D1.1. – First study subject approvals package for the retrospective study

Related Work Package	WP1 - Definition of KPIs for assessing intrinsic capacity and QoL and development of eHealth applications enabling effective monitoring and implementation of behavioral and psychological interventions**.**
Related Task	Task 1.1- Definition of a panel of quality key performance indicators for monitoring health status, intrinsic capacity and QoL for the CARDIOCARE healthcare model
Lead Beneficiary	IEO
Contributing Beneficiaries	BOCOC, UOI, NKUA, KSBC, IOL, IMS, FORTH, HMU
Document version	v.1.0
Deliverable Type	Report
Distribution level	Public
Target Readers	All partners
Contractual Date of Delivery	31/12/2021
Actual Date of Delivery	01/01/2022

Authors	Gabriella Pravettoni, Marianna Masiero, Dario Monzani, Roberto Grasso
Contributors	BOCOC, UOI, NKUA, KSBC, IMS
Reviewers	Michalis Mantzaris, Elisavet Papageorgiou

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 945175

List of Contributing Beneficiaries

No	Organisation name	Short name	Country
1	ISTITUTO EUROPEO DI ONCOLOGIA SRL	IEO	ITALY
2	OGKOLOGIKO KENTRO TRAPEZAS KYPROU	BOCOC	CYPRUS
3	PANEPISTIMIO IOANNINON	UOI	GREECE
4	ETHNIKO KAI KAPODISTRIAKO PANEPISTIMIO ATHINON	NKUA	GREECE
5	REGION STOCKHOLM (KSBC)	KSBC	SWEDEN
6	ONKOLOSKI INSTITUT LJUBLJANA	IOL	SLOVENIA
7	I.M.S. - ISTITUTO DI MANAGEMENT SANITARIO SRL	IMS	ITALY
8	IDRYMA TECHNOLOGIAS KAI EREVNAS	FORTH	GREECE
9	ELLINIKO MESOGEIAKO PANEPISTIMIO	HMU	GREECE

Version history

Version	Description	Date completed
v0.1	Table of Contents (TOC) circulation Marianna Masiero (IEO), Dario Monzani (IEO)	01/12/2021
v0.2	First draft consolidation Gabriella Pravettoni (IEO), Marianna Masiero (IEO), Dario Monzani (IEO), Roberto Grasso (IEO)	20/12/2021
v0.3	Review of the deliverable Michalis Mantzaris (UOI), Constanza Conti (IMS)	27/12/2021
v0.4	Review comments incorporated Marianna Masiero (IEO), Dario Monzani (IEO)	31/12/2021
v1.0	Final version submission	31/12/2021

Statement of Originality

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

Disclaimer

Compliance of Deliverable 1.1 with the Description of Action

DoA Task description[1]	Addressed by D1.1
Essential Information for clinical studies Annex 1: Mandatory deliverables for clinical studies **First study subject approvals package** (prior to enrolment of first study subject): a. Final version of study protocol as approved by first regulator / ethics committee(s)	• Section 2. Retrospective Clinical Study protocol, pages 9-22, describes the final version of the protocol
b. Registration number of clinical study in a WHO- or ICMJE- approved registry that also allows later posting of study results.	• Section 3. Registration of the Retrospective Clinical Study, page 23, describes the registration status of the study
c. Approvals required for invitation / enrolment of first subject in at least one clinical centre: ethics committees, and copies of opinion or confirmation by the competent Institutional Data Protection Officer. If the position of a Data Protection Officer is established, its opinion/confirmation that all data collection and processing will be carried out according to EU and national legislation	• Section 4. Approvals required for enrolment of the first study subject, page 24, provides the approvals from at least one clinical centre and the status for the rest of the centres.

[1] The information that the First study subject approvals package shall provide is described in Annex 1: Mandatory deliverables for clinical studies of the Essential Information for clinical studies template: https://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_2018-2020_en.pdf

Executive summary

Recent advances in early cancer detection and therapy have dramatically changed the natural course of many cancer types transforming them into chronic diseases. However, the success of improving cancer survival has been compromised by the short, or long-term collateral toxic effects caused by different cancer therapies. **CARDIOCARE** will exploit its unique registries of elderly breast cancer patients and perform a new multi-center clinical trial to implement an interdisciplinary and patient-oriented eHealth approach for assessing the efficacy of behavioral and psychological interventions on cardiotoxicity, intrinsic capacity and QoL. Retrospective and prospective data from the clinical studies will be collected including clinical, imaging, -omics, biomarker, psycho-marker, intrinsic capacity, wearable sensor, and eHealth application data and by employing machine learning approaches. The overreaching goal of **CARDIOCARE** will develop a novel cost-effective risk-stratification strategy and healthcare model based on new sets of quality key performance indicators and provide evidence-based best practices and care pathways to improve the management of the elderly multimorbid breast cancer patient at risk for cardiac toxicity.

The current document reflects the work done within the framework of **Task 1.1** of the CARDIOCARE project "**Definition of a panel of quality key performance indicators for monitoring health status, intrinsic capacity and QoL for the CARDIOCARE healthcare model**" (M1-M6). Task 1.1 aims at defining a panel of tools that would be utilized as quality key performance indicators (KPIs) for effectively monitoring cardiotoxicity, health status, intrinsic capacity and QoL in the elderly breast cancer patients during the cardiotoxicity disease continuum. Multi-dimensional data including imaging data, biochemical biomarkers, lab tests and other clinical data will be interrogated for associations with cardiac toxicity, health outcomes and QoL. To achieve these aims a retrospective observational study must be performed. Consistently, this deliverable reports on the First study subject approvals package for the retrospective study that will be performed in the following five clinical centers: European Institute of Oncology (IEO); Bank of Cyprus Oncology Centre (BOCOC); Karolinska University Hospital (KSBC); National and Kapodistrian University of Athens (NKUA); and University of Ioannina (UOI).

Table of Contents

List of Abbreviations

Abbreviation	Explanation
BNP	Brain natriuretic peptide
CRP	C- reactive protein
CT	Chemotherapy
DPIA	Data Protection Impact Assessment
DPO	Data Protection Officer
ECG	electrocardiogram
ECHO	Echocardiography
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
GDPR	General Data Protection Regulation
HER2	human epidermal growth factor receptor 2
HRV	Heart Rate Variability
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IL-6	Interleukin-6
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Event
MRI	Magnetic Resonance Imaging
QoL	Quality of Life
TNF-α	Tumor Necrosis Factor-alpha
WHO	World Health Organization

List of Tables

1 Introduction

The information provided in this deliverable concerns the first study subject approvals package for the retrospective study of the CARDIOCARE project, performed under Task 1.1 and is led by IEO. The deliverable provides information on:

- The final version of retrospective clinical study protocol.
- The registration of the retrospective clinical study in a WHO- or ICMJE- approved registry that also allows later posting of study results.
- The approvals required for invitation / enrolment of the first subject in at least one clinical centre: ethics committee approval, and copies of the Data Protection Officer opinion.

Additional information on the implementation of the ethical standards and guidelines of Horizon 2020 that must be applied in the CARDIOCARE project and the GDPR implementation plan is provided in the **Deliverable D6.1**.

2 Retrospective Clinical Study protocol

2.1 The CARDIOCARE Project

Recent advances in early cancer detection and therapy have dramatically changed the natural course of many cancer types transforming them into chronic diseases. Due to a strong reduction in cancer mortality, it is estimated that there will be more than 25 million cancer survivors in Europe by the year 2026[2] and approximately two-thirds of all cancer survivors will be older than 65 years of age[3]. However, the success of improving cancer survival has been compromised by the short, or long-term collateral toxic effects caused by different cancer therapies. Among several side effects of cancer treatment, cardiotoxicity has emerged as a major cause of co-morbidity and mortality in cancer patients, which further impairs their physical, psychosocial and quality of life (QoL) status[4]. One of the basic clinical problems is the correct definition of what exactly, in the field of oncologic therapies, "cardiotoxicity" means. We think that we can nowadays consider the most comprehensive concept described in what is reported in the ESMO Guidelines 2012 that indicates as potential chemotherapy-related cardiotoxicity: i) LVEF (Echocardiography detected Left Ventricular Ejection Fraction) lower than 55%; ii) A decrease, after chemotherapy, of at least 10% LVEF from baseline value; iii) Occurrence of MACE (Major Acute Cardiovascular Effects) as cardiac death, acute coronary syndromes, acute pulmonary edema, over heart failure and life-threatening arrhythmias[5]. Although breast cancer mortality rates have been declining each year in Europe for two decades, the number one cause of death for women with breast cancer is cardiotoxicity[6,7]. Adding further complexity to the management and care of this population, 50%-60% of the newly diagnosed breast cancer patients are older than 65 years of age[2]. This elderly group of patients is particularly susceptible to co-morbid cardiotoxicity induced by cancer

[2] Miller KD, Siegel RL, Chun, et al: Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 66:271–289, 2016

[3] Reddy P, Shenoy C, Blaes AH: Cardio-oncology in the older adult. J Geriatr Oncol 8:308–314, 2017

[4] Singh A, Kareem H, Devasia T, et al: Breast Cancer and the Heart: Burden on the Chest. J Cardiovasc Dis Res 9:01–04, 2018

[5] Cardinale, D., Colombo, A., Bacchiani, G., Tedeschi, I., Meroni, C. A., Veglia, F., ... & Cipolla, C. M. (2015). Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation*, *131*(22), 1981-1988.

[6] Carioli G, Malvezzi M, Rodriguez T, et al: Trends and predictions to 2020 in breast cancer mortality in Europe. The Breast 36:89–95, 2017

[7] Montazeri K, Unitt C, Foody JM, et al: ABCDE steps to prevent heart disease in breast cancer survivors. Circulation 130:e157–e159, 2014

treatment due to age-related risk factors, pre-existing heart disease, and a high prevalence of multiple co-morbidities. Age-related risk factors including body changes in drug pharmacokinetics and declined kidney function, existing cardiovascular disease with risk factors such as hypertension, diabetes, hyperlipidemia and obesity, as well as cancer and treatment-related factors including metabolic changes and physical inactivity, together with drug-drug interactions as a result of polypharmacy, can promote declines in intrinsic (mental and physical) capacity[8, 9] and exacerbate cardiac toxicity from cancer therapy in older women with breast cancer[2,10]. The challenge of maximizing the clinical benefit from cancer therapies while minimizing the risks of cardiotoxicity has stimulated a close collaboration between clinical oncologists and cardiologists, giving rise to the field of CardioOncology. However, evidence-based best practices for risk stratification and management of elderly cancer patients, including older women with breast cancer, are still lacking. Data are scarce on the unique aspects of this vulnerable group, as patients 65 years or older are systematically underrepresented in clinical oncology trials[11]. As a result, older patients are frequently offered lower doses of chemotherapy due to concerns of cardiotoxicity, frailty bias and high prevalence of multimorbidity, leading to undertreatment and suboptimal outcomes[2,12] with a negative impact on the QoL of the individuals and significant costs to the healthcare systems, patients and families. Furthermore, although advances have been made in the detection and management of cardiotoxicity based on imaging (2D and 3D Echocardiography, Cardiac MRI) and, in

[8] 6. Chang L, Weiner LS, Hartman SJ, et al: Breast cancer treatment and its effects on aging. J Geriatr Oncol 10:346–355, 2019

[9] Mandelblatt JS, Small BJ, Luta G, et al: Cancer-Related Cognitive Outcomes Among Older Breast Cancer Survivors in the Thinking and Living With Cancer Study. J Clin Oncol 36:3211, 2018

[10] Fusco D, Villani ER: An update in breast cancer management for elderly patients. Transl Cancer Res 7:319–328, 2018

[11] Shenoy C, Klem I, Crowley AL, et al: Cardiovascular Complications of Breast Cancer Therapy in Older Adults. Oncologist 16:1138, 2011

[12] Owusu C, Lash TL, Silliman RA: Effect of undertreatment on the disparity in age-related breast cancer-specific survival among older women. Breast Cancer Res Treat 2006 1022 102:227–236, 2006

particular, circulating biomarkers release (troponin, brain natriuretic peptide)[13, 14, 15,16] , we have still a lot to understand about the impact of chemotherapeutic agents on some frails categories of patients, particularly on elderly over 65 and in patients with one or more comorbidities. But let us underline and propose one consideration concerning what we think is a correct longitudinal vision and approach to risk factors, general clinical morbidities, and cancer expression in elderly over 65 patients since these conditions do not obviously "pop up" in one day, but take a long time to express and become someway evident.

We perfectly know that, for women population, there is a psychological and pathophysiological critical age: the peri-post menopausal period; in this clinical subset there is the potential explosion (or become evident and/or diagnosed especially in areas, as Center-Southern Italy, where females prevention knowledge, attitude and socioeconomic issues are lacking) of the most common risk factors, as increased weight, hypertension, coronary arteries diseases and peripheral vascular diseases, diabetes, metabolic and bone disorders, etc. As a matter of fact, epidemiological data clearly show that soon after the menopausal period there is a peak increase in breast cancer occurrence. Because of these reasons we strongly suggest considering in our study population also the decade before the generally defined "elderly over 65" (that anyway is just a conventional definition that not always correctly fits with the real evident or hidden health conditions and the immediate evidence (or not) also of risk factors.

Thus, novel interdisciplinary and holistic patient-oriented approaches are urgently needed, to better monitor the health status and QoL of cancer patients aged over 55, enabling the provision of new evidence-based best practices on the early detection, prevention and management of cardiotoxicity which can particularly be applied to > 55 aged patients with cancer.

Consistently, the **CARDIOCARE** project (H2020 European Project "**An Interdisciplinary Approach for the Management of the Elderly Multimorbid Patient with Breast Cancer Therapy Induced**

[13] Curigliano G, Lenihan D, Fradley M, et al: Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol 31:171–190, 2020

[14] Cardinale D, Sandri MT, Martinoni A, et al: Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. Ann Oncol 13:710–715, 2002

[15] Cardinale D, Caruso V, Cipolla CM: The breast cancer patient in the cardioncology unit. J Thorac Dis 10:S4306, 2018[cited 2021 Dec 17] Available from: /pmc/articles/PMC6328395/

[16] Cardinale D, Colombo A, et al: Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation, J Clin Oncol. 2010 Sep 1;28(25):3910-6. doi: 10.1200/JCO.2009.27.3615. Epub 2010 Aug 2.

Cardiac Toxicity"; Proposal ID: SEP-210653155) investigates cancer therapy-induced cardiotoxicity in elderly multimorbid patients. **CARDIOCARE** will bring together modeling, medical, and social sciences experts to advance current knowledge on the stratification of elderly breast cancer patients at risk for co-morbid cardiotoxicity from cancer therapy and a decline in their QoL. The European partners involved in the projects are:

- **University of Ioannina** (UOI, Greece; Coordinator of the project);
- **European Institute of Oncology** (IEO), Italy;
- **Bank of Cyprus Oncology Centre** (BOCOC), Cyprus;
- **Foundation for Research and Technology-Hellas** (FORTH), Greece;
- **Istituto di Management Sanitario** (IMS), Italy;
- **Philips Electronics Nederland** BV (PHILIPS), Netherlands;
- **Karolinska University Hospital** (KSBC), Sweden;
- **Stremble Ventures LTD** (STREMBLE), Cyprus;
- **Institute of Oncology** Ljubliana (IOL), Slovenia;
- **National and Kapodistrian University of Athens** (NKUA), Greece;
- **European Society of Cardiology** (ESC), France;
- **Hellenic Mediterranean University** (HMU), Greece.

2.2 The Methodology of the Retrospective Data Collection

In this document's section, revealing aspects of the retrospective data procedure and analysis are presented through the example of the European Institute of Oncology (IEO). Similar methodological procedures were adopted by the other clinical partners (respectively BOCOC, KSBC, NKUA, UOI) involved in CARDIOCARE project.

2.2.1 Objectives

The main objective of the CARDIOCARE project is to identify potential risk factors associated with cardiotoxicity and deterioration of QoL in breast cancer patients with previous baseline cardiovascular disease and in patients with no cardiovascular disease, to train and develop the first version of a risk prediction model for the future prediction of cardiotoxicity and QoL, and to provide actionable insights for best practices and cost-effective healthcare pathways by helping clinicians in identifying patient care gaps. It includes two main studies: a retrospective observational study including 180 breast cancer patients over 65 with and without cardiovascular baseline disease before starting any active treatment for cancer and a complete setting of the most important clinical and cardiological data as requested plus 120 female patients over 55 with and without documented cardiovascular risk factors with breast cancer at baseline, who developed cardiotoxicity during or after cancer therapies (see primary endpoints) (**Specific object of the current document**); b) a prospective clinical study will be developed on the results of the retrospective study to validate and fine-tune the risk prediction model (**Not the object of the current document**). The risk prediction model of cardiotoxicity, once it will be developed and tested, will allow early detection, prevention and treatment of cardiotoxicity in elderly breast cancer patients and improve QoL.

