An International Clinical Validation of Radiomics Artificial Intelligence for Breast Cancer Treatment Planning

Deliverable D2.1:
Study initiation package

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Lead Beneficiary	HULAFE
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Date of validation by the Project Coordinator	27.02.2023
Project Coordinator Signature	

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Version log

Issue Date	Version	Involved	Comments
2023.02.06	0.1	HULAFE	Draft
2023.02.14	0.2	HULAFE	Revised Draft v0.1
2023.02.15	0.3	UB	Revised Draft v0.2
2023.02.23	0.4	HULAFE	Revised and corrected final version.
2023.02.27	1.0	UB	Revised and corrected final version to submit to the EC

Executive Summary

This deliverable develops:

Work package WP2 – Multi-faceted evaluation framework, resources and guidelines.

- D2.1 Study initiation package

This deliverable describes the first tasks within work package 2, focused on the Radioval project initiation package.

The document explains the main tasks performed to obtain ethical clearance in each clinical center, as well as the tasks required by the European Commission for all those projects involving clinical studies. All these documents must be approved by the different local committees before the start of the inclusion of patients in the study.

These tasks also include enrollment of the study in a registry that meets the criteria of the WHO Registry. Specifically, the study has been registered in ClinicalTrials.gov PRS.

Table of Contents

Acronyms

Name	Abbreviation
Protocol Registration and Results System	PRS
Horizon Europe	HE
World Health Organization	WHO
Neoadyuvant Chemotherapy	NAC
Breast Cancer	BC
Magnetic Resonance	MR
Positron Emission Tomography–Computed Tomography	PET/CT

1. Registration number of the clinical study in a registry meeting WHO Registry criteria

1.1 Clinical study description

A **Clinical Study** involves clinical projects, trials and cohorts, using any systematic prospective or retrospective collection and analysis of health data obtained from individual patients or healthy persons (also called participants), in order to add medical knowledge related to the understanding, prevention, diagnosis, monitoring or treatment of a disease, mental illness, or physical condition. The results of these studies can make a difference in the care of future patients by providing information about the benefits and risks of therapeutic, preventative, or diagnostic products or interventions.

There are two main types of clinical studies:

1. Clinical Trials (also called interventional studies)
   In a clinical trial, participants receive specific interventions according to the research plan or protocol created by the investigators. These interventions may be medical products (such as drugs or devices), procedures, or changes to participants' behavior (diet). Clinical trials may compare a new medical approach to a standard one that is already available, to a placebo that contains no active ingredients, or to no intervention.

2. Observational Studies
   In an observational study, researchers assess health outcomes in groups of participants according to a research plan or protocol. Participants may receive interventions (which can include medical products such as drugs or devices) or procedures as part of their routine medical care, but participants are not assigned to specific interventions by the investigator (as in a clinical trial).

In both types of studies, researchers attempt to determine the safety and efficacy of the specific intervention by measuring certain outcomes in participants, and to establish whether it will be helpful, harmful, or no different from available alternatives (including no intervention).

The **common reasons for conducting clinical studies** include:

- Evaluating one or more interventions (for example, drugs, medical devices, approaches to surgery or radiation therapy) for treating a disease, syndrome, or condition.
- Finding ways to prevent the initial development or recurrence of a disease or condition. These can include medicines, vaccines, or lifestyle changes, among other approaches.
- Evaluating one or more interventions aimed at identifying or diagnosing a particular disease or condition.
- Examining methods for identifying a condition or the risk factors for that condition.
- Exploring and measuring ways to improve the comfort and quality of life through supportive care for people with a chronic illness.

The **ClinicalTrials.gov Protocol Registration and Results System (PRS)** is a web-based-data-entry-system used to register a clinical study or submit results information for a registered study. It includes both interventional and observational studies.

ClinicalTrials.gov allows the registration of clinical studies with human subjects that assess biomedical and/or health outcomes and that conform to:

- Any applicable human subject or ethics review regulations (or equivalent)
- Any applicable regulations of the national or regional health authority (or equivalent)

Registering clinical trials when they begin, providing timely updates, submitting summary results, and making this information publicly available fulfills a number of purposes and benefits a variety of people (see Table 1).

The Table 1 shows the purposes and who are the main beneficiaries of the trial registry process.

Table 1. Purposes and Benefits of Trial Registry

Registry Purpose	Beneficiary
Fulfill ethical obligations to participants and the research community	Patients, general public, research community
Provide information to potential participants and referring clinicians	Patients, clinicians
Reduce publication bias	Users of the medical literature
Help editors and others understand the context of study results	Journal editors, users of the medical literature
Promote more efficient allocation of research funds	Granting agencies, the research community
Help institutional review boards (IRBs) determine the appropriateness of a research study	IRBs, ethicists

1.2 European Commission mandatory documents for clinical studies

For EU Grants three mandatory deliverables apply to each clinical study included in the proposal:

1. STUDY INITIATION PACKAGE (BEFORE ENROLMENT OF THE FIRST STUDY PARTICIPANT) INCLUDING:

a) Registration number of the clinical study in a registry meeting WHO Registry criteria (e.g. EudraCT Number, or identifier from ISCRTN, or ClinicalTrials.gov if available).
b) Final version of study protocol as approved by the regulator(s)/ethics committee(s).
c) Regulatory and ethics (if applicable, institutional) approvals required for the enrolment of the first study participant.

2. MIDTERM RECRUITMENT REPORT

This report is due when 50% of the study population is recruited. The report shall include an overview of the number of recruited participants by clinical sites, any problems in recruitment and, if applicable, a detailed description of implemented and planned measures to compensate for any incurred delays.

3. REPORT ON THE STATUS OF POSTING RESULTS

Irrespective of the successful completion of the clinical study, summary results must be posted in the applicable registry/ies (where the study was registered) even if the timing of posting of results falls outside of the grant period. The report is to be scheduled for the time results posting is expected or for the last months of the project, whichever comes earlier.

1.3 Process to register/submit a clinical study in ClinicalTrials.gov PRS

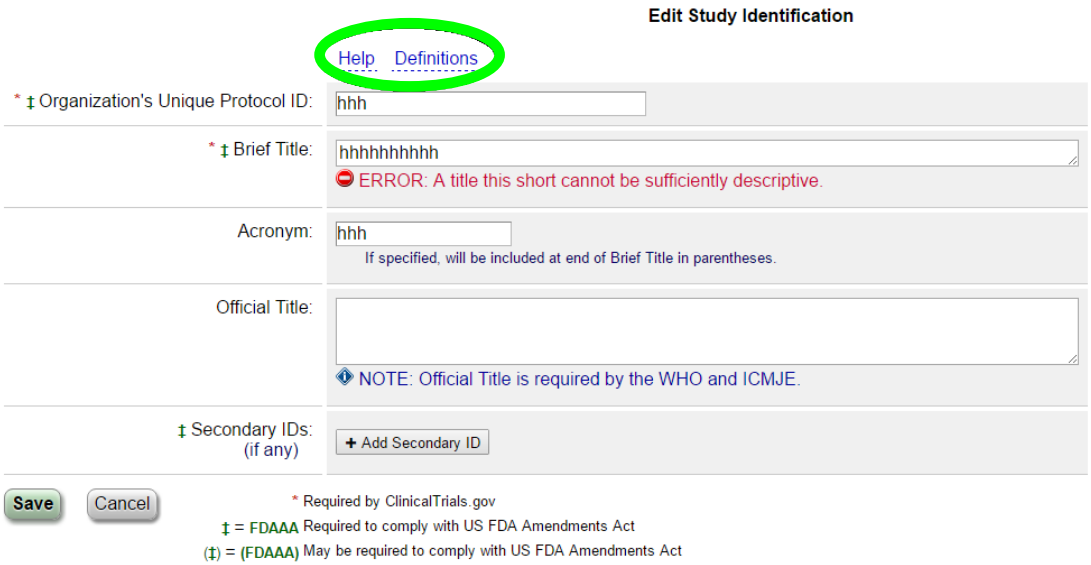
As required by the EU, we carried out to register the clinical study corresponding to the RadioVal project using the platform: ClinicalTrials.gov PRS

Briefly, the steps followed were:

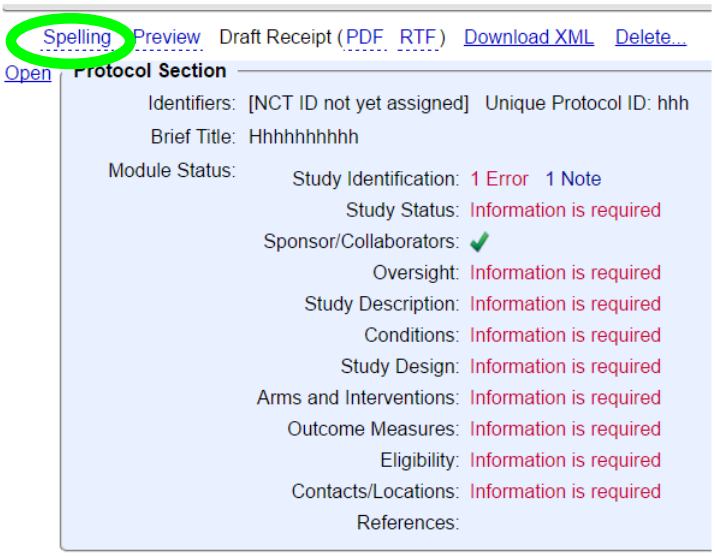
1. Log in to the following link: https://register.clinicaltrials.gov/

2. Once logged in, you can start registering the study/project by selecting "New Record" on the registration page.

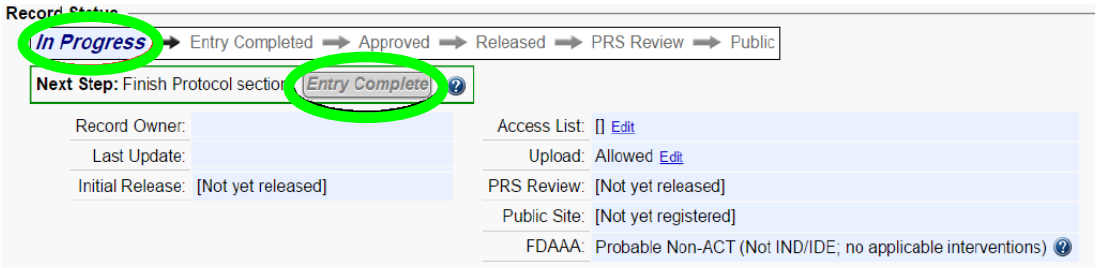
3. Fill in the data requested by ClinicalTrials.gov. In case of doubt, you can select the "Help" and "Definitions" buttons.



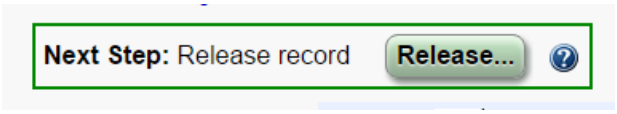
4. Check for grammatical errors by selecting the "Spelling" option.



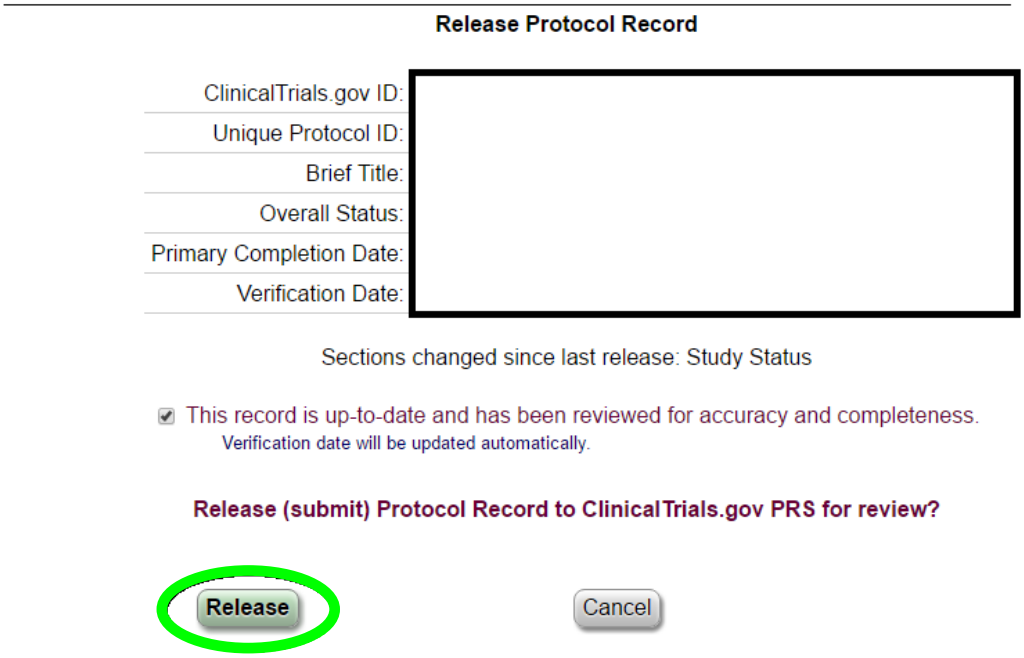
5. Once the information regarding the protocol section has been completed, select the "Entry Complete" option. The registration status will become "Entry Completed".



