SERBIA ACCELERATING INNOVATION AND GROWTH ENTREPRENEURSHIP (SAIGE) PROJECT

Program PRISMA

ENVIRONMENTAL AND SOCIAL MANAGEMENT PLAN (ESMP)

Artificial INTELligence-based Decision Support System for Early and Accurate Diagnosis of HEART Failure

(INTELHEART)

DRAFT DOCUMENT

Belgrade,
30/10/2023

Table of Contents

Abbreviations and acronyms

AI – Artificial Intelligence

BRS – Brief Resilience Scale

CNNs – Convolutional Neural Networks

COVU – Coventry University, Faculty of Health and Life Sciences, UK

CT – Computed Tomography

DASS – Depression, Anxiety and Stress Scale

DSS – decision support system

ECG – Electrocardiography

ESMF –- Environmental and Social Management Framework

ESMP – Environmental and Social Management Plan

ESS – World Bank's Environmental and Social Standard

FE – Finite Element

FINK – Faculty of Engineering, University of Kragujevac

FMSUKG – Faculty of Medical Sciences, University of Kragujevac

GDPR – Data Protection Regulation

Grad-CAM – Gradient-weighted Class Activation Mapping

HF – Heart Failure

IITKG – Institute for Information Technologies Kragujevac

IVI – The Institute for Artificial Intelligence Research and Development of Serbia

MFUB – Faculty of Medicine (School of Medicine), University of Belgrade

MFUN – Faculty of Medicine, University of Nis

MFUNS – Faculty of Medicine, University of Novi Sad

ML – Machine Learning

MRI – Magnetic Resonance Imaging

ORDP – Open research Data Pilot

PI – Principal Investigator

PIU – Project Implementation Unit

RBF – Radial Basis Function

SAIGE – Serbia Accelerating Innovation and Growth Entrepreneurship

SF – Science Fund

SOPs – Standard Operating Procedures

SRO – Scientific and Research Organization

SUNP – State University of Novi Pazar

WP – Work Package

1 Introduction

This draft Environmental and Social Management Plan (ESMP) has been prepared for the PRISMA Program, funded by the Science Fund of the Republic of Serbia. The goal of the PRISMA Program is to support research projects based on excellent ideas that in the future may have a significant impact on the development of science and research, as well as society at large, and clearly stated motivation for research within the framework of modern trends in the development of science in the relevant scientific fields. The draft ESMP document for the project entitled Project "**Artificial INTELligence-based Decision Support System for Early and Accurate Diagnosis of HEART Failure**" (hereinafter: INTELHEART), was prepared in accordance with Environmental and Social Management Framework (ESMF) for the SERBIA ACCELERATING INNOVATION AND GROWTH ENTREPRENEURSHIP (SAIGE) PROJECT.

The INTELHEART project aims to develop, implement and assess the artificial intelligence (AI)-based computerised digital platform for early and accurate diagnosis of heart failure (HF) in both primary and secondary care. The INTELHEART platform will uniquely integrate patient-specific demographic and clinical data using existing and novel technologies and develop an AI-driven intelligent decision support system (DSS) and mobile app for patient stratification and HF prediction using machine learning, computational modelling, voice characteristics and vocal biomarkers. Voice characteristics will also be used to assess the emotional disturbance and physiological resilience which have been associated with cardiovascular diseases.

According to the Environmental Social Management Plan (ESMP), the INTELHEART project is a research project which will perform activities such as the clinical study and development of tools based on Artificial Intelligence (AI) that might have impact on Population, Health and Safety. Also, the project has potential impacts on the Workers and Community Health and Safety, as well as potential Socio-Economic impacts. The ESMP for the INTELHEART project consists of the set of mitigation, monitoring, and institutional measures to be taken during the project implementation to eliminate adverse environmental and social risks and impacts, offset them, or reduce them to acceptable levels.

1.1 Project description

The **INTELHEART** aims to **develop, implement and assess the AI-based computerised digital platform for early and accurate diagnosis of HF in both primary and secondary care**. The **INTELHEART** platform will uniquely integrate patient-specific demographic and clinical data using existing and novel technologies and develop an AI-driven intelligent DSS and mobile app for patient stratification and HF prediction using machine learning, computational modelling, voice characteristics and vocal biomarkers. Voice characteristics will also be used to assess the emotional disturbance and physiological resilience which have been associated with cardiovascular diseases.

<table>
<tr><th colspan="2">INSTITUTIONAL AND ADMINISTRATIVE PART</th></tr>
<tr><td>Country</td><td>Serbia</td></tr>
<tr><td>Project</td><td>Serbia accelerating innovation and growth entrepreneurship (SAIGE) project</td></tr>
<tr><td>Sub-component</td><td>Science Fund of the Republic of Serbia</td></tr>
<tr><td>Program</td><td>Program PRISMA</td></tr>
<tr><td>Subprogram</td><td>Artificial intelligence</td></tr>
<tr><td>Project title</td><td>Artificial INTELligence-based Decision Support System for Early and Accurate Diagnosis of HEART Failure</td></tr>
<tr><td>Acronym</td><td>INTELHEART</td></tr>
<tr><td>Contact email address</td><td>fica@kg.ac.rs</td></tr>
<tr><td>Participating Scientific and Research Organization (SRO):</td><td>Faculty of Engineering, University of Kragujevac</td></tr>
<tr><td>Partner Research Organization on the project:</td><td>
<table>
<tr><th>SRO</th><th>Acronym</th><th>Country</th></tr>
<tr><td>Faculty of Engineering, University of Kragujevac</td><td>FINK</td><td>RS</td></tr>
<tr><td>Institute for Information Technologies Kragujevac</td><td>IITKG</td><td>RS</td></tr>
<tr><td>The Institute for Artificial Intelligence Research and Development of Serbia</td><td>IVI</td><td>RS</td></tr>
<tr><td>Faculty of Medical Sciences, University of Kragujevac</td><td>FMSUKG</td><td>RS</td></tr>
<tr><td>Faculty of Medicine, University of Novi Sad</td><td>MFUNS</td><td>RS</td></tr>
<tr><td>Faculty of Medicine, University of Belgrade</td><td>MFUB</td><td>RS</td></tr>
<tr><td>State University of Novi Pazar</td><td>SUNP</td><td>RS</td></tr>
<tr><td>Faculty of Medicine, University of Nis</td><td>MFUN</td><td>RS</td></tr>
<tr><td>Coventry University, Faculty of Health and Life Sciences, UK</td><td>COVU</td><td>UK</td></tr>
</table>
</td></tr>
</table>

The specific **objectives** of the project are to:

1. **Perform clinical study for heart failure diagnosis in tertiary care to collect and integrate various diagnostic data** (WP1);
2. **Develop AI tools for risk stratification and early diagnosis of heart failure** (WP2);
3. **Design, develop and validate a breakthrough AI technology** (WP3);
4. **Develop a finite element model for the patient-specific whole cardiac working cycle** (WP4);
5. **Develop, evaluate and refine a cloud computational platform and mobile app for early diagnoses of heart failure based on artificial intelligence, computational modelling and voice biomarkers** (WP5);
6. **Implement a pilot of the diagnostic platform in participating clinical centers and inform the Serbian regulatory body for medical device class 2b** (WP6);
7. **Disseminate and exploit the project results and communicate the INTELHEART project** (WP7);
8. **Manage the project and the developed innovations based on the project management methods** (WP7).

Existing research on the patient perspective of HF is limited and many untested assumptions are made about what we think is best for people with HF and what matters to them most – with little confirmation that these are meaningful or correct. Our overall ambition is to improve the quality and length of life for patients and to reduce the economic burden of HF on health care systems. The strategy on how to approach this goal is to offer primary and secondary care with novel technology-based computational tools finite element and AI which will allow early and accurate diagnosis of HF. The concept, ambition and impact assessment of INTELHEART project are presented in Figure 1.