The retrospective observational study is the first step needed to deliver a risk prediction model to assist clinical decision-making for better health and care, economic growth, and sustainability of health systems using specific technics of machine learning and statistical analysis on the collected data. Specifically, this retrospective observational study will aim at: i) Determining the epidemiological characteristics of cardiotoxicity in these patients by evaluating specific trajectories of cardiotoxicity progression; ii) Identifying new biomarkers and psycho-markers of cardiotoxicity progression; iii) Defining a risk stratification model to improve early diagnosis, prevention and

therapy of cardiotoxicity and improve patients' intrinsic capacity and QoL, deriving from available data in existing databases.

2.2.2 Primary Endpoints

- Cardiac damage and toxicity defined as the elevation of cardiac Troponin I levels in plasma, above the threshold in use at the local laboratory (cut-off values suggested by the manufacturer), or a decrease of left ventricular ejection fraction (LVEF) by 10% from baseline or below 55% in the elderly population over 65 years.
- The same endpoints will be considered in breast cancer patients aged from 55 to 65 years to better define the longitudinal onset/evidence/progression of common peri/postmenopausal risk factors and cancer occurrence.

2.2.3 Secondary Endpoints

- Cardiac toxicity registered as BNP elevation above 400 pg/ml.
- Hospital admissions for cardiovascular causes or falls.
- The following continuous variables will be also retrieved to identify predictive factors of disease trajectories and cardiac toxicity related to the objective of developing and defining the risk stratification model:
- Imaging biomarkers of cardiac structural and functional variables by echocardiography.
- Whole blood and plasma biomarkers including biochemical, inflammatory/psychological (platelet activation, IL-6, TNF-α, HRV, CRP, Fibrinogen, Ferritin, alfa2 protein)
- Association of clinical variables with QoL assessments.

2.3 Patient Selection: Criteria for Eligibility/Ineligibility

2.3.1 Participants population

Data will be retrieved on patients with a breast cancer diagnosis and cardiac damage and toxicity and patients with breast cancer and pre-existent cardiovascular disease before starting any active treatment for breast cancer. Available multi-modal retrospective data at different time points of the patient's care pathway (starting of chemotherapy and at each cycle until the end of chemotherapy), including clinical data, cardiac imaging, biochemical and psychological biomarkers as

well as QoL will be retrieved from existing databases of the five clinical centers involved in this retrospective study.

2.3.2 Sample size considerations

The sample size of around 1560 breast cancer patients has been computed based on the number of patients responding to the inclusion criteria and that were admitted to the five clinical centers in the last 15 years. Specific numbers of patients that will be retrospectively collected in each clinical centers: IEO: 300, BOCOC: 600, KSBC: 260, NKUA:300, UOI: 100.

2.3.3 Inclusion criteria

To be eligible for inclusion in the study, each patient must fulfill the criteria below:

- Women or men with a diagnosis of early breast cancer who underwent neoadjuvant and/or adjuvant treatment with regimens including anthracyclines.
- Women or men with a diagnosis of HER2 positive early breast cancer who underwent neoadjuvant and/or adjuvant treatment with anti-HER2 therapy (trastuzumab or trastuzumab and pertuzumab).
- Women or men with HER2 positive metastatic breast cancer who underwent first-line therapy with anti-HER2 agents (trastuzumab or trastuzumab and pertuzumab in combination with taxanes).
- Women or men with age ≥ 65 years with and without baseline cardiovascular or metabolic disease (any) before starting any active treatment for breast cancer
- Women or men eligible who underwent first-line therapy in the metastatic setting with any type of treatment (chemotherapy, immunotherapy, endocrine therapy plus biological agents)
- Age ≥ 55 years with and without cardiovascular risk factors before starting any active treatment for breast cancer.

2.3.4 Exclusion criteria

Patients who meet any of the following criteria will be excluded:

- Patients with blood troponin levels higher than the cut-off suggested by the manufacturer before chemotherapy

2.4 Methods and Study Design

This is a retrospective observational study. Available multi-modal retrospective data at different time points of the patient's care pathway (starting of chemotherapy and at each cycle until the end of chemotherapy), including clinical data, cardiac imaging, biochemical and psychological biomarkers as well as QoL will be retrieved from existing databases of the European Institute of Oncology and of other clinical partners (BOCOC, KSBC, NKUA, UOI) involved in CARDIOCARE project. This data will be used for computing the most prominent variables affecting cardiotoxicity. This, together with the theoretical work will define the initial set of parameters for modeling cardiotoxicity and conducting the aforementioned prospective clinical study. Available retrospective data that will be extracted are presented in **Table 1**.

Table 1: Retrospective data that will be considered.

Cardiac imaging
Baseline: ECHO, ECG
Follow-up: Months 3, 6, 9, 12
All patients the 1st year
Positive patients up to 2nd year
Cardiac Biomarkers (Troponin I, BNPs)
Baseline
During CT
Follow-up: Months 3, 6, 9, 12
All patients the 1st year
Positive patients up to 2nd year
Psycho-markers
Baseline: Platelet, CRP, Fibrinogen
Follow-up: months 3, 6, 9, 12
Blood tests/Samples
Baseline: Blood tests, blood samples
Follow-up: months 3, 6, 9, 12
QoL
Baseline: Distress thermometer, EORTC-QLQ (patient subsample)
Follow-up: End of chemotherapy
Breast imaging
Baseline: Echo, Mammography, CT
Follow-up: months 3, 6, 9, 12
Tissue
Baseline: Biopsy

2.5 Statistical Procedures

All descriptive statistics will be presented as means, medians and standard deviations for numerical variable and as frequencies and proportions for categorical variables. Before proceeding with inferential statistical testing, all numerical data dependent variables, Cardiac imaging (ECHO, ECG) derived biomarkers, Cardiac Biomarkers (Troponin I, BNPs), Psycho-markers (Platelet, CRP, Fibrinogen), Blood tests Blood Samples, Quality of Life (Distress thermometer, EORTC-QLQ), Breast imaging derived biomarkers (Echo, Mammography, CT) and Tissue (Biopsy) will be tested for Normality using the Kolmogorov Smirnov test or the Shapiro Wilk test of Normality. For pairwise comparisons of numerical data at follow-up at months 3, 6, 9 and 12 with respect to the baseline, we will use the paired samples Wilcoxon test (also known as Wilcoxon signed-rank test) where the dependent variable is non-parametric and the paired t-test where the dependent variable is parametric. In the case that we will have two independent groups in our sample which we would like to compare with regards to their measurements with respect to the numerical dependent variable, we will use the Mann Whitney U test, (sometimes called the Mann Whitney Wilcoxon Test or the Wilcoxon Rank Sum Test) for non-parametric dependent variables and the independent sample t-test for parametric dependent variables. Levene's test for the equality of the variances will also be run to allow us to better assess the assumptions of the tests. For comparing more than two independent groups with regards to their measurements with respect to the numerical dependent variable, we will use the Kruskal-Wallis test by rank for non-parametric dependent variables and the ANOVA test for parametric dependent variables. In the case that the equality of the independent groups is rejected by the Kruskal-Wallis test, pairwise comparisons will be performed to pinpoint which of the independent groups differ between themselves. The same will be done in the case that ANOVA rejects the equality of the groups where Post-Hoc tests will be performed. Levene's test for the equality of the variances will once again be run to allow us to better assess the assumptions of the tests whereas the Bonferroni correction will be applied adjusting for multiple testing. The Kaplan Meier test will be used to assess the Survival or Progression of the patients and the Cox Regression will be used to compare the Survival or Progression of the patients from independent groups.

2.5.1 Exploratory data analyses

The data will also be analyzed with artificial intelligence (AI) based methods. The objective here is to go beyond endpoint testing and onto the discovery of potentially novel knowledge and models. In order to prove the superiority of the proposed integrative diagnostic tool, CARDIOCARE will first develop single source predictive models using the available retrospective data categories. To this end, the proposed AI infrastructure will focus on radiomics, machine and deep learning methods to rank variables based on the amount of information that they carry in differentiating groups defined in the study endpoints (such as cardiotoxicity) and make predictions further used in the prospective phase. The model priors will be primarily single modality models since during the retrospective part of the project all data sources might not be available for all patient data gathered in the multi-center setup. However, partially integrative diagnostic models will also be developed in this phase, in particular radiomics-based machine learning and end-to-end deep learning to identify potential associations between imaging signatures and the clinical characteristics of the patients. Subsequently, the single source models will be used for fine-tuning and ensemble learning, aiming to develop novel, multi-modal integrative diagnostics.

2.5.2 Assessment of data quality

Period controls are planned to verify the quality of data collected (verifying missing data, out-of-range values and misalignments). At the end of the data collection a final data quality check will be performed, including the following checks:

1. Extraction of the entire database and manual inspection of the data;
2. Statistical analysis of each variable:
    a. Distribution analysis;
    b. The outliers will be identified according to a statistical analysis of patients' distribution. For categorical data, frequency analysis will be performed to see the incidence.
    c. Identification of putative errors and outliers and queries to the clinical sites;
3. Random selection of patients, for key variables, and confirmation of data set with source documents.
4. Clear identification of missing data (missing values vs. non-available data vs non-collected data).

2.6 Data Management

An electronic case report form (eCRF) will be prepared to collect all the relevant data during the study, to record all characteristics, efficacy and safety endpoints for the study. The eCRF will be integrated with in the CARDIOCARE Data Management Platform, which will be compliant with applicable data privacy and security standards. The CRF will be accessible to all clinical centers and will enable to data collection during the study. The data will be collected in a consistent and standardized way across all clinical sites, in accordance with an agreed CARDIOCARE data model. The collected data elements will be identified by the clinical experts and the model will be refined based on the defined clinical scenarios of the project, ensuring that the objectives of the scenarios are realized, including with respect to the development of analytics. The implementation of the data model will adopt the HL7 FHIR standard and the corresponding medical ontologies as prescribed by the value sets of the FHIR standard. When required by our domain, extensions to the standard will be proposed and implemented.

Data de-identification will be carried out on site, before transfer to the CARDIOCARE Data Management Platform[17, 18] Widely-adopted statistical methods will be applied to compute and ensure that the re-identification risk is very low. The potential sources of bias will be evaluated to avoid bias in data and in the subsequently developed models.

2.7 Regulatory Approval Procedures

The protocol of this retrospective and observational study has been submitted for approval to the Ethics Committees of all clinical sites involved in the study (Table 2).

2.7.1 Protection of the Data Subjects

Each clinical site will have access to personal patient's data and will be able to associate clinical data with patient identifiers, while only anonymized data will be shared with the CARDIOCARE partners for the purposes of the study.

[17] Dankar FK, El Emam K, Neisa A, et al: Estimating the re-identification risk of clinical data sets, BMC Med Inform Decis Mak 12:1–15, 2012

[18] Khaled El Emam, Luk Arbuckle: Anonymizing Health Data: Case Studies and Methods to Get You Started - Khaled El Emam, Luk Arbuckle - Google Libri. O'Reily Media

2.7.2 Ethical issues and data privacy

The present study has been devised to comply with both national (i.e., GCPs) and international declarations (i.e., Declaration of Helsinki) regulating proper ethical research involving human subjects. The protocol was developed in compliance with the STROBE statement and with ISO 14155:2020. By signing this protocol, the investigator declares to conduct the trial in accordance with that regulation and norms. All procedures will comply with National law and the European Union's General Data Protection Regulation (GDPR).

2.7.3 Benefits and risks of the clinical investigation

The study design follows a risk minimization and a benefit maximization requirement, thus promoting non-maleficence and active beneficence towards the category of research participants that are investigated in the CARDIOCARE project: breast cancer patients with cardiotoxicity. First of all, retrospective data research is important to design the next study more accurately, thus allowing us to maximize the chances of actually predicting cardiotoxicity. Moreover, it is harmless to patients, as it makes use of material that exists already and does not require further procedures to patients. The retrospective design also allows gathering long term follow-up data in reasonable time to draw hypotheses that will be further tested and validated in a prospective study.

2.7.4 Risk of bias

Retrospective studies have inherent risks of bias, such as reporting bias, since patients with increased risk of cardiovascular events might have more follow-up visits and better phenotypic characterization or surveillance bias since high-risk patients might have been more thoroughly monitored.

2.7.5 Patient identification

As per GCP, patients have the right to confidentiality. Therefore, no patients' names will be used in any documentation transmitted to the European Institute of Oncology. Items that are used to identify a patient include the year of birth and registration number.

The local data manager will keep an identification log for all patients entered in this trial including:

- Patient's name
- Patient's initials
- Registration number
- Date of birth
- Date of registration

2.7.6 Informed consent procedures

Considering the nature of the study (retrospective) and the high number of patients, we will verify whether one of the following procedures are allowed (in order of preference):

- Assessment of the center data use/reuse policies to assess the possible reuse of large datasets in the context of epidemiological studies without specific informed consent.
- Verify if at the time of cancer treatment and its follow up the patient has signed an Informed Consent Form specifying that his/her clinical data can be used for research purposes
- If the first two options are not feasible, the patient will be re-called and invited to sign the ICF of this study. A signed copy of the ICF will be provided to the recruiting center personally or by mail.

Legal basis for processing retrospective data is based on that processing is necessary for the performance of a task carried out in the public interest according to Article 6(1e) of the GDPR. In case of not a public body processing is necessary for the legitimate interests pursued by the beneficiary according to Article 6(1f). Further processing is based on scientific research purposes as a lawful compatible purpose, in line with Recitals 50 and 159 of the GDPR and additional condition for processing sensitive/special category data is that processing is necessary for scientific research purposes in the public interest and in the area of public health according to Article 9(2j) with appropriate safeguards in line with Article 89(1). A Privacy Notice publicly available via each institution's website provides, where applicable, Article 13 & 14 information to the data subjects enabling them to exercise their rights.

2.8 Data property and publication policy

Property of data will be treated in accordance with the Consortium Agreement of the Horizon 2020 CARDIOCARE project. The main results of the clinical trial may be published in a peer-reviewed scientific journal and presented in scientific workshops only in an anonymous and aggregated way. Co-authors will be the principal investigators of the Study who participate in the design and draw up of the research project, the contributing CARDIOCARE modelers, the investigators of the satellite centers who add their patient retrospective data, and a representative of the European Institute of Oncology Data Management. No contribution from the pharmaceutical industry will be provided.

3 Registration of the Retrospective Clinical Study

The Retrospective Clinical Study will be registered in a WHO- or ICMJE- approved registry, such as the www.clinicaltrials.gov registry allowing later posting of study results. The sponsor of the study is IEO and is responsible for the study registration which requires an Ethics Approval by the competent Ethics Committee. IEO has submitted the protocol however ethics approval is still pending and it is anticipated to be obtained within January 2022.

4 Approvals required for enrolment of the first study subject

The approvals required for the enrolment of the first data subject in at least one clinical centre are the following:

a. Ethical approval by the competent ethics committee,
b. The opinion or confirmation by the competent Institutional Data Protection Officer (DPO), that a Data Protection Impact Assessment (DPIA) has been performed and all data processing activities can proceed in compliance with the GDPR and national legislation.

To this end, all clinical centres participating in the retrospective clinical study have submitted the study protocol to their institution's ethics committees to obtain ethical approval and a comprehensive DPIA to their institutional DPO. The current status of these approvals in each centre is presented in Table 2. For the first study subject approvals package the **Ethical and DPIA Approvals** of the BOCOC clinical centre are provided in the **Appendix**. All other approvals or submitted protocols are also provided.

Table 2: Approvals status for each clinical center.

Country	Centre	Ethics Approval	DPIA Approval	Expected date
Italy	IEO	Pending, (Internal Submission Code 2888)	Pending	January 31st 2022
Cyprus	BOCOC	**APPROVED** **Reference No: ΕΕΒΚ ΕΠ 2021.01.147, 25-11-21**	**APPROVED**	January 15th 2022
Sweden	KSBC	Pending, (Internal Submission Code: Dnr 2021-06616-01)	Pending	January 15th 2022
Greece	UOI	Pending, (Internal Submission Code 1052/22-12-21)	**APPROVED**	January 15th 2022
Greece	NKUA	Attikon - Pending (Internal Submission Code 731/30-12-2021)	Pending	January 15th 2022
		Aretaieio – APPROVED **Reference No: 384/22-12-21**	Pending	January 15th 2022

5 Conclusions

Based on this protocol, in the retrospective study we will extract multi-dimensional data to test for their associations with cardiac toxicity, health outcomes and QoL. Based on statistical analysis as well as machine learning approaches employed in parallel in Task 3.1, specific KPIs presenting high predictive ability will be adopted and further validated in the prospective clinical study in WP4. All retrospective data will be exploited for training and development of the CARDIOCARE Risk prediction model (WP3).