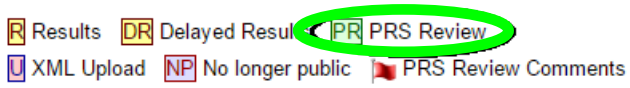
6. Select "Approved".



7. Select "Release" to send the record to ClinicalTrials.gov.



8. Once the registration is sent to ClinicalTrials.gov, the status will become "PRS Review".



9. A review of the registry will ClinicalTrials.gov conducted. They will send you an e-mail with the result (3-5 days).

10. If there are any errors, you will see a red flag ("PRS Review Comments"). Open the appropriate section and make the requested changes. When you finish with the revision, select the "Release" option to resend the record to ClinicalTrials.gov.

11. When the information is correct, ClinicalTrials.gov will provide you with an identification number for your study/project ("Protocol ID").

12. You must keep the registry up to date.

Figure 1 shows the history of events performed during the project registration process.

Figure 1. Review History of RadioVal Project entry

Event	User/Reviewer	Date/Time	
Publish	QA69	02/02/2023 11:28	
Release	IISLAFE	02/01/2023 07:55	View Release
Publish	QA57	10/06/2021 16:06	
Release	IISLAFE	10/04/2021 02:57	View Release
Reset	QA57	09/28/2021 19:29	Review Comments (1) Viewed by AnaPenades 6 time(s) -- last access: 10/04/2021 02:55
Release	IISLAFE	09/20/2021 03:34	View Release

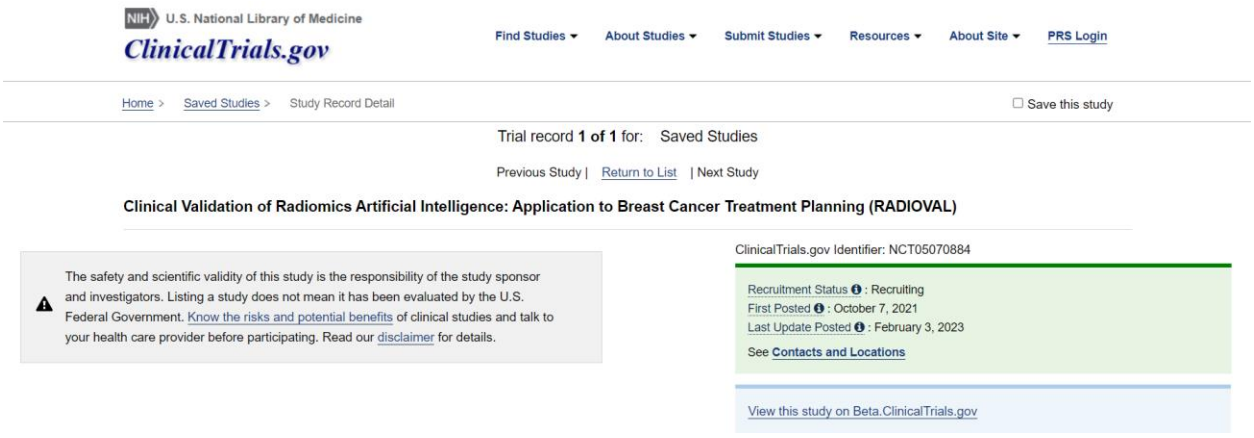
Figure 2 presents a summary table with the main details of the project once it has been registered in ClinicalTrials.gov PRS

Figure 2: Study Record Detail

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Clinical Validation of Radiomics Artificial Intelligence: Application to Breast Cancer Treatment Planning	Recruiting	No Results Available	•Breast Cancer	•Other: The development of new clinical AI solutions to predict treatment response to neoadjuvant chemotherapy (NAC) in breast cancer	•Alexander Fleming, Buenos Aires, Argentina •Medical University of Vienna, Vienna, Austria •University of Zagreb School of Medicine, Zagreb, Croatia •Ain Shams University, El Cairo, Egypt •Medical University of Gdansk, Gda#sk, Poland •Hospital Universitario y Politécnico La Fe de Valencia, Valencia, Spain •Karolinska Institute, Stockholm, Sweden •Hacettepe University, Ankara, Turkey

Figure 3 demonstrates the result obtained after searching for the project by its title in ClinicalTrials.gov application, and the resulting information.

Figure 3: Illustration of searching the RadioVal project in ClinicalTrial.gov



You can also consult the project registered in ClinicalTrials.gov PRS through the following link: https://clinicaltrials.gov/ct2/show/NCT05070884

2. Final version of study protocol as approved by the regulator(s) / ethics committee(s)

The final version of study protocol, data collection and other relevant details of the study, has been described in the document provided by de EU Grants: Information on Clinical Studies (HE): V4.2, which is attached as Annex 2.

3. Regulatory and ethics approvals required for the enrolment of the first study participant

3.1 Clinical description of RadioVal project

The objective of RadioVal is to implement a large-scale, international clinical validation of radiomics-based prediction of Neoadjuvant Chemotherapy (NAC) response from breast cancer (BC) based on Magnetic Resonance (MR). The evaluation study itself, which will assess the clinical value of the radiomics tools in terms of: **F**airness, **U**niversality, **T**raceability, **U**sability, **R**obustness and **E**xplainability (main recommendations from FUTURE-AI guidelines in health imaging). In addition, this tool will evaluate the cost-effectiveness, clinical applicability and

transferability of the radiomics solutions in the real world, not only within Europe but also to other world regions (South America, North Africa and Eurasia).

An "AI for Health Imaging" Network (AI4HI) was established in 2020, consisting of 90 affiliated institutions from 20 countries involved in five large EU-funded projects on big data and AI in cancer imaging. While the AI4HI Network is organized into thematic working groups, its work is driven by a concrete set of clinical use cases. In one of these use cases, namely MR-driven estimation of patient response for NAC in breast cancer, the AI4HI Network is gathering over 4,450 new datasets from over 11 countries and has built a computational pipeline based on FORTH's radiomics model for patient-specific NAC response estimation in breast MR26. Through the AI4HI Network, RadioVal will involve a unique sample of n=4,450 EU training cases and will add n=2,700 multi-continent testing cases to validate the radiomic tool.
RadioVal will involve a wide range of countries, from high-income EU countries (Austria, Sweden and Spain), emerging countries in Europe (Croatia and Poland), as well as international low-to-middle income countries (Egypt, Argentina and Turkey), and thousands of datasets from multiple populations and contexts (see table 2).

To achieve the objectives of RADIOVAL, centers will conduct a retrospective study to provide data that will be useful for analysis. Existing data from medical records, consisting of imaging and clinical data for breast cancer will be collected. More specifically, these data are grouped into the following categories:

1. Medical imaging data: MR compulsory at diagnosis, PET/CT, ultrasound and mammograms if available, providing multiparametric information (anatomical, morphological and functional/physiological) about the tumour. The data format will be provided in *.dicom*.
2. Clinical examinations and laboratory tests: demographic, somatometric and biochemical data as well as pre-existing risk data and treatment information. The format of the data will be in *.csv/.xls*.
3. Histopathological data at diagnosis and surgical specimen biopsy results after NAC treatment. The format of this data will be in *.pdfs/csv/text* (report).

Data from this phase to be used in the project will come from 9 clinical partners who will follow similar ethics procedures.
Each of the clinical centers participating in the project has submitted the required documentation for evaluation by their local ethics committee. Once evaluated and approved, the research project approval reports were sent via email to the project's clinical coordinator contact for supervision and accommodation in the google drive for all participant´s group.
Currently, all the clinical center collaborators have the project approved by the specific ethics committees of their hospital, except for GUMED, which has obtained an ethics committee approval with minor clarifications of the clinical study, and MUW, which has not yet communicated the status of the review process by its ethics committee (see table 3).
Table 2 shows the Clinical Collaborating Institutions that collect data.

Table 2: List of Clinical Collaborating Institutions

Participant Number	Role	Short name	Clinical Site	Country
8	BEN	HULAFE	FUNDACION PARA LA INVESTIGACION DEL HOSPITAL UNIVERSITARIO LA FE DE LA COMUNIDAD VALENCIANA	Spain
9	BEN	KI	KAROLINSKA INSTITUTET	Sweden
10	BEN	GUMED	MEDICAL UNIVERSITY OF GDANSK	Poland
11	BEN	UNIZG	MEDICAL SCHOOL UNIVERSITY OF ZAGREB	Croatia
12	BEN	MUW	MEDICAL UNIVERSITY OF VIENNA	Austria
13	BEN	HUH	HACETTEPE UNIVERSITY HOSPITAL	Turkey
14	BEN	AFI	ALEXANDER FLEMING INSTITUTE	Argentina
15	BEN	ASU	AIN SHAMS UNIVERSITY HOSPITAL	Egypt
17	BEN	GOC	GERMAN ONCOLOGY CENTRE	Cyprus

Table 3 shows the details and process of ethics evaluation of the clinical study from each Clinical Collaborating Institution.

Table 3. Ethics Committee Documentation

Clinical Sites		Retrospective Data	Document preparation (local language)	Document submitted to the local ethics committee	Forseen date of approval	Document approval
Eur 1	HULAFE	PASSED	Spanish	04/02/2022	March 2022	30/03/2022
Eur 2	KI	PASSED	Swedish	09/12/2022	January 2023	16/01/2023
Eur 3	GUMED	PROVISIONAL	Polish	14/09/2022	February 2023	Pending clarifications
Eur 4	UNIZG	PASSED	English	2022	2022	27/06/2022
Eur 5	MUW	Unknown	--	--	--	--
Eur 6	GOC	PASSED	Greek	02/02/2023	February 2023	09/02/2023
Int 1	HUH	PASSED	English	2022	2022	05/07/2022
Int 2	AFI	PASSED	Spanish	18/07/2022	October 2022	28/10/2022

Int 3	ASU	PASSED	Arabic	2022	2022	28/06/2022

1.4 Ethics Committees of RadioVal project

All ethical and regulatory considerations are according to good clinical practise and following GPDR regulations in all countries participating in the study. Approvals by Local Ethics Committees of each participating Clinical Institution are included in the Annex 3 of this document.

This document compiles the regulatory and ethics final approval required in the study. Each institution has sent the application and specific information to its committee for review and evaluation. This documentation is maintained by the local Ethics Committees at each clinical center, and can be consulted if needed.

Throughout the project, the Consortium will also make use of the Legal Working Group to ensure full compliance with the regulatory guidelines.

4. Conclusions

Throughout this deliverable we've presented the first tasks within work package 2, focused on the Radioval project initiation package. We are currently working on building synergies with other projects to collect more data. Said data providers will have to go through ethical approval process.

5. Annexes

ClinicalTrials.gov PRS
Protocol Registration and Results System

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: February 1, 2023

ClinicalTrials.gov ID: NCT05070884

Study Identification

Unique Protocol ID:	RADIOVAL
Brief Title:	Clinical Validation of Radiomics Artificial Intelligence: Application to Breast Cancer Treatment Planning (RADIOVAL)
Official Title:	Clinical Validation of Radiomics Artificial Intelligence: Application to Breast Cancer
Secondary IDs:	

Study Status

Record Verification:	September 2022
Overall Status:	Recruiting
Study Start:	June 1, 2023 [Anticipated]
Primary Completion:	August 2025 [Anticipated]
Study Completion:	December 2025 [Anticipated]

Sponsor/Collaborators

Sponsor:	Instituto de Investigacion Sanitaria La Fe
Responsible Party:	Sponsor
Collaborators:	Karolinska Institutet Medical University of Gdansk Medical School University of Zagreb Medical University of Vienna Hacettepe University Hospital Alexander Fleming Institute Ain Shams University

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: 2022-106-1 Board Name: Ethic Committee La Fe Health Research Insititute Board Affiliation: N/D Phone: 96 124 66 05

Email: ceic@iislafe.es
Address:

Comité Ético de Investigación Clínica
Instituto de Investigación Sanitaria La Fe
Torre A - Planta 7ª - Despacho 7.02
Avenida Fernando Abril Martorell, 106
46026 Valencia (Spain)

Data Monitoring: No

FDA Regulated Intervention: No

Study Description

Brief Summary: RadioVal will develop and implement interoperable solutions for clinical deployment of the radiomics tools, including information, training, and communication packages for clinicians and patients, as well as standard operating procedures for the integration of radiomics in clinical oncology. With this study, we will clinically validate these solutions, by looking at their reliability for precise breast cancer diagnosis, treatment recommendation and prognosis estimate, treatment response, evaluation of residual disease and outcome prediction.

