk for their rights and freedoms.

EU6. There is also a Directive (97/66/EC[12]) that concerns the processing of personal data and the protection of privacy in the telecommunications sector which applies to telephony services only.

EU7. The Commission has also published in December 2012 a staff working document[13] (non-binding legislative instrument) that refers to the application of Data protection rules to telemedicine. i-PROGNOSIS is not directly concerned since telemedicine refers to healthcare services delivered through the use of information and communications technology (ICT), such as teleradiology, teleconsultation or telemonitoring. Although important for i-

[12] EU Directive 97/66/EC http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31997L0066:EN:HTML

[13] EC Staff Working Document on data protection and telemedicine https://ec.europa.eu/digital-single-market/en/news/commission-staff-working-document-applicability-existing-eu-legal-framework-telemedicine

PROGNOSIS, it is not directly covering mHealth applications, such as the ones that will be developed.

3.2.3 The specific case of mHealth

"mHealth or mobile health is a medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices"(Kay, Santos & Takane, 2011, p. 6)

On 10 April 2014 the European Commission published a Green Paper on mobile health (hereafter "mHealth") which launched a public consultation, open until 10 July 2014, in which it invited stakeholders to provide their views on 11 identified barriers to the uptake of mHealth in the EU: data protection, privacy, safety and ethics were among the topics.

Following the consultation, a process was launched to develop tools that will facilitate the implementation of the EU legislation on data protection to the new challenges raised by mHealth. Since it has started before the final adoption of the new regulation and directive, it still refers to the "old" piece of legislation, but will most probably be aligned[14]. Considering the framework of i-PROGNOSIS, this on-going process is highly relevant.

It was agreed that the most appropriate solution would be for the industry to set up a code of conduct on mHealth. The process has been facilitated by the European Commission and involved the different stakeholders.

EU8. *The Code of Conduct on privacy for mobile health apps*[15] was submitted to the Art 29 Data Protection Working Party. This Working Party is actually an independent EU advisory group on the protection of individuals with regard to the processing of personal data and on the free movement of such data, it has been set up under the Directive 95/46/EC[16], i.e., the "old" EU legislation on data protection. The Code is meant to raise awareness on data protection rules regarding mHealth applications as well as to facilitate and increase compliance at EU level for application developers, who will be able to voluntary commit themselves to follow the Code's rules. Issues covered in the document notably include users' consent; data subjects' rights and information requirements; security measures and the use of personal data for secondary purposes. The issues covered by the Code are:

- user's consent,
- purpose limitation and data minimisation,
- privacy by design and by default,
- data subjects rights and information requirements,
- data retention,

[14] EU Code of Conduct on privacy for mHealth apps https://ec.europa.eu/digital-single-market/en/news/code-conduct-privacy-mhealth-apps-has-been-finalised

[15] The draft Code of Conduct for privacy for mobile health apps https://ec.europa.eu/digital-single-market/en/news/mhealth-ehealth-week-2016

[16] EU Directive 95/46/EC http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV%3Al14012

- ❖ security measures,
- ❖ principles on advertising in mHealth applications,
- ❖ use of personal data for secondary purposes,
- ❖ disclosing data to third parties for processing operations,
- ❖ data transfers,
- ❖ personal data breach, and
- ❖ data gathered from children.

The decision of the Art.29 *Data Protection Working Party* is pending, nonetheless the work related to the governance and implementation of the code has started.

EU9. Last but not least, it is interesting to also refer to the work conducted by the European Union Agency for Network and Information Security, a centre of expertise based in Greece, which works with and support both the EU and the Member States. It has extensively worked on data protection, amongst others, in relation to mobile and online products[17].

3.3 NATIONAL REGULATIONS

This section provides an epitomised overview of the ethical regulatory framework in each country, where partners of the i-PROGNOSIS project reside and where a significant amount of data will be collected for the scopes of the project. It must be noted *a priori* that national legislation in all cases is harmonised with international guidelines and key EU regulations such as the Directive 2001/20/EC. Additionally, the new regulations and directives concerning data protection (Section 3.2.2) are expected to be applied and transposed, respectively, at national level.

3.3.1 Belgium

The Belgian laws and royal decrees related to pharmaceutical and medical device research involving human subjects are published by the Federal Agency for Medicines and Health Products (FAMHP). The Belgian regulations integrate the transposition of:

BE1. *The European Directive on Clinical Trials on Medicinal Products* 2001/20/EC (see Section 3.2.1), setting out how those trials must be conducted; it has been transposed in the Belgian law regarding research on human subjects - 7/5/2004.

BE2. *The European Directive on Medical Devices* 93/42/EEC (see Section 4.1.2).

BE3. All studies must be submitted to an accredited REC, normally operating at the hospital of the national coordinator.

The accredited REC is the leading ethics committee, by coordinating the opinion of the local ethics committee of each participating site. Currently, there are around 215 local ethics committees, the majority being associated with hospitals. The Leading Ethical Committee will provide a single opinion within 28 days (15 days for the phase

[17] European Union Agency for Network and Information Security
https://www.enisa.europa.eu/topics/data-protection/online-and-mobile-data-protection

1 trials) with the possibility of one clock stop for questions. RECs and clinical trials abide by:

BE4. *The law dated 7th May 2004*[18]*,* related to experiments on human people that was further modified by a series of laws[19].

BE5. *The Royal decree dated 4th April 2014*[20]*,* determining the measures for carrying out the aforementioned law relating to experiments on human people.

The FAMHP has also published guidelines[21] for ethical committees and investigators relating to the conduct of exploratory (phase 0) trials in Belgium.

As for any other EU Member States, Belgium has started working on the transposition of the new EU regulation and directive on data protection. Until the end of this process, the current legislative framework applies, i.e.:

BE6. *The Privacy Act (8 December 1992) on the protection of privacy in relation to the processing of personal data* aims to protect individuals against abuse of their personal data[22]*:* An independent supervisory authority, Commission for the Protection of Privacy[23], ensures that personal data are used and protected with due care, so that citizens' privacy remains safeguarded. This act has been modified over the year notably to comply with the EU legislation, but also to better take into account the digitalisation of the society.

3.3.2 Germany

In Germany, the ethical regulatory framework is harmonised with international guidelines and European directives. In particular:

DE1. Research involving humans needs to be conducted according to the Declaration of Helsinki (Section 3.1.1).

DE2. Ethical approval for every relevant study in Germany is obligatory.

DE3. Research is differentiated in three main themes and for each a different ethical approval is necessary. The three main themes of research are:

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[18] Belgian Law 7th May 2004 http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=2004050732&table_name=loi (*in French*)

[19] Modifications of Belgian Law 7th May 2004 http://www.fagg-afmps.be/en/human_use/medicines/medicines/research_development/ethic_committee

[20] Belgian Royal decree dated 4th April 2014 http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=fr&la=F&cn=2014040446&table_name=loi (*in French*)

[21] FAMHP Guidelines http://www.fagg-afmps.be/sites/default/files/downloads/Guideline%20for%20exploratory%20clinical%20trials%20in%20Belgium%20v2%202012.pdf

[22] Belgian Privacy Act (8 December 1992) https://www.privacycommission.be/sites/privacycommission/files/documents/Privacy_Act_1992.pdf

[23] Belgian Commission for the Protection of Privacy https://www.privacycommission.be/en

a. Research studies under the German Pharmaceutical Act ("Arzneimittelgesetz")[24]
b. Research studies under the Medicinal Devices Act ("Medizinproduktegesetz")[25]
c. Research studies under the Paragraph 15 Science of the Medical Association's professional code of conduct of Saxony of the 24th of June 1998 ("Berufsordnung der Sächsischen Landesärztekammer, 1998")[26].

Germany has a total of 53 research ethics committees (RECs), 33 attached to Faculties of Medicine/Universities, 17 attached to Medical Associations ("Ärztekammern") in the States and 3 attached to States governments. These RECs are the only legally competent ethics committees to assess all kind of biomedical research including drug research. For studies performed by an investigator attached to a university, the REC of the Faculty of Medicine or of that University is entitled to assess the research. For studies carried out by an investigator outside a university, the REC of the regional Medical Association ("Ärztekammer") is legally competent.

TUD, partner of the i-PROGNOSIS project, can obtain ethical approval through the ethical committee of the Technical University Dresden ("Ethikkommission an der TU Dresden"), based on Paragraph 15 Science of the Medical Association's professional code of conduct of Saxony of the 24th of June 1998 (Berufsordnung der Sächsischen Landesärztekammer, 1998). The ethical committee of the Technical University Dresden is registered as institutional review board (IRB) at the Office for Human Research Protections (registration number: IRB00001473 and IORG0001076).

The application for ethical approval has to contain a covering letter, a study protocol, participant information and consent form. In particular:

DE4. The covering letter has to contain the sponsor protocol number, the title of the trial and should draw attention to any special issues related to the application.
DE5. The study protocol should comply with the guidance of the International Council for Harmonisation[27] (ICH) on Good Clinical Practice (CPMP/ICH/135/95)[28]. The content, format and procedures of the study protocol should comply with Article 8 of Directive 2005/28/EC[29] and the ICH guideline on Good Clinical Practice (CPMP/ICH/135/95). It should be identified by the title, a sponsor's protocol number specific for all versions of it, a

[24] Research studies under the German Pharmaceutical Act https://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf (*in German*)
[25] Research studies under the Medicinal Devices Act https://www.gesetze-im-internet.de/bundesrecht/mpg/gesamt.pdf (*in German*)
[26] Research studies under the Paragraph 15 Science of the Medical Association's professional code of conduct of Saxony of the 24th of June 1998 https://www.slaek.de/media/dokumente/04presse/aerzteblatt/archiv/2006/01/berufsord.pdf (*in German*)
[27] International Council for Harmonisation http://www.ich.org/home.html
[28] CPMP/ICH/135/95 http://ec.europa.eu/health/files/eudralex/vol-10/3cc1aen_en.pdf
[29] EU Directive 2005/28/EC http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF

number and date of version that will be updated when it is amended and by any short title or name assigned to it. The study protocol should be signed by the sponsor and principal investigator (or co-ordinating investigator for multicentre trials). Furthermore, it should describe:

- ❖ the content and procedures of the project based on all available information and evidence of the state of the art of science;
- ❖ include information regarding the sponsor, funding, institutional affiliations, potential conflicts of interest;
- ❖ incentives for subjects and information regarding provisions for compensating subjects who are harmed as a consequence of participation in the research study; and
- ❖ a definition of the end of the trial.

DE6. Participants should be informed about the study aim and content, methods and procedures, anticipated benefits and potential risks by a researcher involved in the study project. This should be performed in a manner and using language that participants understand in a written and oral form with the help of a participant information document. Afterwards, the participant should be able to make an informed decision about participation in the study. Furthermore, participation must be voluntary and participants must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal.

DE7. After ensuring that the potential participant has understood the information, the researcher or another appropriately qualified individual will seek the potential subject's freely-given informed consent in writing in a participant consent form (signature, date, and place).

Concerning the handling of personal information, Germany aims to protect people from having their privacy violated when personal data is processed:

DE8. For clinical trials the *German Data Protection Act*[30] ("Bundesdatenschutzgesetz"), especially Sections 3a, 28 and 40 cover the collection, recording, storage, processing, distribution, extinction of personal data. Additionally, Section 40 Paragraph 2 of the German Data Protection Act regulates the need of anonymisation of personal information as far it is reasonable in connection with the research project. The dissemination of personal data needs explicit consent of the participants.

3.3.3 Greece

In Greece, the National Bioethics Commission[31] (Εθνική Επιτροπή Βιοηθικής), established under the Act 2667/1998[32] and according to Directive 2001/20/EC (see Section 3.2.1), is the highest level bioethics committee of the State that has mainly an

[30] German Data Protection Act http://www.gesetze-im-internet.de/englisch_bdsg/federal_data_protection_act.pdf

[31] National Bioethics Commission (Greece) http://www.bioethics.gr/

[32] Greek Republic Gazette No. 281 on Act 2667/1998 https://nomoi.info/%CE%A6%CE%95%CE%9A-%CE%91-281-1998-%CF%83%CE%B5%CE%BB-1.html (*Automatic English translation available*)

advisory role. Research protocols are reviewed by local research ethics committees (RECs) of the institutions (hospital, research centre or higher education institution) in which the research study is planned to be conducted. In case of hospitals where there is no committee, scientific councils have the corresponding responsibilities.

The National Bioethics Commission has further published guidelines[33] for local RECs relating to and summarising the regulatory and legal framework (described below) based on which they should function. The Commission has also published an epitomised code of research ethics for biological sciences[34] based on international declarations and conventions, European directives - presented in previous sections - and national law (below).

In Greece, the regulatory framework regarding research ethics is harmonised with European directives and international guidelines and it includes mainly the following acts and decisions[35]:

GR1. *Act 3418/2005 - Code of Medical Ethics and Deontology*[36]: According to this Act, the following articles give directions on ethics concerning clinical trials and related issues. According to Article 25, clinical research for new medications or application of new monitoring methods is allowed only if:

- The specifications of the clinical research abide with the specifications and processes that are defined by the respective authorities of the EU.
- There are strong indications that the use of the application will increase the possibility of survival, or health recovery, or generally improve the health of population.
- Moreover, if the subject does not want to participate in the related programme or use the device, the researcher should respect his/her opinion without influencing in any manner the trustful relationship between the researcher and the subject.
- The researcher should not also apply new methods or diagnostic devices to subjects if s/he does not know for sure the consequences of use of these methods or devices. S/he should use them only for the benefits of patients.

