PROJECT DELIVERABLE REPORT

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Advanced personalised, multi-scale computer models preventing osteoarthritis

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2.1	29/0910/2020	HULAFE	Review of initial draft
2.2.	28/10//2020	UNIC	Review of initial draft
3.0	26/04/2021	Timelex	Final version

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1 Summary

This Final Version of the Ethics and Safety Manual (D1.5) defines the ethics, safety, and compliance requirements for the OACTIVE project at a high level. It is intended to support OACTIVE's future alignment with the EU's high standards of ethics and safety, and legal compliance. This task was continuous throughout the project: while a first version of this deliverable aimed to outline key issues and requirements, the Ethics and Safety Manual has been developed and maintained further during the project, as additional requirements and concerns surfaced, and appropriate ways to deal with these issues were identified.

As such, the D1.2 First Version of the Ethics and Safety Manual was not intended to be a fully mature and finalized document, but rather a first iteration of essential requirements and compliance strategies that was enriched throughout the project, based on additional feedback from OACTIVE's partners on national compliance requirements and on lessons learned.

The recommendations identified in the First Version of the Ethics and Safety Manual have been implemented throughout the OActive Action and the results are integrated in this Final Version of the Ethics and Safety Manual (D1.5).

The purpose of this document is to develop an ethics and safety code of conduct that identifies the core requirements for the execution of OACTIVE. This code contributes to the recognition of key ethical and legal issues and the development of a relevant project policy towards resolving them, across 11 specific domains:

- Consent objectives
- Protection of minors and other vulnerable persons
- Anonymisation and pseudonymisation objectives
- Legitimacy and secondary use objectives
- Organizational objectives (including ethics committees and local monitoring)
- Patient rights objectives
- Transparency and communication objectives
- National compliance objectives
- Continuous risk assessment objectives
- Safety and security objectives
- Communication of research results and open access

In each case, the high-level objective (*what* we should achieve?) is linked to several controls (*how* do we show that the objective is achieved?). In this manner, this deliverable can act as an operational manual for data processing activities in OACTIVE and can be reused in future comparable initiatives.

In the course of the OACTIVE project, this deliverable has been further developed and detailed, including by operationalising the objectives (e.g. by assisting in the definition of appropriate consent forms where needed) in cooperation with other tasks and work packages in OACTIVE.

2 Introduction

2.1 Purpose and Scope

As a part of work package 1 (Project Management and Coordination in OACTIVE), Task 1.4 – Ethical, Legal and Safety Management was dedicated to ensuring that OACTIVE was executed in compliance with the EU's high standards of ethics, safety and legal compliance. This task is continuous throughout the project: while a first version of this deliverable aimed to outline at a high level how ethics and safety (including legal compliance) were dealt with in OACTIVE, the Ethics and Safety Manual was developed and maintained further during the project, as additional requirements and concerns surfaced, and appropriate ways to deal with these issues were identified.

As such, the D1.2 First Version of the Ethics and Safety Manual was not intended to be a fully mature and finalized document, but rather a first iteration of essential requirements and compliance strategies to be enriched throughout the project, based on additional feedback from OACTIVE's partners on national compliance requirements and on lessons learned. As such, the first version was enhanced based on feedback from pilot site partners, as well as scientists from UPA, CERTH, KUL and LJMU with relevant experience, taking into account specific national regulatory requirements.

The purpose of the D1.2 First Version of the Ethics and Safety Manual was to develop an initial ethics and safety code of conduct that identifies the core requirements for the execution of OACTIVE, without at that stage delving deep into operational implementation. This code has contributed to the recognition of key ethical and legal issues and the development of a relevant project policy towards resolving these issues.

Methodologically, this has been done by drawing requirements from applicable relevant legislation at the EU level, including notably the EU Charter of Fundamental Rights (as the core document in the EU on fundamental human rights), the General Data Protection Regulation (EU) 2016/679 (as the core document in the EU on data protection and informational privacy protection, including for data concerning health), and the Clinical Trials Regulation (EU) 536/2014 (as the core document on clinical trials, including patient rights and safety issues).