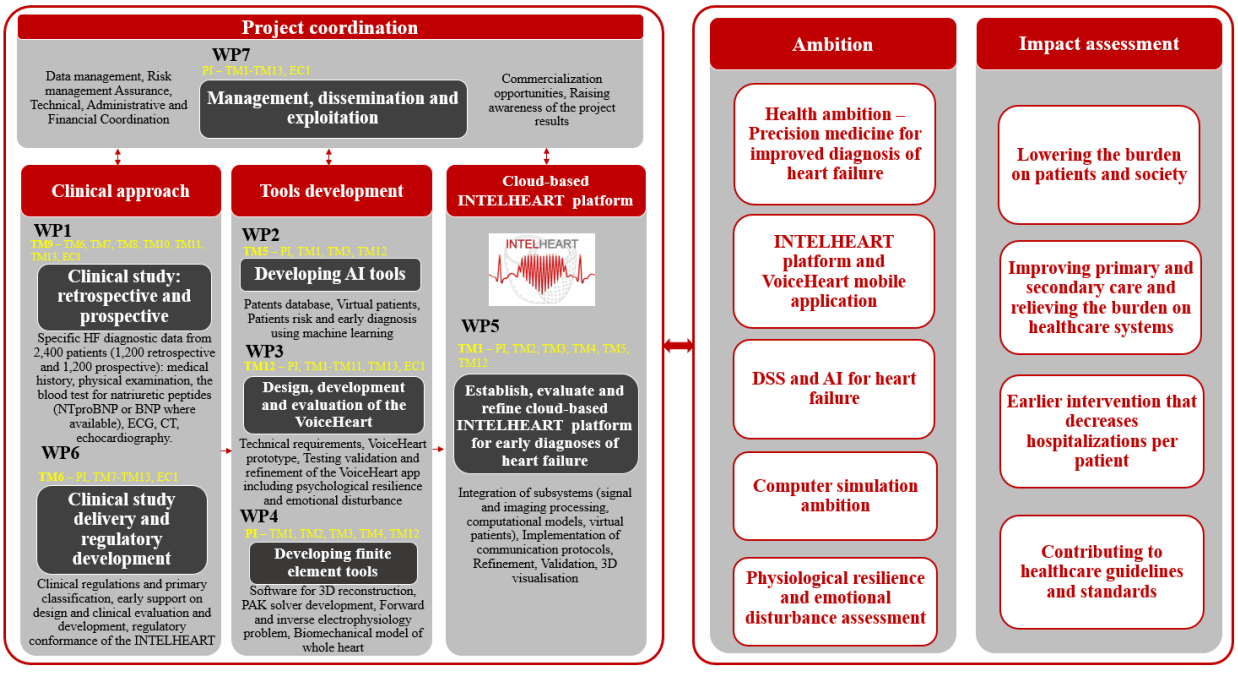

Figure 1. The concept, ambition and impact assessment of INTELHEART project.

Healthcare systems face roadblocks such as lack of appropriate tests and equipment and limited resources at various levels of care that delay diagnosis and treatment for HF in general. **The INTELHEART platform presents a new and innovative AI-DSS solution, which needs fewer resources to diagnose HF accurately and provides patient-centric treatment advice to its primary and secondary care users.**

1.1.1 Project location

Members of the project team are members of nine technical and clinical Institutions located in Kragujevac, Novi Sad, Belgrade, Novi Pazar and Nis. Faculty of Engineering, University of Kragujevac (FINK), Institute for Information Technologies Kragujevac (IITKG) and Faculty of Medical Sciences, University of Kragujevac (FMSUKG) are located in Kragujevac. The Institute for Artificial Intelligence Research and Development of Serbia (IVI) and Faculty of Medicine, University of Novi Sad (MFUNS) are located in Novi Sad. Faculty of Medicine (School of Medicine), University of Belgrade (MFUB) is located in Belgrade. State University of Novi Pazar (SUNP) is located in Novi Pazar. Faculty of Medicine, University of Nis (MFUN) is located in Nis. The project has also a clinical expert from diaspora that is Coventry University, Faculty of Health and Life Sciences, UK (COVU).

The FINK together with technical institutions (IITKG, IVI, SUNP) will bring the expertise in technical science (FE modelling, multiscale modelling, AI, signal processing) and achieve common project objectives with clinical partners (FMSUKG, MFUNS, MFUB, MFUN) and clinical expert from diaspora (COVU) in development of cloud-based computational platform and mobile app for early and accurate diagnosis of heart failure.

1.1.2 Risk Estimation following Environmental and Social Standard (ESS)

During the preparation and implementation phase of the scientific research project INTELHEART, potential environmental and social impacts are listed below (Table 1).

Table 1. Review of the impact on the environment and society for the duration of the INTELHEART project.

INFLUENCE	SIGNIFICANCE	COMMENT
Impacts on land use and settlements	Does not exist	During the realization of the project there will be no expropriation of land
Ground and surface water	Does not exist	During the realization of the project, ground and surface water will not be affected
Air quality	Does not exist	During the realization of the project, the air quality will not be affected
Flora and fauna (protected areas and species)	Does not exist	During the realization of the project, there will be no impact on flora and fauna
Monuments	Does not exist	During the realization of the project, there will be no impact on the cultural heritage

INFLUENCE	SIGNIFICANCE	COMMENT
Noise	Low	Temporary impact
Soil management	Low	With the application of appropriate measures of waste management (medical waste)
Management of Waste (no hazardous)	Low	In accordance with existing waste management plan
Working in the field	Moderate	During the realization of the project, the standardized protocols will be followed to minimize the impact on environment
Management of hazardous materials, including hazardous waste	Low	With the application of appropriate management of hazardous medical waste
Medical waste management	Low	With the application of appropriate management of hazardous medical waste
Working in the laboratory	Moderate	With the application of standard procedures ensuring occupational health and safety
Safe management of chemicals, biohazards and hazardous materials	Low	With the application of appropriate management of hazardous medical waste
Handling of gases under pressure (H&Sat work and prevention of accidents)	Does not exist	During the realization of the project, gases under pressure will not be handled
Health&Safety of the local populations (Field activities)	Low	The impact on health and safety of the local populations and citizens in terms of field activities will be minimized with the application of appropriate project management
Health&Safety of the participants in the clinical study	Moderate	During the realization of the project, the impact on health and safety of the participants in the clinical study will be minimized following the standard clinical procedures, best clinical practice and safety protocols
Data privacy, data security and data processing	Moderate	With the application of confidential handling and storage of medical and other personal data; comprehensive data security strategy; standardised computational methods; interpretable and explainable AI-methods
Ethics in clinical study	Moderate	With the application of clinical protocols in each clinical centre; obtained informed consent from patients for data collection; enabled grievance mechanisms
Use of AI-tools	Moderate	With the application trustworthy AI, addressing EU requirements
Cumulative impacts	Moderate/Low	Cumulative impacts will be monitored (questionnaires and feedbacks from participants and community)

1.2 The planned clinical study

The INTELHEART clinical study is a **non-sponsored and non-interventional, clinical research study** which will be done in four clinical centres (Kragujevac, Nis, Novi Sad and Belgrade), in accordance with national legislation and institutional procedures in the field of academic research in medicine. Study population will consist of adult patients diagnosed and treated of heart failure (HF). For the purpose of the study, we will use clinical data, such as: medical history, physical examination, blood tests (including natriuretic peptides (NTproBNP or BNP where available)), ECG, echocardiography, as well as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) where needed. Those HF patients are already under medical treatment in clinical centres, according to their referral clinical centre. Before regular checkup, educated researchers (treating physicians) of clinical centres of Kragujevac, Nis, Novi Sad and Belgrade, will approach to and introduce each patient about INTELHEART project and the content of informed consent. If patient is willing to participate in the INTELHEART clinical study, after he/she got all relevant information and after needed time for asking about participation, he/she will sign the informed consent.

MFUNS (Novi Sad) will design the prospective diagnostic clinical research study protocol which will then be adopted by other clinical partners from Belgrade (MFUB), Nis (MFUN) and Kragujevac (FMSUKG). The study will be conducted in tertiary care: retrospective clinical data collection (specific HF diagnostic data from 1,200 patients obtained in a standard tertiary care clinical practice: i.e. medical history, physical examination, the blood test for natriuretic peptides (NTproBNP or BNP where available), ECG, CT, and echocardiography) for 8 months and prospective clinical study recruitment of 1,200 HF suspected patients (M6-M29) with the diagnosis of HF confirmed at the time of investigations in order to collect patient-specific data obtained using additional state-of-the-art novel technologies beyond standard clinical practice. In addition to standard clinical investigations, CT MRI, NTproBNP or BNP will be performed where available and needed, while novel technologies will be used across all clinical partners: portable, smartphone-controlled ECG devices and voice recordings. The patient examination will also include Brief Resilience Scale (BRS) and Depression, Anxiety and Stress Scale (DASS) tests. The prospective study will be performed in suspected HF patients undergoing diagnostic clinical investigations for HF. Each clinical partner will recruit 300 patients, which is in total 1,200 patients from four clinical participants, (i.e. 600 patients with a diagnosis of HF with reduced left ventricular ejection fraction (HFrEF), and 600 patients with a diagnosis of HF with preserved ejection fraction (HFpEF)).

The procedures which are not included in standard treatment protocols for HF patients, will be also described in detail in informed consent. Also, patients will be informed that they can withdraw their informed consent during the clinical study. Any procedure will not be performed before informed consent is signed. Inclusion criteria for the participants in the study are age over 18 and written consent to participate in research. Exclusion criteria will be presence of malignant diseases and/or presence of significant renal weakness. Exclusion from research will be carried out if the patients no longer want to participate in the research.