According to Article 26, the following directions are given:

- It is allowed to conduct biomedical research and clinical research on human beings with the prerequisite that the researcher follows, as guiding principle, the protection of human life and the dignity of human being.

[33] Greek National Bioethics Commission Guidelines http://www.bioethics.gr/images/pdf/ENGLISH/OPINIONS_REPORTS/guide.pdf

[34] Greek National Bioethics Commission Code of Research Ethics for biological sciences http://www.bioethics.gr/images/pdf/ENGLISH/OPINIONS_REPORTS/research_ethics_code.pdf

[35] European Network of Research Ethics Committees: Greek Legislation http://www.eurecnet.org/legislation/greece.html

[36] Greek Republic Gazette No. 287 on Act 3418/2005 https://nomoi.info/%CE%A6%CE%95%CE%9A-%CE%91-287-2005-%CF%83%CE%B5%CE%BB-1.html (*Automatic English translation available*)

- ❖ No other kind of interchange is allowed in order to conduct the research except for the purpose of the research.
- ❖ The medical research and clinical trial should be stopped if the extension of the research becomes dangerous for the health of the human being.
- ❖ Researchers should make it open and clear that the results of their research concerning the use of biomedicine tools and methods to the medical community. Before making these results available to the public, they should discuss and listen to the opinion of their colleagues.
- ❖ Researchers should also mention the company or institute that has technically helped or has provided financial help to the research. Researchers may also mention people/colleagues who have helped within the research.
- ❖ Researchers, who are responsible for issuing of medical magazines, should investigate the correctness and the rules that were followed for the result of each medical practice and research.

GR2. *Act 2472/1997 - Data Protection*[37]: The scope of the Act is to establish the terms and conditions under which the processing of personal data is to be carried out, so as to respect the fundamental rights and freedoms of natural persons and, in particular, their right to privacy. According to the National Bioethics Commission guidelines, special attention is given on the following articles of the Act:

- ❖ Article 4 states the provisions in order for personal data to be lawfully processed.
- ❖ Article 5 states that personal data is permitted to be processed only when the data subject has given his/her consent.
- ❖ Article 6 states that the controller of data must notify the Personal Data Protection Authority about the commencement of data processing.
- ❖ Article 7 states that the collection and processing of sensitive data is prohibited unless exceptions apply, including the processing of such data for research and scientific purposes.
- ❖ Article 7a states the types of data controllers that are exempted from the obligations imposed from Articles 6 and 7, including medical personnel and doctors.
- ❖ Article 8 states the terms and conditions for permitting the interconnection of files.
- ❖ Article 9 sets out the conditions and between which entities the transfer of personal data is permitted.
- ❖ Article 10 states that the processing of personal data should be confidential and take place securely.
- ❖ Article 11 states that the controller of data must inform the data subject about his/her identity, the purpose of data processing, the recipients of data and the existence of a right to access.

[37] Greek Act 2472/1997
http://www.dpa.gr/pls/portal/docs/PAGE/APDPX/ENGLISH_INDEX/LEGAL%20FRAMEWORK/LAW%202472-97-APRIL010-EN%20_2_.PDF

- ❖ Article 12 states that every data subject is entitled to the right to access information about their data and the way they are processed.
- ❖ Article 13 states that the data subject is entitled to the right to object at any time to the processing of data relating to him/her.

GR3. *Act 2619/1998 - Ratification of the Oviedo Convention*[38]: This Act has been introduced to ratify the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the application of Biology and Medicine[39], also known as the Oviedo Convention. According to the National Bioethics Commission guidelines, special attention is given on the following guidelines of the Oviedo Convention:

- ❖ Article 15 that presents the terms and conditions for including subjects that are not able to consent to research.
- ❖ Article 16 that presents the terms and conditions regarding the information provided to the authorised legal representative in order for him/her to authorise the participation of a person incapable of given consent in a research study.
- ❖ Article 17 stating that the research carried on persons incapable of giving consent must be of minimal risk and minimal burden.

GR4. *Ministerial Decision DYG3/89292/31.12.2003*[40]: The Decision has been introduced to incorporate the 2001/20/EC Directive relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (see Section 3.2.1) into the domestic law.

GR5. *Additional legislation and regulations*: An informative guide[41] on the procedures for the ethical review and approval of research studies conducted in Greece has been compiled by the European Forum of Good Clinical Practice (EFGCP) in 2012.

AUTH, coordinator and partner of the i-PROGNOSIS project, has its own REC that reviews research protocols planned to be conducted by the institution, i.e., the Bioethics Committee of the AUTH Medical School. Prior to approving a research study involving human subjects, the Bioethics Committee requires the following for review[42]:

GR6. A detailed research protocol.

GR7. The document that will be used to inform candidate research participants.

[38] Greek Republic Gazette No. 132 on Act 2619/1998
https://nomoi.info/%CE%A6%CE%95%CE%9A-%CE%91-132-1998-%CF%83%CE%B5%CE%BB-1.html (*Automatic English translation available*)

[39] Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the application of Biology and Medicine
https://www.coe.int/en/web/conventions/full-list/-/conventions/rms/090000168007cf98

[40] Greek Republic Gazette No. 390 on Ministerial Decision DYG3/89292/31.12.2003
http://www.1dype.gov.gr/wp-content/uploads/2014/10/fek390-klinikes-meletes.pdf (*in Greek*)

[41] European Forum of Good Clinical Practice Guide
http://www.efgcp.eu/Downloads/EFGCPReportFiles/Greece%20definitive%20Updated.pdf

[42] AUTH Bioethics Committee requirements
http://www.med.auth.gr/gram/docs/proypothesi_egkrisis_diatribis.doc (*in Greek*)

GR8. Informed consent documents proving that research participants or their legal representatives participate voluntarily or authorised the participation of a person, respectively, in the research study, after being informed with every detail regarding the scope and nature of the study, as well as its risks.

3.3.4 Portugal

In Portugal, a Bioethics Committee at national level, named "Conselho Nacional de Ética para as Ciências da Vida" (CNECV) [National Ethics Council for the Life Sciences] was created by the Law No. 14/90, of 9th June. In May 29th 2009, the Law No. 24/2009 has been enacted. In general, the CNECV is an independent consulting body that works with the Parliament and whose mission is to analyse the ethical issues raised by scientific progress in the fields of biology, medicine or health (in general) and life sciences.

The Portuguese regulatory framework includes:

PT1. The Law 46/2004 of 19 August 2004, which incorporates the principles of the Clinical Trials Directive 2001/20/EC and creates the "Comissão de Ética para a Investigação Clínica" (CEIC) [National Ethics Committee for Clinical Research], was repealed by a new Law (i.e., Law 21/2014 of April 16). In fact, the Law 21/2014 of 16 April covers all clinical research with humans including not only clinical trials with medicinal products for human use but also studies with medical devices, cosmetics, food supplements and all kind of observational studies[43]. At the same time, this Law creates the National Ethics Committees Network, coordinated by the CEIC, a National Portal for register all clinical research, and a clinical trials database. In this way, all clinical trials must be submitted to this Council.

PT2. In addition, the Faculdade de Motricidade Humana (FMH) has appointed a Research Ethics Council to oversee the safety, rights and welfare of human participants in research. The composition and functions of the Committee meet the standards laid down in the main international requirement in this field, namely:

- International Ethical Guidelines for Biomedical Research Involving Human Subjects: prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) (Section 3.1.2);
- Convention for the protection of Human Rights and Dignity of the Human Being with regard to the application of Biology and Medicine: Convention on Human Rights and Biomedicine (related to GR3 of the previous section);
- World Medical Association (WMA) Declaration of Helsinki (Section 3.1.1);
- Ethics for Researchers: Facilitating Research Excellence in FP7 (Pauwels, 2007); and

[43] Portuguese National Ethics Committee for Clinical Research http://www.ceic.pt/

- ❖ Decree-Law No. 97/95[44] of 10 May on the regulations applying for ethical committees.

Furthermore, the Research Ethics Council adopted the following standards (Harriss & Atkinson, 2013):

PT3. *Basic principles:* Respect the rights and welfare of participants which must take precedence over all other interests.

PT4. *Ethical review:* Before research begins and before amendments are applied, research must be reviewed and approved by an appropriate ethics committee.

PT5. *The research protocol:* The study, research design and statistical analysis must be clearly described, justifiable and appropriate. In drawing up the research protocol, the researcher must:
- ❖ consider ethical issues in accordance with the Declaration of Helsinki;
- ❖ provide information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest;
- ❖ consider the contribution to new knowledge and consider the environment, include details of any incentives for participants and provisions for treating and/or compensating participants who are harmed as a consequence of participation in the research study;
- ❖ describe the arrangements for post-study access by all participants to interventions identified as beneficial in the study or access to other appropriate care or benefits.

PT6. *Consent:* Informed consent/assent should be provided freely by the participant and should ideally be in writing. If written consent/assent cannot be obtained, or is not appropriate, then oral consent/assent should be formally documented and witnessed. Research that involves children or other populations that cannot consent (e.g., vulnerable populations) should seek consent from an appropriate person and assent from the participant. Research involving participants who are physically or mentally incapable of giving consent may be undertaken only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. Informed consent/assent must include the following:
- ❖ aims of the research,
- ❖ methods,
- ❖ sources of funding,
- ❖ conflicts of interest,
- ❖ institutional affiliations,
- ❖ anticipated benefits and potential risks,
- ❖ potential discomfort, and
- ❖ right to refuse to participate or withdraw consent without reprisal.

PT7. *Conduct:* Research must be conducted:
- ❖ in accordance with appropriate risk management,

[44] Decree-Law No. 97/95 of 10 May. Legislação Farmacêutica Compilada. Available at http://www.ceic.pt/documents/20727/38721/Decreto-Lei+n.%C2%BA+97-95,+de+10+de+Maio/286f30dd-6c43-4217-946e-c1cd8f61ee61

- by appropriately qualified researchers and support staff,
- with skill and care,
- in an appropriate setting,
- in order to protect the privacy of participants and confidentiality of their personal information, and
- in accordance with laws and regulations of the country or countries in which the research is to be performed as well as international norms and standards. Specific laws relevant to research ethical may regulate the collection, use and/or storage of human tissue, the protection of individuals that lack the capacity to consent, data protection, and the use of drugs in research.

PT8. *Governance:* Serious adverse events occurring during the study must be reported to the Ethics Committee that ethically reviewed and approved the research. Authors may conduct their research in accordance with principles detailed by professional associations and treaties other than the World Medical Association Declaration of Helsinki such as the International Sociological Association's (ISA) Code of Ethics[45] (2001). This update recognises that differences in ethical principles may exist between professional associations. For example, the ISA's code of Ethics states that:

"The consent of research subjects and informants should be obtained in advance. Covert research should be avoided in principle, unless it is the only method by which information can be gathered, and/or when access to the usual sources of information is obstructed by those in power."

Suggesting that consent in sociological research is less stringent than in experimental research (Hughes et al., 2010). Authors are required to confirm whether aspects of their research abide by ethical principles proclaimed by professional associations or treaties that differ in status to the Declaration of Helsinki.

PT9. Moreover, according to (Hughes et al., 2010), by reading and citing this editorial the author confirms the following aspects:

- Consent to participation was valid, such that the participants were provided with adequate information, the consent was given voluntarily and that those providing consent were competent to do so.
- If research was carried out on participants who were vulnerable or not competent to give consent then the authors confirm that the participants were appropriately identified, there was justification for carrying out the research on these individuals and additional measures were put in place to ensure the research was ethical.
- Issues of privacy and confidentiality have been considered beyond what is legally required:

  "(…) privacy is the protection of control over information about oneself; control over access to oneself, both physically and mentally; and control

[45] International Sociological Association's (ISA) Code of Ethics http://www.isa-sociology.org/about/isa_code_of_ethics.htm

over ones ability to make important decisions about family and lifestyle in order to be self-expressive and to develop varied relationships".

And confidentiality is when the

"(…) participant discloses to the researcher information which the participant regards as confidential or secret [default assumption]; and the researcher undertakes (implicitly or explicitly) not to reveal this information to anyone who does not already possess it."

- Researchers have considered their legal and ethical obligations to privacy and confidentiality.
- If information provided confidentially as part of a research study, and it is intended to be used for other purposes, confidentiality must be preserved by anonymising the information or by seeking the participant's consent.
- Risks relating to harm, inconvenience, time and money and benefits to the participant, to other individuals, to the researchers and organisations have been considered, balanced, communicated to the participants and appropriately managed when relevant.
- Participants have not been exploited and particular groups have not been discriminated regarding the participation in the research.
- There are appropriate governance arrangements and structures in place if participants are asked to donate biological material for use in future research, such as a biobank. This should involve appropriate consideration of broad consent, privacy and confidentiality, feedback to the participant of incidental findings, storage of material, commercial involvement, donor involvement and intellectual property rights.