Beyond these legal documents, issues and potential resolution strategies have also been drawn from non-legislative policy and guidance documents, notably the FP7 Data protection and privacy ethical guidelines, the Opinion of the European Group on Ethics in Science and New Technologies on the ethical implications of new health technologies and citizen participation, the World Medical Association (WMA) Declaration of Helsinki on ethical principles for medical research involving human subjects, and the European Patients Forum Guidance on the new EU Regulation on the protection of personal data.

The recommendations identified in the First Version of the Ethics and Safety Manual have been operationalized throughout the OActive Action, and the observed results are integrated in this Final Version of the Ethics and Safety Manual (D1.5).

2.2 Ethical and safety concerns and challenges in OACTIVE

Prior to examining the high-level ethics, safety, and legal compliance requirements in the following section of this deliverable, it is worth briefly recalling OACTIVE's specific objectives. The OACTIVE project principally intends to permit a significant leap forward in the approach of osteoarthritis, notably through a more holistic consideration of all relevant factors that affect the development and progression of osteoarthritis at different levels of the system (tissue, organ, body) and, most importantly, their interactions. Beyond purely biological factors, OACTIVE incorporates other influences and information sets from different domains such as environmental, social, economic, and lifestyle factors, and their links to physiological, and medical/ biological risk factors in a patient-specific manner.

The goal was to collect and analyse all of this data in order to generate robust predictors for new personalised interventions for delaying the onset and/or slowing down the progression of osteoarthritis, using a combination of mechanistic computational models, simulations, and big data analytics. Once constructed, these models were used to simulate and predict optimal treatments, better diagnostics, and improved patient outcomes. Furthermore, overcoming the limitations of the current treatment interventions, Augmented Reality (AR) empowered interventions were developed in a personalised framework allowing patients to experience the treatment as more enjoyable, resulting in greater motivation, engagement, and training adherence. The AR element was also helpful for the therapists for validating the patients' progress and allow them more adaptive rehabilitation therapy in terms of flexible interactive content. OACTIVE's general mission is to improve healthcare by transforming and accelerating the OA diagnosis and prediction based on a more comprehensive and holistic understanding of disease pathophysiology, dynamics, and patient outcomes.

OACTIVE, therefore, combined many potential ethical, safety and compliance concerns. A first layer is the usual difficulties encountered in a clinical study and medical research setting, including the challenges of ensuring consent, confidentiality and safety, and longer-term monitoring of a potentially vulnerable constituency. However, in the case of OACTIVE, data protection challenges were broader for several reasons: beyond the habitual medical information, additional factors – including lifestyle and economic information, which can be more highly privacy sensitive – were taken into consideration. Furthermore, OACTIVE aimed to apply a big data analytics approach, in which data sets from multiple sources are combined; this created semantic challenges, and also increased the importance of appropriate anonymisation and/or pseudonymisation strategies to mitigate privacy and security challenges. Finally, as OACTIVE aimed to support personalised treatment, it had to be ensured that patients were appropriately protected against automated decision making in a manner that could be detrimental to their patient rights, including by foreseeing additional transparency measures.

Given these considerations, a strict, continuously re-evaluated, and continuously developed risk assessment and risk minimization approach was needed, in which each measure proposed in this code of conduct must be robust, monitored and enforced. In the section below, an updated and final draft of these measures will be presented.

3 Definition of ethical and safety objectives

As noted above, the purpose of this document is to develop an initial ethics and safety code of conduct that identifies the core requirements for the execution of OACTIVE. In the sections below, we will identify and summarily discuss key ethical, safety and legal issues. This will be done by determining high level requirements for each of the issues, in the form of specific objectives, i.e. as specific goals that should be achieved during any piloting initiative which is a part of OACTIVE. This implies that, in the course of the OACTIVE project, for each piloting initiative it is possible to describe how (i.e. through which specific controls) the objective has been achieved. These controls are documented via the DPIAs conducted iteratively in the course of the project (see also D9.4 - Intellectual property laws, licensing, and data protection).

