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Impella vs. VA-ECMO for the treatment of Patients with Cardiogenic Shock. The Impella Network project: Observational Study Protocol for Cost-effectiveness and Budget Impact Analyses

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Note: first and last author names go to the two PIs (Bocconi and San Raffaele), whereas the names of the other clinical centers are ordered alphabetically by surname.

Abstract

Introduction. The treatment of patients with cardiogenic shock (CS), encompasses several health technologies including Impella pumps and veno-arterial extra-corporeal membrane oxygenation (VA-ECMO). However, while they are widely used in clinical practice, information on resource use and quality of life (QoL) associated to these devices is scarce. The aim of this study is therefore to collect and comparatively assess clinical and socio-economic data of Impella versus VA-ECMO for the treatment of patients with severe CS, to ultimately conduct both a cost-effectiveness (CEA) and budget impact (BIA) analyses.

Methods and analysis. This is a prospective plus retrospective, multicenter study conducted under the scientific coordination of the Center for Research on Health and Social Care Management (CERGAS) of SDA Bocconi School of Management and clinical coordination of IRCCS San Raffaele Scientific Institute in Milan. The Impella Network stemmed for the purposes of this study and comprises seventeen Italian clinical centers from Northern to Southern Regions in Italy. The Italian network qualifies as a subgroup of the international Impella Cardiac Surgery (ImCarS) Registry. Patients with CS treated with Impella pumps (CP, 5.0 or 5.5) will be prospectively recruited, and information on clinical outcomes, resource use and QoL collected. Economic data will be retrospectively matched with data from comparable patients treated with VA-ECMO. Both CEA and BIA will be conducted adopting the societal perspective in Italy.

Ethics and dissemination. The Ethical Committee of the clinical PI, IRCCS San Raffaele Hospital, approved the protocol of the ImCarS Registry. Study results will be published in peer-reviewed publications and disseminated through conference presentations.

Conclusion. By comparatively assessing both clinical and socio-economic data associated to two established mechanic circulatory support devices, this study will contribute to generate robust evidence in support of future coverage and reimbursement decisions.

Strengths and limitations of this study

- This is the first study that will collect both clinical and socio-economic data of mechanic circulatory support technologies at the national level in Italy;

- Prospectively, the Impella Network creates an opportunity to expand the scope of research, and to conduct of international comparative studies;
- This study does not consider alternative therapeutic courses for the treatment of patients with cardiogenic shock (e.g., intra-aortic balloon pump), nor the combination of devices (e.g., ECPella).

Introduction

Background

Mechanical circulatory support (MCS) has gained wide application for the treatment of cardiogenic shock (CS) and received a class IIA recommendation by the most recent European Society of Cardiology guidelines on heart failure[1]. In recent years, transcatheter systems have brought great innovation in this field since they enable mechanical left ventricle (LV) unloading, through a lower invasive approach compared to previous generation extracorporeal support devices, equally providing high anterograde flow to reverse the shock status and end-organ damage. They have also the potential to overcome some typical limitations of MCS providing full support up to prolonged period of time and promote patients' recovery at the same time[2–6].

Although both devices are widely used in daily practice, evidence on their uptake and clinical efficacy is constantly evolving. Several meta-analyses evaluated MCS devices for the management of patients with CS[7–9], yet only a few were comparative studies on Impella versus VA-ECMO[10–13]. In this context, conducting comparative studies like randomized controlled trials (RCTs) has proven to be complex, with 5 out of seven RCTs on Impella being discontinued due to inadequate patients' enrollment[14]. Comparative effectiveness studies have become increasingly pivotal since the new Health Technology Assessment Regulation (HTAR 2021/2282) was approved in December 2021 by the EU Parliament[15]. With this regulation, high-risk, life-saving technologies would need to be comparatively assessed at the European level, in line also with the national guidelines of several countries in Europe. However, a prior review by Ardito et al. highlighted that to date virtually no study investigates comparatively socio-economic variables in association to the use of Impella versus VA-ECMO[10]. In light of the new regulatory provisions, the lack of comparative robust clinical and socio-economic evidence might be paralyzing for Member State who are called to take informed coverage and reimbursement decisions[16–18]. As a matter of fact, the limited healthcare resources need to be allocated considering not only the health impact on patient outcomes, but also the financial burden for government budgets. In this context, performing not only economic evaluations (e.g., cost-effectiveness analysis or cost-utility analysis) but also health technology assessments at large, accounting for social, organizational, legal, ethical, or environmental aspects of health technologies, will thus become increasingly pivotal for the uptake of new health technologies and their coverage under national health services. To date, there are only a few

studies investigating the cost effectiveness of MCS devices in the literature. For instance, in a study from 2013 by Roos et al., the cost-effectiveness of Impella was compared to the intra-aortic balloon pump (IABP) in the European perspective, by considering only direct costs[19]. In 2015, the clinical and economic impact of percutaneous ventricular assist devices (pVAD) were compared with IABP for high-risk patients undergoing percutaneous coronary intervention (PCI) by means of conducting a retrospective analysis of published evidence[20]. More recently, another study examined the benefits, harms, cost-effectiveness, and budget impact of the Impella percutaneous ventricular assist device (pVAD) in high-risk PCI and CS[21]. This work builds on the need to conduct more comparative studies in the field of MCS health technologies for the treatment of cardiogenic shock, and to expand the knowledge from existing studies in the Italian framework, which report clinical but not economic data[22–25].

Study objectives

The aim of this study is to generate comparative evidence on the use of Impella versus VA-ECMO for the treatment of patients with severe CS, with the goal to ultimately perform a cost-effectiveness (CEA) and budget impact (BIA) analyses from the national health system (NHS) and societal perspectives in Italy. Both prospective and retrospective data on clinical endpoints and healthcare resource consumption will be collected in Italian heart failure referral centers reunited in what has been named the Impella Network.

The Impella Network

The Impella Network has been created with the purpose of conducting this study. It is a national scientific and medical entity which connects all the Italian institutions within MCS programs and referral for heart failure treatment in which Impella is already used in the clinical practice. All the centers involved in the Impella Network currently run MCS programs and treat patients with CS.

The creation of the Impella Network is promoted under the joint scientific coordination of the Center for Research on Health and Social Care Management (CERGAS) of SDA Bocconi School of Management and IRCCS San Raffaele Scientific Institute in Milan. To answer its specific research question (i.e., assessing the cost-effectiveness and budget impact of Impella versus VA-ECMO for patients with CS), the Impella Network

will leverage the infrastructure of the existing Impella Cardiac Surgery (ImCarS) Registry, therefore qualifying as an ImCarS subgroup analysis of the Italian scenario.

Italian centers were eligible to join the Impella Network if all the following requirements were fulfilled: i) level 2 or 3 center status (with onsite heart failure and mechanical circulatory support program); ii) implantation of Impella 5.0 or Impella CP as standard of care per site; iii) at least one Impella 5.0 or 20 Impella CP implants in the last 3 years (from 2020 to present). The centers meeting the inclusion criteria have been asked to join the Impella Network through a formal invitation from CERGAS SDA Bocconi and IRCCS San Raffaele Scientific Institute as principal clinical center. Table 1 presents the list of clinical centers who agreed to be part of this study.

Table 1 List of clinical centers involved in the data collection

ID	Clinical Center	Location
1	IRCCS Ospedale San Raffaele (PI)	Milano
2	ASST Grande Ospedale Metropolitano Niguarda	Milano
3	San Giovanni Bosco Hospital	Torino
4	Azienda Ospedaliera Universitaria di Padova	Padova
5	Policlinico di Sant'Orsola	Bologna
6	Ospedale Careggi	Firenze
7	Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino	Torino
8	Mater Dei Hospital	Bari
9	Azienda Ospedaliera Sant'Anna e San Sebastiano	Caserta
10	Fondazione IRCCS San Gerardo dei Tintori	Monza
11	Mediterranea Cardiocentro	Napoli
12	IRCCS Ospedale Policlinico San Martino	Genova
13	Azienda Ospedaliera S.Camillo Forlanini	Roma
14	Azienda Ospedaliero-Universitaria delle Marche	Ancona
15	IRCCS Humanitas Research Hospital	Rozzano
16	Azienda Ospedaliera-Universitaria Siena	Siena
17	Ospedale Monaldi, Azienda dei Colli	Napoli

Interestingly, as the field of MCS evolves at high speed and scientific evidence is pivotal to improve clinical practice, the Impella Network might also become a facilitator for prospective analyses of future technologies, and be considered eligible for inclusion in international projects on MCS.

Methods and Analysis

Study design

This will be an observational multicenter study. Patients with severe CS treated either with Impella (CP, 5.0 or 5.5) or with VA-ECMO will represent the study population in the prospective arm. This study population will be compared with a similar population of retrospective patients treated with VA-ECMO for severe CS, which will represent the control group. There is no randomization procedure and all patients will be treated according to the standard of care per site. This protocol has been written following the SPIROS (Standardized Protocol Items: Recommendations for Observational Studies) guidelines[26].

The prospective study foresees a period of six months of follow-up for each patient. Investigators are requested to enroll all patients with CS in their units, according to the inclusion criteria. Data will be collected on a strictly observational basis. The investigators will carry out their usual activity, without any constraints due to the study, both in terms of diagnosis but also regarding patients' management, and the choice of possible treatments. Medical and mechanical circulatory support treatment will be initiated at the discretion of each investigator, according to routine practice. Overall study duration might be variable depending on the time needed for patient enrollment and follow-up in each site, but is estimated to be approximately around 18 months.

Information of comparable patients will be retrieved by retrospectively reviewing the clinical records of patients treated for CS in the Impella Network (retrospective study arm). This information will be retrieved by the clinicians in each participating center and will be inputted within the Impella Cardiac Surgery (ImCarS) Registry, and will ultimately populate the study database together with the information from the prospective study arm. All patients who meet inclusion and exclusion criteria in the appropriate time periods (see "Study population" paragraph) will be included, both for the patients treated with Impella (study arm) and for the patients treated with VA-ECMO (control arm).

It is anticipated that the study protocol might be subject to minor amendments depending on how the data collection unfolds (e.g. fewer patients treated with the technologies in scope to be enrolled in the study, or fewer centers participating in the study).