3.3.5 Sweden

In Sweden research involving humans needs to be executed according to the Act concerning the Ethical Review of Research Involving Humans[46] (Riktlinjer för etisk värdering av medicinsk humanforskning). This Act, in which the EU Clinical Trial Directive 2001/20/EC (see Section 3.2.1) is incorporated, provides an ethical review of research involving humans and human biological material. It also contains provisions regarding consent to such research. The purpose of the Act is to protect the individual and respect human dignity in research. The act also applies to doctoral work in graduate school (relevant in the case of KI). CODEX[47] is the Research Council's portal for research ethics guidelines in Sweden. The site is run in partnership with the Centre for Research Ethics and Bioethics (CRB)[48] (Karolinska Institute &

[46] Riktlinjer för etisk värdering av medicinsk humanforskning Forskningsetisk. (2003). Retrieved July 1, 2016 from http://www.vr.se/download/18.6b2f98a910b3e260ae28000355/medicinsk_humanforskning_13.pdf

[47] CODEX. Rules and guideline for research in Sweden. Retrieved July 1, 2016 from http://www.codex.vr.se/

[48] Centre for Research Ethics & Bioethics (CRB). Retrieved July 1, 2016 from http://www.crb.uu.se

Uppsala University) and contains links to research ethics and to overviews of ethics in research.

SE1. Ethical approval for every relevant study in Sweden is obligatory.

Six Regional Ethical Review Boards[49] are responsible for reviewing the applications for ethical approval. Since KI is located in Stockholm, all the applications for ethical approvals for the i-PROGNOSIS studies in Sweden will be handled by the Stockholm Ethical Review Board[50].

SE2. Concerning the handling of personal information, Swedish legislation is harmonised with the EU directives 95/46/EC[51] and 2002/58/EC[52], and 2009/136/EC[53]. The Swedish Personal Data Act[54] (PUL) aims to protect people from having their privacy violated when personal data is processed. PUL covers the collection, recording, storage, processing, distribution, extinction of data and more. Additionally, the Swedish Data Protection Authority[55] (Datainspektionen), has issued specific guidelines for personal data transfer out of Sweden with electronic means (including cloud storage) and supervises their implementation.

In Sweden guidelines for the information provided to the participants are available by CRB and are also summarised by the Swedish Research Council[56] (Vetenskapsrådet). In summary, in research protocols involving humans in Sweden the following main issues should be addressed:

SE3. *Recruiting participants*: Test subjects must be chosen such that the project results will be useful for society. In conducting research trials, for all intents and proposes, recruiting the appropriate participants is critical. Thus:
- ❖ The research protocol should contain information on participants' eligibility to determine who among them is eligible to be in the study (i.e., well defined inclusion criteria).

[49] Swedish Regional Ethical Review Boards. Retrieved July 1, 2016 from www.epn.se
[50] Stockholm Ethical Review Board. Retrieved July 1, 2016 from www.epn.se/Stockholm
[51] Protection of Personal Data Directive 95/46/EC. (1995). Retrieved July 1, 2016 from http://europa.eu/legislation_summaries/information_society/data_protection/l14012_en.htm
[52] Directive on Privacy and Electronic Communications 2002/58/EC. (2002). Retrieved July 1, 2016 from http://europa.eu/legislation_summaries/information_society/legislative_framework/l24120_en.htm
[53] Directive 2009/136/EC on Privacy and Electronic Communications (2009) Retrieved July 1, 2016 from http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:337:0011:0036:en:PDF
[54] Swedish Personal Data Act (Personuppgiftslag). (1998). Retrieved July 1, 2016 from http://www.riksdagen.se/sv/Dokument-Lagar/Lagar/Svenskforfattningssamling/Personuppgiftslag-1998204_sfs-1998-204/?bet=1998:204
[55] The Swedish Data Protection Authority. Retrieved July 1, 2016 from http://www.datainspektionen.se/in-english/
[56] Good Practice Research. (2011). Retrieved July 1, 2016 from https://publikationer.vr.se/produkt/good-research-practice/

- ❖ The research protocol might also provide reasons that justify why a specific trial procedure is not practicable/ appropriate for some individuals and obtain a Waiver for Recruitment (i.e., well defined exclusion criteria).
- ❖ One possible problematic case arises when data is collected while participants who are later found to be ineligible to participate. In this case, the research protocol should have explicit outlined procedures for dealing with participant and collected data.

SE4. *Information to participants*: The fundamental requirement regarding this issue is the provision of good information to the participants, with researchers ensuring that subjects are informed in a manner and with a language they understand. In general:

- ❖ Information to the participants should be provided using a language that is comprehensible and suitable for each group.
- ❖ The information should be clear and adequate in order for the participant to make a decision about participation, it can be presented in paper/electronic formats or communicated orally through informational meetings and it should take into account the following elements:
  - Title; the title of the protocol (or a simplified version of it).
  - Introductory information; the need for participants, the type of participants needed (i.e., inclusion/exclusion criteria), the location of the study and the number of participants needed.
  - Purpose of the study.
  - Background; a description of the study, the relevance of the study, the stage of development and the product/agent/treatment that is being investigated.
  - Nature and duration of the study.
  - Contents for the study; intervention/s (what, how often), number of visits, questionnaires, test procedures, time investment, study schedule and difference between intervention and research.
  - Disadvantages for the participant; risks, side effects, responsibilities, possible consequences.
  - Advantages for the participant (also mentioning 'no advantages' is relevant).
  - Voluntary participation; before and during a study a participant is allowed to drop-out without giving a reason and with no consequences attached (participation can also be terminated prematurely by the investigator).
  - Insurance (if applicable); amounts, exclusions, insurer contact details, exoneration (if applicable).
  - Resistance of the mentally incompetent: when any resistance is shown, participation is terminated (if applicable).
  - Interim information; timely provision of information that can influence the consent.
  - Results; processing of research data, publication, messages to participants, right to know or not to know and possible use of research material/interventions after the study.

- Confidentiality of personal information & personal information transfer; processing of information, right of access, possible reporting to general practitioner/specialist, storage time, use of excess material.
- Compensations; travel expenses, compensation, possible costs.
- Proof of approval from the ethical authorities.
- Considerations when giving consent; Request for cooperation, time to think about/consider participation, presence/availability of independent physician (if applicable), complaint procedure, contact details and means to reach the investigators/research team.

SE5. *Informed Consent*: In Sweden, according to CRB, the following information shall be provided to each participant:

- ❖ Confirmation on having read the study information.
- ❖ Confirmation on having been able to ask questions, and which were answered satisfactorily.
- ❖ Confirmation on having had enough time to think about and consider participation.
- ❖ Reminder that participation is voluntary and one can withdraw at any time, without giving a reason.

Similarly, the following permissions should be asked from the participant:

- ❖ Permission to inform a general practitioner/treating specialist in case of an identified mishap (if applicable).
- ❖ Permission for authorized persons, approval committees and authorities to access data (if applicable).
- ❖ Permission on transfer of data to another country inside or outside the EU (if applicable).
- ❖ Permission to process the (anonymous) data like mentioned in the information letter.
- ❖ Permission to store data for future research (if applicable).
- ❖ Permission for participation in the study.
- ❖ Date, name, and signature of the subject.
- ❖ Confirmation by or on behalf of the investigator on having offered both oral and written information, and being available for future questions.

3.3.6 United Kingdom (UK)

In the UK, the National Health System (NHS) has a research governance framework that was first issued in 2001 and amended in April 2005. It is now one for the core standards of the NHS organisation. The research governance framework may be defined as the broad range of regulations, principles and standards of good practice that exist to achieve, and continuously improve, research quality in the UK and worldwide. The framework abides by or includes:

UK1. *The EU Clinical Trials Directive (2001/20/EC)* (Section 3.2.1): The Directive was implemented into UK law in May 2004, as the Medicines for Human Use

(Clinical Trials) Regulations 2004[57], and has since been amended, with the last version introduced in 2008[58].

UK2. *The Good Clinical Practice (GCP) Directive (2005/28/EC[59])* supplements the 2001/20/EC Directive, strengthening the legal basis for requiring Member States to comply with the principles and guidelines of good clinical practice, as set out in the ICH GCP guidelines (see DE5, Section 3.3.2).

UK3. *The Declaration of Helsinki* (Section 3.1.1)

UK4. *Data Protection Act, 1998[60]*: Most clinical research requires the processing and/or storage of personal and sensitive information. The Data Protection Act (1998) legislates for the control and protection of personal information relating to living individuals including both facts and opinions about the individual. It is vital that all University research and researchers comply with the Act and process/store all personal information in accordance with it.

UK5. *Caldicott Principles* (Caldicott Committee, 1997): The Caldicott Principles[61] are a key recommendation on how to use NHS data appropriately. Each local trust has a Caldicott guardian[62] who can be consulted for any queries and, depending on the intensity of the research, the Caldicott guardian may also need to review and approve research projects,

UK6. *Mental Capacity Act[63]*: The Mental Capacity Act provides a statutory framework for acting and making decisions on behalf of individuals who lack the capacity to do this for themselves. The Act sets out who can take decisions, in which situations, and how they should go about this.

The current regulatory framework in the UK/EU allows for a range of risk-adapted approaches[64] that may simplify the processes for initiating and conducting some clinical trials. These adaptations are largely related to how much is known about the investigational medicinal product (IMP), and are based on the marketing status of the IMP and standard medical care. Using a simple categorisation of three risk types (safety risks, risk related to participant rights and risk to reliability of results), it is possible to highlight, particularly for lower risk trials, where simplification is possible.

[57] UK Medicines for Human Use (Clinical Trials) Regulations http://www.legislation.gov.uk/uksi/2004/1031/contents

[58] UK Medicines for Human Use (Clinical Trials) Regulations (amended) http://www.legislation.gov.uk/uksi/2008/941/contents

[59] EU Directive 2005/28/EC http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF

[60] UK Data Protection Act (1998) http://www.legislation.gov.uk/ukpga/1998/29/contents

[61] The Caldicott Principles http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4068404.pdf

[62] The Caldicott Guardian http://webarchive.nationalarchives.gov.uk/20130107105354/http://dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_114506.pdf

[63] UK Mental Capacity Act https://www.admin.ox.ac.uk/researchsupport/ctrg/governance/mca/

[64] Clinical trials for medicines: apply for authorisation in the UK https://www.gov.uk/guidance/clinical-trials-for-medicines-apply-for-authorisation-in-the-uk

Regarding RECs, The United Kingdom has 104 RECs (as of April, 2012): 82 in England, 11 in Scotland, 8 in Wales and 3 RECs in Northern Ireland. The United Kingdom Ethics Committee Authority has to approve ethics committees, especially those committees with the competence to review clinical trials of IMPs. The Authority can distinguish two types of RECs: Type 1 Committees are allowed to review phase 1 trials in healthy volunteers and Type 3 Committees are allowed to review trials in patients.

UK7. From 31 March 2016, Health Research Authority (HRA) approval is the process for applying for approvals for all project-based research in the NHS led from England. HRA approval is the process that brings together the assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent REC opinion provided through the UK research ethics service. It replaces the need for local checks of legal compliance and related matters by each participating organisation in England.

3.3.7 Other Countries

The Office for Human Research Protections of the U.S. Department of Health and Human Services has compiled an extensive reference guide on ethics regulations for research involving human subjects. The latter compilation titled "International Compilation of Human Research Standards" (U.S. Department of Health & Human Services, 2016) lists over 1,000 laws, regulations and guidelines that govern human subjects' research in 120 countries and is freely available online[65].

Laws, regulations and guidelines are presented by country and further categorised in eight categories, i.e., "General", "Drugs and Devices", "Clinical Trials Registry", "Research Injury", "Privacy/Data Protection", "Human Biological Materials", "Genetic Research", and "Embryos and Stem Cells". Categories of main focus regarding i-PROGNOSIS are the "General" and the "Privacy/Data Protection" categories.

3.4 THE CASE OF ELECTRONIC INFORMED CONSENT

The electronic informed consent (eIC) - and the electronic consent form (eCF) - is a recently introduced means of seeking for informed consent by using electronic media. The latter is applicable to research studies conducted with remote participants and it significantly speeds up the informed consent process.

In 2015, the Food and Drug Administration (FDA) of the U.S. Department of Health and Human services has issued guidelines on the use of electronic informed consent in clinical investigations (U.S. Department of Health & Human Services, 2015), available online[66]. The guidelines are summarised in the points below:

[65] International Compilation of Human Research Standards (U.S. Department of Health & Human Services, 2016)
http://www.hhs.gov/ohrp/sites/default/files/internationalcomp2016%20.pdf

[66] Guidelines on the use of electronic informed consent in clinical investigations (U.S. Department of Health & Human Services, 2015)
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm436811.pdf

eIC1. The eCF must contain all the elements of an informed consent in a language that is understandable to the concerned subject.
eIC2. The eIC materials may be provided for both on-site and remote access, and the informed consent can be obtained by the subject or the authorised representative either in the presence of the investigator (on site) or in her/his absence (remotely). If the process takes place remotely, all interactive responses must be documented electronically.
eIC3. The process of obtaining eIC must allow the subjects to securely ask questions and request clarifications from the researchers via electronic means, i.e., live chat, video conferencing, electronic messaging etc.
eIC4. Researchers can use multimodal information, including graphics, audio and visual aids to convey the necessary information to the concerned individual, via electronic means. The only prerequisite is that the information, regardless of its form, is adequate and understandable.
eIC5. The FDA also accepts that an electronic signature is considered trustworthy, reliable and generally equivalent to handwritten signatures executed on paper.
eIC6. Subjects should receive a copy of their eIC and they must have easy access to the materials and information included in the eCF.
eIC7. The computerised system that supports eIC process must be secure with restricted access, i.e., only certain members of the research team must have access to the eCF database.
eIC8. A REC must review and approve the eIC and any amendments made to it.
eIC9. The computerised system must archive the obtained eICs in a way that they are easily retrievable. The system must also have versioning capabilities and record who made changes and when they were made.