3.1 Consent objectives

Source:

- Charter of Fundamental Rights of the European Union
- Clinical Trials Regulation
- General Data Protection Regulation
- World Medical Association Declaration of Helsinki
- World Medical Association Declaration of Taipei
- Recommendation CM/Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin (Adopted by the Committee of Ministers on 11 May 2016 at the 1256th meeting of the Ministers' Deputies)
- EDPS, Preliminary Opinion on data protection and scientific research 06 January 2020

Meaning and relevance to OACTIVE:

It is a fundamental principle under EU law that any intervention in the field of biology and medicine cannot be performed without free and informed consent of the person concerned; this principle is stated both in the aforementioned Charter and in the Clinical Trials Regulation.

Furthermore, consent is also one of the grounds of legitimacy for the processing of personal data under the General Data Protection Regulation.

However, it must be clear to all parties involved that consent to participation to a trial or a clinical study and consent to the processing of personal data are different:

- 'consent to participation to a trial or a clinical study' is a procedural ethics requirement. Not only is it a good practice highlighted as necessary by many international conferences and declaration, it is also mandatory under national and European legislation governing clinical trials and studies.
- 'consent to the processing of personal data' is one of the six (6) possible legal grounds provided by the GDPR. Consent to the processing of personal data has several requirements, which are different from those of 'consent for participation to a trial or a clinical study'.

Resulting objective(s):

- Any processing of data concerning health (as defined under the GDPR) in OACTIVE should be authorised on the basis of consent meeting the requirements of clinical trial law. This implies that the consent must indicate a subject's free and voluntary expression of his or her willingness to participate, after having been informed of all aspects that are relevant to the subject's decision to participate.
- The consent should be in writing. When the subject is unable to write, it may be recorded through appropriate alternative means, for instance through audio or video recorders.
- Prior to obtaining informed consent, the potential subject should receive information in a prior interview in a language which is easily understood by him or her. The subject should have the opportunity to ask questions at any moment. Adequate time should be provided for the subject to consider his or her decision.
- The potential subject must be informed that they can withdraw their consent to participate further at any time.
- Proof of consent must be retained in the form of informed consent forms or similar proof.
- In view of the fact that in certain Member States the only person qualified under national law to perform an interview with a potential subject is a medical doctor while in other Member States this is done by other professionals, it is appropriate to provide that the prior interview with a potential subject should be performed by a member of the investigating team qualified for this task under the national law of the Member State where the recruitment takes place.
- Consent to the processing of personal data must be a freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her. In order to certify that informed consent is given freely, the investigator should take into account all relevant circumstances which might influence the decision of a potential subject to participate in an OACTIVE pilot, in particular whether the potential subject belongs to an economically or socially disadvantaged group or is in a situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate.

3.2 Protection of minors and other vulnerable persons

Source:

- Charter of Fundamental Rights of the European Union
- Clinical Trials Regulation
- General Data Protection Regulation

Meaning and relevance to OACTIVE:

The validity of consent is (among other points) determined by the legal capacity of the person concerned to provide their consent. Minors are a typical category of persons whose consent can be questionable in the absence of consent of their parents or legal guardians. Other examples may include persons with diminished mental faculties and/or incapacitated persons.

As osteoarthritis may occasionally occur in minors or in elderly persons with diminished mental capabilities, OACTIVE should ensure that protections are available in these cases.

Resulting objective(s):

- When obtaining consent to participate in OACTIVE, the investigator must assess whether the subject is a minor and subject the person has the mental faculties to provide a freely given, specific, informed, and unambiguous indication of their wishes.
- If the subject is indeed a minor or a person with insufficient mental faculties, their personal data may only be incorporated in OACTIVE with the additional consent of their holders of parental responsibility, legal guardians, or other legal representatives.
- The subjects have received the information in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children;
- The explicit wish of a subject who is capable of forming an opinion and assessing the information to refuse participation in, or to withdraw from, OACTIVE at any time, is respected by the investigator;
- No incentives or financial inducements are given to the subject or his or her legally designated representative except for compensation for expenses and loss of earnings directly related to the participation in OACTIVE;
- The OACTIVE pilot is intended to investigate treatments for a medical condition that only occurs in minors or the OACTIVE pilot is essential with respect to minors to validate data obtained in research on persons able to give informed consent or by other research methods;
- The OACTIVE pilot either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors;
- There are scientific grounds for expecting that participation in the OACTIVE pilot will produce:
    - (i) a direct benefit for the minor concerned outweighing the risks and burdens involved; or
    - (ii) some benefit for the population represented by the minor concerned and such the OACTIVE pilot will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.
- The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.
- If during an OACTIVE pilot, the minor reaches the age of legal competence to give informed consent as defined in the law of the Member State concerned, his or her express informed consent shall be obtained before that subject can continue to participate in the OACTIVE pilot.