Detailed Description:

Conditions

Conditions: Breast Cancer

Keywords:

Study Design

Study Type: Observational

Observational Study Model: Cohort

Time Perspective: Retrospective

Biospecimen Retention: None Retained

Biospecimen Description:

Enrollment: 5000 [Anticipated]

Number of Groups/Cohorts: 1

Groups and Interventions

Groups/Cohorts	Interventions
non respondants of neo treatment those patients with no response or partial response when administered with Chemotherapy prior to sugery	The development of new clinical AI solutions to predict treatment response to neoadjuvant chemotherapy (NAC) in breast cancer Evaluate response to neoadjuvant treatment in advanced breast cancer

Outcome Measures

Primary Outcome Measure:

1. Percentage of patients non-respondents vs respondents in neoadjuvant breast cancer treatment (Estimate tumor aggressiveness)

   Proportion of patients who have complete response evaluating the target lesion according to Miller/Payne Grading system [Ogston et al., 2003]: 1A. Evaluation of target Tumor: G5 as pathological complete response, no tumor left; G4:more than 90% loss of tumor cells; G3: between 30-90% reduction in tumor cells; G2: loss of tumor <30%; G1: no reduction. 1B: Evaluating the lymph nodes: A: negative; B: lymph nodes with metastasis and without changes by chemotherapy; C: lymph nodes with metastasis with evidence of partial response, D: lymph nodes with changes attributed to response without residual infiltration. 1C: Using images to evaluated radiological response: Size and diameter in millimeters of the target lesion using RM and TC or PET/CT for extension analysis (lymph nodes and metastasis).

   [Time Frame: Baseline and after neoadjuvant treatment (4-6 months)]

Eligibility

Study Population:	Patients treated with chemotherapy prior to surgery
Sampling Method:	Non-Probability Sample
Minimum Age:	18 Years
Maximum Age:	85 Years
Sex:	Female
Gender Based:	No
Accepts Healthy Volunteers:	
Criteria:	Inclusion Criteria:

- Females ≥ 18 years up to 85 years old
- Individuals referred to hospitals for diagnosis of breast cancer
- Availability of radiological images: 2D mammography or 2D synthetic digital tomosynthesis, ultrasound, or magnetic resonance
- Availability of pathological report (surgical specimen)
- Availability of (Neoadjuvant) treatment allocation (scheme, duration, benefit)
- Availability of treatment response

Exclusion Criteria:

- Patient with incomplete or low-quality data (radiological, pathological or clinical)

Contacts/Locations

Central Contact Person:	Ana Penades-Blasco, M.Ec Telephone: +34 961245633 Email: ana_penades@iislafe.es
Central Contact Backup:	
Study Officials:	
Locations:	**Spain** Hospital Universitario y Politécnico La Fe de Valencia [Recruiting] Valencia, Spain, 46026

Contact: Gloria Ribas, PHD gloria_ribas@iislafe.es
Principal Investigator: Luis Marti-Bonmati, MD, PhD
Sub-Investigator: Ana Santaballa, MD, PhD
Sub-Investigator: Guillermina Montoliu, MD, PhD
Sub-Investigator: Rosa García, MD

Poland
Medical University of Gdansk
[Not yet recruiting]
Gdańsk, Poland
Principal Investigator: Maciej Bobowicz, MD, PhD

Sweden
Karolinska Institute
[Not yet recruiting]
Stockholm, Sweden
Principal Investigator: Fredrik Strand
Sub-Investigator: Apostolia Tsirikoglou, PhD

Croatia
University of Zagreb School of Medicine
[Not yet recruiting]
Zagreb, Croatia
Principal Investigator: Boris Brkljacic

Austria
Medical University of Vienna
[Not yet recruiting]
Vienna, Austria
Principal Investigator: Pascal Baltzer

Turkey
Hacettepe University
[Not yet recruiting]
Ankara, Turkey
Principal Investigator: Meltem Gulsun Akpinar

Argentina
Alexander Fleming
[Not yet recruiting]
Buenos Aires, Argentina
Principal Investigator: Daniel Cl Mysler

Egypt
Ain Shams University
[Not yet recruiting]
El Cairo, Egypt
Principal Investigator: Abeer Hamed

IPDSharing

Plan to Share IPD: No
N/D

References

Citations:

Links:	
Available IPD/Information:	

Annex 2. EU Grants: Information on Clinical Studies (HE): V4.3 – 22.02.2023

INFORMATION ON CLINICAL STUDIES

(For calls that involve clinical studies[1], project participants must add this document to the application and upload it as separate annex to the proposal part B in the Submission System.)

Clinical studies have a number of methodological, operational and regulatory specificities. Information on these issues is crucial for evaluators to assess the scientific quality and operational feasibility of the proposal. The following set of section headings guide applicants to provide essential information on clinical studies in a standardised format.

Applicability:

For **HE collaborative research and innovation:**

Single-stage and stage-2 proposals: The use of this template is mandatory for single-stage or stage-2 proposals, if the application includes a clinical study[1] AND it concerns a topic including clinical studies[2].

For these topics, you will have the possibility to upload the completed template as a separate part of your application in the submission system.

Stage-1 proposals: In the limited frame of a stage-1 proposal, not all methodological details of clinical studies can be fully elaborated. Depending on the characteristics of the study, however, key aspects of clinical study have to be convincingly addressed already at stage 1. This template cannot be uploaded as a separate document at stage 1, but relevant aspects of this information should be integrated in part B of the stage 1 proposal template.

For **HE IHI Joint Undertaking and Global Health-EDCTP3 Joint Undertaking:**

Single-stage and **stage-2** proposals: The use of this template is mandatory for all clinical studies. You can upload the completed template as a separate part of your application in the submission system.

Stage-1 proposals: see under Horizon Europe collaborative research and innovation

For each[3] clinical study performed within the scope of the proposal, essential information according to the below structure should be provided and compiled into one single document per proposal. Each section must be addressed briefly and concisely. In case one or more sections do not apply to a particular study, please provide a short explanation.

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[1] Clinical study covers clinical studies/trials/investigations/cohorts and means, for the purpose of this document, any systematic prospective or retrospective collection and analysis of health data obtained from individual patients or healthy persons in order to address scientific questions related to the understanding, prevention, diagnosis, monitoring or treatment of a disease, mental illness, or physical condition. It includes but it is not limited to clinical studies as defined by Regulation 536/2014 (on medicinal products), clinical investigation and clinical evaluation as defined by Regulation 2017/745 (on medical devices), performance study and performance evaluation as defined by Regulation 2017/746 (on in vitro diagnostic medical devices).

[2] For proposals containing clinical studies submitted to topics *not* foreseeing clinical studies, you may use the section headings of this template as an orientation and provide the related information in sections B.1 and B.3 of the proposal, if the submission system does not provide the possibility to upload the template.

[3] If the proposal contains more than one clinical study, each study should be described separately, e.g. study A, study B, etc.

When the requested information is currently not available (e.g. a clinical study is planned for a later stage of the project and it will be based on or influenced by future results of other studies), the source and the collection of the relevant input should be described.

Information provided in this template does not need to be repeated elsewhere in the proposal but can be referred to.

There are no page limitations for this template, but explanations should be as concise as possible.

Information outside the scope of this template will not be considered in the proposal evaluation. No other chapters or annexes (containing e.g., complete study protocols) can be added to this template. Section headings should not be changed.

Ethics considerations must be addressed in the appropriate section of the proposal. Similarly, risks and mitigation measures have to be addressed in the respective section of the proposal (part B.3.1 and table 3.1e) and not in this template!

The below three **mandatory deliverables** apply to each clinical study included in the proposal:

1. Study initiation package (before enrolment of the first study participant) including:
    - Registration number of the clinical study in a registry meeting WHO Registry criteria[4] (see also references given in subheading 1.1 of this template)
    - Final version of study protocol as approved by the regulator(s) / ethics committee(s)
    - Regulatory and ethics (if applicable, institutional) approvals required for the enrolment of the first study participant (In case of multicentre clinical studies, submission of approvals for the first clinical site is sufficient.)
2. Midterm recruitment report

    This report is due when 50% of the study population is recruited. The report shall include an overview of the number of recruited participants by clinical sites, any problems in recruitment and, if applicable, a detailed description of implemented and planned measures to compensate for any incurred delays.
3. Report on the status of posting results

    Irrespective of the successful completion of the clinical study, summary results must be posted in the applicable registry/ies (where the study was registered) even if the timing of posting of results falls outside of the grant period. The report is to be scheduled for the time results posting is expected or for the last months of the project, whichever comes earlier.

[4] https://www.who.int/clinical-trials-registry-platform/network/registry-criteria

1 Description of the clinical study

1.1 Title, acronym, unique identifier (e.g. EudraCT Number5, or identifier from ISCRTN6, ClinicalTrials.gov7 if available) of the clinical study

Title: Clinical Validation of Radiomics Artificial Intelligence: Application to Breast Cancer Treatment.
Acronym: (RadioVal)
ClinicalTrials.gov identifier: NCT05070884

1.2 Study rationale

Please provide the overall rationale for conducting the proposed study.

RadioVal will develop and implement interoperable solutions for clinical deployment of the radiomics tools, including information, training and communication packages for clinicians and patients, as well as standard operating procedures for the integration of radiomics in clinical oncology. With this study we will clinically validate these solutions, by looking at its reliability for precise breast cancer diagnosis, treatment recommendation and prognosis estimate, treatment response, evaluation of residual disease and outcome prediction.

1.2.1 Extent and evaluation of current knowledge directly linked to the scientific question(s) to be answered by the clinical study

The development of new clinical AI solutions to predict treatment response to neoadjuvant chemotherapy (NAC) in breast cancer has shown promising results in recent studies. The validation of these studies focused mostly on evaluating model accuracy and in some cases also on evaluating robustness of the radiomic features across multiple centers. Radiomic models should be validated by using a validation data set and a test data set, with the validation set being an unused extension of the training set and the test set being a previously unseen external data set. However, a recent study has shown that only 6% of radiomics studies have performed external validation and none of the external validations looked at diagnostic cohort design, multi-center inclusion and prospective data collection[8]. We will substantially advance the validation of radiomics research by addressing all these shortcomings. We have designed our clinical study to largely validate our radiomic models with respect to the FAIR principles, accuracy, sensitivity, and robustness, but also to look beyond and examine the cost-effectiveness, interpretability, and usability of the clinical applications together with all potential users.

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5 https://www.clinicaltrialsregister.eu/
6 https://www.isrctn.com/
7 https://clinicaltrials.gov/

1.2.1.1 Outcomes (efficacy, safety) of completed and number of ongoing clinical studies utilising the same intervention in the same indication (including review of public registers)

There is only one completed clinical trial regarding the use of radiomic data and prediction of treatment response in breast cancer [Colen et al 2021][9] and the authors describe as outcomes achieved a radiomics-based model for predicting response to pembrolizumab in patients with advanced rare cancers (including breast cancer). Patients are enrolled in a phase II clinical trial of pembrolizumab.

The 10 most relevant radiomics features were selected; XGBoost-based classification successfully differentiated between controlled disease (complete response, partial response, stable disease) and progressive disease with high accuracy, sensitivity, and specificity in patients assessed by RECIST (94.7%, 97.3%, and 90%, respectively; $p<0.001$) and in patients assessed by irRECIST (94.7%, 93.9%, and 95.8%, respectively; $p<0.001$). Additionally, the common features of the RECIST and irRECIST groups also highly predicted pembrolizumab response with accuracy, sensitivity, specificity, and p value of 94.7%, 97%, 90%, $p<0.001$% and 96%, 96%, 95%, $p<0.001$, respectively.

Other completed studies regarding the use of radiomic data and prediction of risk assessment and treatment response in breast cancer are the following:

- Giger et al., 2014 [10]: It is well known that mammographic density is an independent risk factor, and radiomics may provide much more information than breast density. Li et al. investigated breast parenchymal patterns in mammographic images in 456 patients (53 with BRCA1/2 gene carrier, 75 with unilateral cancer and 328 with low risk). They demonstrated that women at high risk tend to have dense breasts with coarse and low-contrast texture patterns.

- Haberle et al., 2012 [11]: Authors performed a case-control study with 864 cases vs. 418 controls. Of the 470 radiomics features explored, 46 remained in the final risk model; the radiomics model outperformed than the conventional risk model with mammographic density. These studies may promote future breast cancer prevention trials to investigate the role of radiomics to measure breast tissue composition in individual woman for personalized risk management.

- Wu et al., 2016 [12]: Authors used dynamic contrast-enhanced-MRI to assess response to neoadjuvant chemotherapy. These images can provide the tumour's kinetic characteristics of the contrast agent by producing pharmacokinetic maps. Based on quantitative, multi-region analysis that identified enhancement characteristics, the proposed imaging predictors achieved a better performance (AUC = 0.79) than conventional imaging predictors (AUC = 0.53) and texture features on whole tumour analysis (AUC = 0.65).

