Project Code: PNRR-MCNT2-2023-12377934	**Call section:** Malattie Croniche non Trasmissibili (MCnT2) ad alto impatto sui sistemi sanitari
Applicant Institution: Toscana	**Applicant/PI Coordinator:** Guarracino Fabio

1 - General information

Project code: PNRR-MCNT2-2023-12377934

Project topic: E2) Malattie croniche non trasmissibili (MCnT2) ad alto impatto sui sistemi sanitari e socio-assistenziali: innovazione in campo terapeutico

Applicant Institution: Toscana

PI / Coordinator: Guarracino Fabio

Istitution that perform as UO for UO1: Azienda Ospedaliera Universitaria Pisana

Call section: Malattie Croniche non Trasmissibili (MCnT2) ad alto impatto sui sistemi sanitari e socio-assistenziali

Proposal title: Prehabilitation to improve heart Rate variability In surgical cancer patients: a randoMized controllEd trial - PRIME TRIAL

Duration in months: 24

MDC primary: Cardiologia-Pneumologia

MDC secondary: Riabilitazione

Project Classification IRG: Surgical Sciences, Biomedical Imaging, and Bioengineering

Project Classification SS: Surgery, Anesthesiology, and Trauma - SAT

Project Keyword 1: Tissue, organ and systemic injury responses to surgery, trauma, burn, sepsis, hemorrhage, ischemia-reperfusion, or resuscitation, including integrating pathways and signals.

Project Request: **Animals:** [ ] **Humans:** [X] **Clinical trial:** [X]

Project total financing request to the MOH: € 980.000

Free keywords:

Declarations

In case of a Synergy grant application 'Principal Investigator'(PI) means 'corresponding Principal Investigator on behalf of all Principal Investigators', and 'Host Institution' means 'corresponding Host Institution'.

1) The Principal Investigator declares to have the written consent of all participants on their participation and on the content of this proposal, as well as of any researcher mentioned in the proposal as participating in the project (either as other PI, team member or collaborator).	[X]
2) The Principal Investigator declares that the information contained in this proposal is correct and complete.	[X]
3) The Principal Investigator declares that all parts of this proposal comply with ethical principles (including the highest standards of research integrity — as set out, for instance, in the European Code of Conduct for Research Integrity — and including, in particular, avoiding fabrication, falsification, plagiarism or other research misconduct).	[X]
4) The Principal Investigator is only responsible for the correctness of the information relating to his/her own organisation. Each applicant remains responsible for the correctness of the information related to him and declared above.	[X]

Personal data protection

The assessment of your grant application will involve the collection and processing of personal data (such as your name, address and CV), which will be performed pursuant to Regulation (EC) No 45/2001 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data. Unless indicated otherwise, your replies to the questions in this form and any personal data requested are required to assess your grant application in accordance with the specifications of the call for proposals and will be processed solely for that purpose. Details concerning the purposes and means of the processing of your personal data as well as information on how to exercise your rights are available in the privacy statement. Applicants may lodge a complaint about the processing of their personal data with the European Data Protection Supervisor at any time.

Abstract

Cancer patients require chronic management and care. For those individuals living with chronic cancer, a comprehensive approach that acknowledges the inter-disciplinary chronic nature of their condition can help guide appropriate care strategies and support their overall well-being. About 45% of patients diagnosed with cancer have surgery to remove their tumor. Despite the advancements in surgical techniques, anesthesia, and perioperative care, major cancer surgeries still pose a significant challenge with a considerable decline in physiological and functional capacity. Traditionally, efforts have been concentrated on postoperative rehabilitation to enhance recovery. In recent years, prehabilitation, a form of rehabilitation which focuses on improving functional capacity before surgery, has gained attention due to its potential benefits in improving surgical outcomes. However, prehabilitation lacks objective assessment measures to evaluate its effectiveness. Developing validated outcome measures is essential to enhance prehabilitation impact on surgical outcomes and long-term care for cancer patients. Heart rate variability (HRV) is a physiological parameter that measures the variation in time intervals between consecutive heartbeats reflecting the autonomic nervous system activity. HRV is commonly used in sport medicine as a potential marker for assessing performance during training and it can predict physiological recovery after training. HRV can therefore serve as a valuable solution for objective outcome measures in evaluating the effectiveness of prehabilitation for cancer patients, as it provides an objective tool to assess and monitor physiological response to stress, recovery capacity, and autonomic nervous system activity. A multicenter randomized controlled trial will be conducted to assess the impact of a multimodal prehabilitation program on HRV. We will randomize patients aged 18 or older, scheduled for elective major cancer surgery to receive either prehabilitation or standard care. The prehabilitation arm will receive a program involving home-based physical, nutritional, and psychological interventions for at least four weeks. Participants allocated to the control group will receive usual care. Patients will be followed throughout the study using an innovative mobile application, allowing for real-time monitoring and data collection during the prehabilitation program. The study has two primary outcomes: A) to assess the impact of prehabilitation on increasing preoperative HRV in chronic cancer patients undergoing surgery; B) to assess the effect of prehabilitation on length of hospital stay (expressed following the modern "days at home within first 30 days after surgery").

In order to best review your application, do you agree that the above non-confidential proposal title and abstract can be used, without disclosing your identity, when contacting potential reviewers? Yes

2 - Participants & contacts

Project Code: PNRR-MCNT2-2023-12377934 | **Call section:** Malattie Croniche non Trasmissibili (MCnT2) ad alto impatto sui sistemi sanitari

Applicant Institution: Toscana | **Applicant/PI Coordinator:** Guarracino Fabio

Operative Units

Institution that perform as UO	CF Institution	Department / Division / Laboratory	Role in the project	Southern Italy	SSN
1 - Azienda Ospedaliera Universitaria Pisana	01310860505	Anesthesia and Intensive Care - Azienda Ospedaliero Universitaria Pisana	Project coordination and patients recruitment		X
2 - Ospedale San Raffaele	07636600962	Cardiothoracic department	Coordination of the feasibility trial and patients recruitment		X
3 - Azienda Ospedaliero Universitaria Policlinico San Marco di Catania	4721290874	Anesthesia and Intensive Care	Patients recruitment	X	X
4 - Università di Foggia	94045260711	Anesthesia and Intensive Care	Patients recruitment	X	

Principal Research Collaborators

Key Personnel Name	Operative Unit	Role in the project
1 - LANDONI GIOVANNI GUGLIELMO	Ospedale San Raffaele	Project coordination and patients recruitment
2 - SANFILIPPO FILIPPO	Azienda Ospedaliero Universitaria Policlinico San Marco di Catania	Patients recruitment
3 - Cinnella Gilda	Università di Foggia	Patients recruitment
4 - BERTINI PIETRO	Azienda Ospedaliera Universitaria Pisana	Project coordination and patients recruitment
5 - BALDASSARRI RUBIA	Azienda Ospedaliera Universitaria Pisana	Project coordination and patients recruitment
6 Under 40 - Sidoti Anna	Azienda Ospedaliera Universitaria Pisana	Project coordination and patients recruitment
7 Under 40 - Costanzo Diego	Azienda Ospedaliera Universitaria Pisana	Project coordination and patients recruitment

Key Personnel Name	Co-PI	Resp. CE	Resp. Animal	Birth Date	Gender
1 - LANDONI GIOVANNI GUGLIELMO				27/11/1971	M
2 - SANFILIPPO FILIPPO				21/06/1981	M
3 - Cinnella Gilda				22/03/1962	F
4 - BERTINI PIETRO	X			07/05/1981	M
5 - BALDASSARRI RUBIA				28/08/1962	F
6 Under 40 - Sidoti Anna				28/08/1987	F
7 Under 40 - Costanzo Diego				30/12/1987	M

Responsible who requests CE authorization: Guarracino Fabio

Additional research collaborators under 40 to hire

Key Personnel Name	Operative Unit	Birth Date	Gender	Role in the project	Degree	Actual Pos. and Inst.
0 - PADALINO SIMONA	Università di Foggia	11/07/1991	F	Patients recruitment	Specialization in Short Dynamic Psychotherapy	AIL - Italian Association against Leukemia Lymphoma and Myeloma - Psycho-oncologist
1 - Lo Giudice Giulia	Azienda Ospedaliero Universitaria Policlinico San Marco di Catania	31/03/1988	F	Patients recruitment	Master's degree in Business Management	Studio Associato Benza Calcagno Puglisi - Tax Due Dilingence: check fiscal documentio

2.1 Administrative data of participating

Operative Unit Number 1:

Address: Via Paradisa, 2, 56123, Pisa (PI) regione Toscana, Italia
PEC: pec-aoupisana@legalmail.it

Operative Unit Number 2:

Address: Via Olgettina, 60, 20132, Milano (MI) regione Lombardia, Italia
PEC: dir.scientifica@hsr.postecert.it

Operative Unit Number 3:

Address: Via Santa Sofia, 78, 95123, Catania (CT) regione Sicilia, Italia
PEC: dirsan@pec.policlinico.unict.it

Operative Unit Number 4:

Address: Viale Gramsci, 89/91 71122, Foggia (FG) regione Puglia, Italia
PEC: protocollo@cert.unifg.it

Operative Unit Number 5 (self financing):

Address: -
PEC: -

2.2 Principal Investigator (PI) Profile

Last Name: Guarracino
First Name: Fabio
Last name at birth:
Gender: M

Title: Principal investigator
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 26/02/1964
Place of Birth: Napoli

Official H index (Scopus or Web of Science): 33.0

Scopus Author Id:55411547300 **ORCID ID:**0000-0002-2562-0199 **RESEARCH ID:**DWR-8366-2022

Contact address

Current organisation name: Azienda Ospedaliera Universitaria Pisana
Current Department / Faculty / Institute / Laboratory name: Anesthesia and Intensive Care - Azienda Ospedaliero Universitaria Pisana

Street: Azienda Ospedaliero Universitaria Pisana, Via Paradisa 2
Postcode / Cedex: 56123 **Town:** Pisa
Phone:+393281652528 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Padova	Specialization / Specializzazione	Cardiology	2000	2004
University of Padova	Specialization / Specializzazione	Anesthesia and Intensive Care	1988	1992
University of Padova	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	1982	1988

Personal Statement:

The project aims to establish the impact of multimodal prehabilitation on heart rate variability and length of hospital stay in chronic cancer patients undergoing surgery. The project aims to determine whether a structured preoperative intervention can lead to improvements in heart rate variability (which is an important indicator of autonomic nervous system function) and to reduction in length of hospital stay. As principal investigator of this study I will oversee the entire research process. My responsibilities will be to coordinate the research teams across other participating hospitals involved in the trial and patients recruitment. Furthermore, I will play a crucial role in organizing investigator meetings and I will be in charge for ethics committee authorization.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Azienda Ospedaliero Universitaria Pisana	Integrated Activity Department (DAI) of Anesthesia and Intensive Care	Pisa, Italy	Director	2016	2023
Azienda Ospedaliero Universitaria Pisana	Anesthesia and Intensive Care Unit	Pisa, Italy	Department Director	2011	2016
Azienda Ospedaliero Universitaria Pisana	Intensive Care Unit	Pisa, Italy	Interdipartimental Coordinator	2008	2011
Azienda Ospedaliero Universitaria Pisana	Cardiothoracic and Vascular Anesthesia and Intensive Care	Pisa, Italy	Director	2002	2023
Hospital of Mestre	Anesthesia and Intensive Care Unit	Mestre, Italy	Senion Anesthesiologist	1996	2002
IRCCS San Raffaele Scientific Institute	Anesthesia and Intensive Care Unit	Milano, Italy	Anesthesiologist	1994	1996
Hospital of Vicenza	Anesthesia and Intensive Care Unit	Vicenza, Italy	Anesthesiologist	1992	1994

Other awards and honors

- Past President EACTAIC 2022
- Board member of SIAARTI - 2016-2018
- Member of the editorial board of several journals
- Active member of ESA, ESICM, EACTA, SCA, EACVI, SIAARTI
- Invited speaker at >100 international meetings and congresses
- Author of >240 publications

Other CV informations

- Reviewer for several scientific journals in the field of anesthesia and resuscitation, cardiology and cardiac surgery
- Author of several chapters in italian and foreing volumes
- Author of 4 volumes published by Elsevier:
  Transesophageal echocardiography in critical care area (2007)
  Hemodynamic monitoring in critical care area (2009)
  Intensive Care in cardiovascular surgery (2011)
  Echocardiography in critical area (2012)

Selected peer-reviewed publications of the PI valid for minimum expertise level

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Venovenous Extracorporeal Membrane Oxygenation in Awake Non-Intubated Patients With COVID-19 ARDS at High Risk for Barotrauma	Article	2975-2982	36	2022	10.1053/j.jvca.2022.03.011	35537972	6	L
Landiolol for managing atrial fibrillation in post-cardiac surgery	Article	A4-A9	20	2021	10.1093/eurheartj/sux038	NOT_FOUND	10	L
Vasopressor Therapy in Cardiac Surgery - An Expert' Consensus Statement	Article	1018-1029	35	2021	10.1053/j.jvca.2020.11.032	33334651	20	F