6 Appendix (Ethics & DPIA Approvals-Protocol submissions)

ΚΥΠΡΙΑΚΗ ΔΗΜΟΚΡΑΤΙΑ

ΕΘΝΙΚΗ ΕΠΙΤΡΟΠΗ ΒΙΟΗΘΙΚΗΣ ΚΥΠΡΟΥ

Αρ. Φακ.: ΕΕΒΚ ΕΠ 2021.01.147
Αρ. Τηλ.: 22809038/039, 22819101
Αρ. Φαξ: 22353878

25 Νοεμβρίου, 2021

Δρ Αναστασία Κωνταντινίδου
Παθολόγος Ογκολόγος
Ογκολογικό Κέντρο Τράπεζας Κύπρου
Λεωφ. Ακροπόλεως 32
2006 Στρόβολος
Λευκωσία

Αγαπητή Δρ Κωνσταντινίδου,

Αίτηση διαφοροποίησης για την πρόταση με τίτλο:
«An interdisciplinary approach for the management of the elderly multimorbid patient with breast cancer therapy induced cardiac toxicity (CARDIOCARE)»

Αναφέρομαι στην αίτηση διαφοροποίησης που υποβάλατε στις 16 Νοεμβρίου 2021 για το πιο πάνω ερευνητικό πρόγραμμα, και επιθυμώ να σας πληροφορήσω ότι εγκρίνεται η προτεινόμενη διαφοροποίηση σε σχέση με τα κριτήρια εισδοχής και αποκλεισμού.

2. Σημειώνεται ότι η εν λόγω έγκριση δίδεται υπό τον όρο ότι η πιο πάνω αναφερόμενη ερευνητική πρόταση είναι αναδρομική με συλλογή δεδομένων από ιατρικούς φακέλους ασθενών χωρίς οποιαδήποτε προοπτική παρέμβαση στους συμμετέχοντες.

3. Παραμένουμε στη διάθεση σας για οποιαδήποτε περαιτέρω πληροφορία ή διευκρίνιση.

Με εκτίμηση,

Καθ. Κωνσταντίνος Ν. Φελλάς
Πρόεδρος
Εθνικής Επιτροπής Βιοηθικής Κύπρου

Data Protection Impact Assessment (DPIA)

This template is an example of how you can record your DPIA process and outcome. It follows the process set out in our DPIA guidance, and should be read alongside that guidance and the Criteria for an acceptable DPIA set out in European guidelines on DPIAs.

You should start to fill out the template at the start of any major project involving the use of personal data, or if you are making a significant change to an existing process. The final outcomes should be integrated back into your project plan.

Submitting controller details

Name of controller	OGKOLOGIKO KENTRO TRAPEZAS KYPROU (BOCOC), established in LEOFOROS AKROPOLEOS 32, STROVOLOS 2006, Cyprus
DPIA subject	Identify and minimize any data protection risks related to the EU's Horizon 2020 project: "CARDIOCARE- AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY".
Name of controller contact	Dr. Anastasia Constantinidou, Department of Medical Oncology, Email: Anastasia.constantinidou@bococ.org.cy, Tel.:+357 22847411

Step 1: Identify the need for a DPIA

Explain broadly what project aims to achieve and what type of processing it involves. You may find it helpful to refer or link to other documents, such as a project proposal. Summarize why you identified the need for a DPIA.

UOI is the Coordinator of and partner in the CARDIOCARE project. The project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No 945175, entitled: "AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY".

CARDIOCARE is an interdisciplinary clinical research project. The project is an international collaboration aiming to improve the monitoring, treatment and overall care provided to the elderly breast cancer patients which are at higher risk of developing cardiac toxicity from cancer therapy. Already available retrospective data from other projects and data collected within a new prospective clinical study will be used for the development and validation of a novel Risk Stratification model for the elderly breast cancer patients.

For the scientific research purposes of the project set under the Grant Agreement No 945175, BOCOC will be one of the six clinical centres of the study and acting as a **Joint Controller** (Data Provider), will share the following of data:

I. Patient data already available from other projects.

II. Newly collected data from patients enrolled in the CARDIOCARE prospective clinical study.

The types of personal data that shall be shared for the purposes of the project include clinical data, cardiac imaging, serum biomarkers and psycho-markers, multi-omics (genomics, epigenomics, metagenomics) data, Quality of Life data and intrinsic (mental and physical) capacity monitoring data including wearable sensor and mobile Health application data. Such data processing involves also 'Profiling' of patients with automated processing of personal data in order to monitor aspects of patients' health, behaviour, location and movements. However, such 'Profiling' DOES NOT involve automated individual decision-making, with legal or similarly significant effects for the patients.

Considering the **special category/sensitive nature** of the personal data that shall be processed, comprising health and genetic data, as well as the requirement to transfer such data to other CARDIOCARE partners (**Data Recipients**) for processing, a need for a DPIA is identified in accordance with Article 35 (3b) of the GDPR. This DPIA is performed in order to assess any potential risks arising from the processing activities planned and to assess the effectiveness of the technical and organisational measures taken for the protection of the rights and freedoms of the data subjects.

Step 2: Describe the processing

Describe the nature of the processing: how will you collect, use, store and delete data? What is the source of the data? Will you be sharing data with anyone? You might find it useful to refer to a flow diagram or other way of describing data flows. What types of processing identified as likely high risk are involved?

In order for the partners to carry out the tasks set under the project's Grant Agreement No 945175, transfers of patient data are necessary between the partners. The partners, as **Joint Controllers** will enter an appropriate **Data Sharing Agreement** in line with Article 26(1) of the GDPR. For the research purposes of the project, BOCOC acting as a **Data Provider** shall share:

I. Patient data already available from other projects.

II. Newly collected data from patients enrolled in the CARDIOCARE prospective clinical study.

More specifically, **pseudonymised** data shall be transferred to Joint Controllers acting as **Data Recipients** to carry out their tasks set under the EC Grant Agreement.

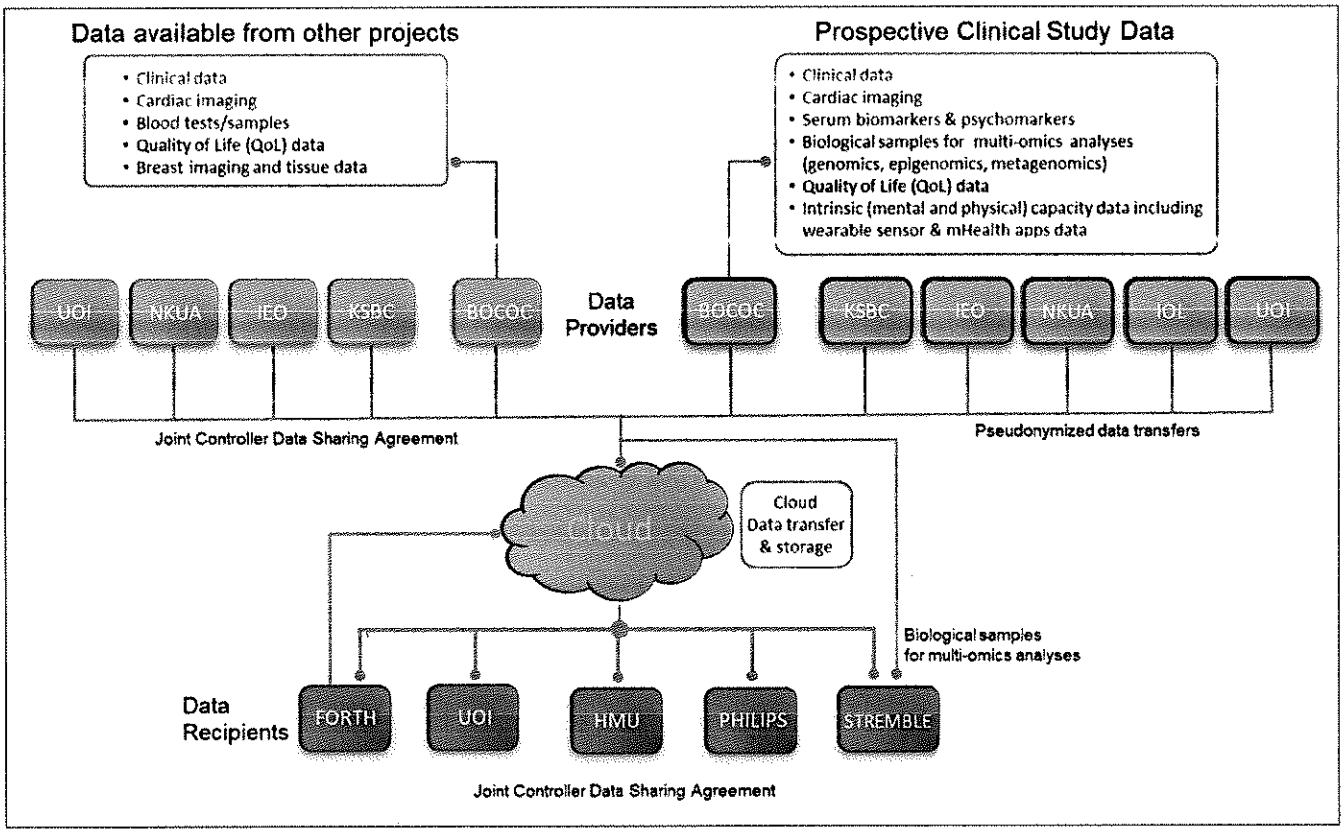
Cloud data processing services including **data transfers and storage** shall be performed using a **Private Cloud infrastructure** provided by the CARDIOCARE partner **FORTH**, acting as a Data Recipient and **Joint Controller**.

The Data Provider will retain the personal data as long as needed for scientific research purposes in line with Article 5(1e) and in accordance with Article 89(1) of the GDPR subject to appropriate technical and organizational measures to safeguard the rights and freedoms of the data subjects.

At the end of the project (for a minimum of 4 years, unless an extension is granted by the European Commission) and at the choice of the Data Provider, the Data Recipients shall return or destroy all the Personal Data transferred, unless legislation imposed upon them prevents them from returning or destroying all or part of the personal data transferred.

Taking into account the special category nature of the data that shall be processed and the requirement to transfer such data to partners in other countries for further processing, via a cloud infrastucture, appropriate technical and organisational measures are needed to mitigate any risks arising from such types of processing activities that involve a likely high risk for the rights and freedoms of the data subjects.

Collectively, the data flows are described in the following diagram.



Describe the scope of the processing: what is the nature of the data, and does it include special category or criminal offence data? How much data will you be collecting and using? How often? How long will you keep it? How many individuals are affected? What geographical area does it cover?

The processing is for personal and special category data. For the research purposes of the project BOCOC shall share the following patient data collected by the Department of Medical Oncology at 32 Acropoleos Avenue,2006 Strovolos in Nicosia -Cyprus:

I. **Pseudonymized** data from **600 patients** available from other projects including the following **special category/sensitive data**:
   a. Clinical data
   b. Cardiac imaging
   c. Blood tests/samples
   d. Quality of Life data
   e. Breast imaging and tissue data

II. **Pseudonymized** newly collected data from **120 patients** enrolled in the CARDIOCARE prospective clinical study including the following **special category/sensitive data**:
   a. Clinical data
   b. Cardiac imaging

c. Serum biomarkers and psycho-markers

d. Biological samples for multi-omics analyses (genomics, epigenomics, metagenomics)

e. Quality of Life data

f. Intrinsic (mental and physical) capacity monitoring data including wearable sensor and mobile Health application data. Such data processing involves also **'Profiling'** of patients with automated processing of personal data in order to monitor aspects of patients' health, behaviour, location and movements. However, such 'Profiling' **DOES NOT** involve automated individual decision-making, with legal or similarly significant effects for the patients.

The patient data will be retained as long as needed for scientific research purposes in compliance with Article 5(1e) and the Member State's applicable law.

Describe the context of the processing: what is the nature of your relationship with the individuals? How much control will they have? Would they expect you to use their data in this way? Do they include children or other vulnerable groups? Are there prior concerns over this type of processing or security flaws? Is it novel in any way? What is the current state of technology in this area? Are there any current issues of public concern that you should factor in? Are you signed up to any approved code of conduct or certification scheme (once any have been approved)?

The relationship with the data subjects is characterized as patient – doctor relationship and as research participant in nature, where the patient is expecting the use of its health data for scientific research purposes in the area of Breast Cancer and Cardio-Oncology research. BOCOC as a Joint Controller and Data Provider ensures that the personal data will be lawfully processed for the public good and for legitimate research activities while protecting the interests of the data subjects. In addition, the Data Provider ensures the processing of personal data to be both fair and transparent in order for the patients to retain control over their personal data. For this reason, the Data Provider undertakes to inform, where applicable, the data subjects with the information listed in Articles 13 and 14 of the GDPR in order to comply with the principles of fairness and transparency.

The data concern elderly breast cancer patients. No children or other vulnerable groups are included as research participants.

The types of processing activities planned for the project include clinical, biochemical, molecular biology, biomedical imaging, machine learning and statistical modelling approaches together with wearable sensor and mHealth applications technologies involving cloud services and information security technologies. No approved code of conduct or certification scheme exists, yet.

Describe the purposes of the processing: what do you want to achieve? What is the intended effect on individuals? What are the benefits of the processing – for you, and more broadly?

Aged-related factors and co-morbidities increase elderly breast cancer patients' vulnerability to cardiotoxicity due to cancer treatment. Lack of best practices and frailty bias in these patients, underrepresented in clinical trials, may lead to inappropriate interventions and undertreatment, resulting in poorer outcomes, deterioration of quality of life and increased healthcare costs. CARDIOCARE will focus on the elderly breast cancer population and through a holistic approach including mHealth applications, wearable sensors, imaging and molecular biomarkers, will provide the ability to patients to take part in their care process and enhance their physical and mental health (intrinsic capacity), contributing to an individualised care plan and a psychological adaptation to their disease. CARDIOCARE will enable the development of an effective risk stratification model in mitigating cardiotoxicity and adverse events, minimizing hospitalisations and enhancing quality of life.

Step 3: Consultation process

Consider how to consult with relevant stakeholders: describe when and how you will seek individuals' views – or justify why it's not appropriate to do so. Who else do you need to involve within your organisation? Do you need to ask your processors to assist? Do you plan to consult information security experts, or any other experts?

EUROPA DONNA – The European Breast Cancer Coalition is an international breast cancer patient advocacy organization which has endorsed the CARDIOCARE project and will participate in the **Ethical Advisory Board** and the **Regulatory Advisory Board** of the project.

This endorsement can be mutually beneficial by encouraging patients' participation to the management of their condition while assisting the medical experts to get a deeper understanding of patients' concerns and expectations regarding their health and the protection of their personal data.

EUROPA DONNA will help communicate the project's results and advise on ethical, privacy, health and quality of life issues concerning breast cancer patients. In addition EUROPA DONNA will help highlight the need for early diagnosis of cardiotoxicity after cancer treatment, inform about care and treatment choices available to improve mental and physical health and QoL, and encourage patients to have an active role in decisions regarding their own health.

The endorsement of the EUROPA DONNA to the CARDIOCARE project is provided below:

To: Prof. Dimitrios I. Fotiadis, Coordinator of the CARDIOCARE consortium

Date: May 18, 2020

Reference:
Subject: Support of the CARDIOCARE research proposal for the H2020 call SC1-BHC-24-2020: Healthcare interventions for the management of the elderly multimorbid patient.

Dear Prof. Dimitrios I. Fotiadis,
Concerning your research proposal entitled "CARDIOCARE - AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY",
We are pleased to inform you that EUROPA DONNA - The European Breast Cancer Coalition, an independent non-profit organisation representing the interests of European women regarding breast cancer, will support your efforts in case the proposal is accepted for funding, in terms of participating in the advisory board. EUROPA DONNA member(s) will advise on ethical, privacy, health and quality of life issues concerning breast cancer patients. All costs for the participation of the EUROPA DONNA member(s) to the advisory board meetings, including any travelling expenses, will be covered by the CARDIOCARE consortium.
We hope for a positive decision for funding this project.

Sincerely,

Susan Knox
CEO/Executive Director

Head Office: Piazza Amendola, 3 - 20149 Milan, Italy - Tel. +39-02.3659 2280 - Fax +39-02. 3659 2284 - E-mail info@europadonna.org
www.europadonna.org

In addition, the medical associations European Society of Cardiology (ESC), a CARDIOCARE partner and the International Cardio-Oncology Society (ICOS) which has also endorsed the project, will have an active role by advising on ethical issues concerning the protection of the patients' data.

All Data Recipients have provided all available information to perform this Data Protection Impact Assessment.

All research staff handling personal data has been made aware of its responsibilities with regards to handling of Personal Data and will commit to a duty of confidence by signing a non-disclosure declaration.

Information Security issues have been addressed by FORTH, a CARDIOCARE technical partner leader of the relevant "**Task 5.3: The CARDIOCARE Security tools and services**".

Step 4: Assess necessity and proportionality

Describe compliance and proportionality measures, in particular: what is your lawful basis for processing? Does the processing actually achieve your purpose? Is there another way to achieve the same outcome? How will you prevent function creep? How will you ensure data quality and data minimisation? What information will you give individuals? How will you help to support their rights? What measures do you take to ensure processors comply? How do you safeguard any international transfers?