3.3 Anonymisation and pseudonymisation objectives

Source:

- General Data Protection Regulation
- Opinion 05/2014 of the Article 29 Working Party on Anonymisation Techniques
- Recommendation CM/Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin (Adopted by the Committee of Ministers on 11 May 2016 at the 1256th meeting of the Ministers' Deputies)
- Recommendation No. R (97) 5 of the Committee of Ministers of the Council of Europe to Member States on the Protection of Medical Data

Meaning and relevance to OACTIVE:

In order to mitigate data protection and privacy harms and to reduce security risks, it is a fundamental principle of EU data protection law that the processing of personal data should always be kept to a minimum. As stated in the GDPR, personal data should be "adequate, relevant and limited to what is necessary in relation to the purposes for which they are processed".

Within OACTIVE, the data minimisation principle is implied that data is pseudonymised wherever possible, i.e. processed only in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Resulting objective(s):

- Clinical data will be pseudonymised so as to ensure a certain k-anonymity (i.e. preventing a data subject from being singled out by grouping them with, at least, k other individuals. To achieve this, the attribute values are generalized to an extent such that each individual shares the same value).
- The k-anonymity methodology must protect against common shortcomings of k-anonymity including inappropriately low k-values, overlooking some quasi-identifiers, and grouping under an uneven set of attributes.
- Specific algorithms must be used that prevent data aggregation when the k-anonymity drops below the required level. Given person-specific field-structured data, a release of the data will be produced with scientific guarantees that the individuals who are the subjects of the data cannot be re-identified while the data remain practically useful.
- A Data anonymisation strategy was prepared in case research data, containing personal data was required to be shared in an uncontrolled environment, or in a manner resulting in risks for the data subjects. The strategy can be found in Deliverable 9.4 Intellectual property laws, licensing, and data protection.

3.4 Legitimacy and secondary use objectives

Source:

- Clinical Trials Regulation
- General Data Protection Regulation
- EDPS, Preliminary Opinion on data protection and scientific research 06 January 2020

Meaning and relevance to OACTIVE:

Research can be based on data which is initially collected specifically for the purposes of OACTIVE pilots, or it can be based on data, which was collected earlier, and which is re-used for the purposes of OACTIVE. The latter is referred to as secondary use. This is possible, provided that measures are taken to ensure the legitimacy of the use of the personal data, particularly in a clinical setting where a specific treatment may be suggested as a result of the secondary use of the data. Informed consent must be the general rule, with any derogations being subject to requirements defined under national law.

Resulting objective(s):

- Any use of patient data, including secondary use of pre-existing data, should be based on consent as a general rule.
- When consent is not reasonably feasible, secondary use is only permissible upon verification at the national level that secondary use is legally permissible, and that the secondary use envisaged in OACTIVE satisfies national exemptions to consent for research purposes, and that technical and organisational safeguards are in places when using patient data (including confirmations on this point by any relevant ethics committee).
- When data is shared between partners, the relevant contractual documents (i.e. data processing agreements) are prepared.

3.5 Organisational objectives (including ethics committees and local monitoring)

Source:

- Clinical Trials Regulation
- Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)"
- EDPS, Preliminary Opinion on data protection and scientific research 06 January 2020

Meaning and relevance to OACTIVE:

Under clinical trial rules, a research protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Resulting objective(s):

- All OACTIVE pilots will be initiated only after obtaining the relevant approval from research ethics committees, i.e. an independent body established in a Member State in accordance with the law of that Member State and empowered to give opinions on the pilots, taking into account the views of laypersons, in particular patients or patients' organisations.
- The ethics committee shall be informed of the outcomes of the pilots as required under national law.
- The follow up of these committees will be incorporated into OACTIVE deliverables as a demonstration that all levels of safety, ethics and security have been considered in the study.