Pertaining to the issue of the use of electronic signatures, the EU has recently issued a regulation on this matter, i.e., Regulation (EU) No 910/2014[67], also referred to as eIDAS Regulation, replacing the existing directive on electronic signatures (1999/93/EC[68]). The regulation will apply from 1 July 2016 and it introduces mutual recognition of e-identification means and electronic trust services (e-signatures, e-seals, e-registered delivery services, time stamping, and website authentication).

Nevertheless, up until now, there is no European regulatory framework concerning the process of obtaining eIC and the responsibility of approving such a process lies on the regulatory authorities and ethics committees of each European country. In 2015, the Health Research Authority of the National Health Service of the United Kingdom has approved for the first time the use of an eIC platform ("eConsent", Mytrus Inc., Davis, CA) for obtaining informed consent for clinical trials[69]. Later in

[67] EU Regulation No 910/2014 http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.257.01.0073.01.ENG
[68] EU Directive 1999/93/EC http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV%3Al24118
[69] "Britain's national health service approves the use of Mytrus technology for electronic informed consent in clinical trials" https://www.mytrus.com/en/news/detail/20150827-bnhs (Mytrus Inc., Press release)

2015, VERKKO[70] in Finland was the first fully remote clinical study including full electronic informed consent that has been approved in Europe.

4 DEVICES SAFETY REGULATIONS

This section presents the international (WHO) perspective and the European regulatory framework regarding medical devices safety, as well as the common standards and certifications on which the design and development of electronic medical devices must conform to.

4.1 MEDICAL DEVICES REGULATIONS

4.1.1 World Health Organisation Perspective

According to the Global Harmonization Task Force (GHTF) - now replaced by the International Medical Device Regulators Forum - (GHTF document SG1/N029R11) and highlighted also by WHO (WHO, 2003), a harmonised definition of medical device is the following (p. vii):

"Medical device means any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes of:

- *diagnosis, prevention, monitoring, treatment or alleviation of disease*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury*
- *investigation, replacement, modification, or support of the anatomy or of a physiological process*
- *supporting or sustaining life*
- *control of conception*
- *disinfection of medical devices*

providing information for medical purposes by means of in vitro examination of specimens derived from the human body and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means."

According to WHO and as reported in its Medical Device Regulations document (WHO, 2003), also available online[71], the optimal assurance of medical devices safety has several essential elements:

MD1. *Absolute safety cannot be guaranteed*: Safety can be considered only in relative terms as medical device problems cannot be detected until extensive market experience is gained.

[70] The VERKKO study https://verkko.clinpal.com/clinpal/app (In Finnish)
[71] Medical Device Regulations (WHO, 2003)
http://www.who.int/medical_devices/publications/en/MD_Regulations.pdf

MD2. *It is a risk management issue*: Device safety can be translated into a risk assessment of the potential for the use of a medical device to result in safety problems and harm. Risk assessment of medical devices is based on the experience of health care professionals and on safety design engineering.

MD3. *It is closely aligned with device effectiveness/performance*: A medical device is clinically effective when it produces the effect intended by the manufacturer relative to the medical condition. Device performance is more general, it may include additional functions, not related to clinical effectiveness, and it is easier to measure objectively. Performance and safety of medical devices are often considered together.

MD4. *It must be considered throughout the life span of the device*: The major phases in the life span of a medical device are: 1) Conception and development; 2) Manufacture; 3) Packaging and labelling; 4) Advertising; 5) Sale; 6) Use; 7) Disposal. During i-PROGNOSIS and regarding the new sensors developed within the project, Phase 1 is of particular interest. Phase 2-7 are part of the exploitation strategy that the project will adopt. In the case of Phase 1, soundness of concept and adequacy of design, construction, and testing require the scrutiny of experts to ensure that design and performance do not impose unwarranted risks.

MD5. *It requires shared responsibility among stakeholders:* The main stakeholders involved throughout the life span of a device are: a) the manufacturer (phases 1-3), b) the vendor (phases 4-5), and c) the user (phases 6-7). All three play critical roles in ensuring the safety of medical devices. The most important factor that ensures the cooperation of all these stakeholders is an informed and common understanding of the issues. Shared understanding and responsibility are achieved through communication and mutual education, which can be effectively achieved by having all stakeholders participate in establishing the process that ensures safety and performance of medical devices.

The WHO Medical Devices Regulations document (WHO, 2003) also presents, amongst other international and national regulations, the respective European regulations (Chapter 3) and offers an introduction to device standards (Chapter 5), two subject areas that are also analysed in Section 4.1.2 and Section 4.2, respectively, of the present report.

4.1.2 EU Regulatory Framework

The medical devices and their corresponding software need to be fully compliant with the EC directives (see below) and the respective National Legislation. In general, a medical device cannot be marketed in Europe without carrying a CE marking. A CE marking is applied by the manufacturer and means that the device meets the relevant regulatory requirements and, when used as intended, works properly and is acceptably safe. For all but the very lowest risk devices, such as unmedicated bandages, this must be verified by an independent certification body, called a Notified Body, before the CE marking can be affixed. National authorities are responsible for appointing Notified Bodies and regularly audit them to ensure that they perform to high standards.

In the EU, medical devices, low voltage equipment, machinery and radio and telecommunications terminal equipment are regulated under the New Approach (NA) directives, which are defined as directives that are required for the affixing of a CE-mark (Tsang, Pollard & Kracov, 2012).

mEU1. NA directives are based on Resolution 85/C 136/01[72] (1985) on a new approach to technical harmonisation, and standards, which sets out a new regulatory approach based on the following agreed guiding principles:
- ❖ Legislative harmonisation is limited to products placed on the EU market that meet the essential requirements and benefit from free movement within the EU.
- ❖ Technical specification for assessing conformity with the essential requirements is set out in harmonised standards.
- ❖ Application of harmonised or other standards remains voluntary and the manufacturer can apply other technical specifications to meet the requirements.
- ❖ Products manufactured in compliance with harmonized standards benefit from a presumption of conformity with the corresponding essential requirements.

Below the main EC directives regarding the safety of medical devices are briefly described:

mEU2. *Directive 85/374/EEC Product Liability*[73]: Council Directive 85/374/EEC of 25th July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products is a directive of the Council of the European Union that establishes the principle of liability without fault applicable to European producers. Where a defective product causes damage to a consumer, the producer may be liable even without negligence or fault on their part. Articles 1 to 12 create a scheme of strict product liability for damage arising from defective products. This liability is in addition to any existing rights that consumers enjoy under domestic law (Article 13). This Directive seeks to protect victims and promote improvements in product safety within the internal market through a regulatory framework, which is as consistent as possible and based on a fair apportionment of the risks inherent in modern production.

mEU3. *Directive 93/42/EEC concerning medical devices*[74]: The Council Directive 93/42/EEC of 14th June 1993 and its subsequent modifications cover the placing on the market and putting into service of medical devices.

Regarding standards in the EU, a harmonised standard is a European standard developed by a recognised European Standards Organisation: Comité Européen de

[72] Resolution 85/C 136/01 http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A31985Y0604(01)
[73] EU Directive 85/374/EEC http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV%3Al32012
[74] EU Directive 93/42/EEC http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A31993L0042

Normalisation (CEN), the European Committee for Electrotechnical Standardization (CENELEC), or the European Telecommunications Standards Institute (ETSI). It is created following a request from the EC to one of these organisations. Manufacturers, other economic operators, or conformity assessment bodies can use harmonised standards to demonstrate that products, services, or processes comply with relevant EU legislation. The references of harmonised standards must be published in the Official Journal of the European Union. For instance, ETSI produces globally-applicable standards for ICT, including fixed, mobile, radio, converged, broadcast and Internet technologies. They have produced numerous standards for the Radio & Telecommunications Terminal Equipment Directive[75]. By adhering to these standards, manufacturers and service providers can demonstrate that they have followed the essential requirements of the concerned Directive and are able to claim "presumption of conformity". This allows them to put their products and services on the market in Europe.

4.2 STANDARDS & CERTIFICATIONS FOR ELECTRONIC DEVICES

4.2.1 Standards

Medical devices are conceived, developed and fabricated according to the requirements of harmonized norm EN 60601-1-2:2014[76], which pertains to the general safety, electromagnetic compatibility and testing. Companies are requested to have a quality management system in place, which includes not only the base ISO 9001:2008[77] or ISO 9001:2015[78] quality management system, but also the ISO 13485:2003[79] (currently revised to ISO 13485:2016[80]), which is a specific extension applicable to medical device manufacturers.

In addition, Medical Devices Directive 93/42/EEC[81] (see also the previous Section) establishes the guidelines for classification of medical devices in the light of four established categories (Class I, Class IIa, Class IIb and Class III) and essential requirements that devices need to comply with in order to be considered medical devices. As a part of the classification process, a risk analysis with foreseen mitigation measures is required also; this is regulated by the harmonized norm ISO 14971:2007[82].

Depending on the power management and communication mode used by the devices, other regulations may be applicable. The IEC 60601-1:2005[83] establishes

[75] Radio & Telecommunications Terminal Equipment Directive http://ec.europa.eu/growth/sectors/electrical-engineering/rtte-directive/
[76] EN 60601-1-2:2014 https://webstore.iec.ch/publication/2590
[77] ISO 9001:2008 http://www.iso.org/iso/catalogue_detail?csnumber=46486
[78] ISO 9001:2015 http://www.iso.org/iso/catalogue_detail?csnumber=62085
[79] ISO 13485:2003 http://www.iso.org/iso/catalogue_detail?csnumber=36786
[80] ISO 13485:2016 http://www.iso.org/iso/catalogue_detail?csnumber=59752
[81] EU Directive 93/42/EEC http://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX%3A31993L0042
[82] ISO 14971:2007 http://www.iso.org/iso/catalogue_detail?csnumber=38193
[83] IEC 60601-1:2005 https://webstore.iec.ch/publication/2606

specific compliance standards regarding internally powered (via battery) and externally powered devices; furthermore, the IEC 61000-3-3:2013[84] defines specific requirements related with electromagnetic compatibility (e.g. voltage fluctuations, flicker emissions, etc.), and the IEC 61000-3-2:2014[85] defines specific requirements regarding harmonic emissions. For devices that use radio as communication channel, the CISPR 11:2015[86] standard establishes compliance requirements in what concerns radiofrequency power and emissions levels.

With the purpose of regulating the complete life cycle of the devices, from their conception until the end of its useful life, the WEEE 2002/96/EC[87] directive establishes the requirements for recycling of electronic and electrical equipment. Electrical and electronic devices are composed of a complex mixture of materials and components; due to their (often) hazardous content (e.g. batteries), if not properly managed in the end of their useful life, they can cause environmental and health problems. Also, many modern electronic devices use scarce and costly resources (e.g. gold). The WEEE 2002/96/EC[87] directive is therefore designed to enhance resource efficiency, treatment and recycling of electronics at the end of their life.

Standards are often transposed from their general formulation to revisions that are specific to each country and which may incorporate other requirements imposed by national regulations. However, the overall spirit is preserved.

4.2.2 Certifications

Once a medical device has been fully developed and its intended use is defined, a technical file is compiled and submitted to a notified body for evaluation and certification of the device. Each country has specific rules and regulations in what concerns certification, although the overall procedures have a common root. In Europe, devices that comply with the product directives and essential requirements of the relevant health, safety and environmental protection legislation are affixed with the CE Mark[88] (see also Section 4.1.2). This means that a product has been approved by government officials to be legally placed on the market in their country, ensures the free movement of the product within the European Free Trade Association (EFTA) & EU single market (total 28 countries) and allows the withdrawal of the non-conforming products by customs and enforcement/vigilance authorities.

Other regions have comparable certification. Just to name a few of the main certifications, in the US there is the Food and Drug Administration (FDA) registration[89] and 510(k) clearance[90], in Brazil medical devices are approved and regulated by

[84] IEC 61000-3-3:2013 https://webstore.iec.ch/publication/4150
[85] IEC 61000-3-2:2014 https://webstore.iec.ch/publication/4149
[86] CISPR 11:2015 https://webstore.iec.ch/publication/22643
[87] WEEE 2002/96/EC http://ec.europa.eu/environment/waste/weee/legis_en.htm
[88] European Conformity Marking http://www.ce-marking.org/
[89] U.S. FDA registration medical devices http://www.fda.gov/MedicalDevices/
[90] U.S. FDA 510(k) clearance http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/510kClearances/

ANVISA[91], in Canada medical devices must obtain a Medical Device Licence (MDL)[92] and the company needs to have a Medical Device Establishment License (MDEL)[93], prior to introduction in the market, and in Russia medical devices need to comply with the GOST and GOST-R[94] standards.

Most certifications systems foresee special exemptions for devices used for investigational purposes, as well as equivalent assessment conditions that allow a device to be characterized in the light of previously approved devices with similar features.