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Right Ventricular Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis	Review	3319-3324	35	2021	10.1053/j.jvca.2021.04.008	33980426	26	L
Short-term treatments for acute cardiac care: Inotropes and inodilators	Article	D3-D11	22	2020	10.1093/EURHEARTJ/SUAA090	NOT_FOUND	4	F
Heterogeneity of Cardiovascular Response to Standardized Sepsis Resuscitation	Review	NOT_FOUND	24	2020	10.1186/s13054-020-2779-9	32204718	4	F
Levosimendan to facilitate weaning from cardiorespiratory support in critically ill patients: Current evidence and future directions	Review	645-651	86	2020	10.23736/S0375-9393.20.14219-6	32013333	5	L
How to assess ventriculoarterial coupling in sepsis	Review	313-318	26	2020	10.1097/MCC.0000000000000721	32348096	6	L
Thoracic Anesthesia of Patients With Suspected or Confirmed 2019 Novel Coronavirus Infection: Preliminary Recommendations for Airway Management by the European Association of Cardiothoracic Anaesthesiology Thoracic Subspecialty Committee	Article	2315-2327	34	2020	10.1053/j.jvca.2020.03.059	32414544	36	L
Evaluation of ventriculo-arterial coupling in ST elevation myocardial infarction with left ventricular dysfunction treated with levosimendan	Article	1-4	288	2019	10.1016/j.ijcard.2019.04.052	31056414	6	L
Cardiovascular determinants of resuscitation from sepsis and septic shock	Article	NOT_FOUND	23	2019	10.1186/s13054-019-2414-9	30987647	38	F
Use of levosimendan in cardiac surgery: An update after the LEVO-CTS, CHEETAH, and LICORN trials in the light of clinical practice	Article	1-9	71	2018	10.1097/FJC.0000000000000551	29076887	40	F
Novel applications of bedside monitoring to plumb patient hemodynamic state and response to therapy	Review	858-864	84	2018	10.23736/S0375-9393.18.12212-7	29338148	4	F
Sepsis after Cardiac Surgery: From Pathophysiology to Management	Review	773-780	30	2016	10.1053/j.jvca.2015.11.009	26947713	12	L
Recent developments in the management of persistent hypoxemia under veno-venous ECMO	Article	508-510	41	2015	10.1007/s00134-014-3579-y	25447805	21	L
Revised ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management. Implications for preoperative clinical evaluation	Review	226-233	81	2015	NOT_FOUND	25384693	25	F
Transesophageal echocardiography during MitraClip® procedure	Article	1188-1196	118	2014	10.1213/ANE.0000000000000215	24842173	33	F
Esmolol administration in patients with VV ECMO: Why not?	Letter with Data	NOT_FOUND	27	2013	10.1053/j.jvca.2012.12.019	23735468	8	L
Non invasive evaluation of cardiomechanics in patients undergoing MitrClip procedure	Article	NOT_FOUND	11	2013	10.1186/1476-7120-11-13	23642140	10	F
Noninvasive ventilation practice in cardiac surgery patients: Insights from a european survey	Letter with Data	e63-e65	27	2013	10.1053/j.jvca.2013.04.005	24054201	15	F

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

Project Code: PNRR-MCNT2-2023-12377934 **Call section:** Malattie Croniche non Trasmissibili (MCnT2) ad alto impatto sui sistemi sanitari

Applicant Institution: Toscana **Applicant/PI Coordinator:** Guarracino Fabio

** Autocertificated

Selected peer-reviewed publications of the PI for the evaluation CV

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**
Lung, Heart, Vascular, and Diaphragm Ultrasound Examination of COVID-19 Patients: A Comprehensive Approach	Review	1866-1874	35	2021	10.1053/j.jvca.2020.06.013	32624431	41
Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe	Article	412-425	5	2017	10.1016/S2213-2600(17)30116-9	28363725	382
Perioperative and periprocedural airway management and respiratory safety for the obese patient: 2016 SIAARTI Consensus	Review	1314-1335	82	2016	NOT_FOUND	27759743	71
Heart rate reduction with esmolol is associated with improved arterial elastance in patients with septic shock: a prospective observational study	Article	1528-1534	42	2016	10.1007/s00134-016-4351-2	27101380	84
Levosimendan beyond inotropy and acute heart failure: Evidence of pleiotropic effects on the heart and other organs: An expert panel position paper	Review	303-312	222	2016	10.1016/j.ijcard.2016.07.202	27498374	84
Preoperative and perioperative use of levosimendan in cardiac surgery: European expert opinion	Review	323-336	184	2015	10.1016/j.ijcard.2015.02.022	25734940	71
International evidence-based recommendations for focused cardiac ultrasound	Article	683.e1-683.e33	27	2014	10.1016/j.echo.2014.05.001	24951446	377
Jugular vein distensibility predicts fluid responsiveness in septic patients	Article	NOT_FOUND	18	2014	10.1186/s13054-014-0647-1	25475099	51
Complications of non-invasive ventilation techniques: A comprehensive qualitative review of randomized trials	Review	896-914	110	2013	10.1093/bja/aet070	NOT_FOUND	200
Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: A randomized clinical trial	Article	1683-1691	310	2013	10.1001/jama.2013.278477	24108526	472

** Autocertificated

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
European Union - Ministry of Health - PNRR 2022 M6/C_CALL	IRCCS San Raffaele Scientific Institute	2022	MAcklin effect, quantitative imaging analysis and CytoKine profiling to predict Lung frailty IN ARDS (MACKLIN ARDS) - PNRR-MAD-2022-12376796	Collaborator	980.000,00	https://www.salute.gov.it/imgs/C_17_bandi_295_3_file.pdf
Ministry of Health	IRCCS San Raffaele Scientific Institute	2018	Acute normovolemic hemodilution in high-risk cardiac surgery patients. A multicenter, randomized trial	Collaborator	450.000,00	http://www.ministerosalute.it/imgs/C_17_pagineAree_5127_listaFile_itemName_7_file.pdf

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
AIFA	Fondazione Centro San Raffaele	2012	Continuous infusion versus intermittent administration of meropenem in critically ill patients. A multicenter randomized double blind trial	Collaborator	738.478,00	https://www.aifa.gov.it/documents/20142/629739/BANDO_AIFA_2012_21.03.2017.pdf

2.3 CO-PI Profile

Last Name: BERTINI
First Name: PIETRO
Last name at birth: Bertini
Gender: M

Title: Project coordination and patients recruitment
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 07/05/1981
Place of Birth: Livorno

Official H index (Scopus or Web of Science): 16.0

Scopus Author Id:35263618300 **ORCID ID:**0000-0002-3878-044X **RESEARCH ID:**H-9910-2019

Contact address

Current organisation name: Azienda Ospedaliera Universitaria Pisana
Current Department / Faculty / Institute / Laboratory name: Anesthesia and Intensive Care - Azienda Ospedaliero Universitaria Pisana

Street: Azienda Ospedaliero Universitaria Pisana - Via Paradisa 2
Postcode / Cedex: 57128 **Town:** Pisa
Phone:+393806820997 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Pisa	PhD	Clinical pathophysiology	2013	2017
University of Pisa	Specialization / Specializzazione	Anesthesia and Intensive Care	2008	2012
University of Pisa	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	2001	2007

Personal Statement:

As CO-PI, I am committed to assisting the project principal investigator and making valuable contributions to the planning and development of the study. I contributed to collecting preliminary data that will be used in this study. Drawing upon my extensive experience in app development, I am well-equipped to contribute my expertise and insights to enhance the project. I firmly believe that this study is characterized by exceptional quality and innovation, with the potential to significantly improve clinically relevant outcomes for cancer patients undergoing surgery, while also contributing significantly to the existing knowledge on prehabilitation.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Azienda Ospedaliero Universitaria Pisana	Department of Anesthesia and Critical Care Medicine	Pisa, Italy	Consultant, Staff	2015	2023
Royal Brompton Hospital	Cardiothoracic Anaesthesia and Critcal Care	London, UK	Local Consultant	2017	2017
Azienda Ospedaliera Toscana Nord Ovest	Department of Anesthesia and Critical Care Medicine	Portoferraio, Livorno, Italy	Consultant, Staff	2014	2015
Azienda Ospedaliera Toscana Nord Ovest	Prehospital Emergency Medicine	Livorno, Italy	Emergency Physician	2012	2013

Other awards and honors

- Author/co-author of more than 100 peer reviewed scientific articles, book chapters and medical software for mobile devices such as iElastance, iGuyton, iCPAP, Procure, TEE Report and TEE Views.
- ITACTA (Italian Association of Cardiothoracic Anesthesiologists) - Board Member in charge of Education and Training Courses, Basic Certification in Transesophageal Echocardiography Course co-Director

Other CV informations

-Member of:
SIAARTI (Italian Society of Anesthesia, Analgesia and Intensive Care Medicine)
EACTAIC (Italian Association of Cardiothoracic Aaesthesiologists)
ELSO (Extracorporeal Life Support Organization)
ESAIC (European Society of Anesthesia)
ASE (American Society of Echocardiography)
-Editor for:
Austin Anesthesiology
Clinical Anesthesia and Pain Management
Advances in Critical Care Medicine
Journal of Anesthesiology and Research
Frontiers Intensive Care Medicine and Anesthesiology
-Peer reviewer for 17 international journals
-Certifications:
European Certification in Adult Transesophageal Echocardiography (EACTA/EACVI)
Licensed as Full Professor of Anesthesia and Critical Care (Italian Ministry of University and Education)2023-2030
GMC Registered Specialist with Full License to Practice

Selected peer-reviewed publications of the Co-PI valid for minimum expertise level

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
The anesthetic management and the role of extracorporeal membrane oxygenation for giant mediastinal tumor surgery	Review	NOT_FOUND	7	2023	10.21037/med-22-35	36926288	0	F
Levosimendan's ability on veno-arterial extracorporeal membrane oxygenation weaning: Evidence says yes!	Letter with Data	193-194	46	2023	10.1177/0391398822114 5502	36726212	0	C

Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Regional Cerebral Oxygen Saturation to Predict Favorable Outcome in Extracorporeal Cardiopulmonary Resuscitation: A Systematic Review and Meta-Analysis	Review	NOT_FOUND	NOT_FOUND	2023	10.1053/j.jvca.2023.01.007	36759264	1	F
ECMO in COVID-19 Patients: A Systematic Review and Meta-analysis	Review	2700-2706	36	2021	10.1053/j.jvca.2021.11.006	34906383	17	F
Preventing Severe Acute Respiratory Syndrome Coronavirus-2 Exhalation Upon Tracheal Extubation in the Intensive Care Unit: A Case Series	Article	e01466	15	2021	10.1213/XAA.0000000000001466	34018993	0	L
Pathophysiology of cardiogenic shock	Review	409-415	27	2021	10.1097/MCC.0000000000000853	34039874	3	F
Percutaneous tracheostomy in COVID-19 critically ill patients: Experience from 30 consecutive procedures	Article	135-140	25	2021	10.1055/s-0040-1718528	33552294	4	F
Improved diagnosis of pulmonary embolism causing cardiac arrest by combined endobronchial ultrasound and echocardiography	Article	NOT_FOUND	18	2020	10.1186/s12947-020-00208-z	32631355	1	F
Editorial: Anticoagulation in extracorporeal membrane oxygenation: Still a challenge	Editorial	7-8	86	2020	10.23736/S0375-9393.19.14265-4	31820880	2	F
Xenon: Towards a tailored anesthetic approach?	Editorial	13-14	85	2019	10.23736/S0375-9393.18.13303-7	30394076	1	F
Dynamic indices of preload and fluid responsiveness: Some certainty in the midst of the uncertain	Editorial	460-461	85	2019	10.23736/S0375-9393.19.13590-0	30762332	1	L
Septic Shock and the Heart	Review	165-173	9	2019	10.1007/s40140-019-00322-3	NOT_FOUND	3	F
Sugammadex: Hunting for new side effects?	Editorial	150-151	84	2018	10.23736/S0375-9393.17.12423-5	29160660	1	F
Heart rate control or tailored heart rate to improve ventriculo-arterial coupling in heart failure?	Letter without Data	171	265	2018	10.1016/j.ijcard.2018.03.073	29885683	1	L
Turning sedation into comfort analgesia: Another skill to learn for the intensivist	Editorial	244-245	83	2017	10.23736/S0375-9393.16.11716-X	27735884	1	F
To ICU or not to ICU: Tailoring postoperative care in the face of reduced resources and increased morbidity	Editorial	134-135	83	2017	10.23736/S0375-9393.16.11803-6	27982556	2	L
Use of echocardiography in critically ill patients: The intensivist's point of view	Editorial	341-343	16	2015	NOT_FOUND	26156695	1	L
Perioperative non-invasive estimation of left ventricular elastance (Ees) is no longer a challenge; It is a reality	Letter without Data	578	112	2014	10.1093/bja/aeu023	24535511	1	F
Reversing severe dilutional coagulopathy: Towards appropriate management and one more nail in the starches' coffin	Editorial	869-870	80	2014	NOT_FOUND	24463945	1	F
Beta-adrenergic antagonists improve oxygen saturation in acute pulmonary edema: A case series in the prehospital setting	Conference Paper	421-423	17	2013	10.3109/10903127.2013.785621	23607890	1	F

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

Project Code: PNRR-MCNT2-2023-12377934	**Call section:** Malattie Croniche non Trasmissibili (MCnT2) ad alto impatto sui sistemi sanitari
Applicant Institution: Toscana	**Applicant/PI Coordinator:** Guarracino Fabio

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
-	-	-	-	Collaborator	0,00	-

2.3 Research Collaborators n. 1

Last Name: LANDONI
First Name: GIOVANNI GUGLIELMO

Last name at birth:
Gender: M

Title: Project coordination and patients recruitment
Nationality: Italia
Date of birth: 27/11/1971

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: milano

Official H index (Scopus or Web of Science): 57.0

Scopus Author Id:7003479273 **ORCID ID:**0000-0002-8594-5980 **RESEARCH ID:**AAH-1881-2019

Contact address

Current organisation name: Ospedale San Raffaele
Current Department / Faculty / Institute / Laboratory name: Cardiothoracic department
Street: Via Olgettina 60
Postcode / Cedex: 20132
Town: milano
Phone:+393472520801
Phone 2: 3472520801

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Milan	Specialization / Specializzazione	Anesthesia and Intensive Care	1996	2000
University of Milan	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	1990	1996

Personal Statement:
As an active member of the research team, I will lend my full support to the project principal investigator, contributing significantly to the meticulous planning and development of the study. Furthermore, I will take on the responsibility of supervising the research team within my institution, actively enrolling patients and conducting study procedures. The exceptional quality and innovative approach of this study are poised to make a transformative impact on the management and clinical outcomes of cancer patients undergoing surgery.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
IRCCS San Raffaele Scientific Institute	Anesthesia and Intensive Care	Milan, Italy	Full Professor	2022	2023
IRCCS San Raffaele Scientific Institute	Scientific Directorate	Milan, Italy	Director Center for Intensive Care and Anesthesiology	2020	2023
Vita-Salute San Raffaele University	Anesthesia and Intensive Care	Milano, Italy	Associate Professor	2013	2022
IRCCS San Raffaele Scientific Institute	Anesthesia and Intensive Care	Milano, Italy	Head of Research	2006	2023
IRCCS San Raffaele Scientific Institute	Anesthesia and Intensive Care	Milano, Italy	Intensive Care specialist and Anesthesiologists (full time physician)	2000	2023
SIAARTI (Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva)	Research	Rome, Italy	Head Clinical Research Committee	2019	2023
Universidad CES	Anesthesia and Intensive Care	Medellín, Colombia	Visiting Professor	2016	2017
EACTA (European Association of Cardiothoracic Anesthesiology)	Cardiothoracic and Vascular Anesthesia	Vienna, Austria	Italian member of the Representative Council of EACTA	2012	2017
AIFA (Agenzia Italiana del Farmaco)	Technical Scientific Commitee (CTS)	Rome, Italy	Member of the CTS	2009	2012
ITACTA (Italian Association of Cardiothoracic Anesthesiologists)	CardioThoracic and Vascular Anesthesia	Milan, Italy	Vice President	2007	2011