3.6 Patient rights objectives

Source:

- Clinical Trials Regulation
- General Data Protection Regulation
- Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare
- EU Charter of Fundamental Rights

Meaning and relevance to OACTIVE:

Even beyond consent and transparency (both of which are dealt with elsewhere as separate objectives), it is critical that patient rights are protected effectively. The patient at all times has the right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices. A high level of human health protection must be ensured in the definition and implementation of all the Union's policies and activities.

Resulting objective(s):

- Within OACTIVE pilots, patient data may only be processed under the supervisions of a health care professional.
- Any treatment options presented to the patient based on OACTIVE's analysis work (including personalised treatment options) need to be validated first by the health care professional before being suggested.
- The health care professional must ensure that patient rights as defined under national law – notably access to the patient record, the right to a second opinion, the right for amendment or correction of a record, as applicable under national law – are respected at all times.

3.7 Transparency and communication objectives

Source:

- World Medical Association Declaration of Helsinki
- Clinical Trials Regulation
- General Data Protection Regulation
- EDPS, Preliminary Opinion on data protection and scientific research 06 January 2020

Meaning and relevance to OACTIVE:

Since OACTIVE's work is principally based on the informed consent of the patient, it is critical that the patient receives information in a manner and at a level of detail which is appropriate to ensure that they adequately understand the project's scope, ambitions and possible impacts. This implies that information must be provided in writing in a sufficiently clear and accessible manner, that key topics are covered, and that a spoken explanation is available to provide further details as required. Furthermore, the information must be continuously available to the patient in a manner that allows them to continue to evaluate and reflect upon their participation, and to express their wishes in this respect (e.g. on the project/ institution website).

Resulting objective(s):

- Information is given to the subject or, where the subject is not able to provide informed consent, his or her legally designated representative for the purposes of obtaining his or her informed consent shall:

  (a) enable the subject or his or her legally designated representative to understand:

  (i) the nature, objectives, benefits, implications, risks, and inconveniences of the OACTIVE pilot;

  (ii) the subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate and the right to withdraw from the OACTIVE pilot at any time without any resulting detriment and without having to provide any justification;

  (iii) the conditions under which the OACTIVE pilot is to be conducted, including the expected duration of the subject's participation in the OACTIVE pilot; and

  (iv) the possible treatment alternatives, including the follow-up measures if the participation of the subject in the OACTIVE pilot is discontinued;

  (b) be kept comprehensive, concise, clear, relevant, and understandable to a layperson;

  (c) be provided in a prior interview with a member of the investigating team who is appropriately qualified according to the law of the Member State concerned.

- The information referred to above shall be prepared in writing and be available to the subject or, where the subject is not able to give informed consent, his or her legally designated representative.
- In the interview referred to above, special attention shall be paid to the information needs of specific patient populations and of individual subjects, as well as to the methods used to give the information. In the interview, it shall be verified that the subject has understood the information.
- The patient's medical and personal data shall not be published in project deliverables and publications in an identifiable manner.

3.8 National compliance objectives

Source:

- Clinical Trials Regulation
- General Data Protection Regulation
- Relevant national legislations

Meaning and relevance to OACTIVE:

While EU laws and policies have significantly harmonised legal and compliance requirements, the harmonisation is not absolute. Certain key topics remain subject to national laws and national interpretations, including the definition of national requirements for the processing of data concerning health, the definition of appropriate safeguards for scientific research, the validity for the consent of minors, and the need for national authorisations. All of these topics are critical for ensuring the legal compliance of OACTIVE, and a methodology must be applied that controls for this potential variation.

Resulting objective(s):

- OACTIVE piloting activities must be subject to national compliance supervision from an ethics committee or a similar organisation which is familiar with national compliance requirements.
- National compliance requirements for OACTIVE pilots will be identified and logged throughout OACTIVE's duration.