5 DATA MANAGEMENT REGULATIONS

5.1 DATA PROTECTION REGULATIONS

In all cases where computers are used to process personal data, such use will be subject to the Data Protection law. As already identified in Section 3 and in particular in Sections 3.2 and 3.3, the EU regulations and directives on data protection (protection of personal data) and their corresponding transpositions in national laws have been outlined. European Commission has reformed the data protection rules in the EU. In May 2016, the official texts of the Regulation and the Directive on Protection of Personal Data have been published. The Regulation entered into force in May 2016, and it shall apply from 25 May 2018. The Directive enters into force on 5 May 2016 and EU Member States have to transpose it into their national law by 6 May 2018. The objective of this new set of rules is to give citizens back control over of their personal data, and to simplify the regulatory environment for business[95]. The data protection reform is a key enabler of the Digital Single Market which the Commission has prioritised.

Under EU law, personal data can only be gathered legally under strict conditions, for a legitimate purpose. Furthermore, persons or organisations which collect and manage personal information must protect it from misuse and must respect certain rights of the data owners which are guaranteed by EU law.

Every day within the EU, businesses, public authorities and individuals transfer vast amounts of personal data across borders. Conflicting data protection rules in different countries would disrupt international exchanges. Individuals might also be unwilling to transfer personal data abroad if they were uncertain about the level of protection in other countries. Therefore, common EU rules have been established to ensure that personal data enjoy a high standard of protection everywhere in the EU.

[91] Brazil ANVISA http://portal.anvisa.gov.br

[92] Canadian Medical Device Licence http://www.hc-sc.gc.ca/dhp-mps/md-im/licen/mdlic-eng.php

[93] Canadian Medical Device Establishment License http://www.hc-sc.gc.ca/dhp-mps/compli-conform/licences/form/frm-0292-eng.php

[94] GOST-R standard http://www.gost-r.info

[95] EU Protection of Persol Data http://ec.europa.eu/justice/data-protection/

EU citizens have the right to complain and obtain redress, if their data is misused anywhere within the EU.

In e-Health, it is not clear (and national laws may differ) whether the research exemption may be used, or whether explicit consent is required from every person whose data may be processed. As identified in Sections 3.2.3, there are on-going efforts in the area of health (e-Health and m-Health), in particular the *Code of Conduct for privacy for mobile health apps,* which covers issues including the user's consent, data transfers and retention, which are key to the i-PROGNOSIS project.

The main points of the new Data Protection Regulation regarding data management are the following[96]:

DP1. *Data processors are also responsible for data protection:* In the previous framework, any data "by which an individual can be identified" was the sole responsibility of the data owner (called the "data controller"). Under the new regulation, any company or individual that processes this data will also be held responsible for its protection, including third parties such as cloud providers.

DP2. *Global effect:* The new regulation affects not only EU organisations, rather every global organisation that may have data on EU citizens and residents.

DP3. *Stricter rules on transferring data on EU citizens outside the EU:* The directive currently prohibits personal data from being transferred outside the European Economic Area (EEA), unless the controller assures an adequate level of privacy protection.

DP4. *Users may request to see the data about them:* Under the directive, users already have the right to see the data collected about them.

DP5. *User may request to erase data about them:* In the new regulation, users can also demand that their data be erased.

DP6. *Controllers are responsible to inform users about their rights:* Under the new regulations, controllers must inform and remind users of their rights. In addition, users must opt-in for their data to be used to the controller's systems.

DP7. *Encryption and pseudo-anonymisation:* Controllers must meet individuals' "reasonable expectations" of data privacy, such as encrypted, tokenised or pseudo-anonymised data.

5.2 DATA EXCHANGE & ACCESS RIGHTS REGULATIONS

Access and exchange of research data must comply with the standard ethical guidelines on data privacy and protection of personal data reported in Section 3 and Section 5.1. In addition, certain definitions and obligations are included in the

[96] EU on the general data protection regulation http://www.consilium.europa.eu/en/policies/data-protection-reform/data-protection-regulation/

Annotated model Grant Agreement[97] (AGA) of the Horizon 2020 Framework. The latter are included in Articles 26, 27, 29, 31, 36, and 37 of the AGA and pertain to:

AGA1. Based on Article 26: Results (including data) are owned by the beneficiary that generates them. If more than one beneficiary generated the data, the ownership becomes joint ownership. In a joint ownership, each of the beneficiaries can licence third parties to exploit the results in agreement with the other owners. If a third party (including personnel) generates results, the beneficiary must obtain all necessary rights on these results. The EC and its concerned agencies may claim ownership to protect the results under certain conditions.

AGA2. Based on Article 27: Each beneficiary must protect its results (including data produced) for an appropriate period and with appropriate territorial coverage.

AGA3. Based on Article 29: Regarding the digital research data generated in an action that participates in the Open Research Data Pilot the beneficiaries can deposit the data in a research repository and make them available to third parties to exploit them. The latter must not infringe Articles 27, 36, 37, and 39

AGA4. Based on Article 31: The beneficiaries must - on royalty free basis - give access to recruited researchers to results necessary for their research training activities under the action.

AGA5. Based on Article 36: The parties must keep confidential any data that is identified as confidential at the time it is disclosed. Confidentiality obligations no longer apply under certain conditions.

AGA6. Based on Article 37: Results with a security recommendation may be disclosed or disseminated only under certain conditions. Before disclosing such results to a third party, the beneficiary must inform the coordinator, who must request written approval from the European Commission (EC).

Ownership of results and access rights are also defined, in detail, in the DESCA Horizon 2020 model Consortium Agreement[98], which has been adopted by the i-PROGNOSIS consortium.

In general, the production of a data management plan[99] and/or a data collection protocol specifying, amongst others, who has access in the collected research data and the type of access/exchange rights is considered good practice, if not mandatory.

Other EU directives that pertain to the processing and sharing of personal data and concern the i-PROGNOSIS project are:

[97] Horizon 2020 Annotated model Grant Agreement http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/amga/h2020-amga_en.pdf#page=213

[98] DESCA Horizon 2020 model Consortium Agreement http://www.desca-2020.eu/fileadmin/content/Desca_2020_1.2/DESCA2020_v1.2_March_2016_with_elucidations.pdf

[99] Guidelines on Data Management in Horizon 2020 http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf

- *Directive 95/46/EC*[100] on the protection of individuals with regard to the processing of personal data and on the free movement of such data.
- *Directive 2002/58/EC*[101] concerning the processing of personal data and the protection of privacy in the electronics communication sector.
- *Directive 97/66/EC*[102] concerning the processing of personal data and the protection of privacy in the telecommunications sector.

The three aforementioned Directives are subject to update based on the new EU data protection directive and regulation (Section 5.1).

5.3 GOOD PRACTICES ON THE USE OF DATA IN DISSEMINATION ACTIVITIES

Sharing of individual related data in the context of scientific research, including dissemination activities, is an increasingly important topic since patient privacy as well as retention of data must be ensured. The International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals require that patient privacy be protected, and maintaining confidentiality and privacy is ingrained in various legal statutes such as the UK Data Protection Act and the Health Insurance Portability and Accountability Act (HIPAA) in the US[103].

In Europe, the *Directive 95/46/EC* (Section 3.2.1) provides some harmony in data protection legislation, while in the US there is no overarching data protection law. Researchers and RECs are often responsible for minimising privacy related risks while researchers are responsible for compliance with all related legal and regulatory requirements - always in line with the ethical and data privacy aspects of the current research projects and the corresponding EU regulations and human rights[104].

In an increasingly global research and publishing industry, universally agreed definitions as to what constitutes anonymised patient information are required. Despite journal and funder policies requiring data sharing, there has been little practical guidance on how data should be shared (Hrynaszkiewicz et al., 2010). Bibliography includes proposals and discussions of various guidelines, frameworks and solutions (Smith, 2015; Chen et al., 2012).

The HIPAA provides a list of 18 items that need to be removed from patient information in order for it to be considered anonymous for the purposes of sharing information between the "covered entities" specified in the act, but the list was not

[100] EU Directive 95/46/EC http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:HTML
[101] EU Directive 2002/58/EC http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32002L0058:en:HTML
[102] EU Directive 97/66/EC http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31997L0066:EN:HTML
[103] Partners Human Research Committee. HIPAA frequently asked questions http://healthcare.partners.org/phsirb/hipaafaq.htm#b5
[104] Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter5-chapitre5/

designed with publication in biomedical journals in mind. A number of publications from UK bodies provide some form of guidance on identifying information[105,106,107] but none is as explicit as the HIPAA.

Indicative guidance includes the following:

- Consent for publication of appropriately anonymised raw data should ideally be sought from participants in clinical research.
- Direct identifiers such as patients' names should be removed from datasets; datasets that contain three or more indirect identifiers, such as age or sex, should be reviewed by an independent researcher or ethics committee before being submitted for publication.
- Data anonymisation/de-identification: Data holders are responsible for generating de-identified datasets which are intended to offer increased protection for patient privacy through masking or generalisation of direct and certain indirect identifiers.
- Controlled access to data, including use of a data sharing agreement: A legally binding data sharing agreement should be in place, including agreements not to download or further share data and not to attempt to seek to identify patients.

6 i-PROGNOSIS COMPLIANCE

This section provides an initial report on the procedures that will be followed in order for the data collection phases of the i-PROGNOSIS project to be ethically compliant with the appropriate regulations and guidelines. Additionally, the general level of concern (low, medium, high) arising from data collection aspects is evaluated. It must be noted that pilot data collection (Task 6.1 - *Pilot Data Collection*) preceding each main data collection phase will not collect research data and it will purely focus on the good operation of the respective technical modules. Thus, the pilot data collection does not involve research participants and it is not discussed in the following sections. For clarifications on i-PROGNOSIS-specific terminology the reader is referred to Section 6 of the deliverable D2.1 - *First version of user requirements analysis*.

6.1 GDATA COLLECTION

Generalised data (GData) are defined as unobtrusive behavioural data reflecting the natural interaction of older adults with their smart mobile devices (smartphone and

[105] National Information Governance Board. Information about patients. http://www.advisorybodies.doh.gov.uk/piag/InformationAboutPatients.pdf

[106] Medical Research Council. Personal information in medical research. http://www.mrc.ac.uk/consumption/idcplg?IdcService=GET_FILE&dID=6233&dDocName=MRC002452&allowInterrupt=1

[107] UK Data Archive. Training module II: Dealing with confidential research information. Data Management and Sharing Workshop, Edinburgh, 17 June 2008. http://www.data-archive.ac.uk/news/eventsdocs/anon17jun08.doc

smartwatch) in everyday living. The GData collection phase (Task 6.1 - *GData Collection and Screening*, month 15 - month 45) will include voice, device handling, typing pattern, exploratory walkability, text and photos affective content capturing (smartphone), as well as physical activity and sleep data capturing (smartphone or smartwatch), and the extraction of the respective features. GData shall be used to develop a decision system that will output the risk of transition from healthy status of adults towards Parkinson's disease (PD), a process that is expected to eventually lead to the establishment of the i-PROGNOSIS first stage of early PD detection. It is planned for GData to be collected through a mobile application that will be available for download from the respective mobile application store (e.g., Google Play Store), depending on the operating system that the application will be developed for. Apart from the in-system data collection, user acceptance will be evaluated too, probably through in-application questionnaires (Task 7.3 - *User acceptance evaluation*).

The initial plan was to make the application available globally. However, due to limitations arising from the ethical and data protection regulatory framework, the application is planned to be initially available in the six countries where i-PROGNOSIS partners reside. Details on this matter are given in the following section.

The target number of GData generating participants is 5,000 healthy people or people with early PD aged 50 years or above (desired age, but not an exclusion criterion). Baseline characteristics will be obtained from each participant that will download the mobile application, through short questions about: age, gender, her/his health status, including if s/he is a PD patient or has a history of PD in the family. As GData reflects the natural use of the smart device in an unobtrusive way, participants will not be asked to do special tasks with their smart device but use it in a normal way during routine daily activities, e.g., at home or at work. Certain participants, based on their location, i.e., in the three countries where i-PROGNOSIS medical partners reside (KCL, United Kingdom; TUD, Germany; AUTH, Greece), and provided that they gave consent for, will be selected randomly and contacted to participate in the medical evaluation sessions following the GData collection phase (Task 6.5 - *Medical Experts Evaluation of the System*) that aims at validating the i-PROGNOSIS first stage of early PD detection through standard PD diagnostic tests correlating with the data types/ PD symptoms that are collected/ targeted in the particular data collection phase.

6.1.1 Research Ethics Compliance

Practical approach: As the GData collection phase is a remote research data collection study, i.e., participants will not have direct contact with the researchers, electronic informed consent (eIC) will be sought after the downloading of the i-PROGNOSIS mobile application and prior to its use. In particular, eIC for the GData collection is planned to be obtained as follows: When an adult opens the i-PROGNOSIS detection application on her/his smartphone for the first time, the adult will be presented with an epitomised consent form at the end of which there will be a link to the detailed consent form on the i-PROGNOSIS website and the options to proceed with acceptance or rejection. If the adult agrees, s/he will be presented with a confirmation screen and the option for the consent to be downloaded and stored locally on the

mobile device. Only after completing the electronic consent process, the adult can participate in the GData collection phase.