- Bian et al., 2020 [13]: 152 patients from 2017 to 2019 underwent a preoperative breast MRI and were graded to evaluate complete pathological response to NAC (Miller-Payne grading system) describes a radiomic signature and nomogram model with potential predictive power to NAC treatment which can aid in the prognosis and guidance of treatment regimens (follow up and may avoid chemotherapy-induced toxicity).

- Lambin P, et al., 2017 [14]: Radiomics is becoming increasingly more important in medical imaging. The explosion of medical imaging data creates an environment ideal for machine-learning and data-based science. Radiomics-based decision-support systems for precision diagnosis and treatment can be a powerful tool in modern medicine. Large-scale data sharing is necessary for the validation and full potential that radiomics represents. Standardized data collection, evaluation criteria, and reporting guidelines are required for radiomics to mature as a discipline.

- Leithner D, et al.,2020 [15]: In this IRB-approved HIPAA-compliant retrospective study 91 patients with treatment-naïve breast malignancies proven by image-guided breast biopsy, underwent multiparametric magnetic resonance imaging (MRI) of the breast at 3 T with dynamic contrast-enhanced MRI, T2-weighted and DW imaging. For lesions that were segmented on DWI and segmentation ROIs were propagated to ADC maps the following classification accuracies > 90% were obtained: luminal B vs. HER2-enriched, 94.7 % (based on COM features); luminal B vs. others, 92.3 % (COM, HIS); and HER2-enriched vs. others, 90.1 % (RLM, COM). For lesions that were segmented directly on ADC maps, better results were achieved yielding the following classification accuracies: luminal B vs. HER2-enriched, 100 % (COM, WAV); luminal A vs. luminal B, 91.5 % (COM, WAV); and luminal B vs. others, 91.1 % (WAV, ARM, COM).

- Han L, et al., 2019 [16]: The radiomic signature based on 12 LN status-related features was constructed to predict LN metastasis, its prediction ability was moderate, with an area under the curve (AUC) of 0.76 and 0.78 in training and validation cohorts, respectively. Based on a radiomic signature and clinical features, a nomogram was developed and showed excellent predictive ability for LN metastasis (AUC 0.84 and 0.87 in training and validation sets, respectively). Another radiomic signature was constructed to distinguish the number of metastatic LNs (less than 2 positive nodes/more than 2 positive nodes), which also showed moderate performance (AUC 0.79). Both nomogram and radiomic signature can be used as tools to assist clinicians in assessing LN metastasis in breast cancer patients.

At the moment, 2 ongoing trials are registered on clinicaltrials.gov only. ISCRTN and EudraCT registries have no trials registered that investigate radiomics for evaluating the prediction of breast cancer outcomes. In contrast to the other studies, the RadioVal study will involve a wide range of countries, from high-income EU countries (Austria, Sweden, and Spain), emerging countries in Europe (Croatia and Poland), as well as international low-to-middle income countries (Egypt, Argentina and Turkey). The wider geographical diversity, much larger data samples, and user-centred multi-disciplinary evaluations will allow to advance the current state-of-the-art.

Registry	Trial Identifier	Description
clinicaltrials.gov	NCT03592004	This is a single-arm, multicentre study that aims to assess whether Radiomics combining multiparametric MRI and clinical data could be a good predictor of the responses to neoadjuvant chemotherapy in Breast Cancer.
clinicaltrials.gov	NCT04021069	This study examines retrospective clinical data on patients diagnosed with breast cancer and

		monitor their response to neoadjuvant chemotherapy, incidence of locoregional recurrence, distant metastasis, and disease-free survival. The hypothesis of this study is that breast cancer patients who achieve a pathological complete response (pCR) to neoadjuvant chemotherapy demonstrate distinct clinicopathomic biomarker signatures.

1.2.1.2 Level of evidence related to the mechanism of action of the intervention in the planned clinical study population.

RadioVal will follow high level of evidence recommendations for designing the study proposed [Marti-Bonmati L 2021][17]. Radiomics quantifies textural information in medical imaging by using advanced mathematical methods from artificial intelligence. Therefore, the study proposed based on "Clinical Validation of Radiomics Artificial Intelligence: Application to Breast Cancer Treatment Planning" will focus on validation of previous developed AI models for breast cancer (from European projects CHAIMELEON, EuCanImage) which are based on large retrospective, non-observational in silico studies. The results obtained in this validation of radiomic models will focus in improving healthcare of breast cancer patients predicting better response to neoadjuvant treatments.

1.3 Objective(s) of the clinical study

Please differentiate between primary and secondary objective(s)

Primary objective:
To predict tumour aggressiveness (non-respondents vs respondents) in the setting of neoadjuvant breast cancer treatment with the application of AI solutions in medical imaging.

Secondary objectives: Use AI models developed to be applied:

- to improve tumour detection (detection and segmentation),
- to use radio-genomic expression,
- to predict local immune reaction,
- to predict lymph node invasion,
- to predict distant metastasis,
- to determine patient prognosis (survival, relapse, response to treatment).

1.4 Characteristics of the study population (size, age group, sex distribution, inclusion, and exclusion criteria; all items with justification!)

The study population will be expected to reach a size larger than 2400 patients with breast cancer diagnosis who have undertaken neoadjuvant chemotherapy treatment. The age distribution will include female patients between 18 and 80 years of age. [Allot et al., 2020][18]. Although there is a small fraction of male diagnosed with breast cancer (1%), they almost certainly have important biological differences in relation to females and, usually patients belong to families with hereditary breast cancer, for this reason the study will only study females with breast cancer (Gucalp et al 2019)[19].

Inclusion criteria:

- Females ≥ 18 years up to 85 years old
- Individuals referred to hospitals for diagnosis of breast cancer
- Availability of radiological images: 2D mammography or 2D synthetic digital tomosynthesis, ultrasound, or magnetic resonance
- Availability of pathological report (surgical specimen)
- Availability of (Neoadjuvant) treatment allocation (scheme, duration, benefit)
- Availability of treatment response

Exclusion criteria:

- Patient with incomplete or low-quality data (radiological, pathological or clinical)

1.4.1 Details on sample size and power calculation

- Through the AI4HI Network and other public databases, we estimated to recruit a unique sample of n=4,450 EU training cases.
- Through multi-continent recruitment sites, we estimated to recruit samples for validation. These clinical sites are from high-income European countries (Austria, Sweden and Spain), emerging countries in Europe (Croatia, Poland and Cyprus), as well as international low-to-middle income countries (Egypt, Argentina and Turkey).

Site, acronym, full name, country, and approximate initial number of cases already enrolled in the study in tabular form. This recruitment will be increase according to the established protocols in each annuity.
In case, it will be necessary, we recruit more cases from public databases.

Clinical Sites			***COUNTRY***	***CASES***
Eur 1	***HULAFE***	*FUNDACION PARA LA INVESTIGACION DEL HOSPITAL UNIVERSITARIO LA FE DE LA COMUNIDAD VALENCIANA*	*Spain*	*600*
Eur 2	***KI***	*KAROLINSKA INSTITUTET*	*Sweden*	*150*
Eur 3	***GUMED***	*MEDICAL UNIVERSITY OF GDANSK*	*Poland*	*350*
Eur 4	***UNIZG***	*MEDICAL SCHOOL UNIVERSITY OF ZAGREB*	*Croatia*	*250*
Eur 5	***MUW***	*MEDICAL UNIVERSITY OF VIENNA*	*Austria*	*1000*
Eur 6	***GOC***	*GERMAN ONCOLOGY CENTRE*	*Cyprus*	*45*
Int 1	***HUH***	*HACETTEPE UNIVERSITY HOSPITAL*	*Turkey*	*200*
Int 2	***AFI***	*ALEXANDER FLEMING INSTITUTE*	*Argentina*	*50*
Int 3	***ASU***	*AIN SHAMS UNIVERSITY HOSPITAL*	*Egypt*	*50*

Prevalence for pathological Complete Response in Neoadjuvant treatment varies according to molecular breast cancer subtypes, representing up to 45% of triple negative. In the case of HER2-positive tumors, several studies have demonstrated a high pCR rate after neoadjuvant therapy that includes anti-HER2 treatment, which can be up to 60% pCR with the newest drug regimens. However, regarding luminal-like tumors, neoadjuvant chemotherapy achieves a lower rate of pCR in

comparison with other subtypes, with a pCR rate of around 10%–24%". [Colomer R. et al., 2019][20]. Other works report more discrete results. Spring et al., 2020, global pCR is 21.1% [increasing to (32.6%) in the Triple Negative Breast Cancer cases and 36.4% for Her2+ breast cancer both with neoadjuvant treatment] [21].

The Breast Cancer Unit at HULAFE received about 200 Breast cancer patients newly diagnosed per year. According to oncologists in the Unit about 25 – 30% of the total patients will follow neoadjuvant treatment (mainly Triple negatives breast cancer and Her2+ subtypes, with some luminal B cases) which could represent between 55 or 65 patients per year. Considering the period of ten years for recruitment (from 2015- up to 2025), in HULAFE we could reach at least 600 neoadjuvant cases, and of those about 180 will have pathological complete responses.

Assuming a similar recruitment in all the 9 clinical sites, we could most probably recruit around 2,400 breast cancer patients with neoadjuvant treatment.
Sample size estimation has been done according to Ridley el al 2020 with the package "pmsize/R". We will use a R-correction factor of 0.3 and 30 as maximum number of predictor parameters. Prevalence for pathological Complete Response of global Neoadjuvant treatment (21.1%) [according to Spring et al., 2020] [13]. The Sample size recommended using these conservative parameters is of 2,300 patients [1,251 training set x 948 validation set x with 200 events (cases with complete pathological response)].

1.5 Design of the clinical study (controlled / uncontrolled; randomised; open / blinded; parallel group / cross over / other; please justify the appropriateness of the selected design)

The RadioVal study will be based on "observational and non-interventional research on data, emulated control trial, longitudinal, retrospective, analytic, case control by presence of exposure with no-enrolment conditions. Clinical cases would be used to develop Guidelines for prediction Model Validation (TRIPOD)[23] will be followed.

1.6 Type of intervention (medicinal product / advanced therapy medicinal product / medical device / in vitro diagnostic medical device / surgical or other invasive procedure / other medical intervention, including, e.g., counselling)

Not applicable. RadioVal will not conduct any interventional studies.

1.7 Description and timing of study procedures

Please provide an overview, preferably in a tabular format, about the schedule of study procedures. Please give a simple statement on how long individual patients or healthy volunteers participate in the clinical study.

Recruitment period will be from 2015 onwards and will consist in real world data of complete clinical, pathological, genetic, and radiological data for each patient. Complete Demographic, diagnosis, treatment, and follow-up (response, relapse, metastasis, outcome) will be recollected.

Study procedures	**Description**	***Timeline***
Define population & collection of data	Breast cancer patients with neoadjuvant treatment	M1-M12
Recruitment of breast cancer data	Automatic extraction using OMOP terminology from EHR in hospitals	M6 – M12
Extract radiomic and genomic data	Handcrafted and deep extraction of features	M12-M18
Split in control and cases by exposure signature	Balance and evaluate distribution for training and validation of data sets	M18-M30
Evaluate relations with clinical endpoints	ML models, fine tuning and transfer learning	M30-M38
Validation and causal relations	Obtaining and validating results with AI tools developed	M38-M42
Publications and reports		M42-M48

2 Preparedness status

2.1 Development of the clinical study protocol

Please describe how the below aspects have been or will be addressed in developing the clinical study protocol (if applicable):

2.1.1 Scientific advice from regulatory and health technology assessment bodies

Scientific advice will be sought from experts in breast cancer and members of European Society of Medical Oncology (ESMO). Guidelines approved by ESMO and leading oncologist in breast cancer will be closely followed.

In addition, leading members of the most prestigious associations in radiomics will advise on ethical and regulatory aspects in project: European Society for Magnetic Resonance in Medicine and Biology (ESMRMB), European Imaging Biomarkers Alliance (Marti-Bonmatí is a leading member.

2.1.2 Clinical efficacy, safety, and methodological guidelines (including guidelines on statistics)

The study will follow guidelines on longitudinal, observational studies: EQUATOR guidelines[24] and Larson et al., 2021 on Artificial Intelligence[25], including to the following guidelines:

1. TRIPOD (Transparent Reporting of studies on prediction models for Individual Prognosis or Diagnosis) reporting guideline (issued in January 2015; www.tripod-statement.org)[26].