3.9 Continuous risk assessment objectives

Source:

- Clinical Trials Regulation
- General Data Protection Regulation
- Guidelines on Data Protection Impact Assessment (DPIA) and determining whether processing is "likely to result in a high risk" for the purposes of Regulation 2016/679, WP248 rev.01

Meaning and relevance to OACTIVE:

Any medical research that aims to result in a specific treatment strategy (including personalised treatment recommendations as envisaged by OACTIVE) presents potential risks to the patients, even if no new medical substances or treatments are piloted. For this reason, risk should be monitored and evaluated on a continuous basis.

This is also a principle of EU data protection law: the GDPR requires that, where a type of processing in particular using new technologies, and taking into account the nature, scope, context and purposes of the processing, is likely to result in a high risk to the rights and freedoms of natural persons, the controller shall, prior to the processing, carry out an assessment of the impact of the envisaged processing operations on the protection of personal data (DPIA).

Resulting objective(s):

- A data protection impact assessment (DPIA) has been conducted and maintained in the course of OACTIVE that identifies risks and proposes mitigation strategies (see D9.4 - Intellectual property laws, licensing, and data protection). The DPIA complies with the requirements of the GDPR, and also encompasses any identified risks that go beyond data protection/privacy challenges.
- Notably, the risks and potential mitigation strategies related to automated decision making are covered. I.e., given OACTIVE's objective of providing personalised treatment recommendations, patients must be appropriately protected against any negative outcomes of automated analysis, including notably through the ensured intervention of an appropriately trained health care professional who can assess and (if necessary) correct inaccurate treatment recommendations before any negative effects on the patient can occur.

3.10 Safety and security objectives

Source:

- Clinical Trials Regulation
- General Data Protection Regulation

Meaning and relevance to OACTIVE:

Data concerning health is considered as inherently privacy sensitive, and any processing activities therefore must be subject to elevated requirements of security and confidentiality. In addition, OACTIVE envisages to apply a 'big data' analytics approach, implying that information from multiple sources will be brought together (albeit in a pseudonymised form as described above) and comparatively analysed. Finally, the fact that personalised treatment options will be suggested on the basis of this process creates additional safety concerns. Therefore, measures are required that safeguard the data from an information privacy perspective, but also from a health protection perspective.

Resulting objective(s):

- Within OACTIVE, patients' data may only be processed as long as the person who does the processing is bound by a legal obligation of professional secrecy and is acting under the supervision of a health professional.
- All processing activities undertaken within OACTIVE must be subject to authentication and authorisation processes in a way that allows the patient data to be protected against access or use by unauthorised parties.
- All processing activities undertaken within OACTIVE must be subject to logging processes in a way that allows access, modification, and deletion of the data to be detected and audited, at least until the termination of the OACTIVE project.
- All processing activities undertaken within OACTIVE must be subject to monitoring at the national level, including by data protection officers operating at local sites (with local DPOs being able to monitor only the processing activities within OACTIVE that relate to their patients).
- All processing activities undertaken within OACTIVE must be subject to appropriate storage and retention controls, ensuring that all data is stored in a manner that renders them accessible only under the control of OACTIVE project partners. Data must be stored in the EU/EEA only, and partners are responsible for ensuring that data will only be retained as long as is permissible under applicable law.
- If a breach of personal data in the OACTIVE project occurs (i.e. a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed in OACTIVE), the OACTIVE Project Coordination Team and Management Board must be informed by the affected OACTIVE partner(s) without undue delay after becoming aware of it, so that appropriate follow-up actions can be undertaken.
- The security of processing is monitored and documented at project level through the performance of a DPIA, with several iterations.

3.11 Communication of research results and open access

Source:

- Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)"
- General Data Protection Regulation
- Guidelines to the Rules on Open Access to Scientific Publications and Open Access to Research Data in Horizon 2020

Meaning and relevance to OActive:

Scientific research supposes communication of the results through publication. The open access requirement of the EU means that the academic publication relating the results of a project should be accessible to the public free of charges. Open access to publication requires in particular that the underlying research data be made available as well. OACTIVE partners have the obligation to make available for access, mining, exploitation, reproduction, and dissemination the research data (as specified in the Data Management Plan) and the associated metadata. Making data available in open access is a processing operation in the meaning of the GDPR. However, personal data are considered as confidential and should not be made accessible to the public as such without restriction, and for an unlimited duration.