In this vein, the presentation of the eIC and the way the participant will interact with it will be based on the following:

- The eIC will present the information as a scrollable text with clear sections in an easy-to-read manner (white background - black font of appropriate size).
- The information presented will be in language understandable to the user, i.e., any scientific or technical terms will be explained with appropriate detail.
- The form will be presented to prospective participants, immediately, after they open the respective application for the first time, clearly stating that it constitutes a consent form (title), and the text will be in their language (based on their location - available through the smartphone settings).
- A means of contact with i-PROGNOSIS members for further clarifications - additional questions will be also provided and it will be highlighted in the eIC user interface.
- At the end of the form, the options of accepting or declining to give consent will be provided as two distinctive buttons. Upon tapping on any of the two buttons, the user will be asked to verify his/her choice with a pop-up message.
- As soon as the process is complete, the user will be informed that an electronic copy (.pdf file) of the accepted consent form will be downloaded to her/his mobile device.
- In case of an amendment or update to the eIC affecting the participant's willingness to continue to participate in the study, he/she will receive a notification in his/her mobile device and he/she will be prompted to read and accept/decline the amended eIC in a timely manner.

Regarding the content of the eIC:

- It will briefly inform the participant about the study aim and content, methods and procedures, anticipated benefits and potential risks.
- Furthermore, a statement will be included stating that participation is voluntary and withdrawal is possible at any time.
- Finally, the prospective participant, if s/he resides in one of the three countries where i-PROGNOSIS medical partners are located (KCL, United Kingdom; TUD, Germany; AUTH, Greece), will be asked if s/he consents to be contacted for participating in the medical evaluation procedure at some point near the end of the GData collection phase. Costs for this procedure (including transportation of participants) will be covered by the project.

Based on the aforementioned, the prospective participant is expected to be able to provide a freely-given informed consent about participation in the study. Additionally, during the use of the application, the user will be free to halt the collection of specific data types (e.g., voice) at will, as well as withdrawing from the data collection phase and (optionally) erase the data s/he generated until this point.

Furthermore, a corner stone of the GData collection phase will be the anonymity of the participants. Thus, the mobile application and the related data management infrastructure will be developed in such a way that no personal identification will be required from the application users (participants in the GData collection phase). Their baseline characteristics and collected data will be labelled for the purpose of storage and processing with a participant (or user) ID. Communication with the participant (if required) will take place within the mobile application in the form of push notifications.

Certain participants may reveal their identity voluntarily if they are selected and notified to participate to the medical evaluation procedure (see Concerns). An extra hard-copy consent will be required for the participation (and the use of data) in the planned GData-related medical evaluation sessions.

Regulatory framework compliance: Each European country for which the i-PROGNOSIS mobile application will be available on the application store, will apply for ethical approval for the GData collection study, including the approval of seeking informed consent through electronic media. Initially, for this procedure to be feasible in the time frame of the project, i-PROGNOSIS partners in six countries (Belgium, Greece, Portugal, Germany, United Kingdom, and Sweden) will ask for ethical approval of the data collection phase from their concerned REC. The i-PROGNOSIS consortium will further investigate practicable ways to make the i-PROGNOSIS mobile application available to additional countries.

Regarding the eIC, its design will be based on the FDA guidelines and its confirmation of acceptance will be evaluated against the EU regulation No 910/2014 (eIDAS Regulation) as pointed out in Section 3.4. As there is no European regulatory framework concerning the process of obtaining eIC and the responsibility of approving such a process lies on the regulatory authorities and RECs of each European country, i-PROGNOSIS researchers will consider a unique ethical argument line guided by the EU Directives/Regulations, but they will also seek separate ethical approval dependent on the country ethical regulatory framework.

The aforementioned approach is expected to ensure i-PROGNOSIS GData collection compliance with international, European and national regulations (Section 3) regarding a procedure of research data sourcing that has been introduced recently, i.e., remote and de-identified data collection through mobile applications, and it is vaguely and fragmentally regulated.

Concerns: A complete anonymisation will not be possible as certain participants, based on the countries where i-PROGNOSIS medical partners reside (KCL, United Kingdom; TUD, Germany; AUTH, Greece), will be contacted via the i-PROGNOSIS application and asked to participate in the medical evaluation procedure. In particular, these participants will be provided with the opportunity to contact a local medical centre taking part in the i-PROGNOSIS research project to undergo further medical evaluation and to participate in the SData collection phase (additional informed consent and ethical approval). Adverse events in the form of psychological burden that these participants may experience due to medical evaluation will be managed according to the procedures reported in Section 6.4. Due to the nature of

the study, a drop-out rate of ~30% is expected, i.e., users that will download the application may uninstall it in short time. However, i-PROGNOSIS partners will attempt to mitigate this issue by strengthening social intervention activities (Task 8.1 - *Build i-PROGNOSIS community*) in order to motivate people to participate in the GData collection phase. As a result, the level of concern for the conduct of the GData collection is considered medium.

6.1.2 Devices Safety Compliance

The general standards and regulations applicable to electronic devices have been previously discussed in Section 4.2. In the scope of the i-PROGNOSIS project, GData collection will take place by using two different kinds of off-the-shelve electronic devices, namely the users' personal smartphones and smartwatches, which are already certified.

Concerns: Based on the aforementioned, the level of concern for the safety of the devices (off-the-shelve) to be used for the GData collection is considered low.

6.2 SDATA COLLECTION

The i-PROGNOSIS specialised data (SData) collection phase will augment the data collected by the GData collection phase towards the development of the second stage of the i-PROGNOSIS early PD detection. The SData collection phase (Task 6.3 - *SData Collection and Screening*, month 23 - month 45) is envisioned as an unobtrusive data collection phase by providing the participant with additional web-connected everyday sensing objects that collect additional to the GData data and which is expected to be deployed mainly in the user's home environment. The SData collection phase will target the detection of diet deterioration, obesity, frequent constipation, and general health deterioration, using web-connected everyday sensing objects, such as a Mandometer (small plate scale to capture eating mechanics), a smart watch (to capture physical activity), a smart belt (to capture bowel sounds) and a smart TV remote control (to capture bowel sounds). SData shall be used to further develop the decision system, already trained with GData, in order for the system to output a more confident risk of adults' transition from healthy status towards Parkinson's disease (PD), based on augmented data. It is planned for SData to be collected through a mobile application (an upgraded version of the mobile application used for the GData collection phase) that will be provided only to those participating in this phase. Apart from the in-system data collection, user acceptance regarding mainly the new sensors will be evaluated as well (Task 7.3 - *User acceptance evaluation*).

The SData collection will take place in three countries, i.e., Greece, Germany and the UK in order to facilitate the medical monitoring of the users and the subsequent medical evaluations. In particular, general data (GData) generating users selected for medical evaluation during the GData collection phase (including PD patients and controls; up to 60 individuals in total, across three countries) forming a balanced sample of end-users, will be asked to participate in the SData collection phase. The latter denote that the SData collection phase will be a more structured study, as

compared to the GData collection phase, due to the limited availability of the web-connected sensors. Note that in this phase, data collection cannot be anonymous and participants will give signed hard copy consent prior to their engagement.

Users that agree to take part in this phase will be provided with the appropriate hardware and instructed by the i-PROGNOSIS investigators on how to use them during their daily activities. All participants in this data collection phase will be asked to give separate hard-copy consent for participating in the medical evaluation procedure (baseline, interim, and final medical evaluation sessions) accompanying the SData collection phase (Task 6.5 - *Medical Experts Evaluation of the System*) that aims at validating the i-PROGNOSIS second stage of early PD detection through standard PD diagnostic tests correlating with the additional data types/ PD symptoms that are collected/ targeted in the particular data collection phase.

6.2.1 Research Ethics Compliance

Practical approach: Upon the recruitment for this phase and after the GData medical evaluation sessions, the interested individuals will meet with i-PROGNOSIS medical partners from KCL in the UK, TUD in Germany and AUTH in Greece, where they will be informed verbally and in writing (in their local language, i.e., English, German or Greek) about the precise requirements and protocols relating to their participation. The individuals, who express their intention to participate, will be required to 1) go through the material, 2) state that they understand it, and 3) provide *written informed consents*, which are to be collected locally by the concerned medical partners. An extra hard-copy consent will be required for the participation (and the use of data) in the planned SData-related medical evaluation sessions.

The basic elements of the informed consent that will be compiled for the needs of the SData collection phase are the following:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any products which are experimental.
- A description of any reasonably foreseeable risks or discomforts to the subject.
- A description of any benefits to the subject or to others which may reasonably be expected from the research.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that external regulatory agencies, such as the Food and Drug Administration, may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation and/or medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

- An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled will be added.

All essential and required approval procedures will be carried out for this data collection phase at where medical partners are located (UK, Greece, and Germany).

Regulatory framework compliance: Ethical and legal issues are a matter of major importance for the i-PROGNOSIS approach since it involves senior users and health-related data acquisition and medical evaluation. Data collection will be conducted in accordance with international and EU Directives/Regulations, as well as, any German, Greek and UK research regulations (Sections 3.3.2, 3.3.3 and 3.3.6). In particular, the i-PROGNOSIS SData collection phase will abide by the clinical trial recommendations and regulations set out by the Declaration of Helsinki (Section 3.1.1), the Universal Declaration on Bioethics and Human Rights (Section 3.1.3), and the European Clinical Trial Directive 2001/20/EC (Section 3.2.1). In addition, the informed consent procedure in the SData collection phase of i-PROGNOSIS will be in line with the relevant European Regulation 2016/679, the European Directive 2016/680 (Section 3.2.2) concerning Data Protection, as well as the respective National Acts (Section 3.3).

For the appropriateness of the medical evaluation and the i-PPROGNOSIS SData collection protocols, the formulation of both the provided informational material and the specifics of the written consent forms, an ethical approval procedure will take place at three countries (UK, Germany and Greece):

- In accordance to UK ethical requirements (presented in detail in Section 3.3.6), ethical approval will be asked by the UK Health Research Authority (HRA) complying with the standard procedure (as of March 31, 2016) of applying for approvals for all project-based research in the NHS led from England.
- In Germany, ethics approval will be asked from the ethical committee of the Technical University Dresden (TUD). The SData collection phase will be based on Paragraph 15 Science of the Medical Association's professional code of conduct of Saxony of the 24th of June 1998 [see Section 3.3.2, DE3-(c)]. The SData collection will be labelled as "non-commercial, investigator initiated clinical trial" as conducted by researchers without the participation of the pharmaceutical or other commercial industry and funded by the EU as a non-profit institution.
- In Greece, ethics approval will be asked from the AUTH Bioethics Committee in compliance with its requirements (GR6-GR8) and the Greek regulatory framework as set out by the National Bioethics Commission (see Section 3.3.3).

Concerns: As in the GData collection phase, adverse events in the form of psychological burden that participants may experience due to medical evaluation will be managed according to the procedures reported in Section 6.4. Issues relating to compliance due to the age of the prospective participants in conjunction with their willingness to use new technology must be also taken into consideration. Furthermore, a moderate drop-out rate (~20%) is also expected due to the nature of the study and the inclusion of medical evaluation sessions. Nevertheless, the direct contact of the i-PROGNOSIS investigators with the participants and the proper screening of each participant before active involvement in the data collection phase will reduce the probability that these concerns actually come true. As a result, the level of concern for the conduct of the SData collection is considered medium, and special attention will be given on the aforementioned matters.

6.2.2 Devices Safety Compliance

The general standards and regulations applicable to medical devices have been previously highlighted in Section 4. In the scope of the i-PROGNOSIS project, SData collection will be done using a number of already certified off-shelve devices (e.g. Microsoft Band 2) and devices that will be purpose-built for the project. The devices to be developed include a smart belt for bowel sounds monitoring and a smart TV remote control.

Off-the-shelve devices are already certified. Given the exploratory nature of the development associated with the novel devices, which will be created in an iterative process of incremental improvement, and the time frame, devices will be developed following all applicable standards and regulations, which in most cases are already adopted by the partners for the production of their certified devices.

Nevertheless, in the scope of the project, the purpose-built SData collection devices will be used as non-certified exploratory and investigational devices as it is not feasible to complete the full process of certification and approval by a notified body in the time frame that spans the completion of the devices and the starting of the deployment with real users.

Concerns: Based on the aforementioned, the level of concern for the safety of the devices (off-the-shelve and novel ones) to be used for the SData collection is considered low.

6.3 INTERVENTION DATA COLLECTION

The i-PROGNOSIS Intervention data collection phase is envisioned as a comprehensive, user-tailored, self-management intervention platform for adults at high-risk or into the early stages of PD, which is expected to be deployed in the user's home environment. The user participation in the intervention will be self-tailored by the PD expert (i-PROGNOSIS medical personnel) and will complement the use of the previously described G/SData collection process (in free living environment) with additional home, behavioural training, mostly through the implementation of the Personalised Game Suite, complemented by the targeted nocturnal intervention (TNI) and the assistive interventions (gait rhythmic guidance

and voice enhancement interventions). Note that the envisioned platform will also have a strong social element, encouraging the interconnection of the i-PROGNOSIS users and that the specific elements and/or the training protocols of the intervention will differ per intervention user, i.e., modular deployment, based on the personalised needs and the stage of PD for each participant.