Other awards and honors

-Ad hoc reviewer for >90 peer reviewed international journals including NEJM, JAMA, and Lancet
-Lectured lessons in > 100 international congresses in 28 countries
-External Reviewer for 10 International Funding Agencies
-Filed 6 patent applications
-Member of the Editorial Board of 9 international Journals
-Participated to 35 RCT as study coordinator and published 670 scientific papers in indexed Journals
-2019-2021 Head of the SIAARTI Clinical Research Committee
-Wrote 4 books for Springer

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
European Union - Ministry of Health - PNRR 2022 M6/C2_CALL	IRCCS San Raffaele Scientific Institute	2022	A new portable device for PRE-hospital non-invasive VENTilatory support in acute respiratory failure (PREVENT)	Coordinator	980.000,00	https://www.salute.gov.it/imgs/C_17_bandi_295_1_file.pdf
Fondazione Cariplo	IRCCS San Raffaele Scientific Institute	2022	Long-term COVID in Regione Lombardia (PI Prof Alessandro Rambaldi)	Collaborator	149.484,00	Rif 2021-4497

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
European Commission H2020 Programme	Politecnico di Milano	2020	H2020-ICT-2020-2 - ARTERY - Autonomous Robotics for Transcatheter dEliveRy sYstems	Collaborator	3.044.437,50	https://cordis.europa.eu/project/id/101017140/it
Canadian Institutes of Health Research	PHRI	2020	VISION Cardiac Surgery - ECG Evaluation Sub-Study - Fund expressed in Canadian Dollars	Collaborator	534.839,00	-
Ministry of Health	IRCCS San Raffaele Scientific Institute	2020	Clinical and biological characterization of patients with COVID-19 - COVID2020-12371617	Collaborator	715.301,00	https://www.salute.gov.it/imgs/C_17_bandi_216_3_file.pdf
Canadian Institutes of Health Research	PHRI - Population health Resarch Institute	2019	Colchicine for the prevention of perioperative atrial fibrillation (COP-AF)trial - Fund expressed in Canadian dollars	Collaborator	1.981.350,00	-
Ministry of Health - Ricerca Finalizzata	IRCCS San Raffaele Scientific Institute	2018	Acute normovolemic hemodilution in high-risk cardiac surgery patients. A multicenter, randomized trial.	Collaborator	450.000,00	https://www.salute.gov.it/imgs/C_17_paginaAree_5127_listaFile_itemName_3_file.pdf
Ministry of Health - Ricerca Finalizzata	IRCCS San Raffaele Scientific Institute	2016	Intravenous amino acid therapy for kidney protection in cardiac surgery: a multicentre randomised blinded placebo controlled clinical trial - PROTection	Coordinator	434.025,50	https://www.salute.gov.it/imgs/C_17_bandi_135_listaFile_itemName_9_file.pdf
CCM (National Centre for Disease Prevention and Control)	IRCCS San Raffaele Scientific Institute	2012	Risk analysis model for the control of nosocomial infections in the ICU	Collaborator	44.000,00	-
EACTA (European Association of Cardiothoracic Anaesthesiology	IRCCS San Raffaele Scientific Institute	2010	Levosimendan to reduce mortality in high risk cardiac surgery patients. A randomized controlled trial	Coordinator	10.000,00	-

2.4 Research Collaborators n. 2

Last Name: SANFILIPPO
First Name: FILIPPO
Last name at birth:
Gender: M

Title: Patients recruitment
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 21/06/1981
Place of Birth: Catania

Official H index (Scopus or Web of Science): 22.0

Scopus Author Id:57210196072 **ORCID ID:**0000-0001-5144-0776 **RESEARCH ID:**HGT-5406-2022

Contact address

Current organisation name: Azienda Ospedaliero Universitaria Policlinico San Marco di Catania
Current Department / Faculty / Institute / Laboratory name: Anesthesia and Intensive Care
Street: via Santa Sofia n 78
Postcode / Cedex: 95100
Town: Catania
Phone:+393289178766
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Catania	PhD	Experimental and Clinical Pharmacology	2010	2013
University of Catania	Specialization / Specializzazione	Anesthesia and Intensive Care	2005	2009
University of Catania	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and surgery	1999	2005

Personal Statement:
As a collaborator of the research team, I will offer unwavering support to the project principal investigator, making valuable contributions to the comprehensive planning and development of the study. Additionally, I will take on the task of supervising the research team within my institution, actively enrolling patients and facilitating study procedures. With its exceptional quality and innovative approach, this study has the potential to significantly enhance the management and clinically relevant outcomes for cancer patients undergoing surgery.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Policlinico-San Marco University Hospital	Anaesthesiology and Intensive Care	Catania, Italy	Assistant Professor	2022	2023
Policlinico-San Marco University Hospital	Anaesthesiology and Intensive Care	Catania, Italy	Medical Doctor	2018	2023
ISMETT (Mediterranean Institute for Transplant&High Specialization Therapies)	Cardiac and Thoracic OR	Palermo, Italy	Attending/Consultant	2016	2018
Morgagni Heart Centre	Cardiovascular ICU and Cardiovascular Anaesthesia	Pedara, Catania, Italy	Consultant	2015	2016
St Georges Hospital NHS Trust	Cardio-thoracic ICU and Cardio-thoracic Anaesthesia	Londra, UK	Consultant	2014	2014
John Radcliffe Hospital, Oxford University Hospitals NHS Trust	Cardio-Thoracic Anaesthesia and Critical Care	Oxford, UK	Senior Clinical Fellow	2012	2014
Addenbrooke's Hospital - Cambridge University Hospitals NHS Foundation Trust	Neuroscience and Trauma Critical Care Unit (NCCU)	Cambridge, UK	Clinical Fellow	2010	2012

Other awards and honors

- Best Oral Communication - "Aggressive post-resuscitation care improves outcome and reduces days of ventilation and ICU stay" - X° WFSICCM 2009 (Florence)
- Runner-up prize - "Hospital acquired H1N1 infection during 2010-2011 pandemic. A single centre experience" - East Anglia Intensive Care Group Meeting (Cambridge)
- Best award - "Excellence in clinical teaching of residents" by the University of Pittsburgh
- Member of the Jury for the Young Lecturer Award - LIVES 2019 (Berlino) ESICM

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
University of Catania	University of Catania	2023	Starting grant	Coordinator	10.000,00	https://www.unict.it/it/ricerca/ricerca-su-fondi-di-ateneo

2.5 Research Collaborators n. 3

Last Name: Cinnella
First Name: Gilda
Last name at birth:
Gender: F

Title: Patients recruitment
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 22/03/1962
Place of Birth: Bari

Official H index (Scopus or Web of Science): 26.0

Scopus Author Id:6603598364 **ORCID ID:**0000-0001-9864-2893 **RESEARCH ID:**GAI-3383-2022

Contact address

Current organisation name: Università di Foggia
Current Department / Faculty / Institute / Laboratory name: Anesthesia and Intensive Care
Street: Viale L pinto 1
Postcode / Cedex: 71100
Town: Foggia
Phone:+393204394598
Phone 2: 3204394598

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Bari	Specialization / Specializzazione	Diseases of the respiratory system	1994	1998
University of Bari	Specialization / Specializzazione	Anesthesia and Intensive Care	1986	1989
University of Bari	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	1980	1986

Personal Statement:
As a research collaborator, I will actively assist the project principal investigator, making substantial contributions to the strategic planning and development of the study. Additionally, I will take on the role of supervising the research team in my institution, actively engaging in patient enrollment and overseeing study procedures. With its exceptional quality and innovative design, this study will make a transformative impact on the management and clinical outcomes of cancer patients undergoing surgery.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
AOU Ospedali Riuniti di Foggia	Integrated Emergency-Urgency Care Department	Foggia, Italy	Director of the Integrated Emergency-Urgency Care Department	2019	2023
University of Foggia - AOU Ospedali Riuniti di Foggia	Department of Medical and Surgical Sciences, Section of Anesthesia	Foggia, Italy	Director of Anesthesia and Intensive Care Unit	2017	2023
University of Foggia	Department of Medical and Surgical Sciences, Section of Anesthesia	Foggia, Italy	Full Professor	2019	2023
University of Foggia	Department of Medical and Surgical Sciences, Section of Anesthesia	Foggia, Italy	Associate Professor	2005	2019
University of Foggia	Department of Surgical Sciences, Section of Anesthesia	Foggia, Italy	Clinical and research activities	1999	2004
Azienda Ospedaliero-Universitaria "Policlinico"	Anesthesia and Intensive Care	Bari, Italy	Clinical and research activities	1989	1999
Université Paris XII- Hopital Henri Mondor	Réanimation Médicale	Créteil, France	Clinical and research activities	1988	1989

Other awards and honors

- SIAARTI Award - "Continuous epidural anaesthesia: levobupivacaine vs levobupivacaine-sufentanyl. Neuroendocrine response effects and gene polymorphism for the opioids receptor." (2005)
- FEDERDOLORE Award - "Symptoms and sensory profiling in 11 patients with trigeminal neuralgia" (2011)
- Award European Society of Anesthesiology-Baxter - "Effects of recruitment maneuver and positive end-expiratory pressure on respiratory mechanics and transpulmonary pressure during laparoscopic surgery" (2014)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
European Commission - EACEA Erasmus + programme - Knowledge Alliances Principal Investigator Proposal EAC/A02/201	University of Foggia, Bucharest, Munchen, Barcelona	2020	Simulation Approach for Education and Training in Emergency (SAFETY)	Coordinator	900.000,00	EACEA
Regione Puglia, project I4W9R64	University of Foggia	2015	Pre.C.I.O.U.S. (Predictive Computer aided scoring support system): Sistema per l'ottimizzazione delle procedure e dei percorsi assistenziali nella pratica clinica ospedaliera	Coordinator	100.000,00	Regione Puglia
PRIN 2004	University of Foggia	2004	Identificazione della componente eredo-familiare nella patogenesi dell'ictus ischemico giovanile	Coordinator	50.000,00	Ministero - Università

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
PRIN 2002	University of Foggia	2002	Effects of general anesthesia on oxidative stress in patients with pre-eclampsia undergoing Caesarean section	Coordinator	50.000,00	Ministero - Università

2.6 Research Collaborators n. 5

Last Name: BALDASSARRI
First Name: RUBIA

Last name at birth:
Gender: F

Title: Project coordination and patients recruitment
Nationality: Italiana
Date of birth: 28/08/1962

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Viareggio

Official H index (Scopus or Web of Science): 9.0

Scopus Author Id:8590732200 **ORCID ID:**- **RESEARCH ID:**ELE-7536-2022

Contact address

Current organisation name: Azienda Ospedaliera Universitaria Pisana
Current Department / Faculty / Institute / Laboratory name: Anesthesia and Intensive Care - Azienda Ospedaliero Universitaria Pisana

Street: Azienda Ospedaliero Universitaria Pisana, Via Paradisa 2
Postcode / Cedex: 56123 **Town:** Pisa
Phone:+393483847177 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Pisa	Specialization / Specializzazione	Anesthesia and Intensive Care	1991	1995
University of Pisa	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	1981	1988

Personal Statement:
As a research collaborator of the team, I will provide dedicated support to the project principal investigator, actively contributing to the planning and development of the study. This study is characterized by its exceptional quality and innovative approach, and I am confident that it has the potential to significantly improve the management and clinically relevant outcomes for cancer patients undergoing surgery.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Azienda Ospedaliero Universitaria Pisana	Cardiothoracic and Vascular Anaesthesia and ICU	Pisa, Italy	Senior consultant	2002	2023

Other awards and honors
-

Project Code: PNRR-MCNT2-2023-12377934	**Call section:** Malattie Croniche non Trasmissibili (MCnT2) ad alto impatto sui sistemi sanitari
Applicant Institution: Toscana	**Applicant/PI Coordinator:** Guarracino Fabio

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
-	-	-	-	Collaborator	0,00	-

2.7 Research Collaborators n. 6 - Under 40

Last Name: Sidoti
First Name: Anna
Last name at birth:
Gender: F

Title: Project coordination and patients recruitment
Country of residence: ITALY
Nationality: italiana
Country of Birth: ITALY
Date of birth: 28/08/1987
Place of Birth: Pisa

Official H index (Scopus or Web of Science): 3.0

Scopus Author Id:55817777300 **ORCID ID:**- **RESEARCH ID:**FZR-8515-2022

Contact address

Current organisation name: Azienda Ospedaliera Universitaria Pisana
Current Department / Faculty / Institute / Laboratory name: Anesthesia and Intensive Care - Azienda Ospedaliero Universitaria Pisana

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Postcode / Cedex: 56123
Town: pisa
Phone:+393336150315
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Pisa	Specialization / Specializzazione	Anesthesiology Reanimation, Intensive Care and Pain Therapy	2013	2018
University of Pisa	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	2006	2012

Personal Statement:

I will provide essential support to the Principal Investigator, actively participating in study planning and development. I will collaborate with the Principal Investigator to ensure successful patient recruitment and assist in the interpretation of collected data. The significance of this high-quality and innovative study lies in its potential to enhance management strategies and improve clinically relevant outcomes for cancer patients undergoing surgery.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Azienda Ospedaliero Universitaria Pisana	Day Surgery Unit	Pisa, Italy	Attending physician - Anaesthetist	2020	2023
University of Pisa	Post-Graduation School in Anesthesiology Rianimation, Intensive Care and Pain Therapy	Pisa, Italy	Medical Resident	2013	2018

Other awards and honors

-

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
-	-	-	-	Collaborator	0,00	-

2.8 Research Collaborators n. 7 - Under 40

Last Name: Costanzo
First Name: Diego

Last name at birth:
Gender: M

Title: Project coordination and patients recruitment
Nationality: Italiana
Date of birth: 30/12/1987

Country of residence: ITALY
Country of Birth: ITALY
Place of Birth: Lamezia Terme