For the purposes of **further processing** patients' data available from other projects (I), lawful processing is based on the following legal grounds:

a. Processing is necessary for the **performance of a task carried out in the public interest** according to Article 6(1e) of the GDPR. The task or function has a clear basis in law in line with Recital 45 of the GDPR. For non-public bodies, processing is necessary for the **legitimate interests in scientific research** pursued by the beneficiaries according to Article 6(1f) of the GDPR.

b. Further processing is based on **scientific research purposes** as a lawful compatible purpose, in line with Recitals 50 and 159 of the GDPR.

c. Additional condition for processing sensitive / special category data including health data is that processing is necessary for **scientific research purposes in the public interest and in the area of public health** according to Article 9(2j) and Recitals 52, 53 and 159 with appropriate safeguards in line with Article 89(1) and Recitals 156 and 157 of the GDPR.

For the purposes of processing newly collected data from patients enrolled to the CARDIOCARE prospective clinical study (II), lawful processing is based on the following legal grounds:

a. Processing is necessary for the **performance of a task carried out in the public interest** according to Article 6(1e) of the GDPR. The task or function has a clear basis in law in line with Recital 45 of the GDPR. For non-public bodies, processing is necessary for the **legitimate interests in scientific research** pursued by the beneficiaries according to Article 6(1f) of the GDPR.

b. Additional condition for processing sensitive / special category data including health data is that processing is necessary for **scientific research purposes in the public interest and in the area of public health** according to Article 9(2j) and Recitals 52, 53 and 159 with appropriate safeguards in line with Article 89(1) and Recitals 156 and 157 of the GDPR.

For the purposes described above the Data Provider (BOCOC) undertakes to inform, where applicable, the data subjects with the **information listed in Articles 13 and 14** of the GDPR in order to comply with the principle of **transparency**.

As far as the further processing of patient data available from other projects (I), based on the legal grounds used, the Data Subjects are entitled to the following **rights**:

a. The right to be informed, the right of access and the right to rectification.

b. Based on the specific legal grounds for processing, the rights to erasure, to data portability, and to object are **NOT** available in line with Recital 65 and Article 17(3d), Recital 68, and Article 21(6) plus Recital 159 of the GDPR respectively.

As far as the processing of newly collected data from patients enrolled to the CARDIOCARE prospective clinical study (II), based on the legal grounds used, the Data Subjects are entitled to the following **rights**:

a. The right to be informed, the right of access and the right to rectification.

b. Based on the specific legal grounds for processing, the rights to erasure, to data portability, and to object are **NOT** available in line with Recital 65 and Article 17(3d), Recital 68, and Article 21(6) plus Recital 159 of the GDPR respectively.

Data Subjects can exercise their rights through a Subject Access Request to the Data Provider. To facilitate the Data Subjects' rights, the Data Provider and Data Recipients shall maintain Records of all Personal Data processed and all processing activities in a structured, commonly used and machine-readable form in accordance with Article 30 of the GDPR.

Data transfers between Joint Controllers shall be performed using the **Cloud infrastructure** provided by FORTH (an EU-based partner) acting as a Data Recipient and Joint Controller.

Considering the risks arising from the processing activities involved, the Joint Controllers shall implement strategies of **data protection by design** including appropriate technical and organisational measures to ensure data quality and minimisation and a level of security appropriate to those risks, including but not limited to:

1. **Pseudonymisation** of the personal data or biological samples by the Data Providers, before uploading the data to the cloud for transferring and/or further processing. The key codes shall be kept in separate location from the Personal Data.
2. **Encryption** of the Personal Data stored within the cloud, to prevent unauthorised and unlawful processing, including Password Storage Encryption, Data Partition Encryption and SSL Host Authentication. Secure and separate access to each joint controller shall be provided only upon entering into this Agreement.
3. Appropriate **back-up procedures** in order to avoid accidental loss, destruction or damage of the Personal Data by a physical or technical incident, enabling to reinstate the system in a timely manner.
4. **Secure biological sample storage** conditions including equipment maintenance and authorised processing of the samples by trained personnel only, in order to avoid accidental loss, destruction or damage of the biological samples by a physical or technical incident.
5. **Audit Log operation** to allow viewing the users' access history to the system

enabling the detection of any potential security or data breaches.

6. Conducting **regular security assessments** on systems to review the effectiveness of the security measures and on biological sample storage conditions.
7. Ensuring that pseudonymised personal data will **not be stored outside the European Economic Area (EEA)**.
8. Ensuring all research personnel have been made aware of their responsibilities concerning the handling of Personal Data only under the instructions laid down in this Agreement and commit to a duty of confidence by signing a **non-disclosure declaration**.

Step 5: Identify and assess risks

Describe source of risk and nature of potential impact on individuals. Include associated compliance and corporate risks as necessary.	**Likelihood of harm** Remote, possible or probable	**Severity of harm** Minimal, significant or severe	**Overall risk** Low, medium or high
1. Impossible or disproportionate effort to directly inform the data subjects of the further processing operations. For the purposes of further processing patients' data available from other projects (I), the Data Provider shall provide the data subjects concerned, and where applicable, with Article 13 and 14 information regarding that further processing operation. Considering that the processing is carried out for scientific research purposes involving a large number of data subjects, data of a certain age, and likely a number of no more valid contact details it might be impossible or involve a disproportionate effort to directly inform the data subjects of that further processing (GDPR Recital 62), in order to enable them to exercise their rights. However, taking into account the compatible nature of further processing for scientific research purposes, the pseudonymization of the personal data by the Data Provider and the existence of appropriate safeguards (see, pages 9-10) in the intended further	Probable	Minimal	Medium

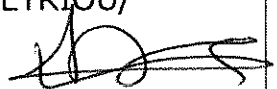
processing operations, the overall risk for the data subjects is considered **medium**.			
2. Illegitimate access to data. Considering the technical and organisational security measures applied (see, pages 9-10), including but not limited to data pseudonymization, encryption, secure and separate access under an Article 26(1) data sharing agreement and an Article 28 contract, the overall risk for the data subjects is considered low.	Remote	Minimal	Low
3. Undesired modification of data Considering the technical and organisational security measures applied (see, pages 9-10), including but not limited to the commitment of the authorized research personnel to a duty of confidence by signing a non-disclosure declaration, the overall risk for the data subjects is considered low.	Remote	Minimal	Low
4. Disappearance of data. Taking into account that the personal data shall be pseudonymised before uploaded to the Cloud, stored encrypted and systematically backed-up in external RAID drives the overall risk for the data subjects is considered Low.	Possible	Minimal	Low
5. Breach of any Data Recipient's obligation to protect the personal data of the data subjects. Considering that the recipients of the pseudonymised data are partners in the CARDIOCARE project under EC Grant Agreement No 755320 and that an appropriate Article 26(1) Data Sharing Agreement for Joint Controllers is in place, the overall risk is considered Low.	Remote	Minimal	Low
6. Patient 'Profiling' involving tracking or observation of participants. Intrinsic capacity monitoring includes wearable sensor and mobile Health application data processing. Such processing involves also 'Profiling' of patients with automated processing of data in order to	Remote	Minimal	Low

monitor aspects of patients' health, behaviour, location and movements. However, such 'Profiling' **DOES NOT** involve automated individual decision-making, with legal or similarly significant effects for the patients. Taking into account the technical and organisational security measures applied (see, pages 9-10), the overall risk for the data subjects is considered low.			

Step 6: Identify measures to reduce risk

Identify additional measures you could take to reduce or eliminate risks identified as <u>medium</u> or <u>high</u> risk in step 5				
Risk	**Options to reduce or eliminate risk**	**Effect on risk** Eliminated reduced accepted	**Residual risk** Low medium high	**Measure approved** Yes/no
1. Impossible or disproportionate effort to directly inform the data subjects of the further processing operations, in order to enable them to exercise their rights.	Making the required information, about further processing operations, publicly available through the Data Provider's website (as a Privacy Notice).	Reduced	Low	Yes

Step 7: Sign off and record outcomes

Item	**Name/date**	**Notes**
Measures approved by:	KALIA DEMETRIOU/ 14-09-21 	Integrate actions back into project plan, with date and responsibility for completion
Residual risks approved by:	KALIA DEMETRIOU/ 14-09-21 	If accepting any residual high risk, consult the DPA before going ahead

DPO advice provided:	KALIA DEMETRIOU 14/09/2021	DPO should advise on compliance, step 6 measures and whether processing can proceed
Summary of DPO advice: The processing can proceed taken into consideration that all the technical and administrative measures described will be applied. Additionally all the risks related to the processing are clearly identified and assessed with a low residual risk except from one with a medium residual risk where action is suggested and will be implemented by the end of September. Data protection obligations have been met.		
DPO advice accepted or overruled by:	PANOS ERGATOUDES 15/09/2021	If overruled, you must explain your reasons
Comments:		
Consultation responses reviewed by:		If your decision departs from individuals' views, you must explain your reasons
Comments:		
This DPIA will kept under review by:	KALIA DEMETRIOU 14/09/2021	The DPO should also review ongoing compliance with DPIA

ΕΘΝΙΚΟ & ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ

ΙΑΤΡΙΚΗ ΣΧΟΛΗ – ΑΡΕΤΑΙΕΙΟ ΝΟΣΟΚΟΜΕΙΟ

ΕΓΚΡΙΣΗ ΕΠΙΤΡΟΠΗΣ ΕΡΕΥΝΑΣ & ΔΕΟΝΤΟΛΟΓΙΑΣ

Αθήνα, 22/12/2021

Προς
Κον Μ. Κωνσταντουλάκη
Καθηγητή Χειρουργικής ΕΚΠΑ

Κύριε Κωνσταντουλάκη,

Η Επιτροπή Έρευνας Ηθικής και Δεοντολογίας του Αρεταιείου Νοσοκομείου μελέτησε το ερευνητικό πρωτόκολλο με τίτλο:

CARDIOCARE – Induced Cardiac Toxicity in the Multimorbid Patient with Breast Cancer Therapy – A Retrospective Study

Η έγκριση για το Ερευνητικό σας πρωτόκολλο καταχωρήθηκε στο Αρχείο της Επιτροπής Έρευνας με τον αριθμό : **384/22-12-21**

Ο Πρόεδρος

Καθηγητής Μανούσος Μ. Κωνσταντουλάκης

6η Υ.ΠΕ.
ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ
ΝΟΣΟΚΟΜΕΙΟ ΙΩΑΝΝΙΝΩΝ

ΠΑΝΕΠΙΣΤΗΜΙΑΚΗ ΟΓΚΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ
ΔΙΕΥΘΥΝΤΗΣ : Επίκουρος Καθηγητής DAVIDE MAURI

Ιωάννινα 22/12/2021

Προς
το Επιστημονικό Συμβούλιο
του ΠΓΝΙ

Θέμα: Αίτηση για έγκριση συμμετοχής στην αναδρομική μελέτη παρατήρησης με τίτλο: Επαγόμενη καρδιακή τοξικότητα σε ασθενείς με συνοσηρότητες και θεραπεία για καρκίνο του μαστού- Μια αναδρομική μελέτη, στο πλαίσιο της πολυεθνικής μελέτης CARDIOCARE

Αγαπητές Κυρίες, Αγαπητοί Κύριοι,

Παρακαλούμε όπως εγκρίνετε τη συμμετοχή της Ογκολογικής και Καρδιολογικής Κλινικής του ΠΓΝΙ στην ως άνω αναδρομική μελέτη παρατήρησης στο πλαίσιο του Cardiocare στο οποίο συμμετέχει το Πανεπιστήμιο Ιωαννίνων με Επιστημονικά Υπεύθυνο τον καθηγητή Δημήτριο Φωτιάδη και το οποίο είναι μία πολυεθνική μελέτη χρηματοδοτούμενη από το HORIZON 2020.

Πρόκειται για ένα πολύ φιλόδοξο ευρωπαϊκό πρόγραμμα που βασικός του στόχος είναι να αναπτυχθεί η πρώτη έκδοση ενός προγνωστικού μοντέλου για τη μελλοντική πρόβλεψη καρδιοτοξικότητας ώστε να βελτιωθεί η γνώση για την εφαρμογή βέλτιστων κλινικών πρακτικών για τους ασθενείς.

Κύριος στόχος αυτής της αναδρομικής μελέτης είναι η αναγνώριση των πιθανών παραγόντων κινδύνου που σχετίζονται με εμφάνιση καρδιοτοξικότητας και επιδείνωση της ποιότητας της ζωής ασθενών με καρκίνο του μαστού με προϋπάρχουσα ή όχι καρδιαγγειακή νόσο.

Σκοπός είναι να αναπτυχθεί η πρώτη έκδοση ενός προγνωστικού μοντέλου για τη μελλοντική πρόβλεψη καρδιοτοξικότητας ώστε να βελτιωθεί η γνώση για την εφαρμογή βέλτιστων κλινικών πρακτικών για τους ασθενείς.

Πρόκειται για χρηματοδοτούμενη μελέτη και θα υπάρξουν αμοιβές ερευνητών.

Η διεξαγωγή της όμως δεν θα έχει καμία οικονομική επιβάρυνση στο Νοσοκομείο δεδομένου ότι πρόκειται για μελέτη παρατήρησης, δεν προβλέπονται πρόσθετα έξοδα

Στοιχεία επικοινωνίας: Τηλ & Φαξ: 2651099394, e-mail: oncolsec@cc.uoi.gr

εργαστηριακών ή και διαγνωστικών εξετάσεων και δεν απαιτείται βεβαίωση ασφαλιστικής κάλυψης.

Οι υπογράφοντες και οι συν ερευνητές, έχουμε την εμπειρία, την εξειδίκευση και τη δυνατότητα διεξαγωγής της μελέτης με συναίνεση των διευθυντών και οι Κλινικές διαθέτουν την υλικοτεχνική υποδομή που προβλέπεται από το πρωτόκολλο, ώστε να παρέχουν την δυνατότητα διεξαγωγής και ολοκλήρωσης της μελέτης.

Επισυνάπτονται:

1. Το πρωτόκολλο της μελέτης
2. Περίληψη στα ελληνικά
3. Τα βιογραφικά των συμμετεχόντων

Είμαστε στη διάθεσή σας για κάθε διευκρίνιση

Με εκτίμηση

Οι Επιστημονικά Υπεύθυνοι

Davide Mauri

Επίκουρος Καθηγητής Ογκολογίας

Διευθυντής Ογκολογικής Κλινικής ΠΓΝΙ

Αικατερίνη Νάκα

Αναπληρώτρια Καθηγήτρια Καρδιολογίας

Data Protection Impact Assessment (DPIA)

This template is an example of how you can record your DPIA process and outcome. It follows the process set out in our DPIA guidance, and should be read alongside that guidance and the Criteria for an acceptable DPIA set out in European guidelines on DPIAs.

You should start to fill out the template at the start of any major project involving the use of personal data, or if you are making a significant change to an existing process. The final outcomes should be integrated back into your project plan.

Submitting controller details

Name of controller	PANEPISTIMIO IOANNINON (UOI), established in PANEPISTEMIOYPOLE PANEPISTEMIO IOANNINON, IOANNINA 45110, Greece
DPIA subject	Identify and minimize any data protection risks related to the EU's Horizon 2020 project: "CARDIOCARE- AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY".
Name of controller contact	Professor Dimitris Fotiadis, Head of the Unit of Medical Technology and Intelligent Information Systems, Department of Materials Science and Engineering, University of Ioannina, Greece Email: dimitris.fotiadis30@gmail.com, Tel:+302651009006

Step 1: Identify the need for a DPIA

Explain broadly what project aims to achieve and what type of processing it involves. You may find it helpful to refer or link to other documents, such as a project proposal. Summarize why you identified the need for a DPIA.

UOI is the Coordinator of and partner in the CARDIOCARE project. The project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No 945175, entitled: "AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY".

CARDIOCARE is an interdisciplinary clinical research project. The project is an international collaboration aiming to improve the monitoring, treatment and overall care provided to the elderly breast cancer patients which are at higher risk of developing cardiac toxicity from cancer therapy. Already available retrospective data from other projects and data collected within a new prospective clinical study will be used for the development and validation of a novel Risk Stratification model for the elderly breast cancer patients.

For the scientific research purposes of the project set under the Grant Agreement No 945175, UOI will be one of the six clinical centres of the study and acting as a **Joint Controller** (Data Provider), will share the following of data:

I. Patient data already available from other projects.

II. Newly collected data from patients enrolled in the CARDIOCARE prospective clinical study.

The types of personal data that shall be shared for the purposes of the project include clinical data, cardiac imaging, serum biomarkers and psycho-markers, multi-omics (genomics, epigenomics) data, Quality of Life data and intrinsic (mental and physical) capacity monitoring data including wearable sensor and mobile Health application data. Such data processing involves also 'Profiling' of patients with automated processing of personal data in order to monitor aspects of patients' health, behaviour, location and movements. However, such 'Profiling' DOES NOT involve automated individual decision-making, with legal or similarly significant effects for the patients.