Resulting objectives:

- Identification of data and results that should be communicated and made available in open access. This process should be documented in a log and included in the data management plan.
- Open access must be considered throughout the project in relation to data protection concerns as well as Intellectual property protection concerns.
- Identification of a data anonymisation strategy outlining the measures and the circumstances framing the release of research data containing personal data in open access, and outline alternatives if full anonymisation would not meet the purposes of the release of data in open access.

4 Implementation of the Ethics and Safety Manual

Based on the requirements of this Manual, the following implementation actions have been undertaken:

Consent objectives

- Any participant to the clinical study has provided consent, participation was strictly on a voluntary basis.
- Data was collected in medical centre by medical personnel.
- Information concerning the study and their participation is provided orally and in written form to the data subjects.
- Consent obtained from the patient did not meet the requirement of the GDPR consent, therefore a different legal base was selected.

Protection of minors and other vulnerable persons

- Data of minors was collected. in one medical centre, with the appropriate safeguards in place.
- It was made clear to the patient to the participation to the study that it was strictly on a voluntary basis and had no impact whatsoever on the course of their treatment.

Anonymisation and pseudonymisation objectives

- Data is pseudonymised upon collection.
- And data necessary to communication of results and dissemination obligation is anonymised according to the data anonymisation strategy developed by the consortium (see D9.4 Intellectual property laws, licensing, and data protection, Appendix 5).

Legitimacy and secondary use objectives

- The data are processed on the legitimate interest legal base.
- Data is only further processed for scientific research purposes (anonymisation for communication of results).

Organisational objectives (including ethics committees and local monitoring)

- The activities only proceeded after approval of ethics committee.

Patient rights objectives

- Patient can withdraw their consent and end their participation at any time.

Transparency and communication objectives

- Information is provided to participant prior to the collect of data, and information notice is to be available on the project website ((see D9.4 Intellectual property laws, licensing, and data protection, Appendix 4).
- Any published data is to be anonymised beforehand.

National compliance objectives

- National compliance is ensured at partner level. Each medical centre acquired independently ethical approval for the study.

Country	Legislation
Cyprus	With the implementation of the GDPR in May 2018 the Cypriote Data protection Legislation was amended. The Law 125 (I) of 2018 Providing for the protection of natural persons with regards to the processing of persona data and for the free movement of such data does not have any specific provision on the processing of special categories of data, such as health data for scientific research purpose. However, 2004 1(I) of 2005 Safeguarding and protection of the Patients' Rights Law article 14 provides the secondary legal basis necessary.
Greece	With the implementation of the GDPR in May 2018 the Greek Data protection Legislation was amended., the new legislation (Law 4624/2019) was adopted in August 2019. Processing of special categories of data, such as health data is allowed without the consent of the person concerned where such processing is necessary for scientific or historical research purposes. However specific measures must be taken to protect the rights and freedoms of the data subjects. Research for health purposes, in general, is governed by the provisions of Law 3418/2005 (Medical Code of Conduct), Chapter VII.
Spain	With the implementation of the GDPR in May 2018 the Spanish Data protection Legislation was amended, and the Organic Law 3/2018 of 5 December on the Protection of Personal Data and the guarantee of digital rights adopted. The 17th Additional provision (2.f) to the Organic Law 3/2018 of 5 December on the Protection of Personal Data and the guarantee of digital rights provides that secondary legal basis for the processing of data concerning health the Law 14/2007 of 3 July on Biomedical Research.
Italy	With the implementation of the GDPR in May 2018 the Italian Data protection Legislation was amended and a new legislative decree was adopted. However, the processing of special categories of data for scientific research purpose is governed by a specific authorisation adopted by the Guarantee. Although this specific authorisation predates the GDPR it has not been repealed by the Garante. Until new guidelines are adopted, the old Authorisation applies and constitutes a secondary legal basis under national legislation. **Authorisation no. 9/2014 - General Authorisation to Process Personal Data for Scientific Research Purposes**
Belgium	With the implementation of the GDPR in May 2018 the Belgian Data protection Legislation was amended and a new legislation was adopted. Loi 30 Juillet 2018 relative à la protection des personnes physique à l'égard du traitement de données à caractère personnel, and more specifically its title 4, article 186 (data subjects rights derogations) The Loi relative aux expérimentations sur la personne humaine of the 7 May 2004, is the lex specialis for the processing of special categories of data for scientific research purposes. The law defines how a clinical study involving human person should be organised. The consent mentioned in this legislation is the ethical consent required by ethical committees and ethical standards, it should however not be understood as consent for the processing of personal data and as valid legal ground under the GDPR.