2. STARD 2015 – An updated list of essential items for reporting diagnostic accuracy studies [27].
3. REporting of studies Conducted using Observational Routinely collected health Data (RECORD) Statement [28].
4. IMDRF standard for clinical investigation[29].
5. SAMPL (Statistical Reporting) Guidelines[30].
6. Radiomics Quality Score
7. In silico trial/virtual trials

2.1.3 Involvement of citizens / patients, carers in drawing up the clinical study protocol

Although no specific patient's association is directly involved in this clinical study, we will follow all ethical and regulatory considerations to obtain the results according to good clinical practise and with the advice of GPDR regulations with the aim to improve health care for patients, without breaching their privacy.

2.2 Regulatory intelligence to ensure timely regulatory approval and ethics clearance of the clinical study in all jurisdictions where its implementation is planned

Please provide information on the following regulatory and ethics aspects:

2.2.1 How the consortium will ensure access to regulatory expertise necessary to get advice on, and management of, regulatory affairs activities in all concerned jurisdictions?

The Consortium partner, NHG, is a pioneer in advisory services for the health and social services sector and as such has an extensive network with access to regulatory expertise. During the course of the entire study, NHG will be in contact with the regulatory agencies of all concerned jurisdictions to collect continuously feedback on the progress of our clinical study.

All ethical and regulatory considerations to obtain the results according to good clinical practise in all countries participating in the study will be followed. Following GPDR regulations, the project will improve health care for patients without breaching their privacy.

2.2.2 How the consortium will ensure access to ethics expertise necessary to get advice on current proceedings and documentation requirements of all concerned ethics committees?

An **Ethics Management Group (EMG)** will be set up at the very beginning of the project, to oversee the ethical clearance of all the project's activities and their adherence to the relevant European regulations. It will include one representative of all partners, as well as **Data Protection Officers (DPOs)** from the institutions providing data, following the recommendation of the GDPR.

Clinical partners will request ethical approval through their responsible local and national ethical committees for all aspects of the research work where approval for specific activities is required on legal and ethical grounds. To be most up to date,

information regarding ethical permission will be collected by the PC and PM at the start of the project.

2.3 How the scientific and operational governance of the clinical study will be ensured?

RadioVal's management structure and procedures have been carefully set up to guarantee smooth cooperation within this highly inter-disciplinary Consortium, effective implementation of the scientific and operational activities of the project. Operational management will be implemented by the Executive Board (EB). Scientific steering will be performed by two themed committees, namely the Clinical Consensus Group (CCC) and the Technical Working Group (TWG).

The **Executive Board (EB)** will act as the operational body of the project, ensuring day-to-day management and coordination of the research. It will include all WP Leaders and will be chaired by the PC with support from the PM. Each WP Leader will be responsible for coordinating all activities relating to the objectives and implementation of the WP, working in close collaboration with the respective task leaders. They will take all operational decisions regarding the WP day-to-day management based on a detailed monitoring of milestones and expected results of the WP. They will also oversee addressing and documenting internal risks which may impair progress towards the objectives of the WP and suggesting strategies to anticipate and minimise such internal risks. The WP Leader will also be responsible for implementing the decisions agreed by the EB, controlling the execution of the project in line with its agreed work plan, and monitoring preventive actions.

The **Clinical Consensus Group (CCG)** will include representatives from all clinical partners, as well as academic and industry representatives from AI. This committee will:

- Coordinate clinical requirements gathering and analysis.
- Collaborate with ELSI experts and Data Protection Officers on EuCanImage's legal governance.
- Coordinate the data deposition compaign from clinical partners, including standards for data annotations.
- Establish procedures for assessing clinical effectiveness and trust in AI for cancer imaging.
- Take into consideration the patient's needs and perspective in the design of AI solutions.
- Contribute to establishing a tool for cost-benefit analysis of AI solutions.

The **Technical Working Group (TWG)** will comprise academic and industry representatives from AI, as well as clinical representatives.
This group will:

- Iteratively discuss and define technical specifications.
- Define the most suitable material and activities for clinical users.
- Finalise and document the standardised metrics, criteria.

2.3 How the scientific and operational governance of the clinical study will be ensured?

2.3.1 Please give details about the sponsor(s) (name, type of entity, seat or country of residence).

The RadioVal project does not involve sponsors.

2.3.2 Please describe the composition, the role and the functioning of the planned board(s), governing bodies.

In addition to the above-mentioned Executive Board, Clinical Consensus Group and Technical Working Group (see 2.3), RadioVal will establish the following boards:

1. The **Governing Board (GB)** will represent the highest management level in the project as the Consortium's main decision making and arbitration body. Chaired by the PC, it is composed of one representative per partner. High level and strategic project topics will be addressed, such as approving re-allocation of the project's budget; discussing and approving requests for major changes proposed to the work description and proposal of amendments, with subsequent effects on the project plan; requesting contractual changes to the EC; proposing and approving resolutions of critical issues and conflicts. Each partner has one vote, and a relative majority system is employed. Such details are defined in an appropriate Consortium Agreement. Given its nature of high-level decision-making body, the Governing Board will convene on a yearly basis, but summoned if required at other times.

2. **Innovation & IPR Committee (IIC)**: This committee will also comprise experienced members in technological and clinical transfer from our industrial partners (NHG, QUIBIM, SHINE), as well as from academia (UM, UB). This committee will:

    a. Coordinate the innovation and IPR management plan and continuously refined as part of WP8.

    b. Define IPR management policy in the Consortium Agreement at the beginning of the project (incl. allocation and protection of IPR, background and foreground IPR, access rights).

    c. Organise bi-yearly (web) meetings to continuously fine-tune the exploitation strategy based on advances of the project and recent novelties in the market.

    d. Facilitate knowledge exchange among partners, by acting as knowledge broker and thus ensuring an appropriate level of trust within the consortium.

    e. Oversee the management of innovative outcomes and preparation of future exploitation activities.

    f. Support of the preliminary market analysis, feeding directly into the overall exploitation strategy.

g. When needed, such as for resolving conflicts, request the opinion of the EU IPR Helpdesk or the External Advisory Board.

3. **Ethics Management Group (EMG)**: This group will oversee the ethical clearance of all the project's activities and their adherence to the relevant European regulations. For details, see 2.2.2.

4. The **External Advisory Board (EAB)**: The EAB has been carefully selected to include highly experienced international experts from a variety field of relevance to RadioVal. The EAB's role will include offering independent assessment and feedback regarding the implementation and robustness of the research activities, as well as providing advice and recommendation on specific technical issues that may arise. The EAB members will perform an annual project review for summarising project outcomes, alongside the annual project review meeting.

3 Operational feasibility

3.1 Please describe how the availability of the intervention(s) (including comparators) is secured throughout the entire implementation phase (give details on manufacturing, packaging / labelling operations, storage, logistical, import/export issues, etc.)

Not applicable

3.2 Please describe how the study population will be recruited.

Please give details on the recruitment strategy, monitoring of progress and potential mitigation measures

The study will use a retrospective recruitment of cases collected through the routine delivery of health care. Provision of cases will start once approved protocols in full ethical and legal compliance will be in place at each centre.
AI based tools for automated data ingestion, curation and annotation will be integrated and designed pipelines will enable the remote data processing. Data will be filtered from the electronic health records through scripts for the systematic analysis of the database in each clinical site. Common protocols for data processing will be established. Common terminologies, vocabularies and coding schemes will be followed for the extraction according to inclusion criteria and objectives to be achieved.

There will be a well-defined strategy for data de-identification compatible with GDPR and each national/regional Data Providing Site. Optimal deidentification process will be adopted to ensure that no personal information remains in the research data.

For data curation, clinical data scientists will evaluate data completeness and harmonization to keep clean and high-quality datasets, evaluating the appropriateness of cases with incomplete data. Automatic tools will be available to facilitate the process (e.g., quality check, automatic segmentation, annotation, text parsing, etc.) to ensure that images correspond to labels; additionally, semi-automatic extraction of clinical features from full text, using continuous learning

approaches to enrich natural language processing engine and ontologies, will be used properly.

3.2.1 How many clinical sites will contribute to the recruitment of the study population in which countries? Are these clinical sites part of an established clinical trial network? Please also describe the selection criteria of the clinical sites.

This clinical study will involve three clinical partners, large hospitals or research institutions of recognised prestige with previous expertise in European projects. They will have the Data provider role for the recruitment of cases for the training set, corresponding to: Medical University of Gdansk (GUMED, Poland), La Fe University Hospital Valencia (HULAFE, Spain), Karolinska Institute (KI. Sweden).

Also, there would be five external centres that will participate as external validations, namely three EU centres (MUW, UMZG and GOC) and three international centres to evaluate scalability in low-to-middle income countries (HUH, AFI and ASU).

Clinical Site	Country
La Fe University Hospital Valencia	Spain
Karolinska Institute	Sweden
Medical University of Gdansk	Poland
Medical School University of Zagreb	Croatia
Medical University of Vienna	Austria
German Oncology Centre	Cyprus
Hacettepe University Hospital	Turkey
Alexander Fleming Institute	Argentina
Ain Shams University Hospital	Egypt

3.2.2 Will recruitment of the study population be of competitive nature between the clinical sites? (Please describe how underperformance of individual clinical sites in recruitment will be managed.)

The samples to be obtained will not follow a competitive nature. The clinical sites will provide their cases to the project. There will be no limitation and therefore no competition between clinical sites in order to obtain the cases. All cases will correspond to real world data. Patients diagnosed in the participant hospitals and data collected through the routine delivery of health care will be part of the study. The clinical partners will make accessible their historical data since 2015.

In the event of under-recruitment, the scientific committee together with clinicians may decide to extend the range of years to include patients or invite other collaborators to cooperate with more cases. In addition, the study will use cases from existing, large-scale datasets from the repositories of the AI for Health Imaging projects.

A number of mitigation measures (data augmentation, image synthesis, image and feature harmonisation, and transfer learning) will be implemented and tested with available datasets as well as by generating synthetic data with varying heterogeneities (artefacts, noise) or segmentations. In particular, several mitigation measures for inter-centre robustness and reproducibility will be

considered, allowing the calibration of the developed AI-powered decision-support tools according to each centre's requirements. Bayesian analysis will be implemented to estimate uncertainty and provide confidence scores for the treatment predictions that will assist the clinician's trust in the decisions.

3.2.3 What evidence supports the ability of the individual clinical sites to recruit the required number of study participants within the planned timeline (e.g., documented performance in previous clinical studies of similar complexity targeting very similar study population)?

All clinical centers are well recognised centers for breast cancer. Since it is a retrospective study and therefore the participating clinical sites will use existing data from patients that gave their consent to participate in research studies.

Clinical Site	Country	Expertise
La Fe University Hospital Valencia	Spain	Radiomics, Breast cancer, radiology
Karolinska Institute	Sweden	Breast cancer, radiology, AI for breast cancer
Medical University of Gdansk	Poland	Breast cancer, radiology, national clinical trials
Medical School University of Zagreb	Croatia	Breast cancer, radiology
Medical University of Vienna	Austria	Breast cancer, radiology
German Oncology Centre	Cyprus	Breast cancer, radiology
Hacettepe University Hospital	Turkey	Breast cancer, radiology
Alexander Fleming Institute	Argentina	Breast cancer, radiology
Ain Shams University Hospital	Egypt	Breast cancer, radiology

3.3 Please describe what additional supply (e.g., an electronic device for remote data capture, a specific instrument for administering the investigational product, etc.) is necessary to carry out the required study procedures and how this supply will be made available to the clinical sites.

RadioVal will use the federated infrastructure of EuCanImage which allows Consortium partners to host their own XNAT archive locally, while federated access will enable the application of AI solutions. If clinical sites prefer to use a centralised solution, the Advanced HPC infrastructure at UB will be used to store pseudonymised/anonymised data.

At the beginning of the structure, the Clinical Consensus Group will establish which clinical sites will opt for which approach and the academic/industrial partners will outline the technical requirements so clinical partners can take an educated decision.

3.4 Please provide plans on data management aspects (data standards, type of data capture, verification of data, central data collection, cleaning, analysis, reporting, security)

Data will be downloaded automatically with, automatic extraction with OMOP terminologies from Clinical sites, following "Common Data Element" infrastructure. Data will be standardized (range, units, description of variables) and curated. We will collect clinical, pathological, genetic, and radiological images (mammography's and MR). All the data will be stored locally at each clinical site, and copies (properly anonymized) will be shared with scientific participants with high security measures.

The standards and models that will be used are: FHIR and SNOMED CT for interoperability of the health data records and OMOP (with oncology and radiology extensions) as the Data Model, DICOM standard and structured reports for the interoperability in medical imaging. To deal with heterogeneous sources of imaging data, the data model will be based on the DICOM-MIABIS structure. The Minimum Information About BIobank Data Sharing (MIABIS), aims to standardise data elements used to describe biobanks and samples. The DICOM-MIABIS joint model proposes a first integration of the international DICOM standards into the MIABIS core model. The DICOM fields will be used to describe heterogeneous information across datasets, such as imaging protocols, modalities, sequences, scanners, and labels. For non-imaging data, the ICGC (International Cancer Genome Consortium) ARGO (Accelerate Research in Genomic Oncology) dictionary will be used as the basis.