Considering the **special category/sensitive nature** of the personal data that shall be processed, comprising health and genetic data, as well as the requirement to transfer such data to other CARDIOCARE partners (**Data Recipients**) for processing, a need for a DPIA is identified in accordance with Article 35 (3b) of the GDPR. This DPIA is performed in order to assess any potential risks arising from the processing activities planned and to assess the effectiveness of the technical and organisational measures taken for the protection of the rights and freedoms of the data subjects.

Step 2: Describe the processing

Describe the nature of the processing: how will you collect, use, store and delete data? What is the source of the data? Will you be sharing data with anyone? You might find it useful to refer to a flow diagram or other way of describing data flows. What types of processing identified as likely high risk are involved?

In order for the partners to carry out the tasks set under the project's Grant Agreement No 945175, transfers of patient data are necessary between the partners. The partners, as **Joint Controllers** will enter an appropriate **Data Sharing Agreement** in line with Article 26(1) of the GDPR. For the research purposes of the project, UOI acting as a **Data Provider** shall share:

I. Patient data already available from other projects.

II. Newly collected data from patients enrolled in the CARDIOCARE prospective clinical study.

More specifically, **pseudonymised** data shall be transferred to Joint Controllers acting as **Data Recipients** to carry out their tasks set under the EC Grant Agreement.

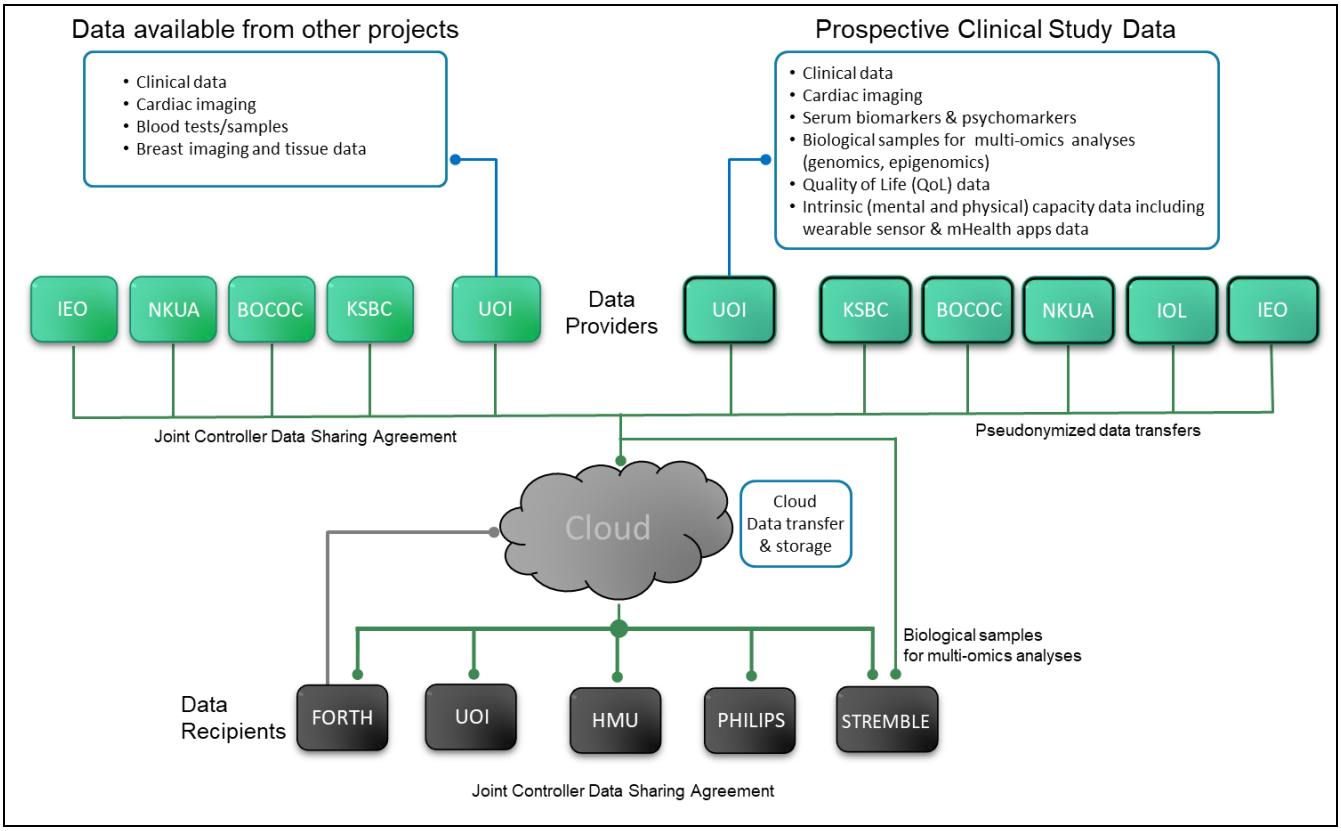
Cloud data processing services including **data transfers and storage** shall be performed using a **Private Cloud infrastructure** provided by the CARDIOCARE partner **FORTH**, acting as a Data Recipient and **Joint Controller**.

The Data Provider will retain the personal data as long as needed for scientific research purposes in line with Article 5(1e) and in accordance with Article 89(1) of the GDPR subject to appropriate technical and organizational measures to safeguard the rights and freedoms of the data subjects.

At the end of the project (for a minimum of 4 years, unless an extension is granted by the European Commission) and at the choice of the Data Provider, the Data Recipients shall return or destroy all the Personal Data transferred, unless legislation imposed upon them prevents them from returning or destroying all or part of the personal data transferred.

Taking into account the special category nature of the data that shall be processed and the requirement to transfer such data to partners in other countries for further processing, via a cloud infrastucture, appropriate technical and organisational measures are needed to mitigate any risks arising from such types of processing activities that involve a likely high risk for the rights and freedoms of the data subjects.

Collectively, the data flows are described in the following diagram.



Describe the scope of the processing: what is the nature of the data, and does it include special category or criminal offence data? How much data will you be collecting and using? How often? How long will you keep it? How many individuals are affected? What geographical area does it cover?

For the research purposes of the project UOI shall share the following patient data collected by the Department of Medical Oncology (Prof. Davide Mauri) and the 2nd Department of Cardiology (Prof. Katerina Naka) at the University Hospital of Ioannina in Greece:

I. **Pseudonymized** data from **100 patients** available from other projects including the following **special category/sensitive data**:
    a. Clinical data
    b. Cardiac imaging
    c. Blood tests/samples
    d. Breast imaging and tissue data

II. **Pseudonymized** newly collected data from **60 patients** enrolled in the CARDIOCARE prospective clinical study including the following **special category/sensitive data**:
    a. Clinical data
    b. Cardiac imaging
    c. Serum biomarkers and psycho-markers

d. Biological samples for multi-omics analyses (genomics, epigenomics)

e. Quality of Life data

f. Intrinsic (mental and physical) capacity monitoring data including wearable sensor and mobile Health application data. Such data processing involves also **'Profiling'** of patients with automated processing of personal data in order to monitor aspects of patients' health, behaviour, location and movements. However, such 'Profiling' **DOES NOT** involve automated individual decision-making, with legal or similarly significant effects for the patients.

The patient data will be retained as long as needed for scientific research purposes in compliance with Article 5(1e) and the Member State's applicable law.

Describe the context of the processing: what is the nature of your relationship with the individuals? How much control will they have? Would they expect you to use their data in this way? Do they include children or other vulnerable groups? Are there prior concerns over this type of processing or security flaws? Is it novel in any way? What is the current state of technology in this area? Are there any current issues of public concern that you should factor in? Are you signed up to any approved code of conduct or certification scheme (once any have been approved)?

The relationship with the data subjects is characterized as patient – doctor relationship and as research participant in nature, where the patient is expecting the use of its health data for scientific research purposes in the area of Breast Cancer and Cardio-Oncology research. UOI as a Joint Controller and Data Provider ensures that the personal data will be lawfully processed for the public good and for legitimate research activities while protecting the interests of the data subjects. In addition, the Data Provider ensures the processing of personal data to be both fair and transparent in order for the patients to retain control over their personal data. For this reason, the Data Provider undertakes to inform, where applicable, the data subjects with the information listed in Articles 13 and 14 of the GDPR in order to comply with the principles of fairness and transparency.

The data concern elderly breast cancer patients. No children or other vulnerable groups are included as research participants.

The types of processing activities planned for the project include clinical, biochemical, molecular biology, biomedical imaging, machine learning and statistical modelling approaches together with wearable sensor and mHealth applications technologies involving cloud services and information security technologies. No approved code of conduct or certification scheme exists, yet.

Describe the purposes of the processing: what do you want to achieve? What is the intended effect on individuals? What are the benefits of the processing – for you, and more broadly?
Aged-related factors and co-morbidities increase elderly breast cancer patients' vulnerability to cardiotoxicity due to cancer treatment. Lack of best practices and frailty bias in these patients, underrepresented in clinical trials, may lead to inappropriate interventions and undertreatment, resulting in poorer outcomes, deterioration of quality of life and increased healthcare costs. CARDIOCARE will focus on the elderly breast cancer population and through a holistic approach including mHealth applications, wearable sensors, imaging and molecular biomarkers, will provide the ability to patients to take part in their care process and enhance their physical and mental health (intrinsic capacity), contributing to an individualised care plan and a psychological adaptation to their disease. CARDIOCARE will enable the development of an effective risk stratification model in mitigating cardiotoxicity and adverse events, minimizing hospitalisations and enhancing quality of life.

Step 3: Consultation process

Consider how to consult with relevant stakeholders: describe when and how you will seek individuals' views – or justify why it's not appropriate to do so. Who else do you need to involve within your organisation? Do you need to ask your processors to assist? Do you plan to consult information security experts, or any other experts?
EUROPA DONNA – The European Breast Cancer Coalition is an international breast cancer patient advocacy organization which has endorsed the CARDIOCARE project and will participate in the **Ethical Advisory Board** and the **Regulatory Advisory Board** of the project. This endorsement can be mutually beneficial by encouraging patients' participation to the management of their condition while assisting the medical experts to get a deeper understanding of patients' concerns and expectations regarding their health and the protection of their personal data. EUROPA DONNA will help communicate the project's results and advise on ethical, privacy, health and quality of life issues concerning breast cancer patients. In addition EUROPA DONNA will help highlight the need for early diagnosis of cardiotoxicity after cancer treatment, inform about care and treatment choices available to improve mental and physical health and QoL, and encourage patients to have an active role in decisions regarding their own health. The endorsement of the EUROPA DONNA to the CARDIOCARE project is provided below:

To: Prof. Dimitrios I. Fotiadis, Coordinator of the CARDIOCARE consortium

Date: May 18, 2020

Reference:
Subject: Support of the CARDIOCARE research proposal for the H2020 call SC1-BHC-24-2020: Healthcare interventions for the management of the elderly multimorbid patient.

Dear Prof. Dimitrios I. Fotiadis,
Concerning your research proposal entitled "CARDIOCARE - AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY",
We are pleased to inform you that EUROPA DONNA - The European Breast Cancer Coalition, an independent non-profit organisation representing the interests of European women regarding breast cancer, will support your efforts in case the proposal is accepted for funding, in terms of participating in the advisory board. EUROPA DONNA member(s) will advise on ethical, privacy, health and quality of life issues concerning breast cancer patients. All costs for the participation of the EUROPA DONNA member(s) to the advisory board meetings, including any travelling expenses, will be covered by the CARDIOCARE consortium.
We hope for a positive decision for funding this project.

Sincerely,

Susan Knox
CEO/Executive Director

Head Office: Piazza Amendola, 3 - 20149 Milan, Italy - Tel. +39-02.3659 2280 - Fax +39-02. 3659 2284 - E-mail info@europadonna.org
www.europadonna.org

In addition, the medical associations European Society of Cardiology (ESC), a CARDIOCARE partner and the International Cardio-Oncology Society (ICOS) which has also endorsed the project, will have an active role by advising on ethical issues concerning the protection of the patients' data.

All Data Recipients have provided all available information to perform this Data Protection Impact Assessment.

All research staff handling personal data has been made aware of its responsibilities with regards to handling of Personal Data and will commit to a duty of confidence by signing a non-disclosure declaration.

Information Security issues have been addressed by FORTH, a CARDIOCARE technical partner leader of the relevant "**Task 5.3: The CARDIOCARE Security tools and services"**.

Step 4: Assess necessity and proportionality

Describe compliance and proportionality measures, in particular: what is your lawful basis for processing? Does the processing actually achieve your purpose? Is there another way to achieve the same outcome? How will you prevent function creep? How will you ensure data quality and data minimisation? What information will you give individuals? How will you help to support their rights? What measures do you take to ensure processors comply? How do you safeguard any international transfers?

For the purposes of **further processing** patients' data available from other projects (I), lawful processing is based on the following legal grounds:

a. Processing is necessary for the **performance of a task carried out in the public interes**t according to Article 6(1e) of the GDPR. The task or function has a clear basis in law in line with Recital 45 of the GDPR. For non-public bodies, processing is necessary for the **legitimate interests in scientific research** pursued by the beneficiaries according to Article 6(1f) of the GDPR.

b. Further processing is based on **scientific research purposes** as a lawful compatible purpose, in line with Recitals 50 and 159 of the GDPR.

c. Additional condition for processing sensitive / special category data including health data is that processing is necessary for **scientific research purposes in the public interest and in the area of public health** according to Article 9(2j) and Recitals 52, 53 and 159 with appropriate safeguards in line with Article 89(1) and Recitals 156 and 157 of the GDPR.

For the purposes of processing newly collected data from patients enrolled to the CARDIOCARE prospective clinical study (II), lawful processing is based on the following legal grounds:

a. Processing is necessary for the **performance of a task carried out in the public interest** according to Article 6(1e) of the GDPR. The task or function has a clear basis in law in line with Recital 45 of the GDPR. For non-public bodies, processing is necessary for the **legitimate interests in scientific research** pursued by the beneficiaries according to Article 6(1f) of the GDPR.

b. Additional condition for processing sensitive / special category data including health data is that processing is necessary for **scientific research purposes in the public interest and in the area of public health** according to Article 9(2j) and Recitals 52, 53 and 159 with appropriate safeguards in line with Article 89(1) and Recitals 156 and 157 of the GDPR.

For the purposes described above the Data Provider (UOI) undertakes to inform, where applicable, the data subjects with the **information listed in Articles 13 and 14** of the GDPR in order to comply with the principle of **transparency**.

As far as the further processing of patient data available from other projects (I), based on the legal grounds used, the Data Subjects are entitled to the following **rights**:

a. The right to be informed, the right of access and the right to rectification.

b. Based on the specific legal grounds for processing, the rights to erasure, to data portability, and to object are **NOT** available in line with Recital 65 and Article 17(3d), Recital 68, and Article 21(6) plus Recital 159 of the GDPR respectively.

As far as the processing of newly collected data from patients enrolled to the CARDIOCARE prospective clinical study (II), based on the legal grounds used, the Data Subjects are entitled to the following **rights**:

a. The right to be informed, the right of access and the right to rectification.

b. Based on the specific legal grounds for processing, the rights to erasure, to data portability, and to object are **NOT** available in line with Recital 65 and Article 17(3d), Recital 68, and Article 21(6) plus Recital 159 of the GDPR respectively.

Data Subjects can exercise their rights through a Subject Access Request to the Data Provider. To facilitate the Data Subjects' rights, the Data Provider and Data Recipients shall maintain Records of all Personal Data processed and all processing activities in a structured, commonly used and machine-readable form in accordance with Article 30 of the GDPR.

Data transfers between Joint Controllers shall be performed using the **Cloud infrastructure** provided by FORTH (an EU-based partner) acting as a Data Recipient and Joint Controller.

Considering the risks arising from the processing activities involved, the Joint Controllers shall implement strategies of **data protection by design** including appropriate technical and organisational measures to ensure data quality and minimisation and a level of security appropriate to those risks, including but not limited to:

1. **Pseudonymisation** of the personal data or biological samples by the Data Providers, before uploading the data to the cloud for transferring and/or further processing. The key codes shall be kept in separate location from the Personal Data.
2. **Encryption** of the Personal Data stored within the cloud, to prevent unauthorised and unlawful processing, including Password Storage Encryption, Data Partition Encryption and SSL Host Authentication. Secure and separate access to each joint controller shall be provided only upon entering into this Agreement.
3. Appropriate **back-up procedures** in order to avoid accidental loss, destruction or damage of the Personal Data by a physical or technical incident, enabling to reinstate the system in a timely manner.
4. **Secure biological sample storage** conditions including equipment maintenance and authorised processing of the samples by trained personnel only, in order to avoid accidental loss, destruction or damage of the biological samples by a physical or technical incident.
5. **Audit Log operation** to allow viewing the users' access history to the system

enabling the detection of any potential security or data breaches.

6. Conducting **regular security assessments** on systems to review the effectiveness of the security measures and on biological sample storage conditions.
7. Ensuring that pseudonymised personal data will **not be stored outside the European Economic Area (EEA)**.
8. Ensuring all research personnel have been made aware of their responsibilities concerning the handling of Personal Data only under the instructions laid down in this Agreement and commit to a duty of confidence by signing a **non-disclosure declaration**.