Official H index (Scopus or Web of Science): 3.0

Scopus Author Id:57201409572 **ORCID ID:**- **RESEARCH ID:**ESP-3466-2022

Contact address

Current organisation name: Azienda Ospedaliera Universitaria Pisana
Current Department / Faculty / Institute / Laboratory name: Anesthesia and Intensive Care - Azienda Ospedaliero Universitaria Pisana

Street: Azienda Ospedaliero Universitaria Pisana, Via Paradisa 2
Postcode / Cedex: 56123 **Town:** Pisa
Phone:+393791595918 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Pisa	Specialization / Specializzazione	Anesthesiology, resuscitation, intensive therapy and pain medicine	2016	2021
University of Pisa	Single-cycle master's degree / Laurea magistrale a ciclo unico	Medicine and Surgery	2009	2015
University of Pisa	Bachelor Degree / Laurea Triennale	Biology	2006	2009

Personal Statement:
In this project, I will assist and collaborate closely with the PI, ensuring effective study planning and development. I will actively contribute to patient recruitment and data interpretation, fully believing in the exceptional quality and innovation of this study. The potential improvement in management strategies and clinically relevant outcomes for cancer patients undergoing surgery makes this research highly valuable.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Azienda Ospedaliera Universitaria Pisana	Department of Anesthesiology and intensive care	Pisa, Italy	Medical executive	2021	2023

Other awards and honors

-

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
-	-	-	-	Collaborator	0,00	-

2.9 Additional Research Collaborators n. 2 - Under 40 to hire

Last Name: PADALINO
First Name: SIMONA
Last name at birth:
Gender: F

Title: Patients recruitment
Country of residence: ITALY
Nationality: ITALIANA
Country of Birth: ITALY
Date of birth: 11/07/1991
Place of Birth: FOGGIA

Official H index (Scopus or Web of Science): 0.0

Scopus Author Id:- **ORCID ID:**- **RESEARCH ID:**-

Contact address

Current organisation name: Università di Foggia
Current Department / Faculty / Institute / Laboratory name: Anesthesia and Intensive Care
Street: VIA HOMS 40
Postcode / Cedex: 71121
Town: FOGGIA
Phone:+393492279645
Phone 2:

Education / training

Educational institution and location	Degree	Field of study	From year	To year
IAF - Institute of Higher Education	Specialization / Specializzazione	Short Dynamic Psychotherapy	2023	2023
University of Chieti	Master's Degree / Laurea Magistrale	Clinical and Health Psychology	2019	2021
University of Chieti	Bachelor Degree / Laurea Triennale	Psychological Sciences and Techniques	2012	2015

Personal Statement:
My active involvement in this project revolves around providing comprehensive support to the Principal Investigator, actively contributing to the planning and development of the study. Additionally, I will assist the PI in various crucial aspects, including patients' enrollment, randomization, follow-up, and data interpretation. Recognizing its exceptional quality and innovation, I firmly believe that this study has the potential to significantly enhance management strategies and improve clinically relevant outcomes for cancer patients undergoing surgery, thus contributing to the advancement of knowledge in the field of prehabilitation.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
AIL - Italian Association against Leukemia Lymphoma and Myeloma	AIL - Italian Association against Leukemia Lymphoma and Myeloma	Foggia, Italy	Psycho-oncologist	2023	2023
AIL - Italian Association against Leukemia Lymphoma and Myeloma	AIL Foggia ODV	Foggia, Italy	Psycho-oncological counselling	2022	2023
Istituto comprensivo "S. Chiara - Pascoli - Altamura"	Istituto comprensivo "S. Chiara - Pascoli - Altamura"	Foggia, Italy	School Counselling	2022	2022
University Hospital of Foggia - Ospedali Riuniti Foggia	University Hospital of Foggia - Ospedali Riuniti Foggia	Foggia, Italy	Clinical Psychology Internship	2021	2022
Manpower Srl	Manpower Srl	Foggia, Italy	Junior Expert in Active Employment Policies	2020	2022
Manpower Srl	Manpower Srl	Foggia, Italy	Sales & Service Representative	2018	2019
Solyda Srl	Solyda Srl	Foggia, Italy	HR Generalist and Personal Senior Advisor	2015	2017
School Counselling Internship	Associazione Crescere Onlus - CID PREVENTION Project	Foggia, Italy	Accompanying training on substance abuse and behavioural addiction prevention to primary and secondary school children, counselling desk at school.	2013	2014

Other awards and honors

Publications:

- "Quality of life after recovery from ICU: COVID-19 vs other critical illness. A pilot study" (2002)
- "Effect of psychological counselling on quality of life in patients with chronic pain under pharmacological therapy. A pilot study" (2022)

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
-	-	-	-	Collaborator	0,00	-

2.10 Additional Research Collaborators n. 3 - Under 40 to hire

Last Name: Lo Giudice
First Name: Giulia
Last name at birth:
Gender: F

Title: Patients recruitment
Country of residence: ITALY
Nationality: Italiana
Country of Birth: ITALY
Date of birth: 31/03/1988
Place of Birth: Catania

Official H index (Scopus or Web of Science): 0.0

Scopus Author Id:- **ORCID ID:**- **RESEARCH ID:**-

Contact address

Current organisation name: Azienda Ospedaliero Universitaria Policlinico San Marco di Catania
Current Department / Faculty / Institute / Laboratory name: Anesthesia and Intensive Care
Street: Piazza Santa Maria della Guardia 28
Postcode / Cedex: 95100 **Town:** Catania
Phone:+393931774548 **Phone 2:**

Education / training

Educational institution and location	Degree	Field of study	From year	To year
University of Catania	Master's Degree / Laurea Magistrale	Business Management	2011	2014
University of Catania	Bachelor Degree / Laurea Triennale	Business Management	2007	2011

Personal Statement:

My active participation in this project involves providing comprehensive support to the Principal Investigator and assist the PI in various essential aspects, including patient enrollment, randomization, follow-up, and data interpretation. Recognizing the study exceptional quality and innovative nature, I firmly believe that it holds significant potential to enhance management strategies and advancement of knowledge in the field of prehabilitation. I am confident that it contributes to the improve clinically relevant outcomes for cancer patients undergoing surgery.

Positions and honors

Positions

Institution	Division / Research group	Location	Position	From year	To year
Studio Associato Benza Calcagno Puglisi	Studio Associato Benza Calcagno Puglisi	Catania, Italy	Tax Due Dilingence: check fiscal documention	2022	2023
Comer Sud SpA	Comer Sud SpA	Catania, Italy	Back office: administrative operational tasks	2021	2022
Fides SpA	Fides SpA	Catania, Italy	Credit collector	2016	2021
Banca Base	Banca Base	Catania, Italy	Banking back office	2015	2015

Other awards and honors

-

Grant

Funded by Institution	Researcher inst. where grant is/was performed	Year	Title	Position in Projects	Fund (euro)	Source website grant listed
-	-	-	-	Collaborator	0,00	-

2.17 Expertise Research Collaborators

Selected peer-reviewed publications of the Research Group / Collaborators

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Costanzo Diego	Macklin effect on baseline chest CT scan accurately predicts barotrauma in COVID-19 patients	Article	NOT_FOUND	197	2022	10.1016/j.rmed.2022.106853	35512457	4	O
Costanzo Diego	Liver transplantation in Jehovah's witnesses: 13 consecutive cases at a single institution	Article	NOT_FOUND	20	2020	10.1186/s12871-020-0945-x	32000668	6	F
Sidoti Anna	Role of lung ultrasound in the preoperative evaluation of surgical patients	Letter with Data	791-793	86	2020	10.23736/S0375-9393.20.14417-1	32154686	3	O
LANDONI GIOVANNI GUGLIELMO	Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis	Article	95-97	22	2020	-	32294809	296	C
LANDONI GIOVANNI GUGLIELMO	Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study	Article	e325-e331	2	2020	10.1016/S2665-9913(20)30127-2	32501454	690	O
LANDONI GIOVANNI GUGLIELMO	Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans	Article	1440-1449	107	2020	10.1002/bjs.11746	32395848	803	O
BALDASSARRI RUBIA	Predictors of hospital-acquired bacterial and fungal superinfections in COVID-19: A prospective observational study	Review	1078-1084	76	2020	10.1093/jac/dkaa530	33374002	76	O
Cinnella Gilda	Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): A multicentre, prospective observational study	Article	129-140	7	2019	10.1016/S2213-2600(18)30294-7	30224322	187	O
Sidoti Anna	Ultrasound- versus landmark-guided subclavian vein catheterization: a prospective observational study from a tertiary referral hospital	Article	NOT_FOUND	9	2019	10.1038/s41598-019-48766-1	31439913	9	F

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
Costanzo Diego	Central Veno-Arterial Extracorporeal Membrane Oxygenation (C-VA-ECMO) After Cardiothoracic Surgery: A Single-Center Experience	Article	1169-1174	32	2018	10.1053/j.jvca.2017.12.003	29428358	24	O
SANFILIPPO FILIPPO	Left ventricular systolic function evaluated by strain echocardiography and relationship with mortality in patients with severe sepsis or septic shock: A systematic review and meta-analysis	Article	NOT_FOUND	22	2018	10.1186/s13054-018-2113-y	30075792	63	F
Cinnella Gilda	Epidemiology, practice of ventilation and outcome for patients at increased risk of postoperative pulmonary complications: LAS VEGAS - An observational study in 29 countries	Article	492-507	34	2017	10.1097/EJA.0000000000000646	28633157	136	O
Cinnella Gilda	Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome: Insights from the LUNG SAFE Study	Article	67-77	195	2017	10.1164/rccm.201606-1306OC	27753501	351	O
Sidoti Anna	Could the use of bedside lung ultrasound reduce the number of chest x-rays in the intensive care unit?	Article	NOT_FOUND	15	2017	10.1186/s12947-017-0113-8	28903756	66	O
SANFILIPPO FILIPPO	Tissue Doppler assessment of diastolic function and relationship with mortality in critically ill septic patients: A systematic review and meta-analysis	Review	583-594	119	2017	10.1093/bja/aex254	29121301	64	F
SANFILIPPO FILIPPO	Incidence and factors associated with burnout in anesthesiology: A systematic review	Review	NOT_FOUND	2017	2017	10.1155/2017/8648925	29318155	86	F
SANFILIPPO FILIPPO	Bivalirudin for Alternative Anticoagulation in Extracorporeal Membrane Oxygenation: A Systematic Review	Review	312-319	32	2017	10.1177/0885066616656333	27356945	105	F
Sidoti Anna	Polymyxin B Direct Hemoperfusion Using Regional Citrate-Calcium Anticoagulation: A Case Report	Article	232-235	7	2016	10.1213/XAA.0000000000000392	27669028	2	F
LANDONI GIOVANNI GUGLIELMO	Global patient outcomes after elective surgery: Prospective cohort study in 27 low-, middle- and high-income countries	Article	601-609	117	2016	10.1093/bja/aew316	27799174	303	O

Collaborato	Title	Type	Pag	Vol	Year	DOI	PMID	Cit.**	P.*
BALDASSARRI RUBIA	The Anesthetic Management of Transcatheter Aortic Valve Implantation	Review	141-146	20	2016	10.1177/1089253215606220	26403787	16	L
Cinnella Gilda	Chronic postsurgical pain in Europe: An observational study	Article	725-734	32	2015	10.1097/EJA.0000000000000319	26241763	304	O
Cinnella Gilda	Physiological effects of the open lung approach in patients with early, mild, diffuse acute respiratory distress syndrome: An electrical impedance tomography study	Article	1113-1121	123	2015	10.1097/aln.0000000000000862	26397017	54	F
SANFILIPPO FILIPPO	Diastolic dysfunction and mortality in septic patients: a systematic review and meta-analysis	Review	1004-1013	41	2015	10.1007/s00134-015-3748-7	25800584	139	F
BALDASSARRI RUBIA	Volatile compared with total intravenous anaesthesia in patients undergoing high-risk cardiac surgery: a randomized multicentre study	Article	955-963	113	2014	10.1093/bja/aeu290	25186820	40	O
BALDASSARRI RUBIA	Ventriculoarterial decoupling in human septic shock	Article	NOT_FOUND	18	2014	10.1186/cc13842	24762124	82	O
BALDASSARRI RUBIA	Effect of fenoldopam on use of renal replacement therapy among patients with acute kidney injury after cardiac surgery: A randomized clinical trial	Article	2244-2253	312	2014	10.1001/jama.2014.13573	25265449	117	O
Sidoti Anna	Rhabdomyolysis following bariatric surgery: A retrospective analysis	Article	51-59	5	2013	10.2174/1876823720130419007	NOT_FOUND	1	C
LANDONI GIOVANNI GUGLIELMO	A meta-analysis of complications and mortality of extracorporeal membrane oxygenation	Article	172-178	15	2013	NOT_FOUND	23944202	378	C

* Position: F=First L=Last C=Correspondent O=Other N=Not applicable

** Autocertificated

3 - Ethics

1. HUMAN EMBRYOS/FOETUSES	
Does your research involve Human Embryonic Stem Cells (hESCs)?	No
Does your research involve the use of human embryos?	No
Does your research involve the use of human foetal tissues / cells?	No

2. HUMANS	
Does your research involve human participants?	Yes
Does your research involve physical interventions on the study participants?	Yes
3. HUMAN CELLS / TISSUES	
Does your research involve human cells or tissues (other than from Human Embryos/ Foetuses?	No
4. PERSONAL DATA	
Does your research involve personal data collection and/or processing?	Yes
Does your research involve further processing of previously collected personal data (secondary use)?	No
5. ANIMALS	
Does your research involve animals?	No
6. ENVIRONMENT & HEALTH and SAFETY	
Does your research involve the use of elements that may cause harm to the environment, to animals or plants?	No
Does your research deal with endangered fauna and/or flora and/or protected areas?	No
Does your research involve the use of elements that may cause harm to humans, including research staff?	No
7. DUAL USE	
Does your research involve dual-use items in the sense of Regulation 428/2009, or other items for which an	No
8. EXCLUSIVE FOCUS ON CIVIL APPLICATIONS	
Could your research raise concerns regarding the exclusive focus on civil applications?	No
9. MISUSE	
Does your research have the potential for misuse of research results?	No
10. OTHER ETHICS ISSUES	
Are there any other ethics issues that should be taken into consideration? Please specify	No

I confirm that I have taken into account all ethics issues described above and that, if any ethics issues apply, I will complete the ethics self-assessment and attach the required documents. [X]

4 - Call-specific questions

Eligibility	
I acknowledge that I am aware of the eligibility requirements for applying as specified in the Call-PNRRXXXX_M6/C2, and certify that, to the best of my knowledge my application is in compliance with all these requirements. I understand that my proposal may be declared ineligible at any point during the evaluation or granting process if it is found not to be compliant with these eligibility criteria.	X
I confirm that the proposal that I am about to submit draws substantially don't repeat on an existing or recently finished GRANT funded.	X
Data-Related Questions and Data Protection (Consent to any question below is entirely voluntary. A positive or negative answer will not affect the evaluation of your project proposal in any form and will not be communicated to the evaluators of your project.)	
For communication purposes only, the MoH asks for your permission to publish,in whatever form and medium, your name, the proposal title, the proposal acronym, the panel, and host institution, should your proposal be retained for funding.	X
Some national and regional public research funding authorities run schemes to fund MoH applicants that score highly in the MoH's evaluation but which can not be funded by the MoH due to its limited budget. In case your proposal could not be selected for funding by the MoH do you consent to allow the MoH to disclose the results of your evaluation (score and ranking range) together with your name, non- confidential proposal title and abstract, proposal acronym, host institution and your contact details to such authorities?	X
The MoH is sometimes contacted for lists of MoH funded researchers by institutions that are awarding prizes to excellent researchers. Do you consent to allow the MoH to disclose your name, non-confidential proposal title and abstract, proposal acronym, host institution and your contact details to such institutions?	X
The Ministry of Health occasionally could contacts Principal Investigators of funded proposals for various purposes such as communication campaigns, pitching events, presentation of their project's evolution or outcomes to the public, invitations to represent the Ministry of Health in national and international forums, studies etc. Should your proposal be funded, do you consent to the Ministry of Health staff contacting you for such purposes?	X
For purposes related to monitoring, study and evaluating implementation of MoH actions, the MoH may need that submitted proposals and their respective evaluation data be processed by external parties. Any processing will be conducted in compliance with the requirements of Regulation 45/2001.	