At the time of writing, the i-PROGNOSIS intervention phase is scheduled to take place in Greece, during the last year in the project lifetime (Task 6.4 - *Intervention data collection and clinical scores*, month 30 - month 45), including around 60 individuals, which will either be recruited through the SData collection phase (~10-15 participants) or recruited locally from the medical i-PROGNOSIS partners, i.e., AUTH, (~45-50 participants). The sample will comprise high-risk/diagnosed men and women, 50+ years old and participant recruitment, compliance and participation will be augmented by the i-PROGNOSIS peripheral social initiatives. Apart from the in-system data collection, user satisfaction and acceptability regarding the whole process will be collected and evaluated too (Task 7.3 - *User acceptance evaluation*).

It is important to note that all participants will be required to consent to parallel medical evaluation by the local medical experts (Task 6.5 - *Medical Experts Evaluation of the System*), in order to: a) validate the SData analyses pointing towards high-risk/initial states of PD, b) evaluate the precise needs of the individual, pointing towards personalised use of the intervention modules and personalised training protocols (e.g., personalised levels of difficulty and duration per task) and c) monitor the progress of the individual and the effects of the interventions/training on the targeted PD symptomatology. In summary, the participants will be required to participate in medical evaluation sessions at the following points around the i-PROGNOSIS interventions phase: 1) one session prior to the interventions onset (maximum two weeks before), 2) one session shortly after the interventions finalisation (maximum two weeks) and 3) 1 to 2 follow-up sessions (e.g., 6 and 12 months after the interventions end). Additionally, a mid-interventions session might be added, based on the feedback from the i-PROGNOSIS intervention platform (e.g., deterioration / transition prediction). The precise medical evaluation protocols will be initially reported in D2.2 - *Data collection and medical evaluation protocol* and they will be finalised closer to the initiation of the respective tasks, but it is conceptually planned that they will comprise baseline, clinical diagnostic tests for motor, non-motor and psychological assessment of PD characteristics, including both self-reported questionnaires (e.g., Parkinson's Disease Non Motor Symptoms Questionnaire, Parkinson's Disease Sleep Scale) and functional testing (e.g., resting EEG, olfactory assessment).

Finally, based on the availability of participants and resources, an age-, sex- and PD-stage matched control group might be recruited locally in order to evaluate, on a group level, the effectiveness of the i-PROGNOSIS interventional approach.

6.3.1 Research Ethics Compliance

Practical approach: Upon the recruitment of the individuals into the i-PROGNOSIS supportive interventions phase, the interested individuals will meet with local medical personnel (AUTH) where they will be informed verbally and in writing (in their local

language, i.e., Greek) about the precise requirements and protocols of their participation. The individuals, who express their intention to participate, will be required to 1) go through the material, 2) state that they understand it, and 3) provide *written informed consents*, which are to be collected locally by the medical partner (AUTH).

For the continuous use of the G/SData platform, the process will be identical to the ones described in the Sections 6.1 and 6.2 respectively. Note that, in case that the specific participant is continuing into the interventions phase through the previous i-PROGNOSIS detection phases, their consent will need to be renewed.

An extra consent (probably in paper format) will be required for the participation (and the use of data) both in the planned medical evaluation sessions and the i-PROGNOSIS intervention platform home use, following the communication of additional information pertaining to the specifics of the medical evaluation protocols to be followed.

Regulatory framework compliance: In general, the intended research protocols concerning the intervention phase in i-PROGNOSIS have been envisioned in accordance to the International, the European and the Greek regulations and guidelines, which are presented in detail in Section 3 of this document. In summary, the i-PROGNOSIS data collection during the intervention phase will abide by the clinical trial recommendations and regulations in the Declaration of Helsinki (Section 3.1.1), the Universal Declaration on Bioethics and Human Rights (Section 3.1.3), the European Clinical Trial Directive 2001/20/EC (Section 3.2.1) and the Code of Medical Ethics and Deontology described in the Greek Act 3418/2005 (Section 3.3.3). In addition, the data management practices in the intervention phase of i-PROGNOSIS will be in line with the relevant European Regulation 2016/679, the European Directive 2016/680 (Section 3.2.2) and the Greek Act 2472/1997 (Section 3.3.3) concerning Data Protection.

For the appropriateness of the medical evlauation and the i-PPROGNOSIS intervention protocols, the formulation of both the provided informational material and the specifics of the written consent forms, an ethical approval will be requested by the appropriate local ethical authority (i.e., the internal Bioethics Committee of the AUTH Medical School). In accordance to Greek ethical requirements (presented in detail in the Section 3.3.3 of this document), the i-PROGNOSIS consortium will make sure that the ethical permission application will include specific information on: GR6) the details of the research protocol, GR7) all the informational material to be provided to prospective participants and GR8) all the specific written consent forms (electronic transcripts and/or paper formats).

Concerns: Finally, the i-PROGNOSIS consortium will need to be careful about participant compliance and mitigation strategies should be in place to avoid this risk. Firstly, a moderate number of participant dropout is expected (~30%) and will be taken into account in the target sample sizes in the power calculations for the intervention trial. Secondly, there is a realistic risk that the participants will not use the provided technology/game suite to the degree planned through the personalised training schemes. These concerns arise due to the age of the target population (50+

years), the PD disease process, its effects on mental capacities of the participants, and the natural resistance of humans to behavioural change. These concerns will be handled through meticulous utilisation of various in- and out-of-system elements, such as social interaction between participants through the interventions platform and the development of a user-friendly interface that fits the needs of older adults. Furthermore, proper screening of each participant before active involvement in the project will reduce the probability that these concerns actually come true. Any adverse effects arising from the use of the interventions, especially, physical exercise games (Exergames) of the Personalised Game Suite, will be handled according to the procedures reported in Section 6.4. Based on the aforementioned, the level of concern for the conduct of the interventions data collection is considered medium.

6.3.2 Devices Safety Compliance

In i-PROGNOSIS a first non-exhaustive list of the hardware to be used during the interventions data collection is provided below:

- Smartphone and/or tablet, smartwatch, web-connected (IoT) everyday objects-sensors (smart TV remote, smart belt, and Mandometer) for the gathering of the interventions users' monitoring data.
- Interventions-specific devices: Microsoft Kinect for interfacing with the Exergames of the Personalised Game Suite and earphones for use with the Targeted Nocturnal Intervention.

Note that most of the aforementioned devices are commercially available so they already have the CE marking. For new devices, where prototypes will have to be developed, i.e., the smart belt and the smart TV remote, the procedure reported in Section 6.2.2 will be followed.

Furthermore, the interventions application and the interventions platform will be developed by taking into account the "Medical device software - Software life-cycle processes" standard[108] (IEC 62304:2006).

Concerns: Based on the aforementioned, the level of concern for the safety of the devices (off-the-shelve and novel ones) to be used for the interventions data collection is considered low.

6.4 GENERAL MANAGEMENT OF ADVERSE EVENTS

While every attempt will be made to ensure the safety of the participants, there are inherent risks associated mainly with the outcomes of the participants' medical evaluation against PD and their exercise training at home through the Exergames of the i-PROGNOSIS intervention platform. In particular, prominent risks are:

Exercise training: Exercise training may lead to muscle tightness, soreness, fatigue, and rarely a pulled muscle. If an interventions participant does develop an injury as a result of their exercise training using the Exergames intervention and since the

[108] IEC 62304:2006 http://www.iso.org/iso/catalogue_detail.htm?csnumber=38421

intervention will take place at home, s/he or her/his caregiver will have to contact the i-PROGNOSIS medical staff at the interventions data collection site, who, in turn, will guide the participant and arrange for her/his treatment through channels of the Greek national health system, based on the participant's health insurance.

Medical evaluation: Participants that will be called for medical evaluation sessions may suffer of additional psychological burden due to the evaluation procedure and/or outcome. In this case, the i-PROGNOSIS medical staff (AUTH, KCL, TUD) in each data collection site (Greece, UK, Germany) should arrange an appointment between the participant and a psychologist/consultant in their institution or through channels of the respective national health system, based on the participant's health insurance and the general practice in each country.

General procedures: If an adverse event does occur it is important that general procedures are followed to eliminate the risk or prevent further harm to the participant. These procedures include:

- The data collection sites should produce a health-safety statement that will include an emergency plan for adverse events. Medical staff from the relevant i-PROGNOSIS partner, responsible for the local data collection, will be responsible for performing the required examinations prior to the data collection onset. Appropriated medical staff will have knowledge of these data, be in touch with participants in the SData and interventions data collection phases, and may instruct a particular data type collection/intervention cessation in case of a foreseeable adverse outcome.
- For the Exergames intervention, i-PROGNOSIS medical staff should inform participants prior to their engagement with the particular intervention that when and if they experience episodes of transient light-headedness, chest discomfort, leg cramps, occasional irregular heartbeats, and abnormal blood pressure response, they should stop immediately exercising and rest. If symptoms persist, participants or their caregivers should contact the medical staff to arrange for an examination appointment.
- For the GData collection phase, during which participants will retain their anonymity and there will be no direct contact between them and the i-PROGNOSIS medical partners, an appropriate procedure for participants to follow in case of minimal adverse events and contact channels with i-PROGNOSIS medical staff will be available through the i-PROGNOSIS website and the i-PROGNOSIS detection mobile application.
- Following an adverse event, the appropriate health and safety forms reporting an incident will be completed and the concerned REC will be informed.

6.5 DATA MANAGEMENT

6.5.1 Data Protection and Anonymisation Compliance

The i-PROGNOSIS project will take every measure to comply with the requirements mentioned in Section 5.1. In particular, the new Data Protection Regulation (Section

5.1) will be taken into consideration that has entered into force in May 2016, but two more years are given before it shall apply to all EU Member States.

Data Management Infrastructure: i-PROGNOSIS will be using Microsoft Azure Cloud services[109] for storing and processing the gathered information. In particular, the European data centres of Microsoft Azure will be used (in Ireland and/or Netherlands). Although a detailed data management architecture for handling the data (personal and non-personal) is a work in progress, and as already stated above, there is a period of two years for applying the regulation for personal data (or transposing the corresponding directive), Microsoft Azure has already provided a document on Security and Privacy, which is regularly updated[110]. The information contained in this document represents the current view of Microsoft Corporation on the issues discussed as of the date of publication.[111]

Regarding the specific points identified in Section 5.1, the following answers can be found or inferred in the Microsoft document:

Data processors are also responsible for data protection - Global effect (DP1, DP2)

- Microsoft has established the operational processes necessary to meet the exacting requirements of the contractual clauses used in agreements between service providers (such as Microsoft) and their customers for the transfer of personal data to processors.
- Regarding the global effect, it is clear that the new regulation affects Microsoft, as it deals not only with EU organisations, rather every global organisation that may have data on EU citizens and residents. Still, the project will be using the EU Microsoft data centres and it will not be necessary to transfer data outside of the EU [except for datasets shared in the context of the Open Research Data Pilot (Section 6.5.2)].

Stricter rules on transferring data on EU citizens outside the EU (DP3)

- As stated above, i-PROGNOSIS will be using European data centres. Microsoft offers customers the EU Standard Contractual Clauses that provide specific contractual guarantees around transfers of personal data for in-scope services. European privacy regulators have determined that the contractual privacy protections Azure delivers to its enterprise cloud customers meet current EU standards for international transfers of data.
- Microsoft asset and data protection procedures provide prescriptive guidance around the protection of logical and physical data and include instructions addressing relocation. Customers control where their data is stored while using Azure services such as Site Recovery and Backup.

Erasure (DP5)

[109] Microsoft Azure https://azure.microsoft.com/
[110] Microsoft Azure Compliance http://www.microsoft.com/download/en/details.aspx?id=26647
[111] A full disclaimer is included in the above document

- Data destruction techniques vary depending on the type of data object being destroyed, whether it may be subscriptions, storage, virtual machines, or databases. In Azure's multi-tenant environment, careful attention is taken to ensure that when a customer deletes data, no other customer (including, in most cases, the customer who once owned the data) can gain access to that deleted data. Azure follows NIST 800-88 Guidelines on Media Sanitisation (Kissel et al., 2014), which addresses the principal concern of ensuring that data is not unintentionally released. These guidelines encompass both electronic and physical sanitisation.

User rights (and acceptable usage policy) (DP4, DP6)

- Microsoft's customer access controls and trust levels are described on the Microsoft Azure Trust Centre website. Before using Azure Services, customers are required to review and agree with the acceptable use of data and the Microsoft Azure service, as well as security and privacy requirements, which are defined in the Microsoft Online Services Use Rights, Microsoft Online Subscription Agreement, Microsoft Azure Platform Privacy Statement and Technical Overview of the Security Features in Microsoft Azure Platform. Microsoft was the first major cloud service provider to make contractual privacy commitments (as well as to incorporate the best practices encompassed by ISO 27018[112]) that help assure the privacy protections built into in-scope Azure services are strong.

Encryption (DP7)

- The following are some capabilities of Azure that are relevant to cryptographic key management:
  Security:
  - Access to secret store is over an encrypted channel
  - Cryptographic key information is stored in an encrypted form
  - Tamper resistant auditing of access to the secret store

  Automated Key Management:
  - Automatic generation of key pairs and certificates
  - Automatic and secure storage of the key pair information in a database
  - Automatic on-demand, minimal downtime key rollovers

  Alerting and Reporting:
  - Alerting on certificates that will expire in next *N* days.
  - Key management encompasses the entire life cycle of cryptographic keys. A key has three phases during its life, namely - Pre-Operational, Operational and Post-Operational.