Step 5: Identify and assess risks

Describe source of risk and nature of potential impact on individuals. Include associated compliance and corporate risks as necessary.	**Likelihood of harm** Remote, possible or probable	**Severity of harm** Minimal, significant or severe	**Overall risk** Low, medium or high
1. Impossible or disproportionate effort to directly inform the data subjects of the further processing operations. For the purposes of further processing patients' data available from other projects (I), the Data Provider shall provide the data subjects concerned, and where applicable, with Article 13 and 14 information regarding that further processing operation. Considering that the processing is carried out for scientific research purposes involving a large number of data subjects, data of a certain age, and likely a number of no more valid contact details it might be impossible or involve a disproportionate effort to directly inform the data subjects of that further processing (GDPR Recital 62), in order to enable them to exercise their rights. However, taking into account the compatible nature of further processing for scientific research purposes, the pseudonymization of the personal data by the Data Provider and the existence of appropriate safeguards (see, pages 9-10) in the intended further	Probable	Minimal	Medium

processing operations, the overall risk for the data subjects is considered **medium**.			
2. Illegitimate access to data. Considering the technical and organisational security measures applied (see, pages 9-10), including but not limited to data pseudonymization, encryption, secure and separate access under an Article 26(1) data sharing agreement and an Article 28 contract, the overall risk for the data subjects is considered low.	Remote	Minimal	Low
3. Undesired modification of data Considering the technical and organisational security measures applied (see, pages 9-10), including but not limited to the commitment of the authorized research personnel to a duty of confidence by signing a non-disclosure declaration, the overall risk for the data subjects is considered low.	Remote	Minimal	Low
4. Disappearance of data. Taking into account that the personal data shall be pseudonymised before uploaded to the Cloud, stored encrypted and systematically backed-up in external RAID drives the overall risk for the data subjects is considered Low.	Possible	Minimal	Low
5. Breach of any Data Recipient's obligation to protect the personal data of the data subjects. Considering that the recipients of the pseudonymised data are partners in the CARDIOCARE project under EC Grant Agreement No 755320 and that an appropriate Article 26(1) Data Sharing Agreement for Joint Controllers is in place, the overall risk is considered Low.	Remote	Minimal	Low
6. Patient 'Profiling' involving tracking or observation of participants. Intrinsic capacity monitoring includes wearable sensor and mobile Health application data processing. Such processing involves also 'Profiling' of patients with automated processing of data in order to	Remote	Minimal	Low

monitor aspects of patients' health, behaviour, location and movements. However, such 'Profiling' **DOES NOT** involve automated individual decision-making, with legal or similarly significant effects for the patients. Taking into account the technical and organisational security measures applied (see, pages 9-10), the overall risk for the data subjects is considered low.			

Step 6: Identify measures to reduce risk

Identify additional measures you could take to reduce or eliminate risks identified as <u>medium</u> or <u>high</u> risk in step 5				
Risk	**Options to reduce or eliminate risk**	**Effect on risk** Eliminated reduced accepted	**Residual risk** Low medium high	**Measure approved** Yes/no
1. Impossible or disproportionate effort to directly inform the data subjects of the further processing operations, in order to enable them to exercise their rights.	Making the required information, about further processing operations, publicly available through the Data Provider's website (as a Privacy Notice).	Reduced	Low	Yes

Step 7: Sign off and record outcomes

Item	**Name/date**	**Notes**
Measures approved by:	Prof. Dimitrios I. Fotiadis / 09-12-2021	Integrate actions back into project plan, with date and responsibility for completion
Residual risks approved by:		If accepting any residual high risk, consult the DPA before going ahead

DPO advice provided:	UOI DPO (dpo@uoi.gr) 09-12-2021	DPO should advise on compliance, step 6 measures and whether processing can proceed
Summary of DPO advice: The processing can proceed. Data protection obligations have been met and no further measures are required.		
DPO advice accepted or overruled by:	Prof. Dimitrios I. Fotiadis / 09-12-2021	If overruled, you must explain your reasons
Comments:		
Consultation responses reviewed by:		If your decision departs from individuals' views, you must explain your reasons
Comments:		
This DPIA will kept under review by:	Michalis D. Mantzaris	The DPO should also review ongoing compliance with DPIA

9-12-2021

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ ΠΡΥΤΑΝΕΙΑ

Α.Π: 1

ΥΠΗΡΕΣΙΑ ΠΡΟΣΤΑΣΙΑΣ ΔΕΔΟΜΕΝΩΝ

ΠΡΟΣΩΠΙΚΟΥ ΧΑΡΑΚΤΗΡΑ

Προς τον κ. Δημήτριο Φωτιάδη,
Καθηγητή Τμήματος Μηχανικών
Επιστήμης Υλικών
Πανεπιστημίου Ιωαννίνων

Υ.Π.Δ: Σταυρούλα Σταθαρά
Τηλέφωνο: 26510 07321 e-
mail: dpo@uoi.gr

ΘΕΜΑ: ΕΓΚΡΙΣΗ ΕΠΕΞΕΡΓΑΣΙΑΣ ΔΕΔΟΜΕΝΩΝ ΠΡΟΣΩΠΙΚΟΥ ΧΑΡΑΚΤΗΡΑ
ΚΑΙ. ΜΕΛΕΤΗΣ ΕΚΤηνΙΗΣΗΣ ΑΝΤΙΚΤΥΠΟΥ (DPIA) ΓΙΑ ΤΟΥΣ ΕΡΕΥΝΗΤΙΚΟΥΣ ΣΚΟΠΟΥΣ ΤΟΥ ΠΡΟΓΡΑΜΜΑΤΟΣ «CARDIOCARE».

Αξιότιμε κ. Φωτιάδη,

Σε απάντηση του υποβληθέντος αιτήματος σας , το οποίο αφορά σε έγκριση της ερευνητικής μελέτης με ακρωνύμιο «CARDIOCARE» , στο πλαίσιο του ερευνητικού Προγράμματος με τίτλο « Μια διεπιστημονική προσέγγιση για την διαχείριση της πολυνοσηρότητας ηλικιωμένων ασθενών με καρκίνο του στήθους που εμφανίζουν καρδιοτοξικότητα επαγόμενη από χημειοθεραπεία» με κωδικό έργου Επιτροπής Ερευνών του Πανεπιστημίου Ιωαννίνων (...ΧΧΙ) και αφού λάβαμε υπόψη μας το περιεχόμενό του, σας ξ\ηημερώνουμε ως ακολούθως:

Το υποβληθέν αίτημα εγκρίνεται άνευ παρατηρήσεων, δεδομένου ότι, πληροί τους όρους και τις προϋποθέσεις που ορίζονται για την επεξεργασία δεδομένων προσωπικού χαρακτήρα στις διατάξεις των άρθρων 5 και 6 (ΕΕ) 2016/679 (ΓΚΠΔ) και των άρθρων 5, 24 και 30 του Ν.4624/2019, τα δεδομένα δε που θα συλλεγού, είναι ανωνυμοποιήμενα, ώστε να μην υπάρχει δυνατότητα ταυτοποίησης των υποκειμένων των δεδομένων.

Για τον σκοπό της ανωτέρω αναφερόμενης επεξεργασίας, διεξήχθη, σύμφωνα με τα οριζόμενα στο άρθρο 35 παρ (1) (ΕΕ) 2016/679 (ΓΚΠΔ) η απαιτούμενη Μελέτη Εκτίμησης Αντίκτυπου(ΌΡΙΑ), αναφορικά με την εκτίμηση των επιπτώσεων και τους κινδύνους για τα δικαιώματα και τις ελευθερίες των συμμετεχόντων στην έρευνα φυσικών προσώπων, τα αποτελέσματα της οποίας ελήφθησαν υπόψη.

Το Πανεπιστήμιο Ιωαννίνων, ως «υπεύθυνος επεξεργασίας», έχει λάβει τα κατάλληλα τεχνικά και οργανωτικά μέτρα, με σκοπό την διασφάλιση της ακεραιότητας και της εμπιστευτικότητας της επεξεργασίας (παρ. (στ) αρ. 5 (ΕΕ) 2016/679).

Επίσης σας ενημερώνουμε ότι η Υπηρεσίας μας, τελεί στη διάθεση σας για οιαδήποτε περαιτέρω διευκρίνιση η πληροφορία.

Με τιμή

Σταυρούλα Σταθαρα

Υ,Π.Δ. Παν/μιου Ιωαννίνων

ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ

ΓΙΝΕΤΑΙ ΑΠΟΔΕΚΤΟ

Ο ΠΡΥΤΑΝΗΣ

ΤΡΙΑΝΤΑΦΥΛΛΟΣ Α.Δ

Σ Α.Δ ΑΛΝΠΙΑΝΗΣ

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ
ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ «ΑΤΤΙΚΟΝ»

Β΄ Πανεπιστημιακή Καρδιολογική Κλινική
Διευθυντής: Καθηγητής Γ. Φιλιππάτος

ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ «ΑΤΤΙΚΟΝ»
ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΜΒΟΥΛΙΟ
ΑΡ. ΠΡΩΤ. Ε.Β.Δ. 731
ΗΜΕΡΟΜΗΝΙΑ 30.12.2021

Αθήνα, 29/12/2021

Προς: Επιστημονικό Συμβούλιο
Πανεπιστημιακό Γενικό Νοσοκομείο "ΑΤΤΙΚΟΝ"
Β' Πανεπιστημιακή Καρδιολογική Κλινική

Κοινοποίηση: Διοικητικό Συμβούλιο

ΘΕΜΑ: Κατάθεση Πρωτοκόλλου της μελέτης CARDIOCARE με Επιστημονικό Υπεύθυνο τον Καθηγητή κ. Γεράσιμο Φιλιππάτο

Τίτλος Μελέτης: ΔΙΕΠΙΣΤΗΜΟΝΙΚΗ ΑΝΤΙΜΕΤΩΠΙΣΗ ΤΗΣ ΜΕΛΕΤΗΣ ΤΟΥ ΗΛΙΚΙΩΜΕΝΟΥ ΑΣΘΕΝΟΥΣ ΜΕ ΣΥΝΝΟΣΗΡΟΤΗΤΑ ΚΑΙ ΚΑΡΚΙΝΟ ΤΟΞΙΚΟΤΗΤΑ ΑΠΟ ΘΕΡΑΠΕΙΑ ΤΟΥ ΚΑΡΚΙΝΟΥ ΤΟΥ ΜΑΣΤΟΥ

Τίτλος Μελέτης: AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY

Acronym: Cardiocare

Κωδικός: H2020-SC1-BHC-2018-2020

Χορηγός: Horizon 2020

Αξιότιμες Κυρίες /Κύριοι,

Κατάθεση του Πρωτοκόλλου της Μελέτης Cardiocare με κωδικό H2020-SC1-BHC-2018-2020 προς έγκριση από το Επιστημονικό Συμβούλιο.
Σημειώνεται ότι λόγω της αναδρομικής μορφής της μελέτης δεν απαιτείται έντυπο συγκατάθεσης του ασθενούς.

Συνημμένα υποβάλλουμε το Πρωτόκολλο.

2ο ΠΓΝ «ΑΤΤΙΚΟΝ»
ΓΕΡΑΣΙΜΟΣ ΦΙΛΙΠΠΑΤΟΣ
ΚΑΘΗΓΗΤΗΣ ΚΑΡΔΙΟΛΟΓΙΑΣ
Β' ΠΑΝ. ΚΑΡΔΙΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ

Με ...
(Υπογραφή & Σφραγίδα)

Ο Επιστημονικός Υπεύθυνος
Καθηγητής Γερασιμός Φιλιππάτος

CARDIOCARE: Ett interdisciplinärt tillvägagångssätt för omhändertagande av äldre multisjuka patienter med bröstcancerbehandling-relaterad hjärttoxicitet

2021-06616-01
Grundansökan
Med biologiskt material, Grundansökan
Validerad

Andri Papakonstantinou

1.2 Ansvarig huvudman för forskningen (forskningshuvudman)

Region Stockholm (232100-0032)

1.3 Behörig företrädare för forskningshuvudman

Robert Bränström

1.3.1 Behörig företrädare – titel som innebär ett verksamhetsansvar

Verksamhetschef

1.4 Har projektet fler forskningshuvudmän?

Ja

1.4.1 Övriga forskningshuvudmän som deltar i projektet:

De övriga forskningshuvudmän är utanför Sverige: European Institute of Oncology (IEO) och utöver de, flera andra europeiska partner är involverade i projektet: University of Ioannina (UOI, Grekland; koordinator för hela CardioCare projektet), Bank of Cyprus Oncology Centre (Cypern), Foundation for Research and Technology- Hellas (FORTH, Grekland), I.M.S. Istituto di Management Sanitario (Italien), Philips Electronics Nederland BV (Nederländerna), Karolinska Universitetssjukhuset (Sverige), Stremble Ventures LTD (Cypern), Institute of Oncology Ljubliana (Slovenien), National and Kapodistrian University of Athens (Grekland), European Society of Cardiology (ESC, Frankrike) och Hellenic Mediterranean University (Grekland)

1.5 Hemvist för forskningen

Tema Cancer, ME Bröst, Endokrina tumörer och Sarkom, Karolinska Universitetssjukhuset

1.6 Huvudansvarig forskare för projektet (kontaktperson)

Andri Papakonstantinou

1.6.1 Institution/hemvist som huvudansvarig forskare är verksam vid

Karolinska Universitetssjukhuset

1.7 Är den huvudansvariga forskaren disputerad?

Ja

1.8 Andra medverkande:

Theodoros Foukakis

Alexios Matikas

Frågor för avgiftskategori

1.9 Hur många forskningshuvudmän kommer att ingå i forskningsprojektet?

Flera

1.9.1 [Om Flera] Har samtliga forskningspersoner ett omedelbart samband med endast en av forskningshuvudmännen?

Ja

1.10 Avser forskningen klinisk läkemedelsprövning?

Nej

1.11 Ska endast befintliga personuppgifter behandlas i projektet?

Nej

2.1 Avser ansökan forskning som inbegriper äggdonation?

Nej

2.2 Avser ansökan forskning med läkemedel för genterapi eller somatisk cellterapi eller läkemedel som innehåller genetiskt modifierade organismer?

Nej

2.3 Avser ansökan forskning med xenogen cellterapi?

Nej

2.4 Kommer joniserande strålning ingå i forskningsprojektet?

Nej

2.5 Kommer biologiskt material från människor att nyinsamlas för projektet?

Nej

2.6 Planerar projektet att använda biologiskt material från människor från en eller flera befintliga provsamlingar?

Nej

2.7 Avser forskningen klinisk prövning av medicinteknisk produkt?

Nej

2.8 Gör en egen bedömning och ange på vilka punkter nedan som forskningen omfattas av 3-4 §§ etikprövningslagen. Observera att myndigheten kan komma att göra en annan bedömning.

✓ 3 § 1 Forskningen kommer att samla in känsliga personuppgifter.

2.8.1 [Om 3 § 1] Gör en egen bedömning och ange vilken typ av känsliga personuppgifter som kommer att behandlas i projektet. Observera att myndigheten kan komma att göra en annan bedömning.

✓ hälsa
✓ biometriska uppgifter som entydigt identifierar en person.

2.9 Önskas ett rådgivande yttrande?

Ja

2.10 Söker projektet förtur med motivering att projektet potential för nytta vad gäller behandling och förebyggande av COVID-19?

Nej

3.1 Skriv en populärvetenskaplig sammanfattning av forskningsprojektet.

Biverkningar av cancerbehandling kan ha en stor påverkan på patienters livskvalitet och även möjlighet att erbjuda lämplig behandling. Hjärttoxicitet är en känd biverkan av exempelvis antracykliner, en typ av cellgifter som är vanligt förekommande i bröstcancerbehandling, samt även målriktade behandlingar mot HER2-positiv bröstcancer, en subtyp av bröstcancer som uttrycker receptorn HER2. Risken för hjärt-och andra biverkningar ökas med åldern och samsjuklighet. Den ansökta studien är en del av ett europeiskt EU H2020-projekt: ”Ett interdisciplinärt tillvägagångssätt för omhändertagande av äldre multisjuka patienter med bröstcancerbehandling-relaterad

hjärttoxicitet” och som namnet säger, syfta till att förbättra omhändertagande av äldre patienter, en grupp som ofta underrepresenteras i kliniska prövningar.

Studien består av två delar: en retrospektiv som presenteras nu och en prospektiv som kommer att kompletteras i senare skedde då kunskap från den retrospektiva delen kommer att användas för att planera den prospektiva studien. Den retrospektiva studien koordineras av European Institute of Oncology (IEO) och utöver de, flera andra europeiska partner är involverade i projektet: University of Ioannina (UOI, Grekland; koordinator för hela CardioCare projektet), Bank of Cyprus Oncology Centre (Cypern), Foundation for Research and Technology- Hellas (FORTH, Grekland), I.M.S. Istituto di Management Sanitario (Italien), Philips Electronics Nederland BV (Nederländerna), Karolinska Universitetssjukhuset (Sverige), Stremble Ventures LTD (Cypern), Institute of Oncology Ljubliana (Slovenien), National and Kapodistrian University of Athens (Grekland), European Society of Cardiology (ESC, Frankrike) och Hellenic Mediterranean University (Grekland).