5 – Description Project

Summary description

In this multicenter randomized controlled trial we will investigate the effectiveness of a multimodal prehabilitation program involving physical, nutritional, and psychological interventions in improving heart rate variability (HRV) and reducing postoperative length of hospital stay in cancer patients undergoing surgery. The hypothesis is that prehabilitation will lead to increased HRV and increase days at home after surgery. Real-time monitoring using a mobile application will be used. The collaboration between four excellent research units, renowned for their innovation capacities and their expertise in conducting multicenter trials ensures a comprehensive approach. The study impact lies in its potential to enhance patient

care and surgical management by providing evidence-based strategies for preoperative intervention, risk assessment, and patient support.

Background / State of the art and Preliminary data (if available)

Cancer patients require long-term management and ongoing care due to the chronic nature of their condition. Major cancer surgeries pose significant challenges, resulting in a decline in physiological and functional capacity. Traditionally, postoperative rehabilitation was the most suitable intervention to improve functional recovery. Prehabilitation, which aims to enhance patients functional capacity before surgery and to improve patients ability to cope with physiological stress, is considered the best form of rehabilitation (Durrand, 2019) Through multi-modal strategies like exercise, nutrition and psychological support, prehabilitation can improve surgical outcomes of cancer patients. However, prehabilitation lacks effectiveness assessment (Orange, 2018). Heart rate variability (HRV), a physiological parameter measuring variation in heartbeats, reflects autonomic nervous system activity and an increase in HRV is associated with fitness and recovery capacity in sport medicine (Lundstorm, 2023). Psychological factors, nutritional status and physical exercise influence HRV (Kemp, 2013). Hence, HRV could be used to objectively assess prehabilitation interventions. In addition, HRV is widely used in risk assessment in cardiology, and a reduction in HRV is recognized to be associated with complications and mortality (Dekker, 2000). Despite its evident potential in risk assessment, HRV has never been utilized in preoperative assessments.

Description and distribution of activities of each operating unit

In this project, the description and distribution of activities of each operating unit play a crucial role in ensuring the successful implementation of the trial. The project involves four operative units, all of which will actively participate in every phase of the trial. Each operating unit will have specific responsibilities and tasks to fulfill throughout the project. The involvement of each unit extends across different areas, ensuring a comprehensive and collaborative approach. Each center will contribute to patients recruitment and screening, and in collecting baseline data.
Azienda Ospedaliero Universitaria Pisana holds a leadership role in the trial and is responsible for overseeing the entire project. We will closely monitor the trial progress, ensure adherence to protocols, and take responsibility of data management and storage. Additionally, this center will play a key role in coordinating the enrollment and in patients recruitment, ensuring the trial success.
IRCCS San Raffaele Scientific Institute brings expertise in digital innovation and will be instrumental in developing an innovative app to monitor and track patients throughout the trial. San Raffaele will also lead the development of the prehabilitation program, working to identify and engage expert professionals who will be employed in the trial. This unit will be responsible for delivering the prehabilitation interventions, coordinating exercise training programs, providing nutritional guidance, and implementing stress reduction techniques. San Raffaele will also closely monitor participants progress and adherence to the prehabilitation program.
Università degli studi di Foggia will focus on outcome assessment and data collection. They will conduct follow up assessments and record relevant data at specified time points during the trial. This unit will play a crucial role in ensuring accurate and standardized data collection across all participating sites. They will also develop strategies to effectively communicate the trial objectives, progress, and outcomes to both patients and the wider community, aiming to involve patients throughout the project.
Azienda Ospedaliero Universitaria "G.Rodolico -San Marco" assumes leadership for statistical analyses and data management. They will employ their expertise in statistical methods to analyze the collected data, interpret the results, and provide valuable insights into the impact of prehabilitation on cancer patients outcomes. They will be responsible for organizing and storing collected data securely, ensuring data quality and integrity, and performing statistical ad interim as well as final analyses to evaluate the effect of prehabilitation on cancer patients outcomes.
Each unit specific roles and expertise will contribute to the success of the project, facilitating robust data collection, rigorous analysis, and effective communication of the trial's findings.
The distribution of activities among these four operative units will be carefully coordinated and managed to ensure seamless collaboration and efficient execution of the trial. Regular communication, team meetings, and shared documentation will facilitate the exchange of information and the integration of efforts among the units. This collaborative approach will enable

the project to leverage the expertise and resources of each operating unit, ultimately leading to valuable insights on the impact of prehabilitation on cancer patients.

5.4 Specific Aims and Experimental Design

Specific aim 1

To evaluate the impact of prehabilitation in increasing heart rate variability (HRV), hence to incorporate an objective measure to evaluate prehabilitation impact. To fulfill AIM 1, a multicentre randomized controlled trial evaluating the effect of a multimodal prehabilitation program on HRV will be conducted. Patients aged 18 years or older scheduled for elective surgery will be eligible for enrolment, if they will not present any exclusion criteria. All patients undergoing major cancer surgery will be screened for eligibility and all eligible patients will be approached for consent. Patients are eligible if they undergo elective major abdominal or thoracic cancer surgery, be schedule to surgery at least 28-days after enrolment and have willingness and ability to use an app. Exclusion criteria include American Society of Anesthesiologists physical status classes 5-6 and other medical conditions that preclude safe training. All eligible patients will be randomized with a 1:1 allocation to receive either prehabilitation or standard of care. Both groups will receive the same standard perioperative care that includes risk assessment, medication management, blood management, and smoking cessation counselling. In addition, prehabilitation arm group will receive a prehabilitation program consisting of home-based physical, nutritional, and psychological interventions. The first visit will be conducted in person and will include recording participants baseline medical, demographic, and HRV. Patients will be monitored for 5 minutes in an isolated room, the day of screening and the day before surgery. HRV time-domain measurement and HRV frequency-domain measurement will be evaluated. To assess HRV the recorded data will be analyzed and processed using the Kubios HRV software (Tarvainen, 2014), which has been previously validated. The analysis will adhere to the guidelines recommended by the Taskforce of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (TFESC and NASPE, 1996), ensuring accurate and reliable evaluation of HRV measurements. During this trial, we will be utilizing an innovative application dedicated and specially developed for the trial to track and monitor our patients progress. This app will be provided only to the prehabilitation group as part of a multimodal management approach. This tool will provide real-time data and insights, and ensure that participants receive the highest quality of care and attention. Furthermore, the app will allow to streamline the entire process, the communication and collaboration among team, ensuring convenience and efficiency for both our patients and our research team. The multimodal prehabilitation program will be implemented by carefully integrating and adapting various components to provide individual needs. The program, designed to last a minimum of four weeks, incorporates exercise training, nutritional therapy, and anxiety reduction techniques as part of the preoperative intervention. To ensure personalized care, a comprehensive assessment is conducted to identify specific physical, nutritional, or psychological challenges. Following the assessment, a customized intervention is prescribed, with a focus on areas such as tailored exercise training, optimized nutrition, and effective distress-coping strategies. The multimodal intervention will be extensively described in the methods of the full application. After completing the four-week programme, patients will continue with a maintenance program until the day of surgery. We expect to observe an increase in HRV in patients receiving prehabilitation.

Specific aim 2

To evaluate the effect of prehabilitation on postoperative clinically relevant outcomes. Prehabilitation, or preoperative rehabilitation, consisting of tailored exercise training, optimized nutrition, and effective distress-coping strategies, is designed to enhance patients physical, nutritional, and psychological well-being prior to surgery. By implementing prehabilitation interventions, several factors can positively influence postoperative outcomes. Through exercises targeting cardiovascular endurance, muscular strength, and flexibility, prehabilitation enhances the individual physical capabilities. Respiratory function is another area addressed in prehabilitation. Respiratory exercises help optimize lung function and strengthen respiratory muscles. Psychological preparedness is also emphasized in prehabilitation programs, reducing anxiety, improving coping strategies, and enhancing psychological well-being. Additionally, prehabilitation often includes nutritional interventions. Addressing malnutrition or nutritional deficiencies before surgery ensures an optimal nutritional

status. Adequate nutrition is crucial for wound healing, immune function, and overall recovery. Overall, prehabilitation aims to optimize the individual physiological and psychological state before surgery (Scheede-Bergdahl, 2019). By addressing physical fitness, respiratory function, psychological preparedness, nutrition, and patient education, prehabilitation can improve surgical outcomes, reduce complications, shorten hospital stays, enhance functional recovery, and improve the individual overall well-being. We will compare patients undergoing prehabilitation with the control group.
This study has two primary endpoints. One was described in the previous section (aim 1) and is to evaluate the effect of prehabilitation on HRV. The other one is represented by "days at home in the first 30-days". The utilization of days at home as an outcome measure represents an innovative approach in this field of research. Traditionally, the length of hospital stay has been the primary measure used to assess postoperative recovery. However, this measure may not capture the full spectrum of patient outcomes. The duration of days spent at home after surgery offers a more comprehensive perspective, considering the patients ability to resume normal daily activities, regain independence, and reintegrate into their home environment. Furthermore, the duration of days spent at home after surgery also accounts for important clinical outcomes such as mortality (which equals to zero days at home) and rehospitalization (Bell, 2019).Secondary endpoints of this study will be represented by quality of life and 30-days postoperative major complication.
The evaluation of quality of life outcomes in a prehabilitation trial holds significant importance as it provides valuable insights into the overall well-being and functional status of patients. Quality of life is a multidimensional construct that encompasses physical, psychological, and social aspects of an individual life. Assessing quality of life allows to understand the impact of the intervention on patients daily functioning, emotional well-being, and social interactions. We will assess quality of life with EuroQol Five-Dimension questionnaire, a widely used and validated instrument for measuring health-related quality of life (Brooks, 1996). Thirty-day postoperative complication will be assessed according Clavien-Dindo classification (Clavien, 2009). The proportion of patients experiencing severe postoperative complications, defined as grade 3 or higher according to the Clavien-Dindo classification, will be compared between groups. By assessing the incidence of severe of complications, we can determine the effectiveness of prehabilitation interventions in reducing the risk of surgery. We expect that prehabilitation increase days at home after surgery and quality of life, and decrease incidence of postoperative complication.

Specific aim 3

To investigate HRV as a preoperative assessment tool for evaluating the risk of surgery. Preoperative HRV will be correlated with postoperative outcomes. HRV is a comprehensive measure that reflects the functioning of the autonomic nervous system, encompassing various physiological processes including inflammation, nutrition, cardiovascular function, and psychological factors (Ernst, 2014). The assessment of HRV provides insights into the dynamic interplay between these systems and can offer valuable information in the preoperative evaluation of patients. Previous research has demonstrated associations between HRV and the severity of disease in cancer patients, highlighting its potential as a prognostic indicator (Zhou, 2016). Additionally, reduced HRV has been identified as an independent marker of mortality in various populations, underscoring its significance in assessing overall health (Jarczok, 2022). While it is essential to include all relevant functions, such as inflammation, nutrition, cardiovascular function, and psychological factors, in the preoperative evaluation of patients, currently, there is a lack of an objective value that comprehensively examines all these aspects. In this observational part of the study, all eligible patients meeting the inclusion criteria will be considered. The day before surgery, all patients will undergo a 5-minute monitoring session in an isolated room. HRV measurements, including both time-domain and frequency-domain analyses, will be conducted. The analysis will strictly follow the guidelines recommended by the Taskforce of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, ensuring the accuracy and reliability of the HRV evaluations. Data collection for the study will be carried out either through medical chart review or by directly contacting the patients. Medical records will be accessed daily to gather relevant information such as surgical details, and postoperative outcomes. One month after the surgery, patients will be contacted to assess the outcomes of interest, which include the number of days spent at home after surgery, the quality of life, and the occurrence of postoperative complications. These three outcomes, including the number of days at home after surgery, quality of life, and postoperative complications, are essential in determining the effectiveness of HRV as an

assessment tool due to their relevance to three fundamental areas of interest. The number of days at home after surgery reflects the patient overall recovery and ability to resume normal daily activities, providing insights into the efficiency of the surgical procedure and postoperative care. Quality of life encompasses various aspects of well-being, such as physical, psychological, and social functioning, indicating the impact of surgery on the patient overall health and satisfaction. Finally, postoperative complications serve as a critical indicator of surgical success and patient safety, assessing the effectiveness of HRV in predicting and preventing adverse events. By considering these comprehensive outcomes, we can obtain a holistic understanding of HRV utility as an assessment tool, covering the functional, psychological, and safety aspects of patient care. Sensitivity analyses will be performed using HRV as a threshold, baseline HRV, DELTA-HRV. Exploratory outcome will be the comparison between the other parameters of HRV (different from SDNN) and the above outcomes.