Diagnosis of HF, as well as treatment procedures and patients' healthcare have been already defined by protocols in each of four clinical centres. Those clinical protocols are well established and standardized, and they are already in clinical practice. We hope that generated knowledge from our research will be beneficial for future clinical practice in diagnosis and treatment of HF.

Once again, we would like to stress out that our clinical research study is not related to sponsored and interventional clinical study. However, the term "clinical" is related to everyday HF patients from our

clinical practice, i.e. HF patients who are already referred for treatment. As INTELHEART clinical study is academic, non-sponsored and non-interventional study, decisions from Ethics Committees of each participating clinical centre cover all ethical issues for such type of study. In the same time, after obtained decisions from Ethics Committees, they are also responsible to monitor conducting of the study, as well as to monitor collected data during and after the study lifetime. Each decision of the local Ethics Committees has issued after the insight into complete study documentation, and careful assessment of potential risks and benefits. Each decision incorporates all relevant documents following the rules for conducting the research in humans. If additional information is needed before conducting the INELHEART clinical study, the project consortium will consult the local Ethics Committees.

1.3 Data usage

What types of data will the Project generate/collect?
The project will collect primary and secondary clinical data. We will get secondary data from the medical history of patients. Primary data will be collected for the first time for each patient. For the purpose of INTELHEART clinical study, data from 2,400 HF patients (1,200 retrospective and 1,200 prospective) will include: medical history, physical examination, the blood test for natriuretic peptides (NTproBNP or BNP where available), ECG, CT & MRI where needed, echocardiography, voice recordings, BRS, DASS tests. Clinical data will be collected by clinical participants FMSUKG, MFUNS, MFUB, MFUN. Beside medical data, the project will generate data as outcome of AI and computer modelling methods (FINK, IVI, SUNP, IIT).
What significant datasets are needed for Project implementation? Specify data types and data size. Specify primary or secondary usage of data
Three different types of datasets will be needed: 1. Standard table dataset that will include discrete and continuous parameters from the medical history, blood tests and various scoring systems (BRS, DASS); 2. Imaging dataset (echocardiography, CT, ECG and MRI where needed); 3. Voice dataset Total of 2,400 patients are needed for project implementation (1,200 retrospective and 1,200 prospective). During the study and collection of data, inclusion criteria are not specific to any vulnerable population. The dataset will consist of **medical images** (CT slices, 300 slices per patient, each slice 500 kB), **medical history**, **blood test** (200kB per patient), **echocardiography** (10MB per patient video file), **ECG** (scanned paper version 10 MB per patient), Brief Resilience Scale (**BRS**) and Depression, Anxiety and Stress Scale (**DASS)** tests. These tests will be filled via mobile app during patients' visits to the hospital. **Patient's voice** will be recorded for 20 seconds (30 MB per patient for MP3 file). Follow up study will be performed 2 times. So, estimated total size of data will be 1 GB per patient, for 2,400 patients there is need for 2,4 TB. Clinical data will be stored at local storage resources of each participating clinical centre. Collected data will be primarily used to feed AI algorithms and FE simulations. The AI algorithms and FE simulation need at least 4-5 TB of memory. The secondary use will be for research purposes and further development of achieved results. Storage resources for generated data using AI algorithms and FE simulations will be provided by the FINK.
How will the data be stored and accessed? What measures will be taken to ensure secure data storage and usage, including data security?
Clinical data will be stored at local storage resources of each participating clinical center. Our aim is to ensure confidentiality (cannot be accessed either over a network or locally by unauthorized people), integrity (data cannot be tempered with or changed) and availability (reduce risk of having storage resources destroyed deliberately or by accident). The project participants will follow the National and European standards for guaranteeing the privacy of any sensitive data handling. Any personal information of the clinical study will be anonymized before being shared between data controllers and data processors. Any data collection will be preceded by signing

informed consent by participants. Standard procedures within ISO27001 will be applied for secure data storage and usage. For Patient Medical Records the CDA Release 2 HL7 Standard (Clinical Reports) will be used following the IHE Cardiology Technical Framework. The network traffic and data upload will be encrypted via TLS/SSL (HTTPS) protocol. For medical images, DICOM standard will be followed. Also, the standardized data mining and statistical stratification models will be used. All the above ensure the required security in information exchange and anonymization as well as interoperability, through the application of well-defined protocols and standards. All generated data during and after the project implementation will be stored and storage systems will be located at FINK.

Who will have access to the data during Project implementation?

Access to all clinical data will be allowed only to authorized personnel from each clinical centre. During INTELHEART project implementation, the anonymized clinical data will be processed by technical participants.

During the conducting of the clinical study, special attention will be paid to the confidential handling and storage of medical and other personal data of the subjects involved in the study. All collected data will be stored in the appropriate research archive and data access will be allowed only to authorized researchers or to other authorized, competent third parties. Personal identifiers (e.g. first and last name, JMBG and LIB number, etc.) of patients found on the printed and electronic media of the research archive will, as a rule, be masked, so that for the purposes of analysis the patients will be marked with an appropriate code (ID). Data masking in printed form will be done by the researcher who collects the original data, and data in electronic form by the researcher (computer operator), authorized by the chief researcher. The list of patients and the corresponding, associated codes will be kept confidential at the research center, under the supervision and responsibility of the main researcher or principal investigator of each clinical center.

All clinical and technical participants (authorized personnel) will have access to the data during INTELHEART implementation: **FINK, IITKG, IVI, FMSUKG, MFUNS, MFUB, SUNP, MFUN, COVU**. The obligations of data controllers and data processors will be defined in the Project Agreement.

How will the data be used regarding the research field?

The data will be used for training and testing the AI algorithms and for computational modelling, i.e only in the research purposes. Additionally, during INTELHEART project implementation all data will be used by all partners in anonymized form for creation on scientific publication, i.e. journal papers, conferences, workshops.

How will the costs of data curation and preservation be covered?

The costs of curation and preservation of clinical data during prospective clinical study will be covered by material costs of each clinical centre.

The costs of curation and preservation of integrated data into the INTELHEART platform, will be covered by material costs of FINK.

How will the stated data be exploited and/or shared/made accessible for verification and re-usage during and after *Project implementation? If data cannot be made available, explain why.*

The data sharing policy will be defined in detail within the Project Agreement. Availability of data for external entities will be evaluated on a case-by-case basis upon approval by the affected participants and PI. All participants will sign the agreement on how the data will be exploited and made accessible for verification and re-usage after INTELHEART project implementation. During project implementation the data will be available to all consortium members. Clinical datasets will remain confidential and will not be published on public repositories, nor during or after the project duration.

Who will have access to the data after Project implementation?

Access to the clinical data will be allowed only to authorised personnel from each clinical centre. The access to the clinical data is enabled after the signed study protocol. The authorised personnel from each clinical centre signs that he/she has studied and understood the clinical study protocol and agrees that the clinical study is being conducted in accordance with that protocol. Authorised personnel from each clinical centre

confirm that they are responsible for conducting clinical research in accordance with the duties and obligations that are based on the clinical study protocol and the appropriate institutional procedures of the quality regulation system. All of the collaborators involved in the conduct of clinical research are aware of their duties and responsibilities in relation to the clinical study and will be provided with all of the necessary information regarding the clinical study in a timely and appropriate manner throughout the period of its implementation. authorised personnel from each clinical centre will handle all clinical research information and documentation in a confidential manner. They will respect all decisions and instructions of the competent Ethics Committee and other competent regulatory bodies related to clinical research.

Regarding all generated and collected data, FINK will have access to the research data after the INTELHEART project implementation. If all participants want to have access to the data, they will have to sign separate agreement with FINK. Nevertheless, following the ORDP initiative, part of the data will be open access for the secondary usage by interested individuals (researchers, software developers, etc.). The type of the license for a newly developed software will be defined in the exploitation plan, that will determine the access level of end-users after the project ends. The identified project stakeholders will be potential end-users of the developed software.

1.4 Legal and institutional framework

Members of the project team **INTELHEART (Artificial INTELligence-based Decision Support System for Early and Accurate Diagnosis of HEART Failure)** are members of nine technical and clinical Institutions: Faculty of Engineering, University of Kragujevac (FINK), Institute for Information Technologies Kragujevac (IITKG), The Institute for Artificial Intelligence Research and Development of Serbia (IVI), Faculty of Medical Sciences, University of Kragujevac (FMSUKG), Faculty of Medicine, University of Novi Sad (MFUNS), Faculty of Medicine (School of Medicine), University of Belgrade (MFUB), State University of Novi Pazar (SUNP), Faculty of Medicine, University of Nis (MFUN), Coventry University, as well as a Faculty of Health and Life Sciences, UK (COVU) as clinical expert from diaspora. The FINK together with technical institutions (IITKG, IVI, SUNP) will bring the expertise in technical science (Finite Element (FE) modelling, multiscale modelling, AI, signal processing) and achieve common project objectives with clinical partners (FMSUKG, MFUNS, MFUB, MFUN) and clinical expert from diaspora (COVU) in development of cloud-based computational platform and mobile app for early and accurate diagnosis of HF.