Huvudsyftet med projektet är att identifiera potentiella riskfaktorer förknippade med hjärttoxicitet och försämring av livskvalitet hos både patienter med tidigare kända kardiovaskulära sjukdomar och hos patienter utan kardiovaskulär sjukdom, för att träna och utveckla den första versionen av en riskprediktionsmodell för att framtiden kunna förutse hjärttoxicitet och livskvalitet, och för att öka kunskap om de bästa tillämpningsmetoder och kostnadseffektiva hälsovårdsvägar genom att hjälpa läkare att identifiera luckor i patientvården. Vi kommer därför använda oss av den Nationellt Kvalitetsregistret för bröstcancer (NKBC) för att identifiera patienter över 55 års ålder vid Karolinska Universitetssjukhuset och deras data kommer att inkluderas i studien, såväl som data från lämpliga patienter som har deltagit i de kliniska studierna Opti-Train och PREDIX HER2. Vi avser samla in information från mammografiundersökningar, hjärtundersökningar såsom Ekokardiografi (EKO) och EKG, biomarkörer (befintliga svar från blodprover som tagits vid diagnos och under uppföljning) samt tumör karakteristiska.

Data kommer att samlas in pseudo-anonymiserade (dvs kodade utan personuppgifter) för att sammanställas. Kodnyckel ska sparas vid Kliniska Prövningsenheten på Karolinska. Insamlade data ska sedan skickas anonymiserade vidare till koordinerande centra i utlandet (inom EU) för analys. Detta eftersom data kommer att kombineras även med insamlade data från andra länder i Europa. Resultat ska hela kohorten kommer att redovisas i vetenskapliga tidskrifter och kongress, gruppvis och anonymiserade.

3.2 Vad är det vetenskapliga syftet med projektet?

Studien är en del av ett europeiskt EU H2020-projekt: ”Ett interdisciplinärt tillvägagångssätt för omhändertagande av äldre multisjuka patienter med bröstcancerbehandling-relaterad hjärttoxicitet”. Den består av två delar: en retrospektiv som presenteras nu och en prospektiv som kommer att kompletteras i senare skedde då kunskap från den retrospektiva delen kommer att användas för att planera den prospektiva studien. Den retrospektiva studien koordineras av European Institute of Oncology (IEO) och utöver de, flera andra europeiska partner är involverade i projektet: University of Ioannina (UOI, Grekland; koordinator för hela CardioCare projektet), Bank of Cyprus Oncology Centre (Cypern), Foundation for Research and Technology- Hellas (FORTH, Grekland), I.M.S. Istituto di

Management Sanitario (Italien), Philips Electronics Nederland BV (Nederländerna), Karolinska Universitetssjukhuset (Sverige), Stremble Ventures LTD (Cypern), Institute of Oncology Ljubliana (Slovenien), National and Kapodistrian University of Athens (Grekland), European Society of Cardiology (ESC, Frankrike) och Hellenic Mediterranean University (Grekland).

CARDIOCARE kommer att sammanföra experter inom modellering, medicin och samhällsvetenskap för att föra fram aktuell kunskap om stratifiering av äldre bröstcancerpatienter som löper risk för samtidig hjärttoxicitet från cancerbehandling och en försämring av deras livskvalitet.
Huvudsyftet med projektet är att identifiera potentiella riskfaktorer förknippade med hjärttoxicitet och försämring av livskvalitet hos både patienter med tidigare kända kardiovaskulära sjukdomar och hos patienter utan kardiovaskulär sjukdom, för att träna och utveckla den första versionen av en riskprediktionsmodell för att framtiden kunna förutse hjärttoxicitet och livskvalitet, och för att öka kunskap om de bästa tillämpningsmetoder och kostnadseffektiva hälsovårdsvägar genom att hjälpa läkare att identifiera luckor i patientvården.

3.3 Vilka är de vetenskapliga frågeställningarna?

Primär effektmått:
Hjärtskada och toxicitet definierad som stegring av troponin I-nivåerna i plasma, över tröskeln som används på det lokala laboratoriet (gränsvärden som föreslås av tillverkaren), eller en minskning av vänsterkammarfunktion (mått som LVEF) med 10 % från baslinjen eller under 55 % i den äldre befolkningen över 65 år.

Sekundära effektmått:
1. Hjärttoxicitet registrerad som stegring av hjärtmarkören brain natrium peptide (BNP) över 400 pg/ml.

2. Sjukhusinläggningar för kardiovaskulära orsaker eller fall.

3. Följande kontinuerliga variabler kommer också att hämtas (där de är tillgängliga) för att identifiera prediktiva faktorer för sjukdomsförlopp och hjärttoxicitet med syftet att utveckla och definiera risk stratifieringsmodellen:
• Avbildning av biomarkörer av hjärtstrukturella och funktionella variabler genom ekokardiografi.
• Helblods- och plasmabiomarkörer inklusive biokemiska, inflammatoriska/psykologiska (trombocytaktivering, IL-6, TNF-α, HRV, CRP, Fibrinogen,
Ferritin, alfa2-protein)
• Korrelation av kliniska variabler med livskvalitetsbedömningar.
• Tumör karakteristiska från PAD svar från brösttumörer.

4.1 Redogör för metod inkl. proceduren, tekniken eller behandlingen.

Inga ingrepp eller prospektiv insamling av prover eller data ska göras för den retrospektiva del av studien.
Data kommer att insamlas om patienter med bröstcancerdiagnos över 55 årsålder. Befintliga och

tillgängliga multimodala retrospektiva data vid olika tidpunkter i patientens väg genom cancerbehandling och uppföljning (före, under och efter cancerbehandling) inklusive kliniska data, hjärt-undersökningar, biokemiska och psykologiska biomarkörer samt livskvalitetsmått kommer att insamlas för patienter med bröstcancerdiagnos vid 55 årsålder eller äldre. Information kommer att inhämtas från Karolinska Universitetssjukhuset och den Nationellt Kvalitetsregistret för bröstcancer (NKBC). Patienter som uppfyller inklusionskriterierna och har diagnostiserats vid Karolinska Universitetssjukhuset kommer att identifieras av NKBC och deras data kommer att inkluderas i studien, såväl som data från lämpliga patienter som har deltagit i de kliniska studierna Opti-Train och PREDIX HER2.

Datan kommer att samlas in pseudoanonymiserade, de ska sammanställas och sedan skickas anonymiserade vidare till koordinerande centra i utlandet (inom EU) för analys. Detta eftersom data kommer att kombineras även med insamlade data från andra länder i Europa.

4.2 Redogör för på vilket sätt metoden skiljer sig från klinisk rutin eller den ordinarie behandlingen.

Inte relevant. Detta är en retrospektiv insamling av data och därmed inte jämförbar med kliniska rutiner.

4.3 Redogör för tidigare erfarenheter (egna och/eller andras) av den använda proceduren, tekniken eller behandlingen.

Medverkande forskare har stor erfarenhet med klinisk och translationell forskning samt insamling och användning av retrospektiva data för forskningsändamål.

5.1 Förväntat startdatum för projektet:

01-01-2022

5.2 Förväntat slutdatum för projektet:

30-06-2025

5.3 Tidsplan för de olika delar som ingår i projektet:

Retrospektiv studie
1. Data extraktion och insamling samt start av dataanalys: start 01-01-2022
2. Slut av data analys 30-06-2024

Prospektiv studie (komplettering för denna ska skickas i senare skedde)
1. Inklusion av patienter : Start 01-07-2022, förväntad slut av inklusion 30-06-2023
2. Upföljning tom 31-03-2025
3. Data analysis, fram till 30-06-2025

6.1 Redogör för datainsamling och datas karaktär.

Då olika typer av retrospektiv data ska samlas in, kommer detta att pseudoanonymiseras för att kunna sammanställa data för samma individer. Dock ska data sedan skickas anonymiserade till koordinerande center inom EU.
Planeras insamling av följande data:
1. NKBC: patienter ska identifieras och baseline tumör data samlas in
2. Mammografi: pseudoanonymiserade data samt själva undersökningen (anonymiserade) ska samlas in
3. Hjärtundersökningar: Ekokardiografi (EKO) och EKG undersökningar ska samlas in från klinisk fysiologi på Karolinska Universitetssjukshuset
4. Biomarkörer: Befintliga svar från blodprover som tagits vid diagnos och under uppföljning ska inhämtas från laboratoriet på Karolinska Universitetssjukhuset och sparas pseudo-anonymiserade.
5. Tumör karakteristiska

Samma data som ovan planeras insamlas även från deltagare i Opti-Train och PREDIX HER2 studien.

6.2 Redogör för det statistiska underlaget för studiepopulationen/ undersökningsmaterialets storlek.

Minst 1560 patienter beräknas inkluderas totalt i studien bland de olika deltagande centra för att tillåta statistik analys och träning av de riskbedömningsverktygen. För Sverige har urvalsstorleken på cirka 260 bröstcancerpatienter har beräknats baserat på antalet patienter som har diagnostiserats med bröstcancer vid 65 års ålder eller äldre på Karolinska Universitetssjukhuset som finns registrerade i NKBC (enl offentliga anonymiserade data) samt antar patienter i Opti-Train och PREDIX HER2 studie i denna ålderskategori. Utöver detta kommer ytterligare antal patienter i åldern 55-65 kommer att inkluderas från samma källor.

6.3 Hur kommer undersökningsprocedurerna att dokumenteras?

Inte relevant.

6.4 Hur kommer insamlad data att hanteras och förvaras?

Data kommer att kodas och kodnyckel kommer att sparas på Cancerstudieenheten på Karolinska Universitetssjukhuset i Solna. Medverkande forskare, data manager och medlemmar i studiegruppen kan få tillgång till data. Som tidigare beskrivet är detta del av en stor europeisk projekt. Data kommer därför att delas anonymiserade med andra forskare utanför Sverige men inom EU.

7.1 Vilka risker kan ett deltagande medföra för de forskningspersoner som ingår i forskningsprojektet?

Vi förväntar oss inte några risker eller nytta för forskningspersoner eftersom vi avser använda material från tester och undersökningar som redan finns insamlade. Data kommer att sparas och

analyseras avidentifierade och därmed förväntar vi oss inte heller några risker för individer vars information kommer att inkluderas i studien.

7.2 Vilken nytta kan ett deltagande medföra för de forskningspersoner som ingår i forskningsprojektet?

Pga studiens retrospektiva karaktär vi förväntar oss inte någon direkt nytta för deltagare. Dock kan resultatet gagna framtida patienter samt även eventuellt aktuella deltagare vid fall av återfall.

7.3 Gör en värdering av förhållandet mellan riskerna och nyttan av projektet.

Samma som punkt 7.1

7.4 Beskriv hur projektet har utformats för att minimera riskerna för forskningspersonerna.

Samma som punkt 7.1. Inga data eller undersökningar planeras för den retrospektiva studien och insamlade data och undersökningsresultat kommer att pseudoanonymiseras hos forskargruppen på Karolinska och ska anonymiseras när de delas med Consortiumet för att analyseras.

7.5 Identifiera och precisera om eventuella etiska problem (nackdelar/fördelar) kan uppstå i ett vidare perspektiv genom forskningsprojektet.

Studiens retrospektiva karaktär gör att vi förväntar oss inte några etiska problem.

8.1 Hur görs urvalet av forskningspersoner?

Kvinnor som har diagnostiserats med bröstcancer mellan 2012 och 2020 och var 55 år eller äldre vid diagnos som identifieras i NKBC eller som ingått i tOpi-Train och/eller PREDIX HER2 studien.

8.2 Hur många forskningspersoner kommer att inkluderas i forskningsprojektet?

Vi förväntar oss ca 260 individer utifrån information som finns på NBKC websida och populationen som hade inkluderats i studierna.

8.3 Vilka urvalskriterier kommer att användas för inklusion?

Inklusionskriterier:

• Kvinnor ≥ 55 år med diagnosen tidig bröstcancer som genomgått neoadjuvant och/eller adjuvant kemoterapi med regimer som innehåller antracykliner.
• Kvinnor ≥ 55 år med nydiagnostiserad metastatisk bröstcancer som kemoterapi, oavsett typ.
• Kvinnor ≥ 55 år med diagnosen HER2-positiv tidig bröstcancer som genomgått neoadjuvant och/eller adjuvant behandling med anti-HER2-terapi.

• Kvinnor ≥ 55 år med HER2-positiv metastaserande bröstcancer som genomgick första linjensbehandling med anti-HER2-medel.

8.4 Vilka urvalskriterier kommer att användas för exklusion?

Ålder <55 år.

8.5 Ange relationen mellan forskare och forskningspersonerna.

Ingen känd relation men forskningspersonerna kan ha eller ha haft en patient-läkare eller patient-vårdare relation med forskarna.

8.6 Vilket försäkringsskydd finns för de forskningspersoner som deltar i forskningsprojektet?

Ej aktuelt

8.7 Redogör för den beredskap som finns för att hantera oväntade bifynd eller händelser under forskningsprocessen som kan äventyra forskningspersonernas säkerhet.

Vi förväntar oss inga bifynd som kan direkt påverka forskningspersonerna då data och undersökningsresultat som ska inhämtas har redan varit känd. Ingen ny information för enskilda individer förväntas från denna analys.

8.8 Kommer ekonomisk ersättning eller andra förmåner betalas ut till forskningspersonerna?

Nej

9.1 Kommer forskningspersonerna att informeras om forskningsprojektet och tillfrågas om de vill vara med eller inte?

Nej

9.1.2 [Om Nej 9.1] Motivera varför forskningspersonerna inte ska informeras och tillfrågas.

Med tanke på studiens retrospektiva karaktär samt kodifieringen av data, finns det ingen förväntad risk för patienten. Ett informerat samtycke kommer därför inte att eftersträvas.

9.2 Kommer barn under 18 år att ingå i forskningsprojektet?

Nej

9.3 Kommer forskningspersoner, vars mening på grund av sjukdom, psykisk störning, försvagat hälsotillstånd eller något annat liknande förhållande inte kan inhämtas, att ingå i forskningsprojektet?

Nej

10.1 Kommer projektet att begära ut uppgifter från ett befintligt register?

Ja

10.1.1 [Om Ja 10.1] Ur vilket eller vilka register kommer uppgifterna att begäras?

Nationella Kvalitetsregister för bröstcancer, Regionala Cancercentrum i samverkan

10.1.2 [Om Ja 10.1] Vilka uppgifter kommer att begäras ut och varför?

Patient uppgifter samt patient och tumör karakteristiska kommer att begäras ut. Patient och tumör karakteristiska behövs för att beskriva kohorten samt eftersom vissa patient karakteristiska såsom ålder kan påverka risk för kardiovaskulära sjukdomar och hjärttoxicitet.
Vi kommer även begära personnummer på de identifierade patienter eftersom detta är nödvändigt för att sedan kunna samla in de övriga parametrar som behövs enligt beskrivning på punkt 6.1.

11.1 Finns det relevanta resultat från djurförsök?

Ej aktuellt

12.1 Hur garanteras tillgång till data för forskningshuvudmannen och medverkande forskare?

Huvudansvarig forskare, medverkande forskare och personal involverad i projektet, såsom data manager, ska ha tillgång till data. Huvudansvarig forskare ansvarar för att tillgång ges enbart till behöriga.

12.2 Vem eller vilka ansvarar för databearbetning och skriftlig redovisning av resultaten?

Forskarna som deltar i Consortiumet CardioCare och ffa koordinerande center i Ioannina ansvarar för databearbetning och redovisning av resultaten.

12.3 Hur och när planeras resultaten att offentliggöras?

Resultaten ska kommuniceras i internationella kongresser samt i vetenskapliga tidskriften.

12.4 På vilket sätt garanteras forskningspersonernas rätt till integritet när materialet offentliggörs?

Data ska bearbetas anonymiserade och resultaten ska redovisas gruppvis och anonymiserade för att skydda forskningspersonernas identitet. Inga icke-anonymiserade data ska lämnas till personer utanför forskningsgruppen på Karolinska Universitetssjukhuset.

13.1 Redovisa eventuella ekonomiska överenskommelser med bidragsgivare eller andra finansiärer (namn och belopp).

Multicentre studie finansierad av EU-Horizon 2020 anslag. Karolinska Universitetssjukhuset har fått 430 000 euro för kostnader relaterade till hela projektet (både retrospektiv och prospektiv del), såsom lönekostnader, material, osv. Inga individer i forskargruppen har enskilda ekonomiska överenskommelser med bidragsgivare utan avser anslag finansiering.