Study population

Patients treated with Impella

The study population will include all patients suffering from CS treated with Impella 5.5, Impella 5.0 or Impella CP at the Impella Network institutions. To be included in the study group (i.e. Impella Intention To Treat group), patients must meet all the following inclusion criteria:

- CS at presentation (as defined by INTERMACS Class 1-2-3 or SCAI Class C-D-E);
- Support as single device strategy;
- Impella support duration of at least 24 hours;
- Patients treated in the last 3 years (2020-2022) (for retrospective data collection);
- Onset of CS from less than 12 hours.

Different primary diseases and etiologies of heart failure are expected: patients will be further stratified according to the cause of heart failure and phenotype of presentation to account for potential bias in the analysis. Patients' shock degree will also be objectified through clinical risk score calculation. Furthermore, patients meeting any of the following exclusion criteria will not be included in the study:

- Impella implantation for elective protected PCI;
- Impella implantation for post-cardiotomy CS;
- Impella support duration for less than 24 hours;

Patients treated with VA-ECMO

The control group will include all patients treated at the Impella Network institutions for severe left ventricular failure with VA-ECMO. To be included in the control group (i.e. VA-ECMO intention to treat group), patients must fulfill ALL the following inclusion criteria:

- CS at presentation (as defined by INTERMACS Class 1-2-3 or SCAI Class C-D-E);
- VA-ECMO support as single device strategy;
- VA-ECMO support duration of at least 24 hours;
- Onset of CS from less than 12 hours.

Different primary diseases and etiologies of heart failure are expected: patients will be further stratified according to the cause of heart failure and phenotype of presentation to account for potential bias in the analysis. Patients' shock degree will also be objectified through clinical risk score calculation. Furthermore, patients meeting any of the following exclusion criteria will not be included in the study:

- VA-ECMO support for post-cardiotomy CS;
- VA-ECMO support duration for less than 24 hours;
- VA-ECMO for refractory prolonged cardiac arrest (ECPR);
- Presence of biventricular failure;
- Onset of CS from more than 12 hours.

In the era of Impella 5.0/5.5, patients with CS treated with VA-ECMO may be indicative of a more severe population compared to the study group counterpart. In order to prevent potential bias, only VA-ECMO patients with isolated LV failure will be included in the study and patients with CS severity profile comparable to the Impella counterpart at baseline will be analyzed

Sample size

For the prospective arms, any patient treated with Impella or VA-ECMO technologies that meets the inclusion criteria will be recruited and considered for the analyses. Therefore, the sample size cannot be estimated ex-ante. For the retrospective arm, based on previous data from the Italian clinical experience, it is expected that data from approximately 200 VA-ECMO patients will be retrieved and included in the analyses.

Outcomes of interest

Clinical parameters

Data related to medical history, shock related hospitalization, mechanical circulatory support characteristics (for Impella or VA-ECMO), clinical and hospital outcomes will be collected from each center and included in a pre-specified structured data set. Short term MCS related adverse events will be defined according to most recent recommendations[27]. The detailed list of clinical parameters to be collected through the study is outlined in the Supplementary Materials.

Healthcare resource use and costs

Direct healthcare resource use will be identified through the analysis of collected clinical data (e.g., number of visits, device implanted, possible management of adverse events, etc.). Monetary quantification will be performed by applying official reimbursement rates (e.g., DRGs for hospitalizations or tariffs for outpatient services).

The collection of "societal costs" will be performed through the administration to patients of a socio-economic questionnaire, developed ad hoc by CERGAS researchers, and it will include information on out-of-pocket (OOP) expenses (e.g. transport costs for carrying out visits or exams), productivity losses and cost of informal care (provided by relatives). The questionnaire will be administered by the clinicians involved in the study to patients before the intervention (at baseline) and during the follow-up visits (e.g., at 30 days).

Direct healthcare resource use will be measured both for prospective and retrospective patients, while information on "societal costs" will only be available for the group of prospective patients as it is collected through patient questionnaires (not available retrospectively). The detailed list of healthcare resource use variables and the questionnaire to assess the societal impact are reported in the Supplementary Materials.

Quality of life

Only for the patients prospectively enrolled in the study, the patient's quality of life will be measured through the EuroQol 5D-5L questionnaires. EuroQol 5D-5L is a questionnaire capable of providing a generic and synthetic measure of the quality of life in relation to health. The questionnaire consists of two parts: the first includes five items that refer to different health aspects: mobility, personal care, usual activities, pain or discomfort, anxiety or depression. For each item there are five levels of response which indicate, for that area, the absence or presence of mild, moderate, severe or extreme problems. The second part of the questionnaire consists of a graduated visual analogue scale (VAS) from 0 to 100 on which the subject indicates his/her perceived state of health. The questionnaire will be administered by the clinicians involved in the study to patients before the intervention (at baseline) if possible and during the follow-up visits (e.g., at 7 days, 30 days) using a paper-based format. The questionnaire has been requested for non-commercial use via the EuroQol website (registration ID 48771), and is reported in its integral version in the Supplementary Materials.

Data collection and management

Data will be collected through the infrastructure of the existing ImCarS Registry. While this study qualifies as an independent study answering a specific research question (i.e., assessing the cost-effectiveness and budget impact of Impella vs. VA-ECMO for patients with CS), it will leverage the ImCarS Registry (i.e., eCRF, IT platform, capabilities) as a facilitator for the data collection phase[28], therefore qualifying as an ImCarS subgroup analysis of the Italian scenario. More in details, each center belonging to Impella Network will join the ImCarS registry and the current project will benefit from the employment of an electronic Case Report Form (eCRF), that will support any activities related to data collection. The company that will handle the eCRF and will ensure data protection is KKS Gießen Marburg. A per-patient fee of approximately 300€ for Impella cases and 100€ for VA-ECMO cases will be provided by the ImCarS Registry to each participating center. Possibly a clinical research organization (CRO) could be involved upon request of the clinical centers for the management of periodic quality controls to ensure completeness and consistency according to a specific plan agreed among the participating centers. Each clinical center will maintain the ownership of the data points of their own patients.

Patient data recorded in each participating clinical center (hospital medical records) as well as responses to quality of life and socio-economic questionnaires will be anonymized and entered by the clinicians in the eCRF of ImCarS Registry. At the end of the applicable operations and checks, the anonymized data set will be transferred to CERGAS researchers in order to perform the cost-effectiveness analysis (CEA) and budget impact analysis (BIA).

Data analysis

Statistical analysis

The data obtained will be analyzed in a descriptive and inferential way using the most suitable statistical model for each variable. Continuous variables with a symmetrical distribution (e.g., age, questionnaire scores) will be expressed as means and standard deviations (SD). As regards the asymmetrically distributed continuous variables (such as, for example, hospital stay) they will be expressed as median and range. The categorical variables (gender, intra and postoperative complications) will be expressed as frequencies and percentages.

Sub-group analyses may be performed depending on the type of data collected, to have consistent results. Possible missing data for the retrospective group of patients will be treated case by case, depending on the quality of the data themselves.

Cost-Effectiveness Analysis (CEA)

The implementation of a CEA model[29] will aim to compare the management of patients with CS with Impella versus VA-ECMO from both NHS and societal perspectives in Italy. The analysis will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[30,31].

The model will project costs, life years (LYs) and quality adjusted life years (QALYs) on a lifetime horizon in order to evaluate the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR). They will be calculated as the difference in the mean expected costs divided by the difference in the mean expected health outcomes (LYs or QALYs) of the considered management strategies.

The CEA model will be developed based on the following phases: 1) Identification of clinical pathways and healthcare resources consumption for the considered strategies; 2) Inclusion of patients' clinical outcomes and possibly quality of life for the considered strategies (available from data collection phase); 3) Monetary quantification of the healthcare resource consumption from both NHS and societal perspectives (e.g., DRG charges/tariffs, productivity losses and out-of-pocket costs reported by the patients); 4) Analysis and interpretation of model results; 5) Sensitivity analyses.

Budget Impact Analysis (BIA)

A BIA model will be developed starting from the CEA model to evaluate the impact on the hospital healthcare expenditure in Italy of the adoption of Impella, possibly differentiating by the type of Impella pumps, over a period of 3 or 5 years, according to the following steps: 1) Identification of patients' pathways and healthcare resources consumption for the considered strategies; 2) Monetary quantification of the healthcare resource consumption from the hospital perspective through a micro-costing analysis; 3) Definition of the current scenario of distribution of patients among the two considered options: Impella 5.0 and VA-ECMO; 4) Definition of future scenarios in which appropriate increased uses of Impella according to different annual penetration rates are considered. The forecasted increased use of Impella may be estimated on the basis of the evidence available in the literature and/or by clinical opinions collected by an ad-hoc e-survey and by

observing market trends in other jurisdictions (e.g., Germany, USA); 5) Analysis and interpretation of model results; 6) Sensitivity analyses (e.g., Impella 5.5).

Patient and public involvement

Being an observational study, patients will be enrolled as part of the research activities. Informed consent will be provided to, and signed by, patients to ensure the purposes of the study are well understood, and the patients' interests protected.

Ethics and dissemination

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Clinical Practices. No specific risks related to the enrolment in the study are expected for patients, since the study is observational and patients will receive best available treatment. Informed consent collection will be performed according to the ImCarS registry protocol and eventually further disciplined according to specific guidelines and/or best practices of the Ethical Committees of each clinical center. Similarly, collection of data at each participating site will be performed according to the policies of the local institutional review board/ethics committee.

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures.

SDA Bocconi received approval of this protocol from Bocconi University's Ethical Committee (EC). IRCCS San Raffaele Hospital Institute also received ethical approval of the ImCarS protocol from its EC. In parallel, each clinical center presented the documentation to join the ImCarS Registry to their own ECs for approval.

The study results will be disseminated through peer-reviewed scientific publications and presentation in international conferences. The economic analyses, namely the results of the CEA and BIA analyses, will be published in one or more scientific publications on top-tier, peer-reviewed journals. The exact publication pipeline depends from the actual start of the data collection. After the end of the data collection, it will take

approximately 9 months for the research team to process the evidence and prepare the aforementioned manuscripts.