The project's activities and objectives are in accordance with the mission and vision of the Science Fund of the Republic of Serbia and with the objectives of the *Strategy of Scientific and Technological Development of the Republic of Serbia for the period from 2021 to 2025*, *Strategy of smart specialization in the Republic of Serbia for the period from 2020 to 2027* and *Strategy for the development of artificial intelligence in the Republic of Serbia for the period 2020-2025* in the following manner:

- Societal needs and priorities;
- Multidisciplinary and interdisciplinary research;
- Ensuring competitiveness, quality, practical value, transparency, and the functionality of the results;
- Professional development of researchers;
- Cooperation with the scientific diaspora.

Ethics and privacy have become key considerations when conducting any form of scientific research that involves personal data. The INTELHEART clinical study is in accordance with the current scientific and professional knowledge in biomedicine and bioengineering in the given field as well as the ethical, scientific and regulatory principles of clinical research, including but not limited to those listed in the Declaration of Helsinki, principles of good clinical practice and other applicable regulations of the Republic of Serbia. When the research is to be done on clinical data, various aspects of law come into play. First, the law on data protection imposes specific requirements on the processing of health data and provides for specific safeguards when clinical data is used for research. Data concerning health, i.e. "*personal data related to the physical or mental health of a natural person, including the provision of health care services, which reveal information about his or her health status*"[1] constitute sensitive data and falls into a special category of personal data, the processing of which is subject to stringent requirements[2]. Thus, at the EU level, the General Data Protection Regulation[3] (hereinafter: GDPR) imposes general prohibition on processing of sensitive data, unless exemptions apply. The GDPR foresees

[1] Article 4 (15) GDPR
[2] Article 9 GDPR.
[3] 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 (General Data Protection Regulation), OJEU, L119, Vol. 59, 4 May 2016.

the possibility of using health data for research, provides however for specific safeguards to protect the fundamental rights and the interests of the data subject[4]. Thus, the legal requirements for the use of health data for research, both the adoption and implementation of organisational and technical measures to safeguard rights of the data subjects need to be considered and implemented into the project. In 2018, Serbia adopted the new *Law on Personal Data Protection ("Official Gazette of RS", no. 87/2018)*, which is compliant with the GDPR.

The implementation of clinical study and handling of health documentation and records will be in compliance with *Law on health documentation and records in the field of health care of the Republic of Serbia ("Official Gazette of RS", no. 123/2014, 106/2015, 105/2017, 25/2019 – other law).* Also, the patients' rights will be fully respected, following the *Law on patients' rights of the Republic of Serbia ("Official Gazette of RS", No. 45/2013 and 25/2019 - other law).* During the INTELHEART clinical study, the grievance mechanism will be enabled to address any concern of the patients. The grievance mechanism is described in Section 4. Section 1.4.1 lists the main legislations which will be followed during the lifetime of INTELHEART project.

In addition, there is a comprehensive understanding of ethical aspects while planning, designing and implementing solutions in the field of AI from a perspective of technical characteristics as well as from a perspective of effects of implementation, while taking into account the principles of preserving the freedom of individuals, fairness and equality, avoidance of damage, openness, transparency and sustainability. As INTELHEART project includes development and validation of AI-tools for HF risk stratification, diagnosis and disease progression, the project activities will follow the recommendations and measures of the *Strategy for the Development of Artificial Intelligence in the Republic of Serbia for the period 2020-2025 ("Official Gazette of RS", No. 96/2019)*. One of the specific objectives of the Strategy is ethical and safe application of AI (Specific objective 5) which should be ensured primarily with regard to the protection of personal data, the protection against discrimination when using AI, and the establishment of responsible AI development in accordance with international ethical principles. At the EU level, the European Commission issued the press release "*Building trust in human-centric AI*" in 2019[5], where the key requirements of "*Ethics Guidelines for Trustworthy Artificial Intelligence*" are supported[6], which have been established by a high-level expert group formed by the Commission. These key requirements are:

- Human agency and oversight
- Technical robustness and safety
- Privacy and data governance
- Transparency
- Diversity, non-discrimination and fairness
- Societal and environmental well-being
- Accountability

The above-mentioned requirements and how to address them are further elaborated in Section 1.5. Challenges for society and individuals require preventive actions for a responsible AI development and consequently the compliance with international guidelines, practice and regulations.

[4] Article 9 (2) (j), Article 89 (1) GDPR.
[5]Building Trust in Human-Centric Artificial Intelligence, COM(2019) 168 final, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2019:0168:FIN
[6]Ethics guidelines for trustworthy AI, High-Level Expert Group on Artificial Intelligence, 2019. Link: https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai

1.4.1 Existing Serbian legislation

All field work, sampling procedures, clinical research, laboratory work, and waste management will be in concordance with the relevant laws and/or management strategies of the Republic of Serbia, including specific rulebooks:

- Law on Science and Research ("Official Gazette of RS" No. 49/19)
- Law on Environmental Protection ("Official Gazette of RS" No. 135/04, 36/09, 72/09, 43/11, 14/16, 76/18 and 95/18)
- Law on Fire Protection ("Official Gazette of RS", Nos. 111/2009, 20/2015, 87/2018 and 87/2018)
- Law on Waste Management ("Official Gazette of RS", 36/09, 88/10, 14/16 and 95/2018)
- Law on Noise Protection ("Official Gazette of RS", 36/09, 88/10 and 96/2021)
- Law on Occupational Health and Safety ("Official Gazette of RS", 101/05, 91/15 and 113/2017)
- Law on Health Care ("Official Gazette of RS", No. 25/2019)
- Law on Health Documentation and Records in the Field of Health Care ("Official Gazette of RS", no. 123/2014, 106/2015, 105/2017, 25/2019 – other law)
- Law on Personal Data Protection ("Official Gazette of RS", no. 87/2018)
- Law on Medical Devices ("Official Gazette of RS", No. 105/2017)
- Law on Patients' Rights ("Official Gazette of RS", No. 45/2013 and 25/2019 - other law)
- Rulebook on Medical Waste Management ("Official Gazette of RS", No. 48/2019)
- Strategy for the Development of Artificial Intelligence in the Republic of Serbia for the period 2020-2025 ("Official Gazette of RS", No. 96/2019)
- Strategy of Scientific and Technological Development of the Republic of Serbia for the period 2021-2025 ("Official Gazette of RS", No. 10/2021)
- Strategy of smart specialization in the Republic of Serbia for the period 2020-2027 ("Official Gazette of RS", No. 21/2020, No. 96/2023)

1.5 Application of artificial intelligence and ethical aspects

Development of AI-tools for HF risk stratification, diagnosis and disease progression will follow Good Machine Learning (ML) practices[7], recommended EU regulatory approaches for use of AI in healthcare[8], and Cross-Industry Standard Process for Data Mining (CRISP-DM) guidelines. The first step of CRISP-DM will implement all phases: domain understanding, data acquisition, data exploration/visualisation, data quality assurance, predictive modelling, evaluation. A patient-specific HF database will be combined with artificial data of virtual patients produced by data generators based on radial basis function (RBF) networks[9]. Supervised and semi-supervised algorithms (such as artificial neural networks, random forest, gradient boosted trees, support vector machines, etc.) will be used for predictive modelling. Boosting ensembles with hybrid loss functions will be trained on the available clinical data to reduce training and testing loss and provide accurate predictions. In addition to CRISP-DM guidelines, each prediction of risk

[7] Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning-Based Software as a Medical Device. FDA, 2021
[8] EU Parliament. Artificial intelligence in healthcare. Applications, risks, ethical and societal impacts. Panel for the Future of Science and Technology 2022.
[9] Robnik-Šikonja, M. Data generators for learning systems based on RBF networks. IEEE Trans Neural Networks Learning Systems, 2015. 27(5): p. 926-938.

will also be supplemented with its reliability estimates. Also, end users (e.g. medical professionals) will be able to better understand the AI-based outputs, by ensuring **Interpretable and Explainable AI**. We will explain the decision models by computing explanations and reliability of estimates of single predictions using local sensitivity analyses. The resulting visualized explanations will facilitate computer-generated explanation for HF and will be used to validate the appropriateness of the generated decision model by clinical partners. Also, the Gradient-weighted Class Activation Mapping (Grad-CAM) method[10] will be implemented in case of processing of medical imaging data. This technique produces "visual explanations" for decisions from a large class of convolutional neural networks (CNNs) - based models, making them more transparent.