Phenotypic and genetic/omic data will be either stored through the EuCanImage federated infrastructure or locally (for institutions who opt for a distributed model). Data submitted should comply with the informed consents and the anonymization sensitive data before submission. The submission request is evaluated by data processors, and after approval, submitters will be guided to comply with the specifications of data submission, including the download, installation, and use of software for encryption of data.

Descriptive information of the data collections available will be presented in the EuCanImage Catalogue. This metadata will comprise:

- Contact information of the institute, owner of the data collection.
- General information regarding the setting within which the data collections were collected.
- Information on the type of imaging data that is available.
- Imaging Modality, Sequences, Type of imaging processing, Type of imaging annotations (anatomical or pathological targets).

The Catalogue will be built in Molgenis (https://www.molgenis.org/) and will be linked to EGA for the phenotype and genomics information.

Metadata and data will be stored in specialised EuCanImage repositories (EGA and EuroBioImaging XNAT) that are duplicated and backed up and provide secure means of data transfer. The security overview of the EGA can be found in the EGA Security Overview Document[31]. The security overview of the Euro-BioImaging XNAT can be found on the Health-RI Security and Privacy measures website[32].

A detailed Data Management Plan will be established during the project.

3.5 Please give details on how reporting obligations (regarding study initiation, safety of study participants, ethical concerns, quality issues, integrity of data, study results) to regulatory bodies and ethics committees will be met.

Security, privacy and data protection is such an important issue that it will have an entire Work Package (WP) dedicated exclusively to "Security and privacy preservation mechanisms, legal and ethical issues". This WP will include all the tasks related to the audits regarding data management protection, especially the information systems and data treatments that will be used. The project will be fully GDPR compliant meaning that it will be data protection oriented by design and by default.

During the execution of this work package, the level of de-identification of the subjects participating in the study (anonymization or pseudonymization) will be defined, functional and technical documentation will be prepared to review the dataflow and its lifecycle and data sharing and processing agreements (Data Management Plan, Data Protection Impact Assessment, Data Sharing Code of Conduct) will be drafted and signed between the different project partners. All this will be oriented to obtain the legitimacy of the use of the data and its treatment in a correct way, guaranteeing the privacy and security of the information under study.

The Ethics Management Group (EMG) led by UB will be set up, including Data Protection Officers (DPOs) from participating centres, to oversee ethical compliance throughout the project. An ethical assessment at the beginning of the project will ensure that all ethical obligations will be met and submitted to regulatory bodies (clinical trial registry) and the ethical committee at UB. Periodic ethical reports will be submitted to the ethical committee at M18, M36 and M48 to ensure the continuous ethical compliance. Each of the ethical reports will include the following deliverables:

1. Study initiation package (before enrolment of the first study participant) including:
2. Midterm recruitment report
3. Report on the status of posting results

3.6 Please list all items of the sponsor's responsibilities (e.g. monitoring clinical sites, meeting regulatory obligations, data management, etc.) that will be supported by entities that are not part of the sponsor's organisation. Please describe how the sponsor will ensure oversight of these activities.

As this study is an observational not private sponsors are involved in the initiation and organization of the clinical study. However, Breast cancer association ESMO association guidelines will be followed to guarantee rightness and accuracy of the data provided.

3.7 What are the plans for major study milestones and what evidence supports its feasibility?

Please describe a realistic plan (based on prior experience) detailing the time necessary for (i) compiling the required regulatory and ethics submission package, (ii) receipt of regulatory and ethics approval, (iii) initiation of clinical site(s), (iv) completion of recruitment of the study population, (v) final assessment of all study participants, (vi) analysis and reporting of the study results.

Milestones	Evidence	Time to complete task
M1. Regulatory/ethics		
1.1 Compiling required regulatory and ethics submission package	previous clinical partners' expertise	6 months (M1 – M6)
1.2Receipt regulatory and ethics approval	As above	2 months (M7- M8)
M2. Patient's recruitment		
2.1 Initiation of clinical site	As above	9th month (M9)
2.2 Completion of recruitment of study population	As above	15 months (M10- M24)
2.3 Final assessment of all study participants	As above	M25
M3. Analysis and reporting of study reports		
3.1 Guidelines on application AI solutions to predict response to treatment, to avoid over-treatment	As above	M46
3.2 Incorporate information predictive of local immune reaction to allow the adjustment of therapy	As above	M46
3.3 Guidelines establishing the need to lymphadenectomy to predict lymph node invasion	As above	M46
3.4 Consensus standards to adjust follow-up criteria to detect distant metastasis	As above	M46
3.5 Consensus standards on treatments according to patient prognosis and give appropriate counselling to them	As above	M46
Results of multi-center clinical evaluation study	As above	M48

HISTORY OF CHANGES		
VERSION	PUBLICATION DATE	CHANGE
1.0	24.03.2021	Initial version (included in the standard HE proposal template)
1.1	08.04.2021	Reference to 'sex distribution' added in section 1.4.
2.0	13.10.2021	Standalone template document.
3.0	15.01.2022	Reformatting changes and change of document name.
4.0	01.05.2022	Removed reference to specific topics for a more generalised template
4.1	13.05.2022	Added reference to Global Health-EDCTP3 Joint Undertaking
4.2	10.02.2023	Added Cyprus Clinical Center
4.3	22.02.2023	Final version

Bibliography

[8] D.W. Kim, H.Y. Jang, K.W. Kim, Y. Shin, S.H. Park, Design characteristics of studies reporting the performance of artificial intelligence algorithms for diagnostic analysis of medical images: results from recently published papers, Korean J. Radiol. 2019; 20 (3): 405–410.
[9] Colen RR, Rolfo C, Ak M, et al. Radiomics analysis for predicting pembrolizumab response in patients with advanced rare cancers. Journal for ImmunoTherapy Cancer. 2021; 9:e001752. doi: 10.1136/jitc-2020-001752.
[10] Li H, Giger ML, Lan L, Janardanan J, Sennett CA. Comparative analysis of image-based phenotypes of mammographic density and parenchymal patterns in distinguishing between BRCA1/2 cases, unilateral cancer cases, and controls. J Med Imaging (Bellingham). 2014;1(3):031009.
[11] Haberle L, Wagner F, Fasching PA, et al. Characterizing mammographic images by using generic texture features. Breast cancer research: BCR. 2012;14(2):R59.
[12] Wu, J, Gong, G, Cui, Y, Li, R. Intratumor partitioning and texture analysis of dynamic contrast-enhanced (DCE)-MRI identifies relevant tumor subregions to predict pathological response of breast cancer to neoadjuvant chemotherapy. J Magn Reson Imaging. 2016;44(5):1107–1115.
[13] Bian T, et al., Radiomic signatures derived from multiparametric MRI for the pretreatment prediction of response to neoadjuvant chemotherapy in breast cancer Br J Radiol. 2020 Nov 1;93(1115):20200287. doi: 10.1259/bjr.20200287. Epub 2020 Sep 2. PMID: 32822542.
[14] Lambin P, et al., Radiomics: the bridge between medical imaging and personalized medicine. Nat Rev Clin Oncol. 2017 Dec;14(12):749-762. doi: 10.1038/nrclinonc.2017.141. Epub 2017 Oct 4. PMID: 28975929.
[15] Leithner D, et al., Radiomic Signatures Derived from Diffusion-Weighted Imaging for the Assessment of Breast Cancer Receptor Status and Molecular Subtypes. Mol Imaging Biol. 2020 Apr;22(2):453-461. doi: 10.1007/s11307-019-01383-w. PMID: 31209778.
[16] Han L, et al., Radiomic nomogram for prediction of axillary lymph node metastasis in breast cancer. Eur Radiol. 2019 Jul;29(7):3820-3829. doi: 10.1007/s00330-018-5981-2. Epub 2019 Jan 30. PMID: 30701328.
[17] Martí-Bonmatí, L. Evidence levels in radiology: the insights into imaging approach. Insights Imaging. 2021; 12: 45. doi.org/10.1186/s13244-021-00995-7.
[18] Allott et al., Bimodal age distribution at diagnosis in breast cancer persists across molecular and genomic classifications, Breast Cancer Res and Treat. 2020; 179:185-195. doi.org/10.1007/s10549-019-05442-2
[19] Gucalp et al., Male breast cancer: a disease distinct from female breast cancer, Breast Cancer Res treat. 2019; 173(1):37-48. doi:10.1007/s10549-018-4921-9.

[20] Colomer R., et al., 2019 Neoadjuvant Management of Early Breast Cancer: A Clinical and Investigational Position Statement Oncologist. 2019 May;24(5):603-611. doi: 10.1634/theoncologist.2018-0228.
[21] Spring et al., Pathological complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis, Clin Cancer Res. 2020 June 15; 26(12): 2838–2848. doi: 10.1158/1078-0432.CCR-19-3492.
[22] Ridley et al., Calculating the sample size required for developing a clinical prediction model, BMJ. 2020; 368:m441 doi: 10.1136/bmj.m441
[23] https://www.equator-network.org/reporting-guidelines/tripod-statement/
[24] https://www.equator-network.org/
[25] Larson DB et al., Regulatory Frameworks for Development and Evaluation of Artificial Intelligence–Based Diagnostic Imaging Algorithms: Summary and Recommendations, J Am Coll of Radiol, 2021, 18(3): 413-424
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7574690/
[26] https://www.tripod-statement.org/wp-content/uploads/2020/03/Heus-et-al-2019-BMJ-Open-TRIPOD-Adherence-Assessment.pdf
[27] https://www.equator-network.org/wp-content/uploads/2015/03/STARD-2015-paper.pdf
[28] https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001885
[29] http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-191010-mdce-n57.pdf
[30] https://www.equator-network.org/wp-content/uploads/2013/07/SAMPL-Guidelines-6-27-13.pdf
[31] https://ega-archive.org/files/European_Genome_phenome_Archive_Security_Overview.pdf
[32] https://www.health-ri.nl/services/xnat#tab4

Annex 3. Approvals by Local Ethics Committee of each participating Clinical Institution

1. Approval by Local Ethics Committee of HOSPITAL UNIVERSITARIO Y POLITÉCNICO LA FE OF VALENCIA (SPAIN)

DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS

MARÍA TORDERA BAVIERA, titular de la Secretaría Técnica del Comité de Ética de la Investigación con medicamentos del **CEIM - HOSPITAL UNIVERSITARIO Y POLITÉCNICO LA FE,**

CERTIFICA

Que este Comité ha evaluado en su sesión de fecha 30/03/2022, el Proyecto de Investigación:

Título: **"RadioVal: International Clinical Validation of Radiomics Artificial Intelligence for Breast Cancer Treatment Planning."**
Nº de registro: **2022-106-1**

Documento	Versión - Fecha
Protocolo	2 de Marzo de 2022

Que dicho proyecto se ajusta a las normativas éticas sobre investigación biomédica con sujetos humanos y es viable en cuanto al planteamiento científico, objetivos, material y métodos, etc, descritos en la solicitud, así como la Hoja de Información al Paciente y el Consentimiento Informado.

En consecuencia, este Comité acuerda emitir **INFORME FAVORABLE** de dicho Proyecto de Investigación que será realizado en el HOSPITAL UNIVERSITARI I POLITÈCNIC LA FE por el/la Dr. / Dra. **LUIS MARTÍ BONMATÍ** del servicio/unidad/grupo de investigación de **AREA DE IMAGEN MEDICA** como Investigador Principal.

Que el CEIM - HOSPITAL UNIVERSITARIO Y POLITÉCNICO LA FE, tanto en su composición como en sus procedimientos, cumple con las normas de BPC (CPMP/ICH/135/95) y con la legislación vigente que regula su funcionamiento, y que la composición del CEIM - HOSPITAL UNIVERSITARIO Y POLITÉCNICO LA FE**,** es la indicada en el anexo I, teniendo en cuenta que, en el caso de que algún miembro participe en el estudio o declare algún conflicto de interés, no habrá participado en la evaluación ni en el dictamen de la solicitud de autorización del estudio clínico.