Continuous risk assessment objectives

- A Data Protection Impact Assessment has been carried out, with two iteration during the project (see D9.4 Intellectual property laws, licensing, and data protection, Appendixes 2 and 3).
- The necessary risk mitigation measures identified during the first iteration were implemented, and positive outcome was observed during the second iteration.

Safety and security objectives

- General compliance with the GDPR has been monitored throughout the projects.
- DPIA has been carried out.

- Contractual provision between partners have implemented to formalise the data flow in compliance with the GDPR.

Agreement:	Parties:
OActive Joint Controller agreement	UNIC – HULAFE – ANIMUS – KU Leuven - RIMED
LEITAT Data processing Agreement	UNIC - LEITAT
CERTH Data processing Agreement	UNIC - CERTH
CETRI Data processing Agreement	UNIC - CETRI
SMARTEX Data processing Agreement	UNIC - SMARTEX
LJMU Data processing Agreement	UNIC - LJMU
UPAT Data processing Agreement	UNIC - UPAT

Communication of research results and open access objectives

- Guidelines on open access have been distributed, and a data anonymisation strategy has been implemented (see D9.4 Intellectual property laws, licensing, and data protection, Appendix 5)

5 Conclusions

This Final Version of the Ethics and Safety Manual (D1.5) defines the ethics, safety, and compliance requirements for the OACTIVE at a high level, across eleven (11) specific domains:

- Consent objectives
- Protection of minors and other vulnerable persons
- Anonymisation and pseudonymisation objectives
- Legitimacy and secondary use objectives
- Organisational objectives (including ethics committees and local monitoring)
- Patient rights objectives
- Transparency and communication objectives
- National compliance objectives
- Continuous risk assessment objectives
- Safety and security objectives
- Communication of research results and open access

This core of this deliverable is divided in two parts. First each high-level objective (*what* we should achieve?) is linked to several controls (*how* do we show that the objective is achieved?). In this manner, this deliverable can act as an operational manual for data processing activities in OACTIVE. In the second part, the main means to implement each high-level principle is summarily addressed.

For specific details in implementation actions, the main document reporting on compliance in OACTIVE is D9.4 Intellectual property laws, licensing, and data protection, as well as the ethics deliverables D11.12 to D11.8 submitted at M6.

Appendix – Principal source materials for ethics, legal and safety issues in this manual

- Charter of Fundamental Rights of the European Union of 26 October 2012; see http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:12012P/TXT
- General Data Protection Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC; see http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.119.01.0001.01.ENG
- Clinical Trials Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC; see https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
- FP7 Data protection and privacy ethical guidelines; see http://ec.europa.eu/research/participants/data/ref/fp7/89827/privacy_en.pdf
- Opinion of the European Group on Ethics in Science and New Technologies on the ethical implications of new health technologies and citizen participation; see https://ec.europa.eu/research/ege/pdf/opinion-29_ege_executive-summary-recommendations.pdf
- World Medical Association (WMA) Declaration of Helsinki on ethical principles for medical research involving human subjects, adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as amended from time to time thereafter; see https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
- European Patients Forum Guidance on the new EU Regulation on the protection of personal data; see http://www.eu-patient.eu/globalassets/policy/data-protection/data-protection-guide-for-patients-organisations.pdf