The INTELHEART AI-powered DSS will be designed to fulfill a set of seven requirements to prove its trustworthiness in terms of compliance with the four ethical principles[6]: (i) respect for human autonomy (the AI systems should be designed to empower human congestive and social skills), (ii) prevention of harm (the AI systems should be designed to protect the human dignity by being safe and secure), (iii) fairness (the AI systems must be developed and deployed in such a way to increase societal fairness), and (iv) explicability (the processes that are implemented by the AI system must be transparent in terms of traceability and auditability).

The seven requirements include the following[6]: (i) accountability, (ii) privacy and data governance, (iii) societal and environmental wellbeing, (iv) technical robustness and safety, (v) human agency and oversight, (vi) diversity, non-discrimination and fairness, and (vii) transparency.

- **Accountability** has to do with the responsibility of the outcomes of the AI system during their development and after their deployment in terms of auditability, risk minimization and respect to the fundamental rights.
- **Privacy and data governance** has to do with the quality of the data in terms of relevance, completeness, integrity, as well as, the fulfillment of the data protection legal and ethical requirements for data sharing.
- **Societal and environmental wellbeing** involves the development of a sustainable and environmental friendly AI system.
- **Technical robustness and safety** involves the prevention or risks and the minimization of any unacceptable harm.
- **Human agency and oversight** involves the support of the human autonomy and oversight through decision-making.
- **Diversity, non-discrimination and fairness** involves the avoidance of biases and the adoption of a global design for accessibility.
- **Transparency** ensures the traceability, explainability and human interaction of the AI system.

The requirements of **privacy and data governance**, **diversity, non-discrimination and fairness**, **technical robustness and safety**[6] will be addressed through the data sharing mechanisms which ensure: (i) the quality of the medical imaging and clinical data in terms of accuracy, relevance and completeness, as well as, the quality of the clinical data through data curation, (ii) the access to the private cloud databases through a "handshaking" process which requires the approval of the data provider to make the data available for the application of AI tools.

[10] R. R. Selvaraju, M. Cogswell, A. Das, R. Vedantam, D. Parikh and D. Batra, "Grad-CAM: Visual Explanations from Deep Networks via Gradient-Based Localization," 2017 IEEE International Conference on Computer Vision (ICCV), Venice, Italy, 2017, pp. 618-626, doi: 10.1109/ICCV.2017.74.

Besides, the fact that the medical imaging and clinical data will be pseudonymized (or anonymized) and maintained in private databases within the cloud instead of a centralized database which enhances the safety of the patient data especially in the case of a privacy breach where the data will not be compromised as a whole.

The requirements of **human agency and oversight**, **transparency**[6] will be addressed by the proposed distributed learning framework through the implementation of machine learning and deep learning algorithms which are able to provide interpretable AI models that can be used for the clinical decision making process.

The requirement of **societal and environmental wellbeing**[6] will be addressed by the fact that the distributed learning framework will be applied in an incremental learning manner which will reduce the resource usage and energy consumption during the training of the deep learning algorithms through a batch processing manner.

The requirement of **applicability**[6] will be addressed by the platform through the definition of a reference model for AI algorithm implementation, as well as, the implementation of trustworthy machine learning and deep learning algorithms, such as, the CNNs which will reduce any potential negative impacts during the development, deployment and application of the AI system.

By developing and integrating AI-based tools and analytics within DSS and mobile app, collecting patient data, we will create a unique knowledge database, facilitating implementation of new trustworthy risk stratification, diagnostic and prognostic, privacy-preserving AI tools to improve the quality of healthcare for both clinicians and patients. This approach ensures use of evidence-based preventive and treatment strategies, data management and curation with their easy access within DSS at primary and secondary care. Our approach will reduce errors, delays and costs associated with current HF care pathway.

2 Issues related to the project considering environmental and social acceptability – baseline data

According to the Environmental Social Management Plan (ESMP), the INTELHEART project is a research project which will perform activities that might have impact on Population, Health and Safety. Also, the project has potential impacts on the Workers and Community Health and Safety, as well as potential Socio-Economic impacts.

More details on how the project impacts the environmental and social aspects are given in the following section (Section 3).

Moreover, in order to mitigate the environmental and social impacts, any individual who feels threatened or harmed by some of the specific activities of INTELHEART project can submit a complaint, following the grievance mechanisms described in Section 4.

3 Potential impact of the project and impact assessment

The INTELHEART project has foreseen potential impacts on environmental and social aspects and measures for its minimization. In addition, the set of measures are given and briefly described.

1. **Environmental and Social Acceptability:**

a. **Impact on Data Privacy:** For the purpose of the INTELHEART clinical study, data from 2,400 HF patients (1,200 retrospective and 1,200 prospective) will include: medical history, physical examination, the blood test for natriuretic peptides (NTproBNP or BNP where available), ECG, CT & MRI where needed, echocardiography, voice recordings, BRS, DASS tests. Clinical data will be collected by clinical participants FMSUKG, MFUNS, MFUB, MFUN. Considering the number of clinical centres and the number of patients involved in the study, it may arise concerns about data privacy.

Mitigation measures: INTELHEART clinical participants will ensure to have obtained informed consent from patients for participating into the clinical study. The project consortium will follow all applicable data privacy and ethical guidelines, such as EU general data protection regulation (GDPR), Regulation (EU) 2018/1725 which sets forth the rules applicable to the processing of personal data and it is aligned with the GDPR, and the Data Protection Law Enforcement Directive. During the clinical study, special attention will be paid to the confidential handling and storage of medical and other personal data of the subjects involved in the study. All collected data will be stored in the appropriate research archive and data access will be allowed only to authorized researchers or to other authorized, competent third parties. Personal identifiers (e.g. first and last name, JMBG and LIB number, etc.) of patients found on the printed and electronic media of the research archive will, as a rule, be masked, so that for the purposes of analysis the patients will be marked with an appropriate code (ID). Data masking in printed form will be done by the researcher who collects the original data, and data in electronic form by the researcher (computer operator), authorized by the chief researcher. The list of patients and the corresponding, associated codes will be kept confidential at the research center, under the supervision and responsibility of the main researcher or principal investigator of each clinical center.

b. **Impact on Ethics in Clinical Study:** The INTELHEART clinical study is a non-sponsored and non-interventional, clinical research study which will be done in four clinical centres (Kragujevac, Nis, Novi Sad and Belgrade) in accordance with national legislation and institutional procedures in the field of academic research in medicine. Study population will consist of adult patients diagnosed and treated of HF. For the purpose of the study, the participants will be invited and the patient-specific demographic and clinical data will be collected which may arise ethical concerns.

Mitigation measures: As INTELHEART clinical study is academic, non-sponsored and non-interventional study, decisions from Ethics Committees of each participating clinical centre cover all ethical issues for such type of study. In the same time, after obtained decisions from Ethics Committees, they are also responsible to monitor conducting of the study, as well as to monitor collected data during and after the study lifetime. Each decision of the local Ethics Committees has issued after the insight into complete study documentation, and careful assessment of potential risks and benefits which mitigated potential negative impact on patients and community. Each decision incorporates all relevant documents following the rules for conducting the research in humans. If additional information is needed before conducting the INELHEART clinical study, the project consortium will consult the local Ethics Committees.

c. **Impact on Data Security:** The INTELHEART project comprehends participants from nine technical and clinical institutions. Also, in includes collection and processing of different type of sensitive patient-specific demographic and clinical data (1,200 retrospective and 1,200 prospective patients). The number and type of collected data may arise the concerns related to data security and storage infrastructure.

Mitigation measures: INTELHEART project will implement robust data security measures to protect sensitive patient data, including voice recordings. This includes encryption, access controls, and regular security audits. Access to all clinical data will be allowed only to authorized personnel from each clinical centre. During INTELHEART project implementation, the anonymized clinical data will be processed by technical participants. INTELHEART platform will have the security layer which provides mechanisms for user access management, authentication, authorization, and encrypted communication. A separate VPN-secured private network will be established for developers and maintainers for accessing the platform's internal infrastructure.

d. **Impact on Data Processing:** The INTELHEART project includes processing of different type of sensitive patient-specific demographic and clinical data (1,200 retrospective and 1,200 prospective patients). The number and type of collected data may arise the concerns related to data processing.

Mitigation measures: INTELHEART project will implement robust measures for implementation of standardised computational methods. Also, interpretable and explainable AI-methods will be ensured, as well as the trustworthy AI.

e. **Impact on Transparency and Informed Consent:** As the INTELHEART project includes both clinical study and AI-tools development using clinical data, the transparency and informed consent are essential for social and ethical acceptability.