Lo que firmo en Valencia, a 30/03/2022

Firmat per Maria Tordera Baviera el 06/04/2022 14:36:54

Fdo.: MARÍA TORDERA BAVIERA
Secretario/a Técnica del Comité de Ética de la Investigación con medicamentos

ANEXO I
COMPOSICIÓN CEIm

Presidente:
ADELA CAÑETE NIETO - Facultativo Especialista en Pediatría. Jefe Sección de Unidad de Hematología y Oncología Pediátrica

Vicepresidente:
OSCAR DÍAZ CAMBRONERO - Facultativo especialista en Anestesiología y Reanimación. Jefe Sección Anestesiología y Reanimación

Secretario:
MARÍA TORDERA BAVIERA - Farmacéutica Especialista en Farmacia Hospitalaria. Farmacéutica adjunta del Servicio de Farmacia

Vocales:
MARÍA VICTORIA PARICIO GÓMEZ - Diplomada Enfermería. Supervisora del Servicio de Hematología y Trasplante de Progenitores Hemáticos
JAVIER LLUNA GONZÁLEZ - Facultativo Especialista en Cirugía Pediátrica. Médico adjunto del Servicio de Cirugía Pediátrica
PAULA RAMÍREZ GALLEYMORE - Facultativo Especialista en Medicina Intensiva. Médico adjunto del Servicio de Medicina Intensiva
JOSÉ MARÍA CANELLES GAMIR - Farmacéutico de Atención Primaria del Departamento de Salud Valencia La Fe
SERAFÍN RODRÍGUEZ CAPELLÁN - Licenciado en Derecho. Técnico de Función Administrativa adscrito a la Dirección de Investigación
VICENTE INGLADA ALCAIDE - Miembro Lego, representante de los intereses de los pacientes
MIGUEL ÁNGEL CANO TORRES - Licenciado en Derecho. Técnico de Función Administrativa adscrito a la Dirección de Investigación
LUIS VICENTE MARTÍNEZ DOLZ - Facultativo Especialista en Cardiología. Jefe de Servicio de Cardiología
BONAVENTURA CASANOVA ESTRUCH - Facultativo Especialista en Neurología. Médico adjunto del Servicio de Neurología
SARA BRUGGER FRIGOLS - Facultativo Especialista en Radiodiagnóstico. Médico adjunto del Área de Imagen Médica
Mª ISABEL IZQUIERDO MACIÁN - Facultativo Especialista en Pediatría (Neonatología). Jefa de Servicio de Neonatología
MATTEO FRASSON - Facultativo Especialista en Cirugía. Médico adjunto del Servicio de Cirugía General y Digestiva
JOSÉ VICENTE SOLANAS PRATS - Facultativo Especialista en Medicina de Familia y Comunitaria. Médico del Centro de Salud Trinitat
ANTONIO ORDUÑA GALÁN - Ing. de aplicaciones y sistemas. Responsable Área de Seguridad y Calidad de Sistemas de Información
ANA PEIRÓ PEIRÓ - Fac. especialista en Farmacología Clínica. Médica Adjunta del Servicio Farmacología Clínica. DSA-HG.

2. Approval by Local Ethics Committee of KAROLINSKA INSTITUTE OF STOCKHOLM (SWEDEN)

BESLUT

2023-01-16

Sökande forskningshuvudman
Region Stockholm

Organisation som ansöker om att bli ny huvudman
Karolinska Institutet

Forskare som genomför projektet
Fredrik Strand

Projekttitel
Datoriserad analys av bilder från MR Bröst (qMRI)

Uppgifter om ansökan
Ansökan om ändring inkom till Etikprövningsmyndigheten 2022-12-09 och blev valid 2023-01-10. Grundansökan med diarienummer 2020-00488 blev godkänd 2020-03-18 av Etikprövningsmyndigheten.

Ändringen avser byte av ansvarig forskningshuvudman, samt förtydligande att data, av typ och med syfte enligt tidigare ansökan, även inhämtas från andra institutioner i Sverige och utomlands.

Etikprövningsmyndigheten beslutar enligt nedan.

BESLUT

Etikprövningsmyndigheten godkänner den forskning som anges i ansökan om ändring.

På Etikprövningsmyndighetens vägnar

Peter Lif
Ordförande

Beslutet har fattats efter föredragning av vetenskaplig sekreterare
Lars-Gunnar Gunnarsson

Beslutet sänds till
Ansvarig forskare: Fredrik Strand
Forskningshuvudmannens företrädare: Eva-Lena Zachrisson, Lars Holmgren

3. Approval by Local Ethics Committee of MEDICAL UNIVERSITY OF GDANSK (POLAND)

NIEZALEŻNA KOMISJA BIOETYCZNA
DO SPRAW BADAŃ NAUKOWYCH
PRZY GDAŃSKIM UNIWERSYTECIE MEDYCZNYM
80-210 Gdańsk, ul. M. Skłodowskiej-Curie 3a
tel. 58 349 10 11, fax 58 349 11 70

*NKBBN/**549**/2022*

Gdańsk, 2022-09-20

Informujemy, że projekt badań pt.: **„RadioVal – Międzynarodowy projekt badawczy oceniający kliniczną przydatność sztucznej inteligencji opartej na radiomice w planowaniu leczenia raka piersi”, *ang.: „International Clinical Validation of Radiomics Artificial Intelligence for Breast Cancer Treatment Planning – RadioVal”***, zarejestrowany pod numerem **549/2022** – był rozpatrywany przez Niezależną Komisję Bioetyczną do Spraw Badań Naukowych przy Gdańskim Uniwersytecie Medycznym na posiedzeniu w dniu 15 września 2022 roku.

Decyzja Komisji zostanie wydana po nadesłaniu do biura Komisji uzupełnienia powyższego projektu zgodnie z załączoną opinią.

SPECJALISTA
Niezależnej Komisji Bioetycznej
do Spraw Badań Naukowych
mgr inż. Maria Abramska-Maresch

Gdańsk 14.09.2022

Opinia wniosku nr 549

Tematem badania jest

„RadioVal - Międzynarodowy projekt badawczy oceniający kliniczną przydatność sztucznej inteligencji opartej na radiomice w planowaniu leczenia raka piersi".

Kierownikiem jednostki organizacyjnej biorącej udział w badaniu

jest Edyta Szurowska, prof. dr hab. n. med., radiologia

Głównym badaczem będzie

- Maciej Bobowicz, dr n. med., chirurgia ogólna, chirurgia onkologiczna, Wydział Nauk o Zdrowiu z Instytutem Medycyny Morskiej i Tropikalnej, II Zakład Radiologii, zaś członkami
- Edyta Szurowska, prof. dr hab. n. med., radiologia, Kierownik II Zakładu Radiologii
- Katarzyna Gwoździewicz, dr n. med., radiologia, II Zakład Radiologii
- Marlena Rygusik, mgr, II Zakład Radiologii
- Elżbieta Senkus-Konefka, dr hab. n. med., onkologia kliniczna, radioterapia, Klinika Onkologii i Radioterapii
- Tomasz Stefaniak, dr hab. n. med., chirurgia ogólna, Klinika Chirurgii Ogólnej, Endokrynologicznej i Transplantacyjnej

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tel. 58 349 10 11, fax 58 349 11 70

Gdańsk, 20.09.2022
Za zgodność z oryginałem
stwierdzam

VERSTE

Miejscem wykonywania badań będzie Wydział Nauk o Zdrowiu z Instytutem Medycyny Morskiej i Tropikalnej, II Zakład Radiologii

Wydział Lekarski, Klinika Onkologii i Radioterapii

Planowany czas trwania badania

01.09.2022 - 31.08.2026 r.

W zamierzeniu ma to być praca

Komisja Europejska; Program Horyzont

RadioVal to nowy europejski projekt badawczy, którego celem jest kliniczna walidacja narzędzi opartych na sztucznej inteligencji służących wsparciu planowania leczenia raka piersi

Pozwolą one na prognozowanie odpowiedzi na wybrane leczenie neoadjuwantowe dostosowane do indywidualnej pacjentki chorującej na miejscowo zaawansowanego raka piersi

Ma to być wielodyscyplinarny i wieloośrodkowy projekt realizowany jednocześnie w ośmiu ośrodkach klinicznych w krajach o dużym zróżnicowaniu socjoekonomicznym, na czterech kontynentach: w Europie (Szwecja, Austria, Hiszpania, Polska, Chorwacja), Ameryce Południowej (Argentyna), północnej Afryce (Egipt) oraz w Eurazji (Turcja).

Celem projektu jest kliniczna walidacja wybranych, opracowanych we wcześniejszych projektach badawczych grupy Artificial Intelligence for Health Imaging (AI4HI) algorytmów sztucznej inteligencji, w które zaangażowany jest też Gdański Uniwersytet Medyczny (projekt EuCanImage) a finansowanych przez Komisję Europejską. Algorytmy sztucznej inteligencji oraz uczenia maszynowego wykorzystujące cechy i parametry obrazów radiologicznych są nazywane radiomiką.

Gdańsk, 20.09.2022
Za zgodność z oryginałem
stwierdzam

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Zadaniem wspomnianych algorytmów jest wsparcie decyzji wielodyscyplinarnego zespołu terapeutycznego w kwalifikacji konkretnych pacjentek mających szansę uzyskania odpowiedzi na leczenie neoadjuwantowe przy jednoczesnym obniżeniu odsetka pacjentek, które nie odniosą korzyści a które mogą odczuć skutki uboczne. Poza oceną klinicznej skuteczności i precyzji badacze chca sprawdzić również bezpieczeństwo technologii w środowisku szpitalnym, jej użyteczność i możliwość zastosowania w codziennej praktyce. Bardzo istotnymi elementami oceny będą również aspekty etyczne i prawne. W ramach projektu opracowana zostanie wystandaryzowana metodologia wieloczynnikowej oceny narzędzi z zakresu radiomiki w oparciu o wytyczne FUTURE-AI (ang. Fairness, Universality, Traceability, Usability, Robustness, Explainability). Zostaną opracowane narzędzia służące ciągłemu i długoterminowemu monitorowaniu i ewaluacji narzędzi radiomicznych.

W trakcie czterech lat projektu zaplanowano trzy następujące po sobie etapy.

Etap 1. W pierwszych dwóch latach przeprowadzone zostanie retrospektywne badanie obejmujące archiwalne dane 200 pacjentek chorych na raka piersi, u których w latach 2010-2022 wykonano przedoperacyjne badanie metodą rezonansu magnetycznego (MRI) i poddano chemioterapii neoadjuwantowej (NAC) w UCK i łącznie około 5000 we wszystkich ośrodkach. Wszystkie dane niezbędne do realizacji tego projektu zostaną pobrane z wewnętrznego systemu elektronicznej dokumentacji medycznej UCK. Po wieloetapowej de-identyfikacji i pseudonimizacji badania MRI i mammograficzne piersi oraz powiązane dane kliniczne i patomorfologiczne zostaną umieszczone na platformie badawczej EuCanImage aby stworzyć docelowy wieloośrodkowy zbiór danych prawie 5000 pacjentek z miejscowo zaawansowanym rakiem piersi.

Gdańsk, 20.05.2022
Za zgodność z oryginałem stwierdzam

NIEZALEŻNA KOMISJA BIOETYCZNA
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Na ich podstawie partnerzy technologiczni opracują zagregowany anonimowy zbiór danych radiomicznych, które posłużą do analizy i opracowania radiomicznej sygnatury czynników predykcyjnych odpowiedzi na leczenie neoadjuwantowe.

Etap 2

Na tym etapie badacze zamierzają przeprowadzić badanie kliniczne przy użyciu komputerów dużej mocy na podstawie danych rzeczywistych bez konieczności bezpośredniego udziału pacjentek. Celem tego etapu jest ewaluacja klinicznej użyteczności opracowanych narzędzi z udziałem onkologów oraz radiologów

Badanie zostanie przeprowadzone w trzecim roku projektu na retrospektywnej próbie 50 pacjentek w każdym z ośmiu uczestniczących ośrodków i potrwa sześć miesięcy.

W trzecim etapie (czwarty rok projektu) badacze planują przeprowadzić półroczne badanie prospektywne oceniające użyteczność i możliwy stopień integracji w systemie wielodyscyplinarnych konsyliów raka piersi w oparciu o dotychczasowy standard opieki. Badaniem zostanie objęte prospektywnie około 50 pacjentek w każdym uczestniczącym ośrodku. Zgodnie z założeniami projektu nie zostanie wprowadzona żadna czynna interwencja medyczna do standardowego procesu opieki nad pacjentkami.

Narzędzie będzie używane podczas konsyliów raka piersi przez badacza celem wygenerowania podpowiedzi klinicznych dotyczących przewidywanej odpowiedzi na leczenie neoadjuwantowe.

Ocenie będą podlegały użyteczność kliniczna, zgodność z decyzjami konsylium, łatwość obsługi i integracji z typowym przebiegiem wielodyscyplinarnego konsylium raka piersi oraz integracji z systemami komputerowymi poszczególnych szpitali.

Gdańsk, 20.09.2022
Za zgodność z oryginałem
stwierdzam

NIEZALEŻNA KOMISJA BIOETYCZNA
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Na podstawie oceny i informacji zwrotnej od zaangażowanych klinicystów zostaną opracowane Standardowe Procedury Operacyjne dla ocenianego narzędzia i przyszłej implementacji narzędzi radiomicznych opartych na sztucznej inteligencji.