Experimental design aim 1

Study design
This is an international, multicenter, parallel-group, randomized, study in chronic cancer patients undergoing surgery. Adult men and women patients who are eligible according to the inclusion/exclusion criteria will be randomized to study the effect of prehabilitation versus standard care on heart rate variability (HRV).

Recruitment and randomization
A total of 600 patients will be recruited by systematic screening of patients scheduled for elective surgical procedures. All patients undergoing major cancer surgery will be screened for eligibility and those who meet the inclusion/exclusion criteria will be approached for consent. Research personnel will use a web-based randomization system to assign patients (1:1 ratio) to either the prehabilitation or control arm. Study personnel will also collect data on recruitment rates, with reasons for non-enrolment.

Eligibility
Inclusion criteria
Patients are eligible if they fulfil all the following criteria:
1. scheduled to undergo elective major abdominal or thoracic cancer surgery (Myles, 2018)
2. scheduled to undergo surgery at least three weeks after enrolment
3. >=18 y;
4. provide written informed consent;
5. willing and able to use smartphone application.

Exclusion criteria
We will exclude patients who meet at least one of the following criteria:
1. presenting with very poor functional capacity (Hlatky, 1989)
2. American Society of Anesthesiologists (ASA) physical status classes 5-6;
3. disabling orthopedic, neuromuscular, and psychiatric diseases or other conditions that preclude participation in a prehabilitation program;

Intervention
Eligible patients will be randomly assigned to 1 of 2 treatments:
1 multimodal prehabilitation program for four weeks started as soon as possible before surgery;
2 standard care.
The multimodal prehabilitation program will be individualized by carefully integrating and adapting various components to provide individual needs. The program will last four weeks (plus maintenance in case of delayed surgery), and will incorporate exercise training, nutritional therapy, and anxiety reduction techniques. After enrollment, patients will receive

initial contact from trained personnel through telemedicine. To ensure personalized care, a comprehensive assessment will be conducted to identify specific physical, nutritional, or psychological challenges. Based on this assessment, a customized intervention plan will be prescribed to achieve tailored exercise training, optimized nutrition, and effective distress-coping strategies. Patients will be requested to download a dedicated smartphone application, which will comprehensively monitor and track their progress towards achieving their prehabilitation goals. After completing the four-week program, patients will continue a maintenance program until surgery.

Outcome
The first (of two) primary outcome will be to determine whether prehabilitation, when compared with standard care, increases HRV in cancer patients undergoing surgery. This primary outcome measure will be the delta standard deviation of normal-to-normal intervals (SDNN) from baseline to the day before surgery.
The first HRV measurement will be performed for 5 minutes in an isolated room, after signing the written consent and before randomization, on the day of screening which occurs several weeks before surgery. The second HRV measurement will be performed the day before surgery. Both HRV time-domain measurements and HRV frequency-domain measurements will be evaluated.

Experimental design aim 2

We will assess the impact of prehabilitation on postoperative outcomes. Adult men and women who are eligible according to the previously described inclusion/exclusion criteria will be randomized to receive either prehabilitation or standard care. Aim 2 is to determine the impact of prehabilitation on "days at home within the first 30 days after surgery".
Prehabilitation will include three domains which we now describe in detail.
Physical training
The individualised exercise program will follow the principles of the American College of Sports Medicine (Thompson, 2013). Patients will engage in a three-day per week training. The exercise modalities will be adapted to individual preference, patient baseline fitness level, surgical procedure, and any pre-existing medical conditions. Each patient will undergo an interview with an expert to identify areas requiring improvement. The intensity, duration, and frequency of the exercises will progressively increase over time. Resistance exercises will be incorporated to enhance muscle strength and endurance. The program will specifically target major muscle groups and include exercises such as squats, lunges, pushups, crunches, and core exercises. Stretching and flexibility exercises will improve joint mobility and enhance the range of motion. These will include static stretches, dynamic stretches, or specific exercises that target tight muscles or restricted joints. Balance exercises and coordination drills will be incorporated to improve stability and reduce the risk of falls. This may involve activities such as standing on one leg, performing heel-to-toe walking, or using balance boards or stability balls. Core exercises will be included to improve core stability and enhance proper posture and movement mechanics. These may involve exercises such as planks, bridges, or pilates-based exercises targeting the abdominal and back muscles. Regular monitoring and reassessment by the expert will allow for adjustments and modifications based on the patient progress and individual needs.
Nutrition Intervention
The individualized nutrition program will follow the ESPEN guideline for clinical nutrition in cancer (Muscaritoli, 2021). An expert will conduct a comprehensive nutritional assessment of each patient to identify their specific nutritional needs, taking into account their medical history, food allergies, cultural considerations, any specific nutritional deficiencies, current dietary habits, and surgical requirements. A detailed daily dietary program will be provided to each patient, emphasizing the optimization of calorie, fiber and protein intake to ensure adequate nutrition and promote optimal healing and recovery (e.g. 25-30 calories/Kg/day, 25-35 grams/Kg/day of fiber, 1.2-1.5 grams/Kg/day of protein). Patients will be advised to choose sources of unsaturated fats. Patients will also be encouraged to drink an adequate amount of water throughout the day and limit the consumption of sugary beverages and caffeine. The program will emphasize obtaining a variety of vitamins and minerals from a balanced diet. During training days, patients will be instructed to consume a whey protein supplement of 20 grams following their exercises. If necessary, the dietitian may recommend nutritional supplementation, such as oral

nutritional supplements or specific micronutrient supplementation, to address any nutrient deficiencies or optimize nutritional status before surgery.
Relaxation Intervention
Participants will be instructed by psychology-trained personnel to stress management techniques and relaxation exercises including deep breathing exercises, progressive muscle relaxation, biofeedback, guided imagery, mindfulness meditation, or other techniques tailored to the individual's preferences (Marinelli, 2020) . Patients will receive information and education about the upcoming surgery, and strategies for coping with stress and anxiety. If needed, referral to a psychiatrist service will be made.

Experimental design aim 3

We will investigate the association between preoperative heart rate variability (HRV) and postoperative outcomes. All patients enrolled in the study, regardless of their group of assignment, will be included in this observational part of the study. The aim 3 of the study is to evaluate the correlation between preoperative standard deviation of normal-to-normal intervals (SDNN) and the following outcomes: days at home within the first 30 days after surgery; quality of life at 30 days postoperative, 30-days postoperative complications.

Heart rate variability assessment
Patients will be monitored for 5 minutes in an isolated room on the day prior the surgery. Both time-domain and frequency-domain measurements of HRV will be evaluated. Data will be analyzed and elaborated with the previously validated Kubios HRV software (version 3.5; University of Kuopio, Kuopio, Finland) (Tarvainen, 2014), according to the guidelines recommended by the Taskforce of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (TFESC and NASPE 1996). The software will extract both the time-domain and frequency-domain of HRV. In the time-domain analysis, parameters such as the SDNN, root mean square of successive differences (RMSSD), and percentage of consecutive intervals differing by more than 50 ms (pNN50) will be measured. Frequency-domain analysis will involve the calculation of power spectral density using the fast Fourier transform. The software will determine the power within specific frequency bands, including high-frequency (HF) power (0.15-0.4 Hz), low-frequency (LF) power (0.04-0.15 Hz), very low frequencies (below 0.04 Hz) power, and Total power (TP). The LF/HF ratio and other derived measures will also be calculate. In addition to these traditional measures, nonlinear HRV analyses will be performed. The Poincaré plot will provide insights into the short-term (SD1) and long-term (SD2) variability, as well as the ratio of SD1 to SD2. Approximate entropy (ApEn) and sample entropy (SampEn) will assess the irregularity and complexity of HRV patterns, while detrended fluctuation analysis (DFA) will evaluate long-range correlations. Recurrence plot analysis will visualize the recurrence of patterns, and multiscale entropy (MSE) will quantify HRV complexity across different time scales.

Picture to support preliminary data

PNRRimage3.0.PNG

Hypothesis and significance

We aim to investigate the effectiveness of prehabilitation in improving heart rate variability (HRV) and the possibility that prehabilitation reduces days at home after surgery and complications and that it improves quality of life. Additionally, we intend to explore the potential role of HRV as a preoperative instrument for risk assessment and the correlation between prehabilitation and postoperative outcomes.
To conduct this research, we will utilize a comprehensive app designed to closely monitor and follow patients throughout their prehabilitation. This app will enable us to collect and analyze a wealth of data exercise regimens, and recovery progress.
Our hypothesis suggests that prehabilitation can effectively enhance HRV. By implementing a structured preoperative exercise program, we anticipate improvements in autonomic regulation, leading to enhanced HRV in patients. HRV serves as an objective outcome measure in assessing the effectiveness of prehabilitation interventions, allowing us to objectively

evaluate the physiological impact of these interventions and determine their efficacy in optimizing patients health prior to surgery.
Furthermore, we hypothesize that there is a correlation between prehabilitation and days spent at home after surgery. We anticipate that patients who undergo prehabilitation will experience shorter hospital stays due to improved physical fitness, reduced complications, and enhanced recovery compared to those who do not receive prehabilitation.
Finally, we hypothesize that there exists a correlation between HRV and postoperative outcomes. Patients with higher preoperative HRV levels are expected to experience fewer complications, shorter hospital stays, and improved quality of life following surgery, compared to those with lower HRV levels. By examining this relationship, we aim to establish HRV as a valuable predictor of postoperative outcomes and provide insights into the potential benefits of prehabilitation in enhancing surgical recovery.
Additionally, we seek to explore the potential role of HRV as a preoperative instrument for risk assessment. Analyzing HRV patterns may enable us to identify patients at a higher risk of postoperative complications, allowing for tailored preoperative management strategies. By detecting patients who may benefit from prehabilitation the most, we can optimize their care and potentially reduce adverse outcomes.
The significance of our study lies in its potential to advance the field of prehabilitation and improve patient care. By investigating the relationship between prehabilitation, HRV, and various postoperative outcomes, we aim to contribute to the existing body of knowledge regarding the importance of preoperative interventions in optimizing surgical outcomes. Through the utilization of our comprehensive patient monitoring app, we aim to provide valuable insights into prehabilitation. By demonstrating the effectiveness and feasibility of using technology apps in prehabilitation, this study has the potential to transform prehabilitation delivery, improve patient engagement, and pave the way for the integration of digital solutions in broader healthcare settings.

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5.5 Methodologies and statistical analyses

Methods of data collection

Patients will be enrolled at least three weeks before the scheduled surgery with the aim to rehabilitate them for four weeks (plus maintenance in case of "delayed" surgery). After inclusion and exclusion criteria assessment, the patient will sign the informed consent and the investigator will ensure that data are recorded in the electronic case report forms. The investigators will record details of all screened patients confirming their eligibility or documenting reasons for screening failure, as applicable. Demographic information and relevant medical history will be recorded and aphysical examination performed. Baseline data includes: demographics; anthropometric (e.g. weight, height), medications, diagnosis, hemodynamic parameters (e.g. heart rate, blood pressure), laboratory findings. This assessment will also include HRV

recording. Patients will be monitored for 5 minutes in an isolated room and data will be analyzed and elaborated with Kubios HRV software (Tavainen, 2014), according to guidelines (TFESC and NAISPE, 1996). The prehabilitation group will have daily contact for the first 3 days after enrollment, and weekly thereafter. The first visit will be scheduled as soon as possible after enrollment, ideally within one day. Each expert will establish telecommunication contact with the patient to conductbaseline assessment and provide instructions for the prehabilitation program. After this initial visit, the patient will be contacted again on the two following days. Visits 2 and 3 will be conducted to assess the patient's adherence to the protocol, identify difficulties, and make adjustments to the prehabilitation program if required. Subsequently, a direct conversation will take place with the patient every seven days to facilitate ongoing evaluation and to make necessary adjustments. During the trial, we will be utilizing an innovative application to track and monitor the progress of our patients. This app will be provided only to the prehabilitation group as a part of its multimodal approach. The app will be developed as a native mobile application for iOS and Android using an operating system framework. The user interface will be designed using UI/UX design tools and include screens for profile creation, workout and nutrition plan management, progress tracking, and resource browsing. The app's backend will be implemented using a server-side programming language (e.g., Python, Node.js) to handle data storage. A relational database management system (e.g., MySQL, PostgreSQL) will be used to store and manage data. User profiles can be created and updated through a registration and login system. Administrators can create and update their workout and nutrition plans through a form-based interface, while users can record their progress. Exercise demonstration videos, and educational and recommended reading materials will be stored either locally or fetched from external sources. Push notifications and messaging will be implemented to send reminders, updates, and motivational messages and to enable communication between users and trainers/coaches. This tool will provide real-time data and insights, guaranteeing that participants receive the highest quality of care and attention, while ensuring accurate and reliable results. Within 24 hours from surgery, the second measurement of HRV will be conducted. Preoperative laboratory data, electrocardiogram; anthropometric, hemodynamic parameters will be collected. Postoperative complications will be extracted from clinical charts and recorded on CRFs. After thirty days from surgery, patients will be contacted and postoperative complications, quality of life, length of hospital stay, hospital readmission, and vital status will be collected. A final follow up at 90-days will assess vital status and quality of life.
With the current follow-up practice and our previous experiences in performing large randomized trials, we expect minimal loss of follow-up in this study.

Statistic plan

An original part of our protocol is the use of two primary outcomes: changes in Heart rate variability (HRV) (measured four weeks and one day before surgery) will allow us to measure the efficacy of prehabilitation and physiological recovery, while days at home within the first 30 days after surgery will measure the impact of this intervention on the healthcare system. To control for type I error, we adopted a significance level of 0.025, using the Bonferroni method to adjust for the two primary outcomes.
For the first primary outcome, our sample size calculation is based on available literature data. Previous studies reported mean standard deviation of normal-to-normal intervals (SDNN) values ranging from 32ms (SD +/- 30) to 52ms (SD +/- 25) in cancer patients (Fadul, 2010; De Couck, 2013). A randomized trial demonstrated that a four-week training program increased SDNN by 10ms in breast cancer patients (Mostarda, 2017). A metanalysis which included non-randomized trials reported that an exercise program increased SDNN in cancer patients by 12.79ms (Lavín-Pérez , 2021). A value of 50 ms was established as the cutoff for normality (TFESC and NASPE, 1996), and SDNN values below this threshold were identified as an independent prognostic marker for mortality, cardiac events, and recovery (Nolan, 1998; ARIC, 1989). The relative risk of mortality in patients with SDNN <50 ms versus those with SDNN >=50 ms was 2.8 (Kleiger, 1987). An increase of 10ms in SDNN was significantly correlated with 6-minutes walk test, work performance, activity index, and VO2 (Larsen, 2004; Kaikkonen, 2014; Leite, 2015). Based on these studies, we estimate a mean SDNN of 40ms (SD 30) in the standard treatment group and an increase to 50ms (SD 30) in the prehabilitation group, which is considered clinically relevant. Using an alpha level of 0.025 and a power of 90%, the estimated sample size per group is 223 participants, resulting in a total study population of 446 patients.