Mitigation measures: INTELHEART clinical participants will provide clear, accessible and transparent information to patients about how their demographic and clinical data, including voice recordings, DASS and BRS tests, will be used. Those HF patients are already under medical treatment in clinical centres, according to their referral clinical centre. Before regular checkup, educated researchers (treating

physicians) of clinical centres of Kragujevac, Nis, Novi Sad and Belgrade, will approach to and introduce each patient about INTELHEART project and the content of informed consent. If patient is willing to participate in the INTELHEART clinical study, after he/she got all relevant information and after needed time for asking about participation, he/she will sign the informed consent. The procedures which are not included in standard treatment protocols for HF patients, will be also described in detail in informed consent. Also, patients will be informed that they can withdraw their informed consent during the clinical study. Any procedure will not be performed before informed consent is signed. Also, if any patient feels harmed by some of the specific activities during the clinical study, the grievance mechanisms will be enabled.

f. **Impact on Ethics in use of AI-tools:** Application of AI-tools raises many ethical concerns and has to fulfil requirements related to trustworthy AI, i.e., to address:

(i) privacy and data governance (quality of the data in terms of relevance, completeness, integrity, as well as, the fulfillment of the data protection legal and ethical requirements for data sharing);
(ii) diversity, non-discrimination and fairness (avoidance of biases and the adoption of a global design for accessibility);
(iii) technical robustness and safety (prevention or risks and the minimization of any unacceptable harm);
(iv) human agency and oversight (support of the human autonomy and oversight through decision-making);
(v) societal and environmental well-being (development of a sustainable and environmental friendly AI system);
(vi) transparency (traceability, explainability and human interaction of the AI system);
(vii) accountability (responsibility of the outcomes of the AI system during their development and after their deployment in terms of auditability, risk minimization and respect to the fundamental rights).

Mitigation measures: The impacts on **privacy and data governance, diversity, non-discrimination and fairness, technical robustness and safety** will be mitigated through the data sharing mechanisms which will ensure: (i) the quality of the medical imaging and clinical data in terms of accuracy, relevance and completeness, as well as, the quality of the clinical data through data curation, (ii) the access to the private cloud databases through a “handshaking” process which requires the approval of the data provider to make the data available for the application of AI tools.

The impact on **human agency and oversight**, **transparency** will be mitigated by the proposed distributed learning framework through the implementation of machine learning and deep learning algorithms which are able to provide interpretable AI models that can be used for the clinical decision making process.

The impact on **societal and environmental wellbeing** will be mitigated by the fact that the distributed learning framework will be applied in an incremental learning manner which will reduce the resource usage and energy consumption during the training of the deep learning algorithms through a batch processing manner.

The impact on **applicability** will be mitigated through the definition of a reference model for AI algorithm implementation in the platform, as well as, the implementation of trustworthy machine learning and deep learning algorithms, such as, the CNNs which will reduce any potential negative impacts during the development, deployment and application of the AI system.

2. **Population, Health, and Safety:**

a. **Impact on Patient Safety and Satisfaction:** INTELHEART prospective clinical study may cause mistrust and discomfort among some of 1,200 foreseen participating patients.

Mitigation measures: Standardised clinical procedures will be performed in order to enable safe and efficient clinical study and clinical data collection. The medical staff will be continuously trained and educated to implemented safeguards and provide support to patients. If any patient feels harmed by some of the specific activities during the clinical study, the grievance mechanisms will be enabled.

b. **Impact on Patient Well-being:** The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society. If there is any question that the prospective participant will not reliably comply with study procedures and/or follow-up, they should not be entered in the study. There is a low probability that INTELHEART can cause negative impact on patients' well-being, as their treatment and monitoring will not be driven by AI decisions, whereas the diagnosis of HF, as well as treatment procedures and patients' healthcare have been already defined by protocols in each of four clinical centres. Considering the number of 1,200 participating patients in prospective clinical study, the consortium will set mitigation measures in case that any of patients feels impaired well-being and discomfort due to INTELHEART clinical study (e.g. voice recordings, imaging diagnostics, DASS, BRS tests).

Mitigation measures: INTELHEART consortium will ensure that patient well-being is prioritized. If imaging methods, voice recordings, DASS, BRS tests, or other data collection methods could potentially cause discomfort or harm, safeguards will be implemented and support will be provided where necessary. Medical staff will provide support and healthcare resources for patients who may experience distress as a result of participation. Clear protocols for handling adverse events will be followed. Also, patients will be informed that they can withdraw their informed consent during the clinical study.

c. **Impact on Patient Inclusivity:** The INTELHEART clinical study will have inclusion and exclusion criteria for taking participation. Inclusion criteria for the participants in the study are age over 18 and written consent to participate in research. Exclusion criteria will be presence of malignant diseases and/or presence of significant renal weakness. Exclusion from research will be carried out if the patients no longer want to participate in the research.

Mitigation measures: INTELHEART clinical participants will consider the diversity of the patient population in the study. Also, we will ensure that the research is inclusive and representative of different demographics to avoid potential biases. During the study and collection of data, inclusion/exclusion criteria are not specific to any vulnerable population.

d. **Impact on Health Monitoring:** There is a low probability that INTELHEART clinical study will have negative impact on the health monitoring or participating patients.

Mitigation measures: INTELHEART clinical participants will monitor the health of participating patients and provide appropriate medical support if any adverse effects are observed during the study.

3. Impacts on Workers and Community Health and Safety:

a. **Impact on Workers Health and Safety:** INTELHEART project activities may have impact on workers' health and safety due to complex data collection and analysis among nine technical and clinical institutions.

Mitigation measures: In case of workers involved in data collection and/or analysis, INTELHEART consortium will ensure they have proper training and protection. Compliance with occupational health and safety regulations will be followed.

b. **Impact on Laboratory Work and Accidents:** INTELHEART project activities may have impact on regular daily work in clinical laboratories, as well as on work in facilities of technical institutions.

Mitigation measures: Preparing of project-specific SOPs for laboratory work. Laboratory safety and emergency procedures. Additional training for laboratory competencies specific to project experts. Consistent safety training sessions and regular equipment servicing. Preparedness for emergency scenarios.

c. **Impact on Waste Management**: During the prospective clinical study, medical waste will be generated.

Mitigation measures: Medical waste management plan will be created according to the rulebook of RS ("Official Gazette of RS", No. 48/2019). Constant education of medical staff will be performed. Measures such as use of proper medical waste containers, wear protective gear, reduced contact via automation, etc. will be taken.

d. **Impact on Community Health and Safety:** INTELHEART project activities has a low negative impact on local community health and safety.

Mitigation measures: During the project lifetime, INTELHEART consortium will monitor if project activities affect the local community. In case of potential discomfort due to performed data collection methods, or evaluation of INTELHEART platform, steps to mitigate the impact on nearby population will be taken (information sessions, explainable AI-methods, enable clear and accessible information materials for patients explaining the purpose of the project, data usage, and risks).

e. **Impact on Preparedness in Emergency Situations:** Emergency situations may be related to fractured parts of infrastructure, communication systems failures, delayed or inefficient deployment of resources.

Mitigation measures: INTELHEART consortium will follow emergency response protocols in case of any unforeseen health or safety incidents during data collection or data analysis. Consistent safety training sessions, regular equipment servicing and preparedness for emergency scenarios will be ensured. Grievance mechanisms will be ensured for any individual who feels threatened or harmed.

4. **Socio-Economic Impacts:**

a. **Impact on Economic Acceptability:** The value and effectiveness of AI in clinical practice remain uncertain, and proper guidance on implementation is crucial. AI applications in healthcare face economic challenges such as investments and increased costs due to additional testing. Developed INTELHEART tools may rise costs for healthcare institutions before their adoption in clinical practice.

Mitigation measures: INTELHEART project will provide measures through validation and verification of developed INTELHEART tools for early detection and diagnosis of HF, which can widely and cost-effectively be used for facilitated and timely initiation of therapy in yet a reversible stage of the disease, thus providing better prognosis and reducing the need for hospitalization and improving the patient's length and quality of life. Moreover, the project will enable job creation and knowledge transfer that may create economic opportunities and benefits for the institutions involved.

b. **Costs to Patients:** Participation in the clinical study should not cause any additional costs for patients. However, in case of any contingency where some of tests have to be repeated (e.g. voice recordings), additional spending for travel to local hospital may be caused.

Mitigation measures: INTELHEART will evaluate any potential costs to patients participating in the study, such as travel or time commitments, and try to minimize these. All participating patients will be referred to the nearest clinical centre of INTELHEART consortium, whereas the clinical study will be performed in a timely and effective manner.

c. **Healthcare Resource Allocation:** INTELHEART clinical study has a low negative impact on healthcare resource allocation. As the prevalence of risk factors and HF is raising, we do not expect delay in the recruitment of achieving expected proposed number of patients across clinical centres participating in the study.