  Azure Crypto algorithms / Key lengths:
  - Symmetric Block: AES >=256 bit
  - Block Cipher Modes: CBC, CCM, GCM
  - Asymmetric: RSA (>=2048bit), Diffie-Hellman (>= 2048bit), ECC (>= 256bit), Elliptic Curve Cryptography P-256 or greater
  - Hash (including HMAC usage): SHA-2 (SHA-256, SHA-384, SHA-512)

[112] ISO/IEC 27018:2014 http://www.iso.org/iso/catalogue_detail.htm?csnumber=61498

- HMAC Key Lengths: >=128 bit

Regarding other Azure compliances, there is an on-line compliance tool as part of the Microsoft Trust Centre[113], which provides available certifications per service, region and discipline. The EU certifications are provided by selecting "EU" as the location. By doing so, it can be seen that Microsoft Azure complies with the ENISA Cloud Computing Information Assurance Framework, identified at the end of Section 3.2.3. Further certifications and updates on the certifications of the new EU data protection regulation will be provided in the next version of the present report.

Anonymisation: A corner stone of the i-PROGNOSIS data collection will be the data anonymisation generated by the participants in all phases. Thus, the mobile application and the related data management infrastructure will be developed in such a way that no personal identification will be required from the application users (participants in the GDATA collection phase). Their baseline characteristics and collected data will be labelled for the purpose of storage and processing with a coded participant (or user) ID. Furthermore, for the data collection phases during which participants cannot be anonymous (SData and Interventions data collection phases), the following actions will be taken:

- ❖ The identity of each participant will be kept confidential at the institution responsible for the data collection and will not be shared amongst consortium partners or any other group.
- ❖ Each participant will be assigned a coded participant ID once they provide written informed consent. The participant ID will be the only way of identifying participants.
- ❖ The mapping of coded participant IDs with personal IDs will be stored in a password-protected electronic file on a secure computer, at each institution responsible for the data collection.
- ❖ All documentation required will have the participant ID and will not contain any information that would identify the participant.
- ❖ Hard-copy documentation will be stored securely in a dedicated space, only accessible to the i-PROGNOSIS investigators at each institution responsible for the data collection.

Concerns: Based on the aforementioned, i.e., the use of certified Cloud services (Microsoft Azure) and the data anonymisation approach to be adopted, the level of concern for incompliance with data protection and anonymisation regulations is considered low.

6.5.2 Data Exchange & Access Rights Compliance

The i-PROGNOSIS project will take every measure to comply with the requirements mentioned in Section 4.2. Thus, for ensuring the maximum possible compliance, specific roles of researchers and developers regarding data access and data exchange will be defined. The latter will be presented in detail in two deliverables of the project:

[113] Microsoft Trust Centre compliance tool https://www.microsoft.com/en-us/trustcenter/Compliance

- *D2.2 - Data collection and medical evaluation protocol* (Month 8): In this deliverable, general roles (e.g., researcher, developer, medical personnel etc.) and sensitive data types based on EU Directives will be defined. Following, the security level and access rights of each role will be matched to each type of data for all data collection phases of the i-PROGNOSIS project. This deliverable will also establish specific data protection measures for each security level.
- *D5.1 - Open research data management plan* (Month 6): This will be the data management plan (DMP) concerning all datasets that are planned to be collected during the project. For each dataset, data sharing procedures will be defined (access type and access procedures) and partners activities and responsibilities will be established. The DMP will also report on the datasets or parts of datasets that will be publicly available in the context of the Open Research Data Pilot, as well as, which parts of the datasets will not be shared due to ethical and privacy reasons, in compliance with DH11 and UN7 (Section 3).

In addition to the aforementioned deliverables, the Consortium Agreement signed by all partners involved in the i-PROGNOSIS project (i-PROGNOSIS Consortium Agreement, 2016), and specifically Sections 8 and 9, has already established the partners' rights and obligations regarding the ownership and access rights to results (including the data generated).

Concerns: Based on the aforementioned, the level of concern for incompliance with data access and exchange regulations is considered low.

6.5.3 Use of Data in i-PROGNOSIS Deliverables and Publications

With regard to the i-PROGNOSIS Deliverables and publications, first of all, the i-PROGNOSIS project will respect and comply with the basic guidelines provided in the Article 29 of the Grant Agreement No 690494 of the project, regarding the use of data in the dissemination activities and more specifically, referring to:

- Article 29.1: Obligation to public dissemination of results, incl. the obligation of, giving advance notice prior to a dissemination activity and the right of any beneficiary to object to it and the obligation of formal notification to the Commission before dissemination takes place (in case of no protection of the results);
- Article 29.2: Provisioning of open access (free of charge online access for any user) to all peer-reviewed scientific publications relating to its results, (unless otherwise identified in the data management plan), the standard format of the bibliographic metadata;
- Article 29.3: Provisioning of open access to research data generated in the action ('data');

while also ensuring the applicability of the standard ethical guidelines on data privacy and protection of personal data (see Article 27 - Protection of results, Article 36 -

Confidentiality, Article 37 – Security related obligations and Article 39 - Processing of personal data).

In addition, based on the related deliverable[114] of the SMARTCARE project (www.pilotsmartcare.eu), the following specific guidance on data privacy regarding scientific dissemination will be applied:

- Data are to be fairly and lawfully processed only for the purposes of the project.
- Only appropriate research/other personnel within the participating organisations should be granted access to the original/raw data.
- All data to be disseminated must be made anonymous.
- Only summaries of the quantitative data should be available. Excerpts (e.g. quotations) from the qualitative data may be included in any results section of any report or academic publication.
- Participants must be treated with respect at all times and their anonymity must be protected. Pseudonyms or codes must be used to replace any identifiers within the data. Every quotation must be made anonymous using e.g., a pseudonym or depersonalised participant ID-code.
- Quotations from interviews may be included in reports and publications arising from the research.
- Any sensitive information that a participant may share with the interviewers must remain confidential and must not be disclosed/ disseminated in any part of the research.
- Reports must only contain selected passages of interview transcripts and must not publish transcripts in their entirety. All quotations will be anonymous.
- Video recordings of persons (if any) will also be separated from identifiers permanently and will not be used publicly.

Concerns: Based on the aforementioned and the experience of the researchers participating in the i-PROGNOSIS regarding the preparation of scientific dissemination material, the level of concern for incompliance with good practices on the use of sensitive data in dissemination activities is considered low.

7 ETHICS MANAGEMENT & DATA CONTROL IN i-PROGNOSIS

From the initiation of i-PROGNOSIS, aspects of the project have been evaluated from an ethical, safety and data management viewpoint, recognising the importance of ethics and data protection in the scheduled data collection phases, especially, when these phases will involve sensitive populations such as PD patients. The product of the latter evaluation is the present manual. In the same vein, two special roles relating to the management of ethical and data protection issues have been defined within the project:

[114] SMARTCARE D10.2-*Ethics and Data Protection Framework*, Version 2.0, 15th April 2014 (Public)

Ethics and Safety Manager (Prof. **Heinz Reichmann, TUD**): He will guarantee that appropriate ethics and safety procedures are in place when individuals are involved in the project, highlighting all the appropriate ethical and safety requirements regarding the participation and recruitment of individuals in the medical evaluation phases of the project.

Data controller (Dr. **Fotis Draganidis, MICROSOFT**): He will monitor compliance with national/European rules for the collection, processing and usage of personal data and with Open Access and data sharing objectives of the Horizon 2020 framework.

Furthermore, the management of ethical and data protection issues during the i-PROGNOSIS project life is planned to take place based on the following actions/guidelines:

- The present report is intended to be used as a reference manual for i-PROGNOSIS investigators regarding ethical, safety and data protection issues. Consultation of this manual is advised when designing aspects of the i-PROGNOSIS system or the data collection phases.
- Ethics and data protection will be on the agenda of i-PROGNOSIS consortium meetings to ensure an on-going discussion about relevant issues throughout the project and facilitating reporting of ethical matters.
- Prior to each data collection phase the responsible investigator at the data collection site will send the data collection protocol, together with the consent form, to the i-PROGNOSIS Ethics and Safety Manager for a final quality check against the guidelines outlined in this document. He will study the protocol in detail and he will provide feedback and instructions for adjustments (if necessary). The Ethics and Safety Manager can consult with the Data Controller about specific issues regarding data management.
- A generic consent form (partly based on UK standards) to be used as the basis for compiling the SData and interventions data collection phases consent forms has been produced (Appendix I). A tentative check-list regarding ethical issues compliance to be used by i-PROGNOSIS investigators, during participant enrolment, has been also compiled (Appendix II).
- Furthermore, if the need arises, the Ethics and Safety Manager and the Data Controller are responsible for initiating contact with the Ethics Helpdesk of the EC[115] and the European Data Protection Supervisor (EDPS)[116], respectively. The Help Desk will provide information, expert advice and guidance on ethics, should ethical issues arise in the course of the project. Finally, the EDPS provides more general advice on the policies and legislation that affect privacy of personal data and will be contacted if the need arises.

The aforementioned actions are expected to support and ensure the compliance of the i-PROGNOSIS data collection phases and the effective mitigation of certain issues of concern as reported in Section 6.

[115] EC Ethics Helpdesk https://ec.europa.eu/research/participants/portal/desktop/en/support/other_help_services.html#ohs4

[116] European Data Protection Supervisor https://secure.edps.europa.eu/EDPSWEB/edps/EDPS

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APPENDIX I - GENERIC CONSENT FORM

A generic consent form (template in English) is presented below that will be adapted and translated for the needs of the SData and Interventions data collection phases, prior to which the prospective participant must give hard-copy informed consent:

CONSENT FORM

Please initial each box and print, sign and date the end of the form

I understand that my participation in the i-PROGNOSIS project <e.g., specialised data (SData) or Interventions data collection > study will involve: <provide brief description of what is required in bullets, e.g.:	☐
● Processing my voice during a phone call when talking on my mobile phone.	☐
● Processing of how I type (not the actual keys pressed) using my mobile phone keyboard.	☐
● ...>	☐
I understand that participation in this study is entirely voluntary and that I can withdraw from the study at any time without justification.	☐
I understand that I am free to ask any questions at any time. I am free to withdraw from the study or discuss my concerns with <Name of investigator responsible>.	☐
I understand that the information provided by me will be anonymised, so that it is impossible to trace this information back to me individually. I understand that this anonymised information may be archived and retained as permitted by the legal authorities.	☐
I also understand that at the end of the study I will be provided with additional information and feedback about the outcomes of the study if I like to.	☐
<Other conditions>	☐

I, <Full name>

consent to participate in the study conducted by <Partner>

Signature

_____

Date

___/___/_____

Medical staff member counter signature:

Print

_____

Signature

_____

Date

___/___/_____

APPENDIX II - TENTATIVE PARTICIPANT ENROLMENT CHECK-LIST

A tentative check-list[117], to be used by i-PROGNOSIS investigators during the enrolment of participants in the SData or interventions data collection phases in order to evaluate compliance with ethical issues, individually, for each prospective participant:

PARTICIPANT ID	*<Coded ID>*	
DATE	*<DD/MM/YYYY>*	
i-PROGNOSIS INVESTIGATOR	*<Full Name>*	
General (Circle YES or NO)		
The participant received correct information and accurate explanations about the study design.	**YES**	**NO**
It was discussed with the participant that selection and inclusion in the study is voluntary, consistent with the preferences, freedom, dignity and expectations of the individuals.	**YES**	**NO**
Information and explanation provided/received on	*<DD/MM/YYYY>*	
Provided by	*<Full Name of i-PROGNOSIS investigator>*	
Needs and safety of participant relevant to her/his eligibility to participate in the study have been discussed and evaluated with full, yet confidential, transparency within the research team that is responsible for the participant throughout the data collection study.	**YES**	**NO**
Date	*<DD/MM/YYYY>*	
By	*<Full Name of i-PROGNOSIS investigator>*	
The following topics were actively discussed by the data collection team and were concluded as follows (Circle YES or NO)		
The participant was found eligible by the data collection team.	**YES**	**NO**
No extra/additional physical and/or other health risks were identified for the participant by enrolling in the study.	**YES**	**NO**
No extra/additional risks in electronic data protection/sharing were identified for the participant by enrolling in the study.	**YES**	**NO**
The participant is not/does not feel in a dependent position or suffers from cognitive impairments, which could influence the informed consent process.	**YES**	**NO**
Continuity of service and technology after the end of the project will not jeopardize the participant unacceptably.	**YES**	**NO**

[117] The check-list was based on the one compiled by the SMARTCARE project and reported in the public deliverable D10.2-*Ethics and Data Protection Framework*, Version 2.0, 15th April 2014.

The participant does not reveal extra 'dropout risks'.	**YES**	**NO**
Conflict of Interest (Circle YES or NO)		
The participant has declared no conflict of interest by enrolling in the study.	**YES**	**NO**
Informed Consent (Circle YES or NO)		
The participant has given consent after being thoroughly informed by the responsible i-PROGNOSIS investigator.	**YES**	**NO**
Informed consent has been provided in writing, as a hard-copy, and is securely stored at the institution responsible for the study.	**YES**	**NO**
The participant has been informed that s/he is free to withdraw her/his consent of participation at any time.	**YES**	**NO**
The participant has been informed about and has access to means for asking questions and making complaints.	**YES**	**NO**
The participant is aware that s/he enrols in the study voluntarily.	**YES**	**NO**