For the other primary outcome (days at home within the first 30 days after surgery), there is a large observational study on 636,885 patients documenting 25 +/- 6.6 days spent at home in the first 30 days after elective surgery (Bell, 2019). A metanalysis of randomized controlled trials reported that in cancer surgery the prehabilitation group had a 2-days reduction in length of hospital stays compared to the control group (Lambert, 2021). Based on these data, we estimated that the prehabilitation group would spend 27 +/- 6.6 days at home, compared to 25 days +/- 6.6 in the control group. Using a power of 90% and an alpha level of 0.025, our sample size calculation resulted in a requirement of 270 participants per group, with a total sample size of 540, rounded up to 600 to account for potential dropouts.
Therefore, the total sample size of our study (which comprises two primary outcomes, each one with a statistically significant threshold of 0.025) corresponds to the largest of the two sample size calculation: 600 patients (300 patients in the control group and 300 patients in the treatment group). Of these, at least 446 patients (223 per group) will have HRV measurements performed at baseline and the day before surgery.
An independent data and safety monitoring board will oversee and review the results of one planned interim analysis after half of the target sample size will complete follow-up for the primary outcome. In this interim analysis the p value will be 0.0015.

Statistical analysis

Demographic and baseline disease characteristics will be summarized using descriptive statistics. Continuous variables will be reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Continuous variables will be analyzed using t-tests or Mann-Whitney U tests, depending on the data distribution. Normality will be tested using Shapiro-Wilk test. Between-group differences will be evaluated using the t-test or Wilcoxon signed rank test, in accordance with normality of the distribution. Categorical variables will be reported as absolute numbers and percentages and will be analyzed using chi-square tests or Fisher's exact tests, as appropriate. Pearson's correlation coefficient or Spearman's rank correlation coefficient will be used depending on the distributional characteristics of the variables. The level of statistical significance will be set at $p<0.025$ for the primary outcomes. Data will be stored electronically via a web-based case report form and analyzed by use of STATA (Stata Statistical Software: version 16, College Station, TX, USA).

Timing of analysis data

The study will have an overall duration of 24 months (two years). We will start enrolling patients as soon as approval for Ethics Committee will be obtained. Duration of intervention will be guided by surgical planning, and will ideally last for four weeks. Prospectively enrolled patients will be followed-up 30-days after surgery and this will correspond to study completion. An additional 90-days follow-up phone call to assess vital status and quality of life will be performed outside the strict timelines of this grant application. Data review and cleaning to ensure data quality will be continuously performed throughout the project course. Data analysis will start once study enrolment is complete and after a final round of data cleaning and quality checks. We plan to submit the final study manuscript(s) for publication shortly after the end of enrollment.

5.6 Expected outcomes

This study includes two primary outcomes: delta standard deviation of normal-to-normal intervals (SDNN) and days at home within first 30 days after surgery (DAH-30). The delta SDNN from baseline to the day before surgery will be compared between groups. For "days at home within first 30 days after surgery" the mean number of days at home in the first 30 days after surgery will be compared between groups.
Secondary outcomes measure will be: (i) quality of life at 30 days; (ii) 30-days postoperative complication; (iii) correlation between preoperative SDNN and: DAH-30; quality of life at 30 days postoperatively; postoperative complication.
DAH-30 is a composite measure that accounts for the length of stay in the hospital following index surgery (Day 0), readmission to either the index or any other hospital, hospital discharge to a rehabilitation center/hospital or nursing facility, and early deaths after surgery within a single metric. DAH-30 (which is a number between 0 and 30) will be calculated by considering mortality and hospitalization data from the date of the index surgery (day 0) to postoperative day 30. For

example, if a patient is discharged from the hospital on day six after surgery but later readmitted for a period of four days before being discharged again, the patient will be assigned 20 (= 30 minus 6 minur 4) of DAH-30. If a patient experiencing postoperative complications spends 16 days in the hospital, then is transferred to a nursing facility for rehabilitation and spends 24 days there before finally being discharged to their own home, the DAH-30 would be 0 because the patient never stayed at home during the first 30 days after surgery. Deaths within the initial 30 days will be assigned zero of DAH-30 (Bell, 2019; Myles, 2017). The Days at Home (DAH-30) outcome measure is a valuable indicator of postoperative recovery and patient well-being. It provides insights into the duration of hospital stay and the ability of patients to resume their normal daily activities in the comfort of their own home. It considers significant factors such as extended hospital stay, discharge from rehabilitation facilities, complications leading to readmission, and early mortality following surgery.
Quality of life at postoperative day 30 will be assessed by EuroQol Five-Dimension questionnaire (EQ-5D). EQ-5D is a multidimensional questionnaire that encompasses the subjective perception of an individual physical, mental, and social well-being, as influenced by their health status and the impact of any associated conditions or treatments. EQ-5D measures evaluate various domains, including mobility, self-care, usual activities, pain and discomfort, and anxiety and depression.. These measures can be self-reported by individuals through interviews, and provide insights into the impact of health conditions, treatments, and interventions on a person's overall well-being (Brooks, 1996).
Thirty-days postoperative complication will be defined using Clavien-Dindo classification (Claiven, 2009).
We expect that in the prehabilitation group we will observe an increase of days at home in the first 30-days after surgery and an improvement in quality of life together with a reduction in postoperative complications at 30-days.
In addition, we expect that SDNN before surgery will be associated with: increased days at home within the first 30 days after surgery; improved quality of life at 30 days; reduced 30-days postoperative complications.

5.7 Risk analysis, possible problems and solutions

In this study addressing prehabilitation and its impact on surgical outcomes in cancer patients, several potential risks and challenges should be considered and addressed to guarantee the credibility and consistency of the findings.
One possible risk lies in the possibility of patients' non-compliance or withdrawal from the study, which can introduce biases and compromise the validity of the results. To address this issue, it is important to prioritize patient engagement and support throughout the research process. Maintaining frequent communication and offering clear explanation of the study's objectives and potential benefits can contribute towards enhanced patient participation and decreased attrition rate. Using a dedicated monitoring application allows to monitor patients with the net effect to increase the adherence to the protocol.
The heterogeneity of prehabilitation can also pose challenges. To ensure consistency and comparability, our study will centralize prehabilitation through the app and through dedicated experts which will follow all the patients in the prehabilitation arm, confirming treatment consistency and minimizing variations in care. The application will facilitate this centralized approach by enhancing communication and enabling streamlined and standardized delivery of prehabilitation interventions. The experts will also provide standardized education on prehabilitation protocols, guide patients through the intervention process, and solve any questions or concerns that may arise. This approach will help mitigate the potential variability in patient education, ensuring a uniform understanding of the study requirements and expectations. By having central figures dedicated to patient education, we can enhance compliance and adherence to the prehabilitation program, thereby improving the overall effectiveness and reliability of the study's intervention.
We also anticipate potential challenges related to data management and analysis, including data errors, missing data, and data quality control. To tackle these issues, we plan to implement robust data collection systems, with regular checks for accuracy and completeness. Employing appropriate statistical methods and involving experienced biostatisticians will further enhance the validity and reliability of the data analysis.
In order to timely reach the planned sample size, additional centers might participate to the study. Our previous experience in other perioperative RCTs published in the NEJM (Landoni, 2017; Landoni, 2019) showed an enthusiastic participation from several centers. We therefore will explore the possibility to include other recruiting centers at no cost for the donor.
The Site Initiation Visits will be conducted by teleconference, video conference, or face-to-face meetings. All site personnel

will receive training explaining the protocol, the procedures, the web-based randomization system, and the electronic case report forms. Written and electronic materials will be supplied for study staff and for education of clinical staff at each participating site. All sites will receive app and devices in order to carry out all trial's procedures.

5.8 Significance and Innovation

The significance and innovation of this study lie in its potential to revolutionize the care of chronic cancer patients. By investigating the impact of prehabilitation on heart rate variability (HRV) and its correlation with postoperative outcomes, this study aims to provide evidence-based strategies to improve cancer care quality. The study's innovation resides in incorporating HRV as an objective measure of recovery, offering insights into the effectiveness of prehabilitation and preoperative assessment. This approach goes beyond conventional outcome measures, identifying a more comprehensive and personalized assessment of patients' readiness for surgery. An additional innovation is the integration of an application into the protocol, which provides a digital delivery of prehabilitation, making it more accessible and applicable. Notably, this study also represents one of the largest trials and a breakthrough in the field of prehabilitation.

5.9 Bibliography

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5.10 Timeline / Deliverables / Payable Milestones

Study Time plan
PHASE 1. Ethical Approval-Identification of personnel and contracts. Organization of tools and supplies for patient management. Identification of technological applications for patients' monitoring at home- Preparation of data entry form- Months 1-2
PHASE 2. Patient recruitment. Intervention. Follow-up visits. Months 3-23.
PHASE 3. Investigators meetings. Every two months
PHASE 4. Monitoring activities on Helsinki declaration and Good Clinical Practice (GCP). Months 1-24.
PHASE 5. Interim analysis and Final statistical analysis. Months 18/-24.
PHASE 6. Dissemination: writing and publication of methodology and final paper. Months 23-24

Milestones 12 month

Milestone 1: Ethical Committee approval for other UOs
Milestone 2: Contracts of study personnel
Milestone 3: Application development
Milestone 4: Starting patients' recruitment.

Milestones 24 month

Milestone 5: Completion recruitment and intervention
Milestone 6: Investigators meetings.
Milestone 7: Completion of data extraction and statistical analysis
Milestone 8: Communication and Dissemination report

Gantt chart

GANTT_PRIME.PNG

5.11 Equipment and resources available

Facilities Available

The Institutions participating to this study are equipped with state-of-the-art resources and infrastructure to conduct the study. All centers have dedicated clinical spaces, such as examination rooms, researcher dedicated areas, and sophisticated data management systems.
The coordinating center has a well-established network and collaborations with the other healthcare institutions and specialists, enabling seamless coordination and multi-center participation in the study. This will ensure access to a diverse patient population, enhancing the generalizability and impact of the research findings. Overall, the available facilities provides a optimal environment for conducting rigorous prehabilitation research and facilitate the integration of findings into clinical practice for the benefit of patients undergoing surgery. Through collaboration with San Raffaele Institute, over the years we have created and consolidated a network of Italian Hospitals performing academic, no profit high quality research on patients centered outcomes. Over 50 Italian hospitals have been participating over the years in multiple successful mRCTs studies recruiting thousands of patients (Landoni, 2017; Landoni, 2019; Monti, 2023)

Subcontract

Monitoring activities are mandatory for RCTs. Our institute are not 'know-how' to perform those actions. An independent CRO will perform monitoring activities through research assistants. All four UOs will stipulate a subcontract with the same

CRO to perform this service.

5.12 Desc. of the complementarity and sinergy of secondary collab. researchers

The collaboration among the researchers brings together a wealth of complementary expertises and resources, leading to a synergistic partnership in the field of prehabilitation research.
Azienda Ospedaliero Universitaria Pisana stands out for its excellence in various areas, including cancer surgery. It is renowned as one of the leading centers in Italy for the surgical treatment of cancer, with the largest public center for robotic surgery in Europe. The Principal investigator Dr Fabio Guarracino, an esteemed anesthesiologist and past president of EACTAIC and current Chair in the ESAIC Forum 3, rises the expertise and value of the team at an international level. He had a prominent role in large perioperative networks, conducting multicenter studies.
The collaboration between the this unit and the other three, has a longstanding history of clinical and scientific collaboration, spanning over 20 years. This extensive experience fosters a strong synergy among the teams, facilitating communication, coordination, and shared knowledge.
Moreover, the collaboration between the units has yielded successful completion of high-quality randomized controlled trials published in top-rated journals, including the NEJM, demonstrating their collective commitment to rigorous research.
IRCCS Ospedale San Raffaele, located in Milan, is the Italian largest biomedical science park. With a robust clinical scientific structure, this unit collaborates with numerous esteemed research bodies and institutes worldwide. With a highly specialized hospital boasting 1,318 beds and a research institute comprising 1,600 scientists, it remains at the forefront of scientific advancements. With more than 150 peer reviewed published articles per year, the Anesthesia and Intensive Care Unit stands out as the most prolific group in Italy. Prof. Giovanni Landoni led successful multicenter randomized studies published in prestigious journals such as NEJM and JAMA. The center showcases leadership in innovation, development technology and demonstrates a strong focus on patient-centered approaches. The expertise of this center adds significant value to the collaboration in terms of innovation, network and experience.

The participation of the Department of Anesthesia of Azienda Ospedaliero Universitaria Policlinico "G.Rodolico - San Marco" and of the University of Foggia represents a remarkable added value to the project. These entities have established a strong partnership, characterized by extensive collaboration and a shared commitment to excellence in research and patient care. Both the departments have a rich international background, fostering a deep understanding of global healthcare practices and enabling fruitful collaborations with researchers and institutions worldwide. Moreover, their strong connections with national and international societies, as well as patients associations, reflect their dedication to engaging with diverse stakeholders and incorporating their perspectives into the research process. Prof. Gilda Cinnella was the principal investigator of several projects funded by European Union.
By leveraging the complementary competencies and resources of the collaborating centers, this research project is well-positioned to achieve its objectives and generate impactful findings. Their combined expertise ensures a comprehensive and multidisciplinary approach to improve patient outcomes, advance clinical practice, and contribute to the field of medical research.

5.13 Translational relevance and impact for the national health system (SSN)

What is already know about this topic?

Prehabilitation programs have gained attention for their potential impact on healthcare. Evidence suggests that prehabilitation interventions improve patients physical and psychological fitness before surgery. Benefits include reduced postoperative complications, shorter hospital stays, and faster recovery. This can lead to fewer hospital readmissions, reduced length of hospital stay, and a lower necessity of post-surgical rehabilitation or extended care facilities. These factors contribute to cost savings by reducing healthcare resources utilization. However, the lack of standardization and validation of prehabilitation programs still represent a main issue. Evaluating the efficacy of prehabilitation can present

certain challenges due to the complexity of the intervention and the diverse nature of patient populations and surgical procedures. Moreover, there are few high-quality studies, leading to gaps in evidence based medicine.