List of abbreviations

BIA: Budget impact analysis

CEA: Cost-effectiveness analysis

CERGAS: Center for Research on Health and Social Care Management

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

CRO: Clinical research organization

CS: Cardiogenic shock

DRG: Diagnosis related groups

EC: Ethical Committee

eCFR: electronic Case Report Form

HTAR: Health Technology Assessment Regulation

IABP: Intra-aortic balloon pump

ICER: Incremental cost-effectiveness ratio

ImCarS: Impella Cardiac Surgery

IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico (research hospital)

LV: Left ventricle

LYs: Life years

MCS: Mechanical circulatory support

NHS: National Health System

OOP: Out-of-pocket

PCI: Percutaneous coronary intervention

pVAD: Percutaneous ventricular assist devices

QALYs: Quality adjusted life years

QoL: Quality of life

RCTs: Randomized controlled trials

SD: Standard deviation

SPIROS: Standardized Protocol Items: Recommendations for Observational Studies

VA-ECMO: Veno-arterial extra-corporeal membrane oxygenation

VAS: Visual analogue scale

Footnotes

Authors contributions

RT and AMS developed the initial study concept. VA, CR and MP devised the study design, drafted the protocol and contributed to critical revisions of the manuscript. RT and AMS are the Scientific Coordinator of the study and take overall responsibility for all aspects of study design, the protocol and the study conduct. All authors contributed to revisions of the protocol and have read and approved this manuscript.

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Conflict of interest

None to declare.

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Supplementary Materials

Supplementary Materials 1. Clinical parameters

Table 1 reports the comprehensive list of clinical variables to be collected for both prospective and retrospective patients. Specifically, the relevant variables for the Impella and ECMO groups are specified, along with the timing for measurements during the observation period.

	Target patients		Timing of measurement			
Patients' characteristics	Impella group	ECMO group	T0 (Baseline)			
Age (years)	X	X	X			
Sex (male/female)	X	X	X			
BMI (kg/m2)	X	X	X			
Arterial Hypertension (yes/no)	X	X	X			
Diabetes Mellitus (yes/no)	X	X	X			
Chronic kidney disease (yes/no)	X	X	X			
Peripheral artery disease(yes/no)	X	X	X			
ICD/CRT (yes/no)	X	X	X			
Previous PTCA (yes/no)	X	X	X			
Previous CABG (yes/no)	X	X	X			
Chronic heart failure (yes/no)	X	X	X			
Cause of acute heart failure:						
*Acute coronary syndrome (yes/no)	X	X	X			
*Myocarditis (yes/no)	X	X	X			
*End stage dilatative cardiomyopathy (yes/no)	X	X	X			
*Arrhythmia/ arrhythmic storm(yes/no)	X	X	X			
*Other (specify)	X	X	X			
Phenotype of cardiogenic shock:						
* LV dominant (yes/no)	X	X	X			
*RV isolated (yes/no)	X	X	X			
* Biventricular failure(yes/no)	X	X	X			
Onset of shock (hours)	X	X	X			
Hemodynamic presentation of shock:						
* Wet and cold (classic CS) (yes/no)	X	X	X			

* Wet and warm (vasodilatory CS) (yes/no)	X	X	X			
* Dry and cold (euvolemic CS) (yes/no)	X	X	X			
Revascularization procedure with stent implantation (yes/no)	X	X	X			
Cardiac arrest(yes/no)	X	X	X			
eGFR (ml/min/m2)	X	X	X			
AKI requiring CRRT yes/no)	X	X	X			
Mechanical ventilation yes/no)	X	X	X			
Days of mechanical ventilation yes/no)	X	X	X			
Mortality risk score	Impella group	ECMO group	T0 (Baseline)			
NYHA	X	X	X			
INTERMACS score	X	X	X			
SCAI class	X	X	X			
CARDshock score (see below)	X	X	X			
RESCUE SCORE	X	X	X			
SAVE score	X	X	X			
MCS strategy and data	Impella group	ECMO group	Event (Y/N)			
Implantation pathway:						
* MCS escalation (yes/no)	X	X	X			
* MCS de-escalation (yes/no)	X	X	X			
* First support (yes/no)	X	X	X			
Device implantation pre PCI (yes/no)	X	X	X			
Device implantation post PCI (yes/no)	X	X	X			
Implantation strategy[1]*:*						
* Bridge to recovery (yes/no)	X	X	X			
* Bridge to LVAD (yes/no)	X	X	X			
* Bridge to transplant (yes/no)	X	X	X			
* Bridge to candidacy (yes/no)	X	X	X			
Implantation route:						
*Axillar (yes/no)	X	X	X			
* Femoral (yes/no)	X	X	X			
Successful implantation (yes/no)	X	X	X			

[1] Typically reassessed also at the end of the patient journey, as it might be subject to changes from the original plan

Need for surgical implant (yes/no)	X	X	X			
Duration of implantation (min)	X	X	Y, minutes			
Hemodinamic and Lab Parameters Trend	Impella group	ECMO group	T0 (Baseline)	24 h post implantation	48-72 h post implantation	First measurement after device removal
Mean arterial pressure (mmHg)	X	X	X	X	X	X
Systolic arterial pressure (mmHg)	X	X	X	X	X	X
Heart rate (bpm)	X	X	X	X	X	X
CVP (mmHg)	X	X	X	X	X	X
CI (l/min/mq)	X	X	X	X	X	X
PCWP (mmHg)	X	X	X	X	X	X
SvO2 (%)	X	X	X	X	X	X
RVSWI (g/m/beat/m^2)	X	X	X	X	X	X
Creatinine (mg/dl)	X	X	X	X	X	X
Lactates (mmol/L)	X	X	X	X	X	X
Troponin (pg/ml)	X	X	X	X	X	X
Inotropic score	X	X	X	X	X	X
NT-proBNP (ng/L)	X	X	X	X	X	X
Platelets (per microliter)	X	X	X	X	X	X
D-dimers (µg/mL)	X	X	X	X	X	X
Bilirubin (mg/dl)	X	X	X	X	X	X
LV EF (%)	X	X	X	X	X	X
RV EF (%)	X	X	X	X	X	X
Mechanical ventilation (yes/no)	X	X	X	X	X	X
Safety in-hosp complications	Impella group	ECMO group	Event during support(yes/no)	Eventual comments/event description		
Bleeding (and site):						
*Major (yes/no)	X	X				
*Moderate (yes/no)	X	X				
*Minor (yes/no)	X	X				
Bleeding requiring surgery (yes/no)	X	X				
Bleeding from Impella (ECMO insertion site (yes/no)	X	X				
Limb ischemia (yes/no)	X	X				
Vascular complication requiring intervention/surgery (yes/no)	X	X				
Ischemic stroke (yes/no)	X	X				
Device malfunction(yes/no)	X	X				
LV perforation (yes/no)	X					

Aortic valve injury (yes/no)	X			
Mitral valve injury (yes/no)	X			
Lesion to other intracardiac structure (yes/no)	X	X		
aortic dissection (yes/no)	X	X		
Other device related injury (yes/no)	X	X		
Major Hemolysis (yes/no)	X	X		
Minor Hemolysis (yes/no)	X	X		
AKI requiring CRRT (yes/no)	X	X		
Sepsis (yes/no)	X	X		
Extracorporeal purification (i.e. Cytosorb) (yes/no)				
EC transfusion, numbers of unit	X	X		
FFP transfusion, numbers of unit	X	X		
PLT transfusion, numbers of unit	X	X		
Device related outcomes	Impella group	ECMO group	Variable	Eventual comments/event description
Duration of MCS support (days)	X	X		
mobilization (chair) with MCS and physiotherapy (yes/no)	X	X		
mobilization (walk) with MCS and physiotherapy (yes/no)	X	X		
Major device malfunction (yes/no)	X	X		
Device exchange (yes/no)	X	X		
Reason for device exchange	X	X		
Survival and cardiac outcomes	Impella group	ECMO group	Event (yes/no)	Eventual comments/event description
30-day mortality (yes/no)	X	X		
ICU mortality (yes/no)	X	X		
Hospital mortality (yes/no)	X	X		
Survival to next therapy (yes/no)	X	X		
Weaning from MCS (yes/no)	X	X		
Myocardial recovery (yes/no)	X	X		
Bridge to LVAD (yes/no)	X	X		
Bridge to Transplant (yes/no)	X	X		
Cause of death	X	X		
Duration of ICU stay, days	X	X		
Duration of hospital stay, days	X	X		
Sequelae of hospital complication at discharge (yes/no)	X	X		

Details of sequelae	X	X		
Duration of mechanical ventilation(days)	X	X		
Tracheostomy (yes/no)	X	X		
Able to perform self-care at discharge (yes/no)	X	X		
Able to return to work at discharge (yes/no)	X	X		

CARDshock score calculation:

Age > 75 years (yes/no)

Confusion at presentation (yes/no)

Prior myocardial infarction of CABG (yes/no)

Acute coronary syndrome ethology (yes/no)

Blood lactate level (<2/2-4/>4)

eGRF (>60/30-60/<30 ml/min/m2)

To the eCRF section dedicated to DTI, it should be added bivalirudin.

It should be added a section that recaps the types of antibiotics use and the duration of therapy (to estimate costs):

Antibiotic class	**Use (yes/no)**	**Duration of therapy (days)**
Cephalosporines (yes/no)		
Pennicillins (yes/no)		
Penicillins (yes/no)		
Glycopeptides (yes/no)		
Fluoroquinolones (yes/no)		
Macrolides (yes/no)		
Carbapenems (yes/no)		
Lyncosamids (yes/no)		
Aminoglicosides (yes/no)		
Tetracyclins (yes/no)		
Sulfonamides (yes/no)		
Oxazolidinones (yes/no)		
Polypeptides (yes/no)		
Other (yes/no) – specify class		
Second line antibiotic therapy needed (yes/no)		

Supplementary Material 2. Healthcare resource use variables (hospital data)

The health services performed to follow-up the patients will be measured by recording the number of assessments performed over the study observation period. These data represent the items necessary to determine the direct healthcare costs incurred by the healthcare system which will be included in the Cost Effectiveness Analysis (CEA). These data are normally traced by hospital records (e.g., eHRs, administrative data), and should be only transferred into the Register platform from treating clinicians. These data are not to be asked to patients. These variables will be measured throughout the patient's the hospital stay. In this study, the following data will be recorded by the doctors during the 6-month follow-up period.