13.2 Redovisa forskningshuvudmannens, huvudansvarig forskares och medverkande forskares egna ekonomiska intressen.

Inga finns att rapportera

14.1 Kommer biologiskt material från människor att nyinsamlas för projektet?

Nej

14.2 Planerar projektet att använda biologiskt material från människor från en eller flera befintliga provsamlingar?

Nej

Forskningsplan

Den sammanfattande beskrivningen av forskningsprojektet ska förstås av fackmän. Den kan lämpligen utformas enligt följande:
Vetenskaplig frågeställning: En redogörelse för det övergripande syftet med det föreslagna forskningsprojektet samt specifika mål (primära och sekundära frågeställningar).
Områdesöversikt: Ge ett sammandrag av egna och andras forskning och tidigare resultat inom forskningsområdet. Översikten ska tydliggöra det aktuella projektets relevans. Nyckelreferenser ska anges.
Projektbeskrivning: Gör en sammanfattning av projektets/motsvarande uppläggning. Urval av forskningspersoner, procedurer, metoder med mera ska tydligt redovisas. Det ska framgå hur metoder, urval och procedurer kan ge svar på de specifika frågeställningarna. Om flera delprojekt avses anges sekvens för genomförande och på vilket sätt ett efterföljande delprojekts uppläggning kan bero av resultaten av ett föregående.
Betydelse: Ge en kortfattad redogörelse för projektets betydelse för forskningsområdet.

Preliminära resultat: Kan i förekommande fall anges.
SKA VARA PÅ SVENSKA ELLER ENGELSKA.

Study_description.pdf
9.59MB

RetrospectiveStudy_Protocol_CARDIOCARE_08.12.021_KSBC.pdf
248.73KB

Variabellista

Variabellista bör bifogas ansökan om data ska begäras ut från befintliga register.
SKA VARA PÅ SVENSKA.

Variabel_lista_NKBC.pdf
84.4KB

CV för ansvarig forskare

Bifoga CV för ansvarig forskare.
I undantagsfall kan icke disputerad forskare godtas om annan medverkande disputerad forskare uttalat att forskningen sker under aktivt överinseende av denne. Uttalandet ska vara skriftligt och bifogas. CV för den disputerade ska även bifogas.
SKA VARA PÅ SVENSKA ELLER ENGELSKA.

CV_Andri_Papakonstantinou_eng.pdf
88.81KB

Kompletterande bilageförteckning

1. Study description: Projektbeskrivning för hela projektet CardioCare.
2. RetrospectiveStudy Protocol_CardioCare: Projektbeskrivning för retrospektiva delen av projektet och det som berör Sverige och Karolinska Universitetssjukhuset.
3. Variabel lista NKBC: Lista med variabler/data som ska inhämtas från NKBC

I och med att ansökan undertecknas intygar du som är ansvarig forskare samt du som är behörig företrädare följande;

- Att den information som lämnas i ansökan om etikprövning och samtliga medföljande bilagor är riktig och fullständig.
- Att verksamhetsansvariga i samtliga medverkande verksamheter är informerade om forskningsprojektets innehåll och utförande och att de har samtyckt till att delta i studien.
- Att du säkerställt att det i samtliga medverkande verksamheter finns resurser som garanterar forskningspersonernas säkerhet och integritet vid genomförandet av den forskning som beskrivs i ansökan.

- Att ansvarig forskare ges rätt att företräda huvudmannen i alla framtida kontakter med Etikprövningsmyndigheten som rör detta forskningsprojekt samt ansöka om ändringar i forskningsprojektet.
- Att du tagit del av Etikprövningsmyndighetens information om hantering av personuppgifter på myndighetens webbplats.

Behörig företrädare för forskningshuvudmannen

Robert Olof Bränström

Signatur behörig företrädare

Signatur-behorig-foretradare.pdf
30.76KB

Är behörig företrädare ordinarie eller tillförordnad?

Ordinarie företrädare

Signatur huvudansvarig forskare

Signatur-huvudansvarig-forskare.pdf
29.69KB

Signatur-huvudansvarig-forskare.pdf
30.18KB

Signatur-huvudansvarig-forskare.pdf
30.22KB

Beslut och handlingar från Etikprövningsmyndigheten

Beslutsbrev och andra handlingar från Etikprövningsmyndigheten i relation till denna ansökan

2021-06616-01_Avgiftsavisering.pdf
35.88KB

2021-06616-01_Begaran_om_administrativt_tillagg.pdf
41.67KB

2021-06616-01_Begaran_om_administrativt_tillagg.pdf
36.39KB

Nationellt Kvalitetsregister för Bröstcancer (NKBC)

Variabellista för data som planeras insamlas i CardioCare

Diagnosdatum

Diagnostiserande sjukhus

Screeningupptäckt eller symptom

Kön (bara kvinnor ska inkluderas)

Personnummer

Operation: typ av operation

Sentinel Node Operation

Axill Utrymning

Bröstbevarande operation

Bröstrekonstruktion

Neoadjuvant behandling (ja, nej, vilken-om tillgänglig)

Adjuvant behandling (ja, nej, vilken-om tillgänglig)

Cytostatika

Endokrin behandling

Strålbehandling

AntiHER2 behandling

ER-status (Östrogenreceptor status)

PgR-status (Progesteronreceptor status)

HER2 –status

Ki67 % (Markör för cellproliferation

Subtyp av bröstcancer

TNM – (System för stadieindelning av cancer, som försöker klarlägga utbredningen av patientens tumörsjukdom. Parametern T relaterar till storlek och utbredning av primärtumören, N till utbredning i regionala lymfkörtlar och M till förekomst av fjärrmetastaser.)

Tumörgrad (histologisk grad)

Överlevnadsdata

CURRICULUM VITAE

Andri (Antroula) Papakonstantinou, MD, MSc, PhD.

Andri.papakonstantinou@ki.se

Education

- April 2020, PhD Karolinska Institutet, Title "Studies of side effects related to adjuvant breast cancer regimens with focus on chemotherapy"
- 2010 - 2014: MSc Clinical Trials awarded with Distinction, University of London, International Programmes
- April 2013, board certified Clinical Oncology, Sweden
- 2001-2007: Aristotle University Medical School, Thessaloniki, Greece
- December 2007, licence to practice medicine (läkarlegitimation) in Sweden

Academic achievements

- ESMO Research Fellowship 2020, for the Project "Impact of microbiota on breast cancer prognosis and treatment efficacy", ongoing at Vall d´Hebron Institute of Oncology.
- Participant ESMO Leaders Generation Programme 2020-2021
- Recipient of the ESMO Virtual Mentorship Programme 2020 (Mentor Prof Paolo Casali)
- November 2020, ESMO Virtual Advanced Course on Biomarkers for Precision Medicine
- January 2019, selected for the ESMO Translational Research Unit (TRU) visit Institut Jules Bordet
- May 2018, ESMO Preceptorship on AYA malignancies
- 2001-2007, received the "Dr Lenas Loizou Kakkouras Foundation" Scholarship, Cyprus, for all the six years of medical studies.
- August 2007: Research Exchange Program by IFMSA, University of Alexandria, Department of Surgery, Egypt
- July 2006: Professional Exchange Program held by IFMSA, in University of Pecs, Institute of Oncology and Radiotherapy, Hungary
- Fall of 2003: Erasmus student at Karolinska Institute Stockholm, Sweden

Work Experience

- September 2017 – today: In charge of the sarcoma flow, with responsibility for structural

planning including oncology, surgical and orthopedic treatments.

- October 2013 – today: Consultant Clinical Oncology, Section for breast cancer and sarcomas, Karolinska University Hospital, Stockholm.
- April 2013 – September 2013: Consultant Clinical Oncology, Linköping's University Hospital
- March 2008 – April 2013: Residency in Clinical Oncology
- Local and national PI and sub-investigator for various sarcoma and breast cancer trials.
- Founding member of the cardio-oncology group at Karolinska University Hospital

Languages

Native language: **Greek.** Other languages in advanced level: **English**, **Swedish**, **Spanish**

Other related activities

- September 2020, Chairman national guidelines committee for extremity sarcomas
- September 2019, GCP course, Karolinska University Hospital
- Autumn 2019, Co-Director PhD course 3194 "Basic principles in clinical and translational research", Karolinska Institutet, Stockholm
- Autumn 2018, Co-Director PhD course 3103 "Breast cancer research and treatment", Karolinska Institutet, Stockholm
- Member of the working group of the Scandinavian Sarcoma Group (SSG) and ESMO
- Member of the local organizing committee "Onkologidagarna 2013 (National Oncology Conference, Sweden)".
- Teaching activities at Karolinska University Hospital
- Mentoring of residents at Karolinska University Hospital and co-supervised student scientific project

Mobile: 00467 62732847
E-mail: andri.papakonstantinou@ki.se

Signering av etikprövningsansökan

Grundansökan

Forskningshuvudman: Region Stockholm
Projekttitel: CARDIOCARE: Ett interdisciplinärt tillvägagångssätt för omhändertagande av äldre multisjuka patienter med bröstcancerbehandling-relaterad hjärttoxicitet Original titel- CARDIOCARE: AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY

I och med att ansökan undertecknas intygar du som är behörig företrädare följande:

- Att den information som lämnas i ansökan om etikprövning och samtliga medföljande bilagor är riktig och fullständig.
- Att verksamhetsansvariga i samtliga medverkande verksamheter är informerade om forskningsprojektets innehåll och utförande och att de har samtyckt till att delta i studien.
- Att du säkerställt att det i samtliga medverkande verksamheter finns resurser som garanterar forskningspersonernas säkerhet och integritet vid genomförandet av den forskning som beskrivs i ansökan.
- Att ansvarig forskare ges rätt att företräda huvudmannen i alla framtida kontakter med Etikprövningsmyndigheten som rör detta forskningsprojekt samt ansöka om ändringar i forskningsprojektet.
- Att du tagit del av Etikprövningsmyndighetens information om hantering av personuppgifter på myndighetens webbplats.

Behörig företrädare har signerat.

Signerat av Robert Olof Bränström 2021-12-08 19:54:48

Signering av etikprövningsansökan

Grundansökan

Forskningshuvudman: Region Stockholm
Projekttitel: CARDIOCARE: Ett interdisciplinärt tillvägagångssätt för omhändertagande av äldre multisjuka patienter med bröstcancerbehandling-relaterad hjärttoxicitet Original titel- CARDIOCARE: AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY

I och med att ansökan undertecknas intygar du som är ansvarig forskare följande:

- Att den information som lämnas i ansökan om etikprövning och samtliga medföljande bilagor är riktig och fullständig.
- Att verksamhetsansvariga i samtliga medverkande verksamheter är informerade om forskningsprojektets innehåll och utförande och att de har samtyckt till att delta i studien.
- Att du säkerställt att det i samtliga medverkande verksamheter finns resurser som garanterar forskningspersonernas säkerhet och integritet vid genomförandet av den forskning som beskrivs i ansökan.
- Att du tagit del av Etikprövningsmyndighetens information om hantering av personuppgifter på myndighetens webbplats.

Ansvarig forskare har signerat.

Signerat av Andri Papakonstantinou 2021-12-08 14:07:30

Signering av etikprövningsansökan administrativt tillägg

Grundansökan

Forskningshuvudman: Region Stockholm
Projekttitel: CARDIOCARE: Ett interdisciplinärt tillvägagångssätt för omhändertagande av äldre multisjuka patienter med bröstcancerbehandling-relaterad hjärttoxicitet

I och med att ansökan undertecknas intygar du som är ansvarig forskare samt du följande:

- Att den information som lämnas i ansökan om etikprövning och samtliga medföljande bilagor är riktig och fullständig.
- Att verksamhetsansvariga i samtliga medverkande verksamheter är informerade om forskningsprojektets innehåll och utförande och att de har samtyckt till att delta i studien.
- Att du säkerställt att det i samtliga medverkande verksamheter finns resurser som garanterar forskningspersonernas säkerhet och integritet vid genomförandet av den forskning som beskrivs i ansökan.
- Att du tagit del av Etikprövningsmyndighetens information om hantering av personuppgifter på myndighetens webbplats.

Ansvarig forskare har signerat.

Signerat av ANDRI PAPAKONSTANTINOU (198311176823)
2021-12-21 16:03:04

Signering av etikprövningsansökan administrativt tillägg

Grundansökan

Forskningshuvudman: Region Stockholm
Projekttitel: CARDIOCARE: Ett interdisciplinärt tillvägagångssätt för omhändertagande av äldre multisjuka patienter med bröstcancerbehandling-relaterad hjärttoxicitet

I och med att ansökan undertecknas intygar du som är ansvarig forskare samt du följande:

- Att den information som lämnas i ansökan om etikprövning och samtliga medföljande bilagor är riktig och fullständig.
- Att verksamhetsansvariga i samtliga medverkande verksamheter är informerade om forskningsprojektets innehåll och utförande och att de har samtyckt till att delta i studien.
- Att du säkerställt att det i samtliga medverkande verksamheter finns resurser som garanterar forskningspersonernas säkerhet och integritet vid genomförandet av den forskning som beskrivs i ansökan.
- Att du tagit del av Etikprövningsmyndighetens information om hantering av personuppgifter på myndighetens webbplats.

Ansvarig forskare har signerat.

Signerat av ANDRI PAPAKONSTANTINOU (198311176823)
2021-12-29 21:51:12

Avgiftsavisering

Etikprövningsmyndigheten har tagit emot din ansökan med titel CARDIOCARE: Ett interdisciplinärt tillvägagångssätt för omhändertagande av äldre multisjuka patienter med bröstcancerbehandling-relaterad hjärttoxicitet Original titel- CARDIOCARE: AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY om etikprövning. Ansökan har diarienummer 2021-06616-01 vilket alltid ska anges i framtida kontakter i ärendet.

Avgiften för ansökan, som är 5000 kronor, ska omgående betalas in enligt nedan:

- Inbetalning sker till bankgironummer 406-1107
- Vid inbetalning ska OCR-nummer 2021066160130 anges som referens.
- Inga andra bokstäver eller siffror får anges i raden för referens.

Först när ärendet kompletterats enligt ovan kommer vi att påbörja handläggningen.

Etikprövningsmyndigheten
Telefon: 010 - 475 08 00
Webbplats: www.etikprovning.se

Begäran om administrativt tillägg

2021-12-21

Sökande forskningshuvudman
Region Stockholm

Forskare som genomför projektet
Andri Papakonstantinou

Projekttitel
CARDIOCARE: Ett interdisciplinärt tillvägagångssätt för omhändertagande av äldre multisjuka patienter med bröstcancerbehandling-relaterad hjärttoxicitet Original titel- CARDIOCARE: AN INTERDISCIPLINARY APPROACH FOR THE MANAGEMENT OF THE ELDERLY MULTIMORBID PATIENT WITH BREAST CANCER THERAPY INDUCED CARDIAC TOXICITY

Uppgifter om ansökan
Ansökan inkom till Etikprövningsmyndigheten 2021-12-08.

Etikprövningsmyndigheten begär administrativt tillägg av din ansökan om etikprövning enligt följande:

Hej!

Etikprövningsmyndigheten har tagit emot din komplettering för ansökan om etikprövning. Ansökan har genomgått en administrativ granskning. Granskningen visar att ansökan måste kompletteras enligt följande:

1. Ta bort den engelska delen av titeln för forskningsprojektet i ansökan.

2. Under punkten 1.4.1 har ni endast skrivit flera centra i centrala Europa, alla dessa ska redovisas i detalj. Komplettera med information kring detta.

3. Under punkten 1.9 har ni uppgett att avgiftskategorin är en forskningshuvudman trots ni har uppgett under punkt 1.4 att forskningsstudien har flera forskningshuvudmän. Korrigera detta och beskriv sambandet mellan forskningshuvudmännen för att bestämma avgiftskategori.

4. Under punkten 14.2 har ni kryssat nej på frågan om ni ska samla in biologiskt material för att sen under punkt 14.2.1 uppgett att ni ska samla in vävnad. Korrigera så att dessa två punkter överensstämmer med varandra.

Kompletteringen ska vara myndigheten tillhanda senast 2021-12-28 och ni gör denna i Ethix via ert konto. Först när kompletteringen mottagits kommer vi fortsätta handläggningen av din ansökan.

Frågor kan ställas via e-post till registrator@etikprovning.se

Vänliga hälsningar

Petter Cedergren

Telefon: 010 - 475 08 00

Webbplats: www.etikprovning.se

Begäran sänds till

Ansvarig forskare: Andri Papakonstantinou

Begäran om administrativt tillägg

2021-12-22

Sökande forskningshuvudman
Region Stockholm

Forskare som genomför projektet
Andri Papakonstantinou

Projekttitel
CARDIOCARE: Ett interdisciplinärt tillvägagångssätt för omhändertagande av äldre multisjuka patienter med bröstcancerbehandling-relaterad hjärttoxicitet

Uppgifter om ansökan
Ansökan inkom till Etikprövningsmyndigheten 2021-12-08.

Etikprövningsmyndigheten begär administrativt tillägg av din ansökan om etikprövning enligt följande:

Hej!

Den inkomna reviderade ansökan ska signeras av behörig företrädaren för forskningshuvudmannen.

Med vänliga hälsningar

Tanja Gyldén

Handläggare

Etikprövningsmyndigheten

Begäran sänds till

Ansvarig forskare: Andri Papakonstantinou