Details on what is already know about this topic

Several trials demonstrated that prehabilitation can enhance outcomes across different patient cohorts. Chronic cancer patients, who often experience functional decline during their clinical course, are an ideal target population for prehabilitation interventions. However, due to several factors, prehabilitation has not yet gained widespread adoption in this population. Firstly, the available evidence comes from small-sized studies and is not specifically focused on cancer populations. Secondly, there is a lack of validated measures to monitor patients' functional reserve and ensure that they are optimally prepared for surgery. The existing evidence suggests that prehabilitation has the potential to address the functional impairment experienced by chronic cancer patients. However, further studies are needed to evaluate the impact of prehabilitation in cancer patients and establish standardized efficacy measures.

What this reasearch adds?

Firstly, HRV can contribute to the standardization of prehabilitation by providing an objective tool to assess physiological response to stress and recovery. Incorporate HRV measurements into prehabilitation protocols, healthcare professionals can monitor and adjust interventions based on individual patients HRV. Secondly, HRV can be a valuable outcome measure in evaluating the impact of prehabilitation interventions. Using HRV as a tool for validate prehabilitation and an outcome measure, healthcare professionals can enhance the effectiveness of prehabilitation interventions, leading to improved outcomes and a more comprehensive understanding of the benefits of prehabilitation. In addition, validating HRV as a reliable assessment tool in preoperative patients, can improve risk stratification, optimize surgical planning, and enhance patient outcomes. Finally, the use of apps represents a significant advancement in the prehabilitation program.

Details on what this reasearch adds

This research will significantly contribute to chronic cancer care by addressing the evidence gap in prehabilitation studies in this specific population. The integration of heart rate variability (HRV) into prehabilitation will provide a standard measure to evaluate its efficacy on cancer patients.
This research aims to provide evidence-based recommendations on incorporating prehabilitation into standard cancer care, potentially transforming clinical practice and improving patient outcomes. This research will introduce the integration of an application for monitoring and delivering the prehabilitation program. The introduction of HRV in preoperative assessment will enrich the evaluation of patients' readiness for surgery and on preoperative risk. Hence, this research represents a breakthrough, providing crucial insights and advancements in the field of prehabilitation and chronic cancer patients care.

What are the implications for public health, clinical practice, patient care?

Using validated outcome measures, healthcare providers can evaluate prehabilitation effectiveness, guiding evidence-based decision-making and promoting effective strategies. HRV assessment provides physiological insights, allowing personalized interventions and optimized surgical planning. By improving outcomes and reducing hospital stay, prehabilitation reduces additional treatments and postoperative care costs. In addition, introducing HRV in preoperative assessment adds a new dimension to patient care. HRV assessment identifies high-risk patients, preventing adverse events and optimizing resource utilization. Integrating app into prehabilitation programs enhances efficiency by streamlining monitoring and communication, leading to fewer in-person visits, reduced costs, and improved accessibility. In conclusion, validated prehabilitation interventions, objective outcomes, and HRV assessment can contribute to cost reduction, enhanced patient outcomes, and efficient healthcare delivery.

Details on what are the implications for public health, clinical practice, patient care

This research carries profound implications for public health, clinical practice, and patient care. From a public health viewpoint, our study will provide pioneering insights on the efficacy of perioperative prehabilitation to enhance routine care and improve patient outcomes. Such improvements could alleviate financial burdens on healthcare systems and individuals. Clinically, this study will offer healthcare professionals a refined prehabilitation, also providing an additional measure for

preoperative risk assessment using heart rate variability.
In the context of patient care, prehabilitation can empower patients by actively involving them in their own care and recovery process. Besides enhancing overall well-being, prehabilitation promotes a holistic patient-centered approach, potentially improving long-term prognosis. Our research, therefore, stands to redefine standard practices and advance patients well-being.

6 - Budget

Total proposed budget (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	0,00	-0,00	not permitted	0,00
2 Researchers' Contracts	588.000,00	0,00	588.000,00	60,00
3a.1 Equipment (Leasing -	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	143.368,00	0,00	143.368,00	14,63
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts *	78.400,00	0,00	78.400,00	8,00
5 Patient Costs	31.120,00	0,00	31.120,00	3,18
6 IT Services and Data Bases	50.000,00	0,00	50.000,00	5,10
7 Travels	4.000,00	0,00	4.000,00	0,41
8 Publication Costs	4.000,00	0,00	4.000,00	0,41
9 Dissemination	4.000,00	0,00	4.000,00	0,41
10 Overheads *	63.112,00	0,00	63.112,00	6,44
11 Coordination Costs	14.000,00	0,00	14.000,00	1,43
Total	980.000,00	0,00	980.000,00	100,00

* percentage calculated as average value between all the Operating Units.

Report the Co-Funding Contributor:

no co-fund

Budget Justification	
1 Staff Salary	no cost
2 Researchers' Contracts	UO1 - UO2 - UO3 - UO4: Research contracts for 24 months to conduct project's activities;
3a.1 Equipment (Leasing - Rent)	no cost
3a.2 Equipment (buying)	no cost
3b Supplies	UO1 - UO2 - UO3 - UO4: tablets; devices for heart rate variability monitoring; computer; instruments for fitness actvities; posters and depliants;

3c Model Costs	no cost
4 Subcontracts	UO1 -UO2 -UO3 UO4: CRO subcontract cost - Each UO will contribute its own part
5 Patient Costs	UO1 patients insurance; UO2-UO3-UO4: no cost
6 IT Services and Data Bases	UO2 : Software for: 1 database; 2 Online randomization system and database for data collection; 3 -statistical analysis; 4- Heart rate variability; Costs for application development and maintenance; UO1 - UO3 - UO4: no cost
7 Travels	UO2 - UO3 - UO4: Travel cost for meeting/congress/conference travel; UO1: no cost
8 Publication Costs	UO2: Publication costs on open access journal;UO1 - UO3 - UO4: no cost
9 Dissemination	UO1 - UO2 - UO3 - UO4: Congress fee and training courses.
10 Overheads	Overhead - 7%
11 Coordination Costs	UO1: Investigator Meeting and other organization costs; UO2 - UO3 - UO4: no cost

Proposed total budget UO1 Institution: Azienda Ospedaliera Universitaria Pisana (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	0,00	-0,00	not permitted	0,00
2 Researchers' Contracts	120.000,00	0,00	120.000,00	60,00
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	5.000,00	0,00	5.000,00	2,50
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	16.000,00	0,00	16.000,00	8,00
5 Patient Costs	31.120,00	0,00	31.120,00	15,56
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	0,00	0,00	0,00	0,00
8 Publication Costs	0,00	0,00	0,00	0,00
9 Dissemination	1.000,00	0,00	1.000,00	0,50
10 Overheads	12.880,00	0,00	12.880,00	6,44
11 Coordination Costs	14.000,00	0,00	14.000,00	7,00
Total	200.000,00	0,00	200.000,00	100,00

Budget Justification

1 Staff Salary	no cost
2 Researchers' Contracts	UO1: Research contracts for 24 months to conduct project's activities;
3a.1 Equipment (Leasing - Rent)	no cost
3a.2 Equipment (buying)	no cost
3b Supplies	UO1: tablets; devices for heart rate variability monitoring; computer; instruments for fitness actvities; posters and depliants;
3c Model Costs	no cost
4 Subcontracts	UO1: CRO subcontract cost for monitoring activites; Each UO will contribute its own part
5 Patient Costs	UO1: Patients insurance;
6 IT Services and Data Bases	UO1 : no cost
7 Travels	UO1: no cost;
8 Publication Costs	UO1: no cost
9 Dissemination	UO1: no cost
10 Overheads	UO1: overhaed - 7%
11 Coordination Costs	UO1: Investigator Meeting and other organization costs;

Proposed total budget UO2 Institution: Ospedale San Raffaele (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	0,00	-0,00	not permitted	0,00
2 Researchers' Contracts	232.800,00	0,00	232.800,00	60,00
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	42.173,00	0,00	42.173,00	10,87
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	31.040,00	0,00	31.040,00	8,00
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	50.000,00	0,00	50.000,00	12,89
7 Travels	2.000,00	0,00	2.000,00	0,52
8 Publication Costs	4.000,00	0,00	4.000,00	1,03
9 Dissemination	1.000,00	0,00	1.000,00	0,26
10 Overheads	24.987,00	0,00	24.987,00	6,44
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	388.000,00	0,00	388.000,00	100,00

Budget Justification

1 Staff Salary	no cost
2 Researchers' Contracts	UO2:Research contracts for 24 months to conduct project's activities;
3a.1 Equipment (Leasing - Rent)	no cost
3a.2 Equipment (buying)	no cost
3b Supplies	UO2: tablets; devices for heart rate variability monitoring; computer; instruments for fitness actvities; posters and depliants;
3c Model Costs	no cost
4 Subcontracts	UO2: CRO subcontract for monitoring activites - each UO will contribuite its own part
5 Patient Costs	no cost
6 IT Services and Data Bases	UO2: Software for: 1 database; 2 Online randomization system and database for data collection; 3 - statistical analysis; 4- Heart rate variability monitoring; Costs for application development and maintenance;
7 Travels	UO2: Travels expenses for partecipation at national/international meetings to comunicate project results and to participate Investigators meetings
8 Publication Costs	UO2: Publication cost;
9 Dissemination	UO2: congress fee
10 Overheads	UO2: Overhead;
11 Coordination Costs	no cost

Proposed total budget UO3 Institution: Azienda Ospedaliero Universitaria Policlinico San Marco di Catania (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	0,00	-0,00	not permitted	0,00
2 Researchers' Contracts	80.000,00	0,00	80.000,00	60,00
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	32.080,00	0,00	32.080,00	24,06
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	10.667,00	0,00	10.667,00	8,00
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	1.000,00	0,00	1.000,00	0,75
8 Publication Costs	0,00	0,00	0,00	0,00
9 Dissemination	1.000,00	0,00	1.000,00	0,75
10 Overheads	8.587,00	0,00	8.587,00	6,44
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	133.334,00	0,00	133.334,00	100,00

Budget Justification

1 Staff Salary	No cost
2 Researchers' Contracts	UO3: Research contracts for 24 months to conduct project's activities;
3a.1 Equipment (Leasing - Rent)	no cost
3a.2 Equipment (buying)	no cost
3b Supplies	UO3: tablets; devices for heart rate variability monitoring; computers; instruments for fitness actvities; posters and depliants;
3c Model Costs	no cost
4 Subcontracts	UO3: CRO subcontract for monitoring activites; Each UO will contribute its own part;
5 Patient Costs	no cost
6 IT Services and Data Bases	no cost
7 Travels	UO3: Travels expenses for coordination of the project, partecipation at national/international meetings to comunicate project results and to participate Investigators meetings;
8 Publication Costs	no cost
9 Dissemination	UO3: congress fee and training courses.
10 Overheads	UO3: Overhead 7%
11 Coordination Costs	no cost

Proposed total budget UO4 Institution: Università di Foggia (Euro)

Costs	TOTAL BUDGET	Co-Funding	List of costs proposed for funding to the MOH	Percentage of total proposed to the MOH
1 Staff Salary	0,00	-0,00	not permitted	0,00
2 Researchers' Contracts	155.200,00	0,00	155.200,00	60,00
3a.1 Equipment (Leasing - Rent)	0,00	0,00	0,00	0,00
3a.2 Equipment (buying)	0,00	0,00	0,00	0,00
3b Supplies	64.115,00	0,00	64.115,00	24,79
3c Model Costs	0,00	0,00	0,00	0,00
4 Subcontracts	20.693,00	0,00	20.693,00	8,00
5 Patient Costs	0,00	0,00	0,00	0,00
6 IT Services and Data Bases	0,00	0,00	0,00	0,00
7 Travels	1.000,00	0,00	1.000,00	0,39
8 Publication Costs	0,00	0,00	0,00	0,00
9 Dissemination	1.000,00	0,00	1.000,00	0,39
10 Overheads	16.658,00	0,00	16.658,00	6,44
11 Coordination Costs	not permitted	not permitted	not permitted	0,00
Total	258.666,00	0,00	258.666,00	100,00

Budget Justification

1 Staff Salary	no cost
2 Researchers' Contracts	UO4: Research contracts for 24 months to conduct project's activities;
3a.1 Equipment (Leasing - Rent)	No cost
3a.2 Equipment (buying)	no cost
3b Supplies	UO4: tablets; devices for heart rate variability monitoring; computers; instruments for fitness actvities; posters and depliants;
3c Model Costs	no cost
4 Subcontracts	UO4: CRO subcontract for monitoring activites; Each UO will contribute its own part
5 Patient Costs	no cost
6 IT Services and Data Bases	no cost
7 Travels	UO4: Travels expenses for coordination of the project, partecipation at national/international meetings to comunicate project results and to participate Investigators meetings;
8 Publication Costs	no cost
9 Dissemination	UO4: congress fee and training courses;
10 Overheads	UO4: Overhead 7%
11 Coordination Costs	no cost

Principal Investigator Data

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Struttura: UOC Anestesia e Rianimazione cardiotoracovascolare
Istituzione: Regione Toscana
Datore/ente di lavoro? Yes
Datore/ente di lavoro SSN? Yes
Nome datore/ente di lavoro non SSN:
Nome istituzione SSN: Azienda Ospedaliero Universitaria Pisana
Tipo contratto: Lavoro Subordinato a Tempo Indeterminato

Con l'invio della presente proposta si dichiara che la stessa o parti significative di essa non sono oggetto di altri finanziamenti pubblici o privati e che di conseguenza vi è assenza del c.d. doppio finanziamento ai sensi dell'art. 9 del Regolamento (UE) 2021/241, ossia che non ci sia una duplicazione del finanziamento degli stessi costi da parte di altri programmi dell'Unione, nonché con risorse ordinarie da Bilancio statale.

By submitting this proposal, I declare that no significant part or parts of it are recipient of any other public or private funding and that consequently there isn't any so-called double financing pursuant to art. 9 of Regulation (EU) 2021/241, i.e. that there is no duplication in the financing of the same costs by other Euopean Union programs or any other ordinary resources from the State budget.

Project validation result