Mitigation measures: INTELHEART consortium will assess whether the project may impact the allocation of healthcare resources, and work with healthcare providers to ensure it does not burden the existing healthcare system (minimize delays in project tasks). In case there is delay in recruitment phase and availability of the eligible patients, the contingency measures will include recruitment of patients from local neighbouring clinics where the project will be communicated.

Throughout the project, INTELHEART consortium will continuously engage with stakeholders, including patients, healthcare professionals, and the local community, to address concerns and make adjustments as needed. The Ethics Committees will also provide guidance and monitoring of ethical and safety considerations. By taking a proactive approach to these issues, INTELHEART consortium will enhance the social acceptability and overall success of this multi-institutional project.

4 Grievance mechanisms

Any individual who feels threatened or harmed by some of the specific activities of "Artificial INTELligence-based Decision Support System for Early and Accurate Diagnosis of HEART Failure" - INTELHEART project can submit a complaint. The grievance mechanisms will be established for all persons involved in the project and will be harmonized with the existing mechanisms. The main goal of grievance mechanisms is the timely, effective and efficient resolution of complaints, appeals and suggestions related to the rights of persons engaged in the implementation of the project. The grievance mechanisms will be organized in such a way as to enable transparency, confidentiality and prevent abuse in the form of retaliation.

Complaints, objections or comments in written form can be submitted by filling out the complaint form (.docx file) which will be available at the project website, in two ways:

- The electronic form should be filled out, saved and sent via email to contact e-mail address provided at the project website;
- The printed form should be filled out manually and sent via post office to the project address provided at the project website.

Authorized persons of INTELHEART project will consider all complaints responsibly and will take timely and appropriate actions in relation to received complaints. The project will only deal with objections directly related to this project.

All personal data any individual provides will be used in accordance with applicable regulations on the protection of personal data and will not be made public. We will use the contact data exclusively for future communication regarding complaint.

5 Mitigation plan

The following table provides set of mitigation measures for the foreseen environmental and social risks and impacts related to INTELHEART project. All mitigation measures are related to the INTELHEART project lifetime.

Issue – environmental and social risks and impacts	Mitigation Measure	Institutional Responsibility	Supervision
Data Privacy	• Ensure compliance with relevant data privacy regulations (*Law on Personal Data Protection ("Official Gazette of RS", no. 87/2018)).* • Ensure compliance with *Law on health documentation and records in the field of health care of the Republic of Serbia ("Official Gazette of RS", no. 123/2014, 106/2015, 105/2017, 25/2019 – other law)* • Implement robust encryption and access controls to protect sensitive patient data. • Ensure confidential handling and storage of medical and other personal data of the subjects involved in the study.	FMSUKG MFUNS MFUB MFUN COVU PIU/SF/FINK	
Ethics in Clinical Study	• Clinical protocols in each clinical centre. • Obtain informed consent from patients for data collection. • Enabled grievance mechanisms. • Withdraw of patients' informed consent during the clinical study.	FMSUKG MFUNS MFUB MFUN PIU/SF/FINK	
Data Security	• Implement a comprehensive data security strategy, including regular security audits. • Restrict access to sensitive data to authorized personnel only. • Educate all project stakeholders about data security best practices. • INTELHEART platform will have the security layer which provides mechanisms for user access management, authentication, authorization, and encrypted communication. • A separate VPN-secured private network will be established for	FMSUKG MFUNS MFUB MFUN COVU PIU/SF/FINK	

Issue – environmental and social risks and impacts	Mitigation Measure	Institutional Responsibility	Supervision
	developers and maintainers for accessing the platform's internal infrastructure.		
Data processing	• Implement standardised computational methods. • Ensure Interpretable and Explainable AI-methods. • Ensure the trustworthy AI.	FINK IVI SUNP IIT	PIU/SF/FINK
Transparency and Informed Consent	• Develop clear and accessible information materials for patients explaining the purpose of the project, data usage, and risks. • Establish a grievance mechanism for patients to submit a complaint, ask questions and provide feedback. • Periodically review and update consent forms and informational materials.	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Ethics in use of AI-tools (privacy and data governance, diversity, non-discrimination and fairness, technical robustness and safety, human agency and oversigh, societal and environmental wellbeing, transparency, accountability)	Ensure trustworthy AI through: • quality of the medical imaging and clinical data in terms of accuracy, relevance and completeness, • data sharing mechanisms and data curation, • access to the private cloud databases through a "handshaking" process, • implementation of machine learning and deep learning algorithms which are able to provide interpretable AI models that can be used for the clinical decision making process, • applied learning framework in an incremental learning manner which will reduce the resource usage and energy consumption during the training of the deep learning algorithms through a batch processing manner • definition of a reference model for AI algorithm implementation in the platform, as well as, the implementation of trustworthy ML and deep learning algorithms, such as, the CNNs which will reduce any potential negative impacts during the development, deployment and application of the AI system, • Development of AI-tools for HF risk stratification, diagnosis and disease progression which follow Good ML practices,	FINK IVI SUNP IIT	

Issue – environmental and social risks and impacts	Mitigation Measure	Institutional Responsibility	Supervision
	• Implementation of CRISP-DM guidelines, • Visual explanations, making AI-based models transparent		
Patient Safety and Satisfaction	• Provide standardised clinical procedures. • Provide trainings and education for medical staff. • Provide grievance mechanisms for patients.	FMSUKG MFUNS MFUB MFUN PIU/SF/FINK	
Patient Well-being	• Implement measures to ensure patient well-being during data collection, including monitoring for any discomfort. • Provide medical support and healthcare resources for patients who may experience distress as a result of participation. • Develop clear protocols for handling adverse events.	FMSUKG MFUNS MFUB MFUN PIU/SF/FINK	
Inclusivity	• Ensure diverse representation within the patient population. • Address potential biases by actively recruiting and engaging underrepresented groups. • Analyse and report result by demographic variables.	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Health Monitoring	• Provide appropriate medical support if any adverse effects are observed during the study. • Regularly follow-up the patients according to clinical study protocol.	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Workers Health and Safety	• Provide training to workers involved in data collection or analysis regarding safety and ethical considerations. • Equip workers with necessary protective gear and tools. • Establish a reporting system for safety concerns and incidents.	FMSUKG MFUNS MFUB MFUN FINK	PIU/SF/FINK
Laboratory Work	• Preparing of project-specific SOPs for laboratory work. • Laboratory safety and emergency procedures. • Additional training for laboratory competencies specific to project experts.	FMSUKG MFUNS MFUB MFUN FINK	PIU/SF/FINK

Issue – environmental and social risks and impacts	Mitigation Measure	Institutional Responsibility	Supervision
Laboratory Accidents	• Consistent safety training sessions. • Regular equipment servicing. • Preparedness for emergency scenarios.	FMSUKG MFUNS MFUB MFUN FINK	PIU/SF/FINK
Management of Hazardous Medical Waste	• Medical waste management plan (valid) according to rulebook of RS. • Constant education of medical staff. • Take measures such as use of proper medical waste containers, wear protective gear, reduced contact via automation, etc.	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Community Impact	• Monitor and mitigate any potential discomfort due to performed data collection methods, or evaluation of INTELHEART platform. • Engage with the local community to address concerns and provide regular updates on the project's progress. • Introduce the local community with INTELHEART AI-tools and methods.	FMSUKG MFUNS MFUB MFUN FINK	PIU/SF/FINK
Emergency Response	• Develop and communicate emergency response protocols to all project clinical personnel. • Ensure all team members are aware of the nearest healthcare facilities and contact information. • Maintain emergency contact lists and equipment for quick response. • Ensure grievance mechanisms for any individual who feels threatened or harmed.	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Economic Benefits	• Collaborate with local institutions to create job opportunities related to the project. • Promote knowledge transfer and skill development to enhance economic benefits. • Monitor economic impacts and adjust strategies accordingly.	FINK	PIU/SF/FINK
Costs to Patients	• Minimize the financial and time burdens on patients participating in the study.	FMSUKG MFUNS	PIU/SF/FINK

Issue – environmental and social risks and impacts	Mitigation Measure	Institutional Responsibility	Supervision
	• Consider offering compensation or incentives for their participation, if feasible. • Provide resources for patients to access healthcare services without significant disruption.	MFUB MFUN	
Healthcare Resource Allocation	• Collaborate with healthcare providers to ensure that the project does not strain existing healthcare resources. • Explore partnerships to improve healthcare services for heart failure patients.	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Access to Healthcare	• Aim to improve access to healthcare services for heart failure patients in the study area. • Partner with local healthcare organizations to expand services where needed.	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Stakeholder Engagement	• Establish regular communication channels with all stakeholders, including patients, healthcare professionals, and the community. • Maintain an ethics committee or review board for ongoing guidance on ethical and safety matters.	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Continuous Monitoring and Adaptation	• Continuously monitor project activities and impacts. • Be prepared to adjust strategies and mitigation measures based on emerging challenges and feedback from stakeholders.	ALL	PIU/SF/FINK