Section 1. Hospitalizations

1.1 Reason for hospitalization

- Heart failure: yes/no/unknown + number
- Ictus ischemic: yes/no/unknown + number
- Ictus hemorrhagic: yes/no/unknown + number
- Bleeding: yes/no/unknown + number
- Renal failure: yes/no/unknown + number
- Respiratory failure: yes/no/unknown + number
- Arrhythmia: yes/no/unknown + number
- Other (please specify): _____ [maximum 5 reasons]

1.2 Number of bed-days in regular ward (e.g., cardiac care ward, other): n (units)

1.3 Number of days in ICU (i.e., intensive care unit): n (units)

1.4 Procedures performed (0 if no procedures are performed)

- Blood transfusion: yes/no/unknown + number
- Dialysis: yes/no/unknown + number
- Ventilatory support: yes/no/unknown + number
- Surgery: yes/no/unknown + number
- Type of surgery (qualitative comment)
- Local interventions: Gastroscopy: yes/no/unknown + number
- Local interventions: Thoracic drainage: yes/no/unknown + number
- Local interventions: Endoscopy: yes/no/unknown + number
- Local interventions: other (please specify name and units): _____
- Physiotherapy: yes/no; nr. of weekly cycles: n (units)
- Ambulatory visit: n (units)

1.5 Exams

- CT Scan: yes/no; n (units)
- MRI: yes/no; n (units)
- Angiography: yes/no; n (units)
- Other (please specify): _____

Section 2: Pharmaceutical consumption during hospitalization

2.1 Drugs used

- Antibiotics: yes/no; days on antibiotics (units)

2.2 Medical devices used

- Nr. of Impella devices used (units)
- Nr. of ECMO devices used (units)
- Dialysis: yes/no
- Extracorporeal purification: yes/no
  - (If yes) Cytosorb: yes/no
  - (If yes) Other (please specify): yes/no + name
- Other (please specify) _____

Section 3: Emergency department

- ER access for heart failure-related symptoms: yes/no
- ER access with no subsequent hospitalization: yes/no + number
- ER access leading to hospitalization: yes/no + number
- Use of the ambulance services: yes/no

Section 4: Other relevant information

- Recovery time needed to go back to work or to "normal life" (from clinician's perspective): 30 days/60 days/120 days/NA

Supplementary Material 3. Patient questionnaire to assess the societal impact of the disease

The following questionnaire will be answered by patients. It has been translated in Italian and will be administered to patients in Italian, however it will be inserted in the Register in English. Both Italian and English versions are provided hereafter. The questionnaire is comprised of two parts:

A. baseline questionnaire, to be administered at signature of informed consent/at ICU-discharge (typically in-person);
B. follow-up questionnaire, to be administered at 6 months, typically over the phone.

*****

A. Baseline questionnaire

1. Employment status:
1.1 What is your current employment status?
If employee:
- factory worker
- employee
- manager, director

If self-employed:
- businessman/woman, freelancer
- other self-employed

If non-professional status:
- retired
- student
- housewife
- other, not employed

1.2 If you are a worker, what is your employment status?
- Full time
- Part-time: 20 hours/week
- Part-time: 24 hours/week
- Part-time: 30 hours/week
- Part-time: 36 hours/week

2. Travel information:
2.1 How much do you spend on average to reach the hospital?
€ _____

2.2 How do you typically reach the hospital?
- By car
- By public transport
- By taxi

- Other (specify)

***

B. Follow-up questionnaire

1. Out-of-pocket (OOP) expenses information:
1.1 In the past 3 months, did you sustain any expense due to cardiogenic shock?
Yes
No
1.2 If yes, what where the healthcare expenses related to?
Medical care
- Specialty visits/exams (e.g., second opinion)
- Drugs (e.g., non-reimbursable drugs, supplements)
- Psychological support
- Other (specify)

1.3 If yes, how much did you spend for each health event?
€ _____
€ _____
€ _____

2. Hospitalizations outside the clinical site of study:
2.1 In the past 3 months, were you hospitalized in a different hospital from this one?
- Yes
- No

2.2 If yes, please indicate the reason: _____ and the hospitalization duration (days): _____

2.3 Did you use emergency services?
- Emergency department
- Ambulance
- None

2.4 Did you pay for any of these services?
- Yes
- No

2.5 If yes, how much did you spend?
€ _____

3. Informal or formal assistance:
3.1 Who gave you informal assistance following your episode of cardiogenic shock? If more than one person, please indicate the one who gives you the most help.
- No one
- Spouse/cohabitant/partner

- Child
- Parent
- Brother/Sister
- Friend
- Other

3.2 If you indicated that someone assists you, how many days does this person assist you, on average, each month, due to issues related to cardiogenic shock? If you want to indicate half a day, write 0,5.
_____ days

3.3 If you indicated that someone assists you, considering the total time you receive as informal assistance from this person, please indicate what percentage you are assisted in the following activities (the sum of the percentages must make 100%):

Activities	%
Nursing activities (eg. drugs administration) and personal care (eg. getting dressed, personal washing)	
Daily activities (eg. work, study, house works, family activities, entertainment, travel)	
Psychological support	

3.4 In the past 3 months, because of complications following your case of cardiogenic shock, have you turned to paid contractors/workers for household help (e.g., babysitter, domestic helper)? (1 answer only)
1. No
2. Yes; How much did you spend? ____ €

4. Limitations caused by the pathology:
4.1 In the past 3 months, approximately how many days of work (professional or home) have you lost due to problems related to cardiogenic shock (if half a day, indicate 0.5)? Exclude any days you have missed for visits, examinations or hospitalizations.
_____ days

4.2 In the past 3 months, how many days have you missed out on activities related to your personal and social life (e.g., going out with friends, hobbies, sports, family activities, etc.) due to problems related to cardiogenic shock (if half a day, indicate 0.5)? Exclude any days you have missed for visits, examinations or hospitalizations.

_____ days

Supplementary Material 4. Patient questionnaire to assess quality of life (EQ-5D-5L)

The EQ-5D-5L questionnaire will be administered to patients included prospectively in the study. The Italian validated version of the questionnaire will be employed. The questionnaire will be administered in a paper-based format, with the clinicians supporting the administration phase (e.g., reading out loud the questions to the patients and making their answers). The questionnaire will be administered to patients in Italian, and inputted in English in the Register. The questionnaire will be administered in three time points following Impella or ECMO implantation: i) after 7 days (i.e., while the patient is still in the hospital); ii) after 30 days; iii) after 6 months of follow-up.A formal request to use the EQ-5D-5L questionnaire has been submitted via the official website (ID: 48771).

Questionario sulla salute

Versione italiana per l'Italia

(Italian version for Italy)

VERSIONE PER LA SOMMINISTRAZIONE DA PARTE DELL'INTERVISTATORE/INTERVISTATRICE

Nota per l'intervistatore/intervistatrice: sebbene si debba tenere conto del particolare stile di conversazione dell'intervistatore/intervistatrice, il testo delle istruzioni del questionario dovrà essere seguito il più fedelmente possibile. Nel caso del sistema descrittivo EQ-5D-5L a pagina 2 del questionario, il testo deve essere seguito fedelmente.

Se l'intervistato/a ha difficoltà nello scegliere una risposta, o chiede chiarimenti, l'intervistatore/intervistatrice dovrà ripetere la domanda parola per parola e chiedere all'intervistato/a di rispondere in un modo che sia il più vicino ai suoi pensieri sulla sua salute oggi.

INTRODUZIONE

(Nota per l'intervistatore/intervistatrice: legga quanto segue all'intervistato/a.)

Desideriamo conoscere ciò che pensa della sua salute. Le spiegherò cosa fare man mano che procedo, ma mi interrompa pure nel caso in cui non dovesse comprendere qualcosa o ritenesse che qualcosa non le fosse chiaro. Non ci sono risposte giuste o sbagliate. Siamo interessati solo al suo personale punto di vista.

Per prima cosa, leggerò alcune domande. Ogni domanda ha una scelta di cinque risposte. Mi dica quale risposta descrive meglio la sua salute OGGI.

Non scelga più di una risposta per ogni gruppo di domande.

(Nota per l'intervistatore/intervistatrice: per prima cosa, legga tutte e cinque le opzioni per ogni domanda. Quindi, chieda all'intervistato/a di scegliere quella che pensa si applichi a se stesso/a. Ripeta la domanda e le opzioni se necessario. Contrassegni la casella appropriata sotto ciascun titolo. Potrebbe essere necessario ricordare regolarmente all'intervistato/a che l'intervallo di tempo è OGGI.)

SISTEMA DESCRITTIVO EQ-5D

Per prima cosa, vorremmo chiederle della CAPACITÀ DI MOVIMENTO. Direbbe che:

1. Non ha difficoltà nel camminare ❑
2. Ha lievi difficoltà nel camminare ❑
3. Ha moderate difficoltà nel camminare ❑
4. Ha gravi difficoltà nel camminare ❑
5. Non è in grado di camminare ❑

Quindi, vorremmo chiederle della CURA DELLA PERSONA. Direbbe che:

1. Non ha difficoltà nel lavarsi o vestirsi ❑
2. Ha lievi difficoltà nel lavarsi o vestirsi ❑
3. Ha moderate difficoltà nel lavarsi o vestirsi ❑
4. Ha gravi difficoltà nel lavarsi o vestirsi ❑
5. Non è in grado di lavarsi o vestirsi ❑

Quindi, vorremmo chiederle delle ATTIVITÀ ABITUALI, per es. lavoro, studio, lavori domestici, attività familiari o di svago. Direbbe che:

1. Non ha difficoltà nello svolgimento delle attività abituali ❑
2. Ha lievi difficoltà nello svolgimento delle attività abituali ❑
3. Ha moderate difficoltà nello svolgimento delle attività abituali ❑
4. Ha gravi difficoltà nello svolgimento delle attività abituali ❑
5. Non è in grado di svolgere le attività abituali ❑

Quindi, vorremmo chiederle quanto DOLORE O FASTIDIO prova. Direbbe che:

1. Non prova alcun dolore o fastidio ❑
2. Prova lieve dolore o fastidio ❑
3. Prova moderato dolore o fastidio ❑
4. Prova grave dolore o fastidio ❑
5. Prova estremo dolore o fastidio ❑

Infine, vorremmo chiederle dell'ANSIA O DEPRESSIONE. Direbbe che:

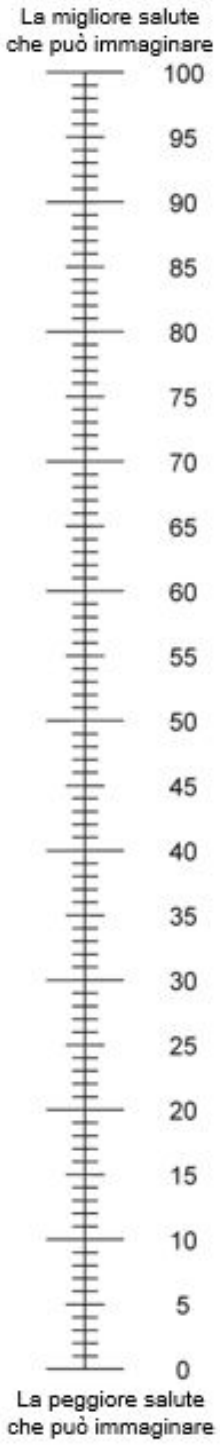
1. Non è ansioso/a o depresso/a ❑
2. È lievemente ansioso/a o depresso/a ❑
3. È moderatamente ansioso/a o depresso/a ❑
4. È gravemente ansioso/a o depresso/a ❑
5. È estremamente ansioso/a o depresso/a ❑

EQ-5D VAS

- **Adesso, vorremmo sapere quanto è buona o cattiva la sua salute OGGI.**
- **Vorremmo che immaginasse una linea verticale numerata da 0 a 100.**
  (Nota per l'intervistatore/intervistatrice: in caso di intervista faccia a faccia, mostrare all'intervistato/a la linea VAS.)
- **100 in cima alla linea rappresenta la migliore salute che può immaginare.**

  0 in fondo alla linea rappresenta la peggiore salute che può immaginare.
- **Vorrei che ora mi indicasse un punto sulla linea per indicare com'è la sua salute OGGI.**
  (Nota per l'intervistatore/intervistatrice: contrassegni la linea nel punto che indica la salute dell'intervistato/a OGGI. Ora, scriva il numero indicato sulla linea nella casella sottostante.)

LA SALUTE DELL'INTERVISTATO/A OGGI = ☐



Grazie per il tempo dedicato a rispondere a queste domande.

SPIROS (Standardized Protocol Items: Recommendations for Observational Studies) checklist

Section and topic	Description / sub-categories	Addressed in the manuscript (Paragraph name)
i) General information		
Title	Descriptive title identifying study design	Title page
Protocol version	Version or amendment number and date and summary of changes	NA
Protocol summary	Brief summary of protocol research	Abstract
Sponsor and partner institute name	Name of sponsor and participating institutes (if applicable)	Title page; Funding
Investigators name	Name of principal and co investigators.	Title page
Affiliations of investigators	Affiliated institutions of investigators	Title page
Principal researcher contact detail	Name, email address, affiliation of Principal researcher for correspondence	Title page
Table of content	Table of content	NA
Page number	Page number on each page of protocol	Yes
List of abbreviations	A detailed List of all abbreviations used in protocol with full form.	List of abbreviations
ii) Introduction		
Background of study	Scientific background of study	Background
Review of prior research	Summary of all previous relevant research	Background
Rationale of study	Justification for conducting the study	Background
Aim	Broader aims and specific objectives of the study	Study objectives
Objective of study	Primary and secondry objectives of study	Study objectives
Prespecified hypothesis	Prespecified null or alternative hypothesis	NA
iii) Methods		
Study design	Description of type/design of study	Study design
Study setting	Description of setting, locations, relevant dates, including periods of recruitment/survey, exposure, follow-up, and data collection. Schedule of study procedure – Figure or table	The Impella Network
Sample size	Estimated number, calculation and assumptions Power calculation	Sample size
Sampling procedure	Description of sampling strategy to ensure representativeness and control of potential bias	Study population
Participants	**Cohort study**—eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. For matched studies, give matching criteria and number of exposed and unexposed	Study population

	Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case **Cross-sectional study**—Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	• All outcomes • Exposures- definition of exposure of interest, • Predictors • Potential confounders • Effect modifiers	Outcomes of interest (Clinical parameters; Healthcare resource use and cost; Quality of life)
Data Sources/Measurement	• For each variable of interest, give sources of data and details of methods of assessment (measurement). • Describe comparability of assessment methods if there is more than one group • Data collection points table • Blinding procedure	Supplementary material
Bias	Describe any efforts to address potential sources of bias. More specifically: • Information bias • Selection Bias • Control for confounding	NA
Statistical analysis plan	• Method of primary / secondary outcomes and additional analysis • Handling of missing data • Post-hoc analysis	Data analysis (Statistical analysis; Cost-effectiveness analysis; Budget impact analysis)
Handling of withdrawals and lost to follow up	Describe the procedures to be followed when a participant ceases participation in the study prematurely or is lost to follow up	NA
Replacements	Provide information on whether or not participants who discontinue the study will be replaced via additional recruitment to maintain the required sample size.	NA
Outcome	Define and describe all primary and secondary outcome or lost to follow up	Outcomes of interest (Clinical parameters; Healthcare resource use and cost; Quality of life)
Database management	Detail plan of database management including: • Data collection (electronic or paper based), • Source data • Data entry • Data editing • Coding • Data storage	Data collection and management

	• Record retention • Data confidentiality	
Validation of instrument	Reliability / validity of instrument or plan to establish validation	NA
Follow up	Plan of follow up and addressing lost to follow up	Study design
Quality control	• Method of quality control • Monitoring (internal and external) • Training of surveyors	NA
Quality assurance	Plan of quality assurance	NA
Expected outcome / results	A brief description of expected outcome or results	NA
iv) Ethical consideration		
Ethical approval	Weather it has been obtained and name of ethical committees. If approval not sought , Reason	Ethics and dissemination
Agreement and consent	Method of taking consent. Reason if consent not sought	Patient and public involvement; Ethics and dissemination
Risk / Harm to participants	Any potential risk or harm to study participants	NA
Adverse event and Severe adverse event reporting	Outline how Adverse Event and Severe adverse event information will be collected.	NA
v) Reporting and dissemination		
Protocol amendments	Methods of communicating to investigators/IRBs and documenting	Study design
Dissemination	How results will be disseminated to participants, practitioners, public	Ethics and dissemination
Publication Plan	Who has right to publish; restrictions; authorship guidelines Open Access	Ethics and dissemination
Reporting of early stopping	Dissemination of results if trial is stopped early (for any reason)	NA
vi) Others		
Limitations	Limitations of proposed study, including risk of bias	Strengths and limitations of this study
Strength of study	Highlight strengths of proposed study	Strengths and limitations of this study
References	List of references cited in protocol	References
Data collection forms	Summary table of all forms used for data collection at each point of study	Supplementary materials
Inform consent forms	Sample of informed consent form, translated into local language	NA
Funding	Source of funding and the role of the funders for the present study	Funding
Acknowledgement for protocol development	Acknowledgement of persons involved in protocol preparation	Acknowledgements
Data sharing policy	To describe how data will be made available in public domain.	
Contributions of authors to protocol	Listed authors should have participated sufficiently in preparation of protocol with details of their contribution.	Authors contribution
Trial registry	For observational studies also registered as trial	NA
Annexures	Data collection form /instruments	Supplementary materials

	Informed consent form Standard operating procedures (SOPs) Detailed Statistical analysis plan (SAP)	

BMJ Open

Impella vs. VA-ECMO for the treatment of Patients with Cardiogenic Shock. The Impella Network project: Observational Study Protocol for Cost-effectiveness and Budget Impact Analyses

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Primary Subject Heading:	Health economics
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Keywords:	CARDIOLOGY, HEALTH ECONOMICS, Observational Study

Impella vs. VA-ECMO for the treatment of Patients with Cardiogenic Shock. The Impella Network project: Observational Study Protocol for Cost-effectiveness and Budget Impact Analyses

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Note: first and last author names go to the two PIs (Bocconi and San Raffaele), whereas the names of the other clinical centers are ordered alphabetically by surname.

Abstract

Introduction. The treatment of patients with cardiogenic shock (CS), encompasses several health technologies including Impella pumps and veno-arterial extra-corporeal membrane oxygenation (VA-ECMO). However, while they are widely used in clinical practice, information on resource use and quality of life (QoL) associated to these devices is scarce. The aim of this study is therefore to collect and comparatively assess clinical and socio-economic data of Impella versus VA-ECMO for the treatment of patients with severe CS, to ultimately conduct both a cost-effectiveness (CEA) and budget impact (BIA) analyses.

Methods and analysis. This is a prospective plus retrospective, multicenter study conducted under the scientific coordination of the Center for Research on Health and Social Care Management (CERGAS) of SDA Bocconi School of Management and clinical coordination of IRCCS San Raffaele Scientific Institute in Milan. The Impella Network stemmed for the purposes of this study and comprises seventeen Italian clinical centers from Northern to Southern Regions in Italy. The Italian network qualifies as a subgroup of the international Impella Cardiac Surgery (ImCarS) Registry. Patients with CS treated with Impella pumps (CP, 5.0 or 5.5) will be prospectively recruited, and information on clinical outcomes, resource use and QoL collected. Economic data will be retrospectively matched with data from comparable patients treated with VA-ECMO. Both CEA and BIA will be conducted adopting the societal perspective in Italy. This study will contribute to generate new socio-economic evidence to inform future coverage decisions.

Ethics and dissemination. The Ethical Committee of 3 clinical centers already approved the protocol, while the other centers are in the process of getting Ethical Committee approval. Study results will be published in peer-reviewed publications and disseminated through conference presentations.

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Strengths and limitations of this study

- This is an observational multicenter study that will evaluate the cost-effectiveness and budget impact associated to use of Impella against VA-ECMO in the treatment of patients with cardiogenic shock;

- The analyses will be performed with the two-fold perspective of the national health system and the larger society in Italy;
- Data collection will leverage the existing infrastructure of the Impella Cardiac Surgery (ImCarS) Registry;
- The outcomes of interests that will be collected are both clinical parameters and socio-economic data, including healthcare resource use and costs, and quality of life;
- This study does not consider alternative therapeutic courses for the treatment of patients with cardiogenic shock (e.g., intra-aortic balloon pump, pharmacological therapy alone), nor the combination of devices (e.g., ECPELLA), as primary therapeutic strategy.

Introduction

Background

Mechanical circulatory support (MCS) has gained wide application for the treatment of cardiogenic shock (CS) and received a class IIA recommendation by the most recent European Society of Cardiology guidelines on heart failure [1]. In recent years, transcatheter systems have brought great innovation in this field since they enable mechanical left ventricle (LV) unloading, through a lower invasive approach compared to previous generation extracorporeal support devices, equally providing high anterograde flow to reverse the shock status and end-organ damage. They have also the potential to overcome some typical limitations of MCS providing full support up to prolonged period of time and promote patients' recovery at the same time [2–6].

Although both devices are widely used in daily practice, evidence on their uptake and clinical efficacy is constantly evolving. Several meta-analyses evaluated MCS devices for the management of patients with CS [7–9], yet only a few were comparative studies on Impella versus VA-ECMO [10–13]. In this context, conducting comparative studies like randomized controlled trials (RCTs) has proven to be complex, with 5 out of seven RCTs on Impella being discontinued due to inadequate patients' enrollment [14]. Comparative effectiveness studies have become increasingly pivotal since the new Health Technology Assessment Regulation (HTAR 2021/2282) was approved in December 2021 by the EU Parliament [15]. With this regulation, high-risk, life-saving technologies would need to be comparatively assessed at the European level, in line also with the national guidelines of several countries in Europe. However, a prior review by Ardito et al. highlighted that to date virtually no study investigates comparatively socio-economic variables in association to the use of Impella versus VA-ECMO [10]. In light of the new regulatory provisions, the lack of comparative robust clinical and socio-economic evidence might be paralyzing for Member State who are called to take informed coverage and reimbursement decisions [16–18]. As a matter of fact, the limited healthcare resources need to be allocated considering not only the health impact on patient outcomes, but also the financial burden for government budgets. In this context, performing not only economic evaluations (e.g., cost-effectiveness analysis or cost-utility analysis) but also health technology assessments at large, accounting for social, organizational, legal, ethical, or environmental aspects of health technologies, will thus become increasingly pivotal for the uptake of new health technologies and their coverage under national health

services. To date, there are only a few studies investigating the cost effectiveness of MCS devices in the literature. For instance, in a study from 2013 by Roos et al., the cost-effectiveness of Impella was compared to the intra-aortic balloon pump (IABP) in the European perspective, by considering only direct costs [19]. In 2015, the clinical and economic impact of percutaneous ventricular assist devices (pVAD) were compared with IABP for high-risk patients undergoing percutaneous coronary intervention (PCI) by means of conducting a retrospective analysis of published evidence [20]. More recently, another study examined the benefits, harms, cost-effectiveness, and budget impact of the Impella percutaneous ventricular assist device (pVAD) in high-risk PCI and CS [21]. This work builds on the need to conduct more comparative studies in the field of MCS health technologies for the treatment of cardiogenic shock, and to expand the knowledge from existing studies in the Italian framework, which report clinical but not economic data [22–25].

Study objectives

The aim of this study is to generate comparative evidence on the use of Impella versus VA-ECMO for the treatment of patients with severe CS, with the goal to ultimately perform a cost-effectiveness (CEA) and budget impact (BIA) analyses from the national health system (NHS) and societal perspectives in Italy. Both prospective and retrospective data on clinical endpoints and healthcare resource consumption will be collected in Italian heart failure referral centers reunited in what has been named the Impella Network.

The Impella Network

The Impella Network has been created with the purpose of conducting this study. It is a national scientific and medical entity which connects all the Italian institutions within MCS programs and referral for heart failure treatment in which Impella is already used in the clinical practice. All the centers involved in the Impella Network currently run MCS programs and treat patients with CS.

The creation of the Impella Network is promoted under the joint scientific coordination of the Center for Research on Health and Social Care Management (CERGAS) of SDA Bocconi School of Management and IRCCS San Raffaele Scientific Institute in Milan. To answer its specific research question (i.e., assessing the cost-effectiveness and budget impact of Impella versus VA-ECMO for patients with CS), the Impella Network

will leverage the infrastructure of the existing Impella Cardiac Surgery (ImCarS) Registry, therefore qualifying as an ImCarS subgroup analysis of the Italian scenario.

Italian centers were eligible to join the Impella Network if all the following requirements were fulfilled: i) level 2 or 3 center status (with onsite heart failure and mechanical circulatory support program); ii) implantation of Impella 5.0 or Impella CP as standard of care per site; iii) at least one Impella 5.0 or 20 Impella CP implants in the last 3 years (from 2020 to present). The centers meeting the inclusion criteria have been asked to join the Impella Network through a formal invitation from CERGAS SDA Bocconi and IRCCS San Raffaele Scientific Institute as principal clinical center. Table 1 presents the list of clinical centers who agreed to be part of this study.

Table 1 List of clinical centers involved in the data collection

ID	Clinical Center	Location
1	IRCCS Ospedale San Raffaele (PI)	Milano
2	ASST Grande Ospedale Metropolitano Niguarda	Milano
3	San Giovanni Bosco Hospital	Torino
4	Azienda Ospedaliera Universitaria di Padova	Padova
5	Policlinico di Sant'Orsola	Bologna
6	Ospedale Careggi	Firenze
7	Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino	Torino
8	Mater Dei Hospital	Bari
9	Azienda Ospedaliera Sant'Anna e San Sebastiano	Caserta
10	Fondazione IRCCS San Gerardo dei Tintori	Monza
11	Mediterranea Cardiocentro	Napoli
12	IRCCS Ospedale Policlinico San Martino	Genova
13	Azienda Ospedaliera S.Camillo Forlanini	Roma
14	Azienda Ospedaliero-Universitaria delle Marche	Ancona
15	IRCCS Humanitas Research Hospital	Rozzano
16	Azienda Ospedaliera-Universitaria Siena	Siena
17	Ospedale Monaldi, Azienda dei Colli	Napoli

Interestingly, as the field of MCS evolves at high speed and scientific evidence is pivotal to improve clinical practice, the Impella Network might also become a facilitator for prospective analyses of future technologies, and be considered eligible for inclusion in international projects on MCS.

Methods and Analysis

Study design

This will be an observational multicenter study. Patients with severe CS treated either with Impella (CP, 5.0 or 5.5) or with VA-ECMO will represent the study population in the prospective arm. This study population will be compared with a similar population of retrospective patients treated with VA-ECMO for severe CS, which will represent the control group. There is no randomization procedure and all patients will be treated according to the standard of care per site. This protocol has been written following the SPIROS (Standardized Protocol Items: Recommendations for Observational Studies) guidelines [26].

The prospective study foresees a period of six months of follow-up for each patient. Investigators are requested to enroll all patients with CS in their units, according to the inclusion criteria. Data will be collected on a strictly observational basis. The investigators will carry out their usual activity, without any constraints due to the study, both in terms of diagnosis but also regarding patients' management, and the choice of possible treatments. Medical and mechanical circulatory support treatment will be initiated at the discretion of each investigator, according to routine practice. Overall study duration might be variable depending on the time needed for patient enrollment and follow-up in each site, but is estimated to be approximately around 18 months.

Information of comparable patients will be retrieved by retrospectively reviewing the clinical records of patients treated for CS in the Impella Network (retrospective study arm). This information will be retrieved by the clinicians in each participating center and will be inputted within the Impella Cardiac Surgery (ImCarS) Registry, and will ultimately populate the study database together with the information from the prospective study arm. All patients who meet inclusion and exclusion criteria in the appropriate time periods (see "Study population" paragraph) will be included, both for the patients treated with Impella (study arm) and for the patients treated with VA-ECMO (control arm).

It is anticipated that the study protocol might be subject to minor amendments depending on how the data collection unfolds (e.g. fewer patients treated with the technologies in scope to be enrolled in the study, or fewer centers participating in the study).

Study population

Patients treated with Impella

The study population will include all patients suffering from CS, according to clinically relevant classifications (Interagency Registry for mechanically assisted circulatory support (INTERMACS) and International Society for Cardiovascular Angiography and Interventions (SCAI)) treated with Impella 5.5, Impella 5.0 or Impella CP at the Impella Network institutions. To be included in the study group (i.e. Impella Intention To Treat group), patients must meet all the following inclusion criteria:

- CS at presentation (as defined by INTERMACS Class 1-2-3 or SCAI Class C-D-E);
- Support as single device strategy;
- Impella support duration of at least 24 hours;
- Patients treated in the last 3 years (2020-2022) (for retrospective data collection);
- Onset of CS from less than 12 hours.

Different primary diseases and etiologies of heart failure are expected: patients will be further stratified according to the cause of heart failure and phenotype of presentation to account for potential bias in the analysis. Patients' shock degree will also be objectified through clinical risk score calculation. Furthermore, patients meeting any of the following exclusion criteria will not be included in the study:

- Impella implantation for elective protected PCI;
- Impella implantation for post-cardiotomy CS;
- Impella support duration for less than 24 hours;

Patients treated with VA-ECMO

The control group will include all patients treated at the Impella Network institutions for severe left ventricular failure with VA-ECMO. To be included in the control group (i.e. VA-ECMO intention to treat group), patients must fulfill ALL the following inclusion criteria:

- CS at presentation (as defined by INTERMACS Class 1-2-3 or SCAI Class C-D-E);
- VA-ECMO support as single device strategy;
- VA-ECMO support duration of at least 24 hours;

- Onset of CS from less than 12 hours.

Different primary diseases and etiologies of heart failure are expected: patients will be further stratified according to the cause of heart failure and phenotype of presentation to account for potential bias in the analysis. Patients' shock degree will also be objectified through clinical risk score calculation. Furthermore, patients meeting any of the following exclusion criteria will not be included in the study:

- VA-ECMO support for post-cardiotomy CS;
- VA-ECMO support duration for less than 24 hours;
- VA-ECMO for refractory prolonged cardiac arrest (ECPR);
- Presence of biventricular failure;
- Onset of CS from more than 12 hours.

In the era of Impella 5.0/5.5, patients with CS treated with VA-ECMO may be indicative of a more severe population compared to the study group counterpart. In order to prevent potential bias, only VA-ECMO patients with isolated LV failure will be included in the study and patients with CS severity profile comparable to the Impella counterpart at baseline will be analyzed.

Sample size

For the prospective arms, any patient treated with Impella or VA-ECMO technologies that meets the inclusion criteria will be recruited and considered for the analyses. Therefore, the sample size cannot be estimated ex-ante. For the retrospective arm, based on previous data from the Italian clinical experience, it is expected that data from approximately 200 VA-ECMO patients will be retrieved and included in the analyses.

Outcomes of interest

Clinical parameters

Data related to medical history, shock related hospitalization, mechanical circulatory support characteristics (for Impella or VA-ECMO), clinical and hospital outcomes will be collected from each center and included in a pre-specified structured data set. Short term MCS related adverse events will be defined according to most recent recommendations [27]. In addition to data registered at specific time points (for example, at baseline)

and outcome measures, several hemodynamic, laboratory and clinical data will be assessed regularly during the treatment with Impella or VA ECMO to assess the evolution of the condition of shock during support. The detailed list of clinical parameters to be collected through the study is outlined in the Supplementary Materials.

Healthcare resource use and costs

Direct healthcare resource use will be identified through the analysis of collected clinical data (e.g., number of visits, device implanted, possible management of adverse events, etc.). Monetary quantification will be performed by applying official reimbursement rates (e.g., DRGs for hospitalizations or tariffs for outpatient services).

The collection of "societal costs" will be performed through the administration to patients of a socio-economic questionnaire, developed ad hoc by CERGAS researchers, and it will include information on out-of-pocket (OOP) expenses (e.g. transport costs for carrying out visits or exams), productivity losses and cost of informal care (provided by relatives). The questionnaire will be administered by the clinicians involved in the study to patients before the intervention (at baseline) and during the follow-up visits (e.g., at 30 days).

Direct healthcare resource use will be measured both for prospective and retrospective patients, while information on "societal costs" will only be available for the group of prospective patients as it is collected through patient questionnaires (not available retrospectively). The detailed list of healthcare resource use variables and the questionnaire to assess the societal impact are reported in the Supplementary Materials.

Quality of life

Only for the patients prospectively enrolled in the study, the patient's quality of life will be measured through the EuroQol 5D-5L questionnaires. EuroQol 5D-5L is a questionnaire capable of providing a generic and synthetic measure of the quality of life (QoL) in relation to health. The questionnaire consists of two parts: the first includes five items that refer to different health aspects: mobility, personal care, usual activities, pain or discomfort, anxiety or depression. For each item there are five levels of response which indicate, for that area, the absence or presence of mild, moderate, severe or extreme problems. The second part of the questionnaire consists of a graduated visual analogue scale (VAS) from 0 to 100 on which the subject indicates his/her perceived state of health. The questionnaire will be administered by the clinicians involved in the study to patients before the intervention (at baseline) if possible and during the follow-up visits (e.g., at 7 days, 30 days)

using a paper-based format. The clinicians will choose an appropriate timing to fill in the questionnaire, namely when patients are awake, conscious and willing to respond. However, should the patients be too weak to respond, or should they fail to recover from the shock, they will be excluded from the QoL analyses.

The questionnaire has been requested for non-commercial use via the EuroQol website (registration ID 48771), and is reported in its integral version in the Supplementary Materials.

Data collection and management

Data will be collected through the infrastructure of the existing ImCarS Registry. While this study qualifies as an independent study answering a specific research question (i.e., assessing the cost-effectiveness and budget impact of Impella vs. VA-ECMO for patients with CS), it will leverage the ImCarS Registry (i.e., eCRF, IT platform, capabilities) as a facilitator for the data collection phase [28], therefore qualifying as an ImCarS subgroup analysis of the Italian scenario. More in details, each center belonging to Impella Network will join the ImCarS registry and the current project will benefit from the employment of an electronic Case Report Form (eCRF), that will support any activities related to data collection. The company that will handle the eCRF and will ensure data protection is KKS Gießen Marburg. A per-patient fee of approximately 300€ for Impella cases and 100€ for VA-ECMO cases will be provided by the ImCarS Registry to each participating center. Possibly a clinical research organization (CRO) could be involved upon request of the clinical centers for the management of periodic quality controls to ensure completeness and consistency according to a specific plan agreed among the participating centers. Each clinical center will maintain the ownership of the data points of their own patients.

Patient data recorded in each participating clinical center (hospital medical records) as well as responses to quality of life and socio-economic questionnaires will be anonymized and entered by the clinicians in the eCRF of ImCarS Registry. At the end of the applicable operations and checks, the anonymized data set will be transferred to CERGAS researchers in order to perform the cost-effectiveness analysis (CEA) and budget impact analysis (BIA).

Data analysis

Statistical analysis

The data obtained will be analyzed in a descriptive and inferential way using the most suitable statistical model for each variable. Continuous variables with a symmetrical distribution (e.g., age, questionnaire scores) will be expressed as means and standard deviations (SD). As regards the asymmetrically distributed continuous variables (such as, for example, hospital stay) they will be expressed as median and range. The categorical variables (gender, intra and postoperative complications) will be expressed as frequencies and percentages. Sub-group analyses may be performed depending on the type of data collected, to have consistent results. Possible missing data for the retrospective group of patients will be treated case by case, depending on the quality of the data themselves.

Cost-Effectiveness Analysis (CEA)

The implementation of a CEA model [29] will aim to compare the management of patients with CS with Impella versus VA-ECMO from both NHS and societal perspectives in Italy. The analysis will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [30, 31].

The model will project costs, life years (LYs) and quality adjusted life years (QALYs) on a lifetime horizon in order to evaluate the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR). They will be calculated as the difference in the mean expected costs divided by the difference in the mean expected health outcomes (LYs or QALYs) of the considered management strategies. It has to be specified that QoL will be measured as long as patients stay alive. Interpolation techniques might be used to manage missing data (e.g., to carry forward QoL measurements occurred prior to death); however, patients who never completed QoL measurements will be excluded from QALYs analyses.

The CEA model will be developed based on the following phases: 1) Identification of clinical pathways and healthcare resources consumption for the considered strategies; 2) Inclusion of patients' clinical outcomes and possibly quality of life for the considered strategies (available from data collection phase); 3) Monetary quantification of the healthcare resource consumption from both NHS and societal perspectives (e.g., DRG charges/tariffs, productivity losses and out-of-pocket costs reported by the patients); 4) Analysis and interpretation of model results; 5) Sensitivity analyses. In addition, if collected data will allow it, centers will

be clustered based on the number of implanted Impella devices and patients treated, to investigate if there is a relationship between cost-effectiveness and the volumes of device use in each center. The definition of the clusters and conduct of sub-group analyses will depend on the data that will be actually collected.

Budget Impact Analysis (BIA)

A BIA model will be developed starting from the CEA model to evaluate the impact on the hospital healthcare expenditure in Italy of the adoption of Impella, possibly differentiating by the type of Impella pumps, over a period of 3 or 5 years, according to the following steps: 1) Identification of patients' pathways and healthcare resources consumption for the considered strategies; 2) Monetary quantification of the healthcare resource consumption from the hospital perspective through a micro-costing analysis; 3) Definition of the current scenario of distribution of patients among the two considered options: Impella 5.0 and VA-ECMO; 4) Definition of future scenarios in which appropriate increased uses of Impella according to different annual penetration rates are considered. The forecasted increased use of Impella may be estimated on the basis of the evidence available in the literature and/or by clinical opinions collected by an ad-hoc e-survey and by observing market trends in other jurisdictions (e.g., Germany, USA); 5) Analysis and interpretation of model results; 6) Sensitivity analyses (e.g., Impella 5.5).

As a final note, it has to be highlighted that the BIA will be conducted from an Italian perspective, based on the cost framework observed within Italian facilities. Therefore, extending the study results to other geographical contexts should be done with caution, and marginal adjustments might be needed to account for country-specific differences in the costs sustained at the local level.

Patient and public involvement

Being an observational study, patients will be enrolled as part of the research activities. Informed consent will be provided to, and signed by, patients to ensure the purposes of the study are well understood, and the patients' interests protected. We plan on involving relevant patient associations when disseminating the study results.

Ethics and dissemination

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Clinical Practices. No specific risks related to the enrolment in the study are expected for patients, since the study is observational and patients will receive best available treatment. Informed consent collection will be performed according to the ImCarS registry protocol and eventually further disciplined according to specific guidelines and/or best practices of the Ethical Committees of each clinical center. Similarly, collection of data at each participating site will be performed according to the policies of the local institutional review board/ethics committee.

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures.

SDA Bocconi received approval of this protocol from Bocconi University's Ethical Committee (EC). IRCCS San Raffaele Hospital Institute also received ethical approval of the ImCarS protocol from its EC. In parallel, each clinical center presented the documentation to join the ImCarS Registry to their own ECs for approval: currently, Azienda Ospedaliera San Camillo Forlanini (Rome) and Clinica Mediterranea (Naples) among participanting centers already received the approval of ethical committee.

The study results will be disseminated through peer-reviewed scientific publications and presentation in international conferences. The economic analyses, namely the results of the CEA and BIA analyses, will be published in one or more scientific publications on top-tier, peer-reviewed journals. The exact publication pipeline depends from the actual start of the data collection. After the end of the data collection, it will take approximately 9 months for the research team to process the evidence and prepare the aforementioned manuscripts.

List of abbreviations

BIA: Budget impact analysis

CEA: Cost-effectiveness analysis

CERGAS: Center for Research on Health and Social Care Management

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

CRO: Clinical research organization

CS: Cardiogenic shock

DRG: Diagnosis related groups

EC: Ethical Committee

eCFR: electronic Case Report Form

HTAR: Health Technology Assessment Regulation

IABP: Intra-aortic balloon pump

ICER: Incremental cost-effectiveness ratio

ImCarS: Impella Cardiac Surgery

IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico (research hospital)

LV: Left ventricle

LYs: Life years

MCS: Mechanical circulatory support

NHS: National Health System

OOP: Out-of-pocket

PCI: Percutaneous coronary intervention

pVAD: Percutaneous ventricular assist devices

QALYs: Quality adjusted life years

QoL: Quality of life

RCTs: Randomized controlled trials

SD: Standard deviation

SPIROS: Standardized Protocol Items: Recommendations for Observational Studies

VA-ECMO: Veno-arterial extra-corporeal membrane oxygenation

VAS: Visual analogue scale

Footnotes

Authors contributions

RT and AMS developed the initial study concept. VA, CR and MP devised the study design, including methodology, and wrote the original draft of the protocol. AB, CB, EC, GG, MI, AL, MM, AM, JO, DP, MP, VP, IP, PS, GT, SV, PV contributed to critical revisions of the manuscript. RT and AMS are the Scientific Coordinators of the study and take overall responsibility for all aspects of study design, the protocol and the study conduct. RT acquired funding for the study. All authors VA, CR, MP, AB, CB, EC, GG, MI, AL, MM, AM, JO, DP, MP, VP, IP, PS, GT, SV, PV, RT and AMS contributed to review and editing of the protocol and have read and approved this manuscript.

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Conflict of interest

None to declare.

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Supplementary Materials

Supplementary Materials 1. Clinical parameters

Table 1 reports the comprehensive list of clinical variables to be collected for both prospective and retrospective patients. Specifically, the relevant variables for the Impella and ECMO groups are specified, along with the timing for measurements during the observation period.

	Target patients		Timing of measurement			
Patients' characteristics	Impella group	ECMO group	T0 (Baseline)			
Age (years)	X	X	X			
Sex (male/female)	X	X	X			
BMI (kg/m2)	X	X	X			
Arterial Hypertension (yes/no)	X	X	X			
Diabetes Mellitus (yes/no)	X	X	X			
Chronic kidney disease (yes/no)	X	X	X			
Peripheral artery disease(yes/no)	X	X	X			
ICD/CRT (yes/no)	X	X	X			
Previous PTCA (yes/no)	X	X	X			
Previous CABG (yes/no)	X	X	X			
Chronic heart failure (yes/no)	X	X	X			
Cause of acute heart failure:						
*Acute coronary syndrome (yes/no)	X	X	X			
*Myocarditis (yes/no)	X	X	X			
*End stage dilatative cardiomyopathy (yes/no)	X	X	X			
*Arrhythmia/ arrhythmic storm(yes/no)	X	X	X			
*Other (specify)	X	X	X			
Phenotype of cardiogenic shock:						
* LV dominant (yes/no)	X	X	X			
*RV isolated (yes/no)	X	X	X			
* Biventricular failure(yes/no)	X	X	X			
Onset of shock (hours)	X	X	X			
Hemodynamic presentation of shock:						
* Wet and cold (classic CS) (yes/no)	X	X	X			

* Wet and warm (vasodilatory CS) (yes/no)	X	X	X			
* Dry and cold (euvolemic CS) (yes/no)	X	X	X			
Revascularization procedure with stent implantation (yes/no)	X	X	X			
Cardiac arrest(yes/no)	X	X	X			
eGFR (ml/min/m2)	X	X	X			
AKI requiring CRRT yes/no)	X	X	X			
Mechanical ventilation yes/no)	X	X	X			
Days of mechanical ventilation yes/no)	X	X	X			
Mortality risk score	Impella group	ECMO group	T0 (Baseline)			
NYHA	X	X	X			
INTERMACS score	X	X	X			
SCAI class	X	X	X			
CARDshock score (see below)	X	X	X			
RESCUE SCORE	X	X	X			
SAVE score	X	X	X			
MCS strategy and data	Impella group	ECMO group	Event (Y/N)			
Implantation pathway:						
* MCS escalation (yes/no)	X	X	X			
* MCS de-escalation (yes/no)	X	X	X			
* First support (yes/no)	X	X	X			
Device implantation pre PCI (yes/no)	X	X	X			
Device implantation post PCI (yes/no)	X	X	X			
Implantation strategy[1]*:*						
* Bridge to recovery (yes/no)	X	X	X			
* Bridge to LVAD (yes/no)	X	X	X			
* Bridge to transplant (yes/no)	X	X	X			
* Bridge to candidacy (yes/no)	X	X	X			
Implantation route:						
*Axillar (yes/no)	X	X	X			
* Femoral (yes/no)	X	X	X			
Successful implantation (yes/no)	X	X	X			

[1] Typically reassessed also at the end of the patient journey, as it might be subject to changes from the original plan

Need for surgical implant (yes/no)	X	X	X			
Duration of implantation (min)	X	X	Y, minutes			
Hemodinamic and Lab Parameters Trend	Impella group	ECMO group	T0 (Baseline)	24 h post implantation	48-72 h post implantation	First measurement after device removal
Mean arterial pressure (mmHg)	X	X	X	X	X	X
Systolic arterial pressure (mmHg)	X	X	X	X	X	X
Heart rate (bpm)	X	X	X	X	X	X
CVP (mmHg)	X	X	X	X	X	X
CI (l/min/mq)	X	X	X	X	X	X
PCWP (mmHg)	X	X	X	X	X	X
SvO2 (%)	X	X	X	X	X	X
RVSWI (g/m/beat/m^2)	X	X	X	X	X	X
Creatinine (mg/dl)	X	X	X	X	X	X
Lactates (mmol/L)	X	X	X	X	X	X
Troponin (pg/ml)	X	X	X	X	X	X
Inotropic score	X	X	X	X	X	X
NT-proBNP (ng/L)	X	X	X	X	X	X
Platelets (per microliter)	X	X	X	X	X	X
D-dimers (µg/mL)	X	X	X	X	X	X
Bilirubin (mg/dl)	X	X	X	X	X	X
LV EF (%)	X	X	X	X	X	X
RV EF (%)	X	X	X	X	X	X
Mechanical ventilation (yes/no)	X	X	X	X	X	X
Safety in-hosp complications	Impella group	ECMO group	Event during support(yes/no)	Eventual comments/event description		
Bleeding (and site):						
*Major (yes/no)	X	X				
*Moderate (yes/no)	X	X				
*Minor (yes/no)	X	X				
Bleeding requiring surgery (yes/no)	X	X				
Bleeding from Impella (ECMO insertion site (yes/no)	X	X				
Limb ischemia (yes/no)	X	X				
Vascular complication requiring intervention/surgery (yes/no)	X	X				
Ischemic stroke (yes/no)	X	X				
Device malfunction(yes/no)	X	X				
LV perforation (yes/no)	X					

Aortic valve injury (yes/no)	X			
Mitral valve injury (yes/no)	X			
Lesion to other intracardiac structure (yes/no)	X	X		
aortic dissection (yes/no)	X	X		
Other device related injury (yes/no)	X	X		
Major Hemolysis (yes/no)	X	X		
Minor Hemolysis (yes/no)	X	X		
AKI requiring CRRT (yes/no)	X	X		
Sepsis (yes/no)	X	X		
Extracorporeal purification (i.e. Cytosorb) (yes/no)				
EC transfusion, numbers of unit	X	X		
FFP transfusion, numbers of unit	X	X		
PLT transfusion, numbers of unit	X	X		
Device related outcomes	Impella group	ECMO group	Variable	Eventual comments/event description
Duration of MCS support (days)	X	X		
mobilization (chair) with MCS and physiotherapy (yes/no)	X	X		
mobilization (walk) with MCS and physiotherapy (yes/no)	X	X		
Major device malfunction (yes/no)	X	X		
Device exchange (yes/no)	X	X		
Reason for device exchange	X	X		
Survival and cardiac outcomes	Impella group	ECMO group	Event (yes/no)	Eventual comments/event description
30-day mortality (yes/no)	X	X		
ICU mortality (yes/no)	X	X		
Hospital mortality (yes/no)	X	X		
Survival to next therapy (yes/no)	X	X		
Weaning from MCS (yes/no)	X	X		
Myocardial recovery (yes/no)	X	X		
Bridge to LVAD (yes/no)	X	X		
Bridge to Transplant (yes/no)	X	X		
Cause of death	X	X		
Duration of ICU stay, days	X	X		
Duration of hospital stay, days	X	X		
Sequelae of hospital complication at discharge (yes/no)	X	X		

Details of sequelae	X	X		
Duration of mechanical ventilation(days)	X	X		
Tracheostomy (yes/no)	X	X		
Able to perform self-care at discharge (yes/no)	X	X		
Able to return to work at discharge (yes/no)	X	X		

CARDshock score calculation:

Age > 75 years (yes/no)

Confusion at presentation (yes/no)

Prior myocardial infarction of CABG (yes/no)

Acute coronary syndrome ethology (yes/no)

Blood lactate level (<2/2-4/>4)

eGRF (>60/30-60/<30 ml/min/m2)

To the eCRF section dedicated to DTI, it should be added bivalirudin.

It should be added a section that recaps the types of antibiotics use and the duration of therapy (to estimate costs):

Antibiotic class	**Use (yes/no)**	**Duration of therapy (days)**
Cephalosporines (yes/no)		
Pennicillins (yes/no)		
Penicillins (yes/no)		
Glycopeptides (yes/no)		
Fluoroquinolones (yes/no)		
Macrolides (yes/no)		
Carbapenems (yes/no)		
Lyncosamids (yes/no)		
Aminoglicosides (yes/no)		
Tetracyclins (yes/no)		
Sulfonamides (yes/no)		
Oxazolidinones (yes/no)		
Polypeptides (yes/no)		
Other (yes/no) – specify class		
Second line antibiotic therapy needed (yes/no)		

Supplementary Material 