W dwóch pierwszych etapach projektu, dane niezbędne do realizacji projektu zostaną poddane wieloetapowemu procesowi de-identyfikacji oraz pseudonimizacji przy użyciu odpowiedniego programu. Procedura spełnia kryteria zgodności z przepisami o ochronie danych osobowych na poziomie pełnej anonimizacji.

W związku z powyższym badacze zwracaja się z prośbą o odstąpienie od obowiązku uzyskania zgody pacjentów na udział w badaniu.

Badacze powinni uzupełnić dokumentacje o deklaracje objęciu procedur anonimizacji również pacjentki z grupy prospektywnej trzeciego etapu. Brak jest również formularza zgody szpitala UCK

Poszczególne elementy planowanego badania opierają się na dotychczasowej praktyce klinicznej a wyniki mogą przyczynić się do lepszej kwalifikacji do leczenia.

Proponuję akceptację wniosku po uzupełnieniu dokumentacji o zwieszczo słowy tytułowej, zgodnie „badanie naukowe" które

się różni od wersji protokołu klinicznej poprzez dodanie 4 nowych autorów, brakuje tytułu protokołu

NIEZALEŻNA KOMISJA BIOETYCZNA
DO SPRAW BADAŃ NAUKOWYCH
PRZY GDAŃSKIM UNIWERSYTECIE MEDYCZNYM
80-210 Gdańsk, ul. M. Skłodowskiej-Curie 3a
tel. 58 349 10 11, fax 58 349 11 70

Gdańsk, 20.09.2022
Za zgodność z oryginałem
stwierdzam

SPECJALISTA
Niezależnej Komisji Bioetycznej
do Spraw Badań Naukowych
mgr inż. Maria Abramska-Maresch

4. Approval by Local Ethics Committee of MEDICAL SCHOOL UNIVERSITY OF ZAGREB (CROATIA)

University of Zagreb
School of Medicine

ADRESS
Šalata 3
10000 Zagreb

PHONE
+385 1 45 66 777

FAX
+385 1 49 20 053

E-MAIL
mf@mef.hr

WEB
www.mef.unizg.hr

ETHICS COMMITTEE

Case number: 380-59-10106-22-111/100
Class: 641-01/22-02/01

Zagreb, 27 June 2022.

Pursuant to Article 23 of the Ethics Committee Regulations, and with regard to application for ethical approval for project proposal titled **"International Clinical Validation of Radiomics Artificial Intelligence for Breast Cancer Treatment Planning – RadioVal"** the Ethics Committee of the University of Zagreb, School of Medicine brought on its meeting held on 27 June 2022 the following

OPINION

The above-referenced project proposal led by **Professor Boris Brkljačić** conforms to the ethical principles and is therefore given ethical approval.

Professor Zdravka Poljaković
Ethics Committee president

6. Approval by Local Ethics Committee of HACETTEPE UNIVERSITY HOSPITAL OF ANKARA (TURKEY)

Hacettepe

HACETTEPE UNIVERSITY HOSPITALS

HACETTEPE UNIVERSITY
Non-interventional Clinical Research Ethics Board

Number : 16969557

HACETTEPE UNIVERSITY

NON-INTERVENTIONAL CLINICAL RESEARCHES ETHICS COMITTEE CERTIFICATE OF APPROVAL

This is to certify that;

Document ID: 16969557-2409

Meeting Date: 05 JULY 2022

Meeting No: 2022/12

Decree No: 2022/12-46

Project no: GO 22/688

Project Title: Evaluation of the response to therapy in breast cancer patients receiving neoadjuvant chemotherapy and development of artificial intelligence platform based on radiomics in order to support accurate patient management (Radioval; Horizon 2020 European Union Project)

Principal Investigator: Prof. Dr. Meltem Gülsün Akpınar, **Co-Investigators**: Prof. Dr. Figen Demirkazık, Prof. Dr. Deniz Akata, Prof. Dr. Sercan Aksoy, Prof. Dr. Ömer Dizdar, Assoc. Prof. Dr. Gamze Durhan

The abovementioned research proposal of the investigators was considered by Non-interventional Clinical Researches Ethics Committee of Hacettepe University, meet the requirements of the National and Universal Statements on Ethical Conduct in Human Research (2007) and was **APPROVED** on 05/07/2022.

It is the Principal Researchers' responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved. The Principal Researchers are required to notify the Secretary of the Ethics Committee, via amendment, progress report and on completion of the project.

Prof. Dr. G. Burça Aydın

Chair of Non-interventional Clinical Researches Ethics Committee

7. Approval by Local Ethics Committee of ALEXANDER FLEMING INSTITUTE OF BUENOS AIRES (ARGENTINA)

Instituto Médico Especializado Alexander Fleming
COMITÉ DE ÉTICA EN INVESTIGACIÓN

Buenos Aires, 28 de Octubre de 2022

De acuerdo con lo establecido en la normativa vigente, este Comité ha evaluado el proyecto de investigación que a continuación se menciona.

Código de registro: 7692

Título del protocolo: RadioVal. Validación Clínica Internacional de Inteligencia Artificial para el plan de tratamiento de cáncer de mama

Patrocinador: no corresponde

Investigador principal: Daniel Claudio Mysler

Institución donde se desarrollará: Instituto Médico Especializado Alexander Fleming

Con relación al mismo se ha recibido la siguiente documentación:

- Autorización de la Dirección de la Institución con caracter previo al dictamen
- Protocolo Fecha: 18 / 07 / 2022 Versión: 1.0
- Consentimientos / asentimientos Detalle: *Hoja de información al paciente y consentimiento informado V 5-jul-2022. *Hoja de información al paciente y consentimiento informado V 5-jul-2022 (1.1)
- Material que se entrega a los sujetos, avisos de reclutamiento y otros documentos Detalle: -
- Declaración jurada conforme modelo del Anexo III, Resolución 2476/MSGC/2019
- Declaración jurada para ANMAT
- CV del investigador principal

Categorización de riesgo asignado por el CEI: Riesgo mínimo
Los miembros del Comité han discutido convenientemente el proyecto. Se han realizado observaciones en el formulario de consentimiento informado, las cuales han sido resueltas favorablemente.

De igual forma, han procedido a evaluar la documentación que respalda la idoneidad del investigador principal,

incluyendo título profesional, matrícula profesional, curriculum vitae, certificación de especialista y capacitación en buenas prácticas clínicas. También se ha considerado la adecuación de las instalaciones para el desarrollo del estudio en evaluación.

Luego de considerar todo lo antes mencionado, el Comité de Ética en Investigación del Instituto Médico Especializado Alexander Fleming ha decidido aprobar el protocolo de referencia para su realización en Instituto Médico Especializado Alexander Fleming, dirigido por Mysler , Daniel Claudio como investigador principal. El presente dictamen tiene una vigencia de un (1) año.

Con relación a esta aprobación, se deja constancia que se han aprobado específicamente los documentos que se mencionan a continuación:

- Protocolo, fecha: 18 / 07 / 2022, versión: 1.0
- Consentimientos/asentimientos: *Hoja de informacin al paciente y consentimiento informado V 5-jul-2022 (1.1)
- Material que se entrega a los sujetos, avisos de reclutamiento y otros documentos: -

La investigación de referencia será supervisada de manera continua por este Comité de acuerdo con lo contemplado en sus Procedimiento Operativos Estandarizados.

Firmas por el CEI

Dr. José Mordoh
Presidente Ceiaf

Instituto Médico Especializado Alexander Fleming
COMITÉ DE ÉTICA EN INVESTIGACIÓN

8. Approval by Local Ethics Committee of AIN SHAMS UNIVERSITY HOSPITAL OF EL CAIRO (EGYPT)

MASRI
Faculty of Medicine Ain Shams University
مركز أبحاث طب عين شمس

السيد الأستاذ الدكتور / مدير لجنة أخلاقيات البحث العلمي

تحية طيبة وبعد،،،

نحيط سيادتكم علماً بأن خطة البحث الاكلنيكى المقدم من الباحث الرئيسى

د/ عبير حامد عبد الحميد

واسم البحث الاكلنيكى باللغة العربية :
التحقق السريري الدولي من الذكاء الاصطناعي الإشعاعي لتخطيط علاج سرطان الثدي

اسم البحث الاكلنيكى باللغة الانجليزية:-

International clinical validation of radiomics artificial intelligence for breast cancer treatment planning

وقد تم تسجيله بواسطة وحدة الابحاث الاكلنيكية وحفظ بقسم الحفظ بالمركز.

وتفضلوا سيادتكم بقبول فائق الاحترام،

المدير التنفيذي لوحدة الأبحاث الإكلينيكية	مدير وحدة الابحاث الإكلنيكية	مدير المركز
أ.د/ فاطمة عبيد	أ.د/ منال حمدي السيد	أ.د/ هشام الغزالى

28/3/22

9. Approval by Local Ethics Committee of GERMAN ONCOLOGY CENTRE OF CYPRUS

ΚΥΠΡΙΑΚΗ ΔΗΜΟΚΡΑΤΙΑ

ΕΘΝΙΚΗ ΕΠΙΤΡΟΠΗ ΒΙΟΗΘΙΚΗΣ ΚΥΠΡΟΥ

Αρ. Φακ.: ΕΕΒΚ ΕΠ 2023.01.49
Αρ. Τηλ.: 22809038/039, 22819101/122
Αρ. Φαξ: 22353878

9 Φεβρουαρίου, 2023

Δρ Κρίστης Βέβης
Διαχειριστής Ερευνητικών Προγραμμάτων
Γερμανικό Ογκολογικό Κέντρο
Λεωφ. Νίκης 1
4108 Άγιος Αθανάσιος
Λεμεσός

Αγαπητέ Δρ Βέβη,

Αίτηση γνωμοδότησης για την πρόταση με τίτλο:
«Radio Val: International Clinical Validation of Radiomics Artificial Intelligence for Breast Cancer Treatment Planning»

Αναφορικά με την αίτηση σας ημερομηνίας 3 και 6 Φεβρουαρίου 2023 για το πιο πάνω θέμα, επιθυμώ να σας πληροφορήσω ότι από τη μελέτη του περιεχομένου των εγγράφων που έχετε καταθέσει η Εθνική Επιτροπή Βιοηθικής Κύπρου (ΕΕΒΚ) **γνωμοδοτεί θετικά υπέρ της διεξαγωγής της εν λόγω έρευνας.**

2. Η Επιτροπή επιθυμεί να τονίσει ότι παραμένει ευθύνη δική σας η διεξαγωγή της έρευνας με τρόπο που να τηρούνται οι πρόνοιες του νέου Ευρωπαϊκού Γενικού Κανονισμού Προστασίας Προσωπικών Δεδομένων (2016/679) και του περί της Προστασίας των Φυσικών Προσώπων Έναντι της Επεξεργασίας των Δεδομένων Προσωπικού Χαρακτήρα και της Ελεύθερης Κυκλοφορίας των Δεδομένων αυτών Νόμος του 2018 (Ν. 125(Ι)/2018), ως αυτός εκάστοτε τροποποιείται.

3. Σας ενημερώνουμε ότι για σκοπούς καλύτερου συντονισμού και αποφυγής επανάληψης ερευνών με το ίδιο θέμα ή/και υπό εξέταση πληθυσμό μέσα σε σύντομο σχετικά χρονικό διάστημα, η ΕΕΒΚ δημοσιεύει στην ιστοσελίδα της το θέμα της έρευνας, τον φορέα και τον υπό εξέταση πληθυσμό.

4. Κατά τη διάρκεια εκπόνησης της έρευνας, ο συντονιστής / επιστημονικός υπεύθυνος θα ενημερώνει την ΕΕΒΚ για κάθε τροποποίηση των αρχικά κατατεθειμένων εγγράφων (πρωτόκολλο ή άλλα ερευνητικά έγγραφα) και θα υποβάλλει τις απαιτούμενες έντυπες τροποποιήσεις στην Επιτροπή.

5. Σε περίπτωση διακοπής της έρευνας, ο συντονιστής / επιστημονικός υπεύθυνος θα ενημερώσει γραπτώς την Επιτροπή κάνοντας αναφορά και στους λόγους διακοπής της έρευνας.

.../2

6. Ο συντονιστής / επιστημονικός υπεύθυνος θα ενημερώσει την Επιτροπή σε περίπτωση αδυναμίας να συνεχίσει ως συντονιστής και θα υποβάλει τα στοιχεία επικοινωνίας του αντικαταστάτη του.

7. Με το πέρας της ερευνητικής πρότασης, ο συντονιστής / επιστημονικός υπεύθυνος θα ενημερώσει εγγράφως την Επιτροπή ότι το υπό αναφορά ερευνητικό πρωτόκολλο ολοκληρώθηκε.

8. Σας ευχόμαστε κάθε επιτυχία στη διεξαγωγή της έρευνάς σας.

Με εκτίμηση,

Καθ. Κωνσταντίνος Ν. Φελλάς
Πρόεδρος
Εθνικής Επιτροπής Βιοηθικής Κύπρου