6 Monitoring plan

What *Parameter is to be monitored?*	**Where** *Is the parameter to be monitored?*	**How** *Is the parameter to be monitored/ type of monitoring equipment?*	**When** *Is the parameter to be monitored- frequency of measurement or continuous?*	**Who** *Is responsible for monitoring?*	**Supervision**
Preparation phase					
Data Privacy and Ethical Compliance	Project headquarters or institutional offices	Regularly review data security measures and ethical compliance to ensure that patient data is protected and that all regulations are being adhered to	Ongoing, with quarterly reviews	MFUNS	PIU/SF/FINK
Stakeholder Engagement	Meetings and communication channels with stakeholders	Monitor the level of engagement and feedback from patients, healthcare professionals, and the community to ensure that concerns and questions are being addressed	Ongoing, with monthly status updates	FINK MFUNS	PIU/SF/FINK
Workforce Safety	Data collection and analysis sites	Regularly inspect and assess safety measures for workers involved in the project, including their access to protective gear and safety training	Weekly safety checks and monthly safety training sessions	ALL	PIU/SF/FINK

Execution phase					
Data Security	Data storage and processing facilities	Continuously monitor data security protocols, including encryption, access controls, and incident reports	Daily monitoring, with monthly security audits	ALL	PIU/SF/FINK
Clinical data collection	Data collection sites at clinical institutions	Continuously monitor data collection at local clinical sites	Monthly monitoring	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Health and Safety	Laboratories, clinical sites	Continuously monitor the health and safety protocols	Monthly monitoring	ALL	PIU/SF/FINK
Hazardous medical waste	Clinical institutions	Continuously monitor the acting according to the medical waste management plan	Monthly monitoring	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Data processing using AI and computational methods	Data storage and processing facilities	Continuously monitor data processing at local sites of technical participants	Bi-monthly monitoring	FINK IVI SUNP IIT	PIU/SF/FINK
Community Impact	Areas surrounding data collection and procession sites	Assess and address any potential discomfort and community concerns by engaging with local community	Quarterly community feedback sessions	FMSUKG MFUNS MFUB MFUN FINK	PIU/SF/FINK
Patient Well-being	Data collection sites	Monitor patient well-being during data collection activities and provide support as needed	Continuous monitoring during data collection, with weekly well-being assessments	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Economic Benefits	Collaborating institutions and job creation sites	Assess the economic benefits generated by the project and track	Quarterly economic impact assessments	FINK	PIU/SF/FINK

		job creation and knowledge transfer			
Inclusivity	Patient recruitment and engagement sites	Monitor the diversity of the patient population and ensure underrepresented groups are actively engaged	Monthly diversity assessments and outreach efforts as needed	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Emergency Response	All project sites	Review and practice the emergency response protocols, ensuring that all team members are aware of healthcare facilities and contacts	Monthly emergency response drills and quarterly protocol reviews	ALL	PIU/SF/FINK
Access to Healthcare	Local healthcare organizations and service points	Assess whether the project enhances or hinders access to healthcare services for heart failure patients	Quarterly access assessments and immediate response to barriers	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Cost to Patients	Patient recruitment and engagement sites	Evaluate and minimize the financial and time burdens on patients, and consider compensation or incentives	Ongoing cost assessments and monthly adjustments	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Healthcare Resource Allocation	Local healthcare institutions	Collaborate with healthcare providers to ensure the project doesn't strain resources and explore ways to improve healthcare services.	Quarterly resource allocation reviews and immediate coordination as needed	FMSUKG MFUNS MFUB MFUN	PIU/SF/FINK
Stakeholder Engagement	Meetings and communication channels with	Maintain open lines of communication with stakeholders, actively	Ongoing, with regular engagement sessions	FINK MFUNS	PIU/SF/FINK

	stakeholders	addressing concerns and providing updates			
Life and fire safety (LFS) procedures in laboratory	Laboratory of the institution implementing the project	Visual inspections and checks of the documentation	Periodically during the implementation of the project	Responsible person for LFS in SRO	PIU/SF/FINK

7 Capacity building and training plan

The INTELHEART has created the initial capacity building and training plan structured as "What, Where, How, When" as follows:

1. Identify Training Needs:

- **What:** Identify the specific knowledge and skills required for project team members, researchers, and other stakeholders.
- **Where:** Conduct surveys, interviews, and assessments to determine training needs.
- **How:** Collaborate with project leads and key stakeholders to identify knowledge gaps and skills required.
- **When:** At the beginning of the project and periodically throughout.

2. Develop Training Modules:

- **What:** Create training modules and materials tailored to the identified needs.
- **Where:** Develop training content at the project headquarters or in collaboration with partner institutions.
- **How:** Engage subject matter experts and instructional designers to create high-quality training materials.
- **When:** Prior to the project's execution phase.

3. Training Delivery:

- **What:** Deliver training to project personnel, ensuring they have the necessary knowledge and skills.
- **Where:** Conduct training sessions at central locations, remote sites, or virtually as needed.
- **How:** Utilize a combination of in-person training, webinars, online courses, and workshops, depending on the nature of the content.
- **When:** Before and during the execution phase, with periodic refresher courses.

4. Assess and Evaluate:

- **What:** Assess the effectiveness of training programs and gather feedback.
- **Where:** Conduct assessments and evaluations at the training locations or virtually.

- **How:** Use surveys, quizzes, and practical assessments to gauge participants' understanding and competence.
- **When:** After each training module, and periodically throughout the project.

5. Continuous Learning:

- **What:** Encourage continuous learning and knowledge sharing among project team members.
- **Where:** Foster a culture of learning within the project teams.
- **How:** Establish forums for knowledge sharing, such as regular team meetings, seminars, and peer-to-peer learning.
- **When:** Throughout the project, with scheduled knowledge-sharing sessions.

6. Support and Resources:

- **What:** Provide ongoing support and resources to facilitate learning.
- **Where:** Ensure access to resources and experts required for project tasks.
- **How:** Offer access to libraries, online databases, mentorship programs, and expert consultations.
- **When:** Continuously throughout the project's duration.

7. Certification and Recognition:

- **What:** Provide certifications or recognition for training completion and exceptional contributions.
- **Where:** Certificates can be awarded at training sites or in formal ceremonies.
- **How:** Develop a system to track and issue certifications or recognize outstanding contributions.
- **When:** Upon the completion of training modules and at project milestones.

8. Feedback Loops:

- **What:** Establish feedback loops for participants to provide input on training quality and relevance.
- **Where:** Feedback mechanisms can be electronic or in-person.
- **How:** Create a structured process for collecting, analysing, and acting upon feedback.
- **When:** After each training module and periodically throughout the project.

9. Revision and Enhancement:

- **What:** Revise and enhance training materials and methods based on feedback and evolving project needs.
- **Where:** Revise content at the project headquarters or in collaboration with partners.
- **How:** Continuously update training modules to stay current with best practices and emerging technologies.
- **When:** As needed, based on feedback and emerging trends.

10. Monitoring and Reporting:

- **What:** Monitor the progress of capacity building and training efforts.
- **Where:** Monitoring can be done centrally or by individual institutions involved.
- **How:** Use key performance indicators to assess the effectiveness of training programs.
- **When:** Regularly, with quarterly and annual reports.

8 Implementation plan and cost assessment

The implementation of project activities will be performed according to the Work Packages (WPs) distribution presented in the Table 2. During the project lifetime, the INTELHEART consortium will continuously take the set of mitigation, monitoring, and institutional measures according to the Environmental Social Management Plan (ESMP) to eliminate adverse environmental and social risks and impacts, offset them, or reduce them to acceptable levels. Special attention will be paid to conducting the clinical research study and development of AI-based tools and platform. The costs related to conducting the ESMP will be covered by the foreseen INTELHEART budget.

Table 2. List of Work Packages (WPs).

WP No	WP title	WP leader	Start month	End month	Total calendar months of WP duration
1	Clinical study: retrospective and prospective	MFUNS	M1	M36	36
2	Developing AI tools	IVI	M1	M31	31
3	Design, development and evaluation of the VoiceHeart	SUNP	M1	M34	34
4	Developing finite element tools	FINK	M6	M29	24
5	Establish, evaluate and refine cloud and mobile app AI-based INTELHEART platform for early diagnoses of heart failure	FINK	M12	M36	25
6	Clinical study delivery and regulatory development	FMSUKG	M1	M36	36
7	Management, dissemination and exploitation	FINK	M1	M36	36

Kragujevac, 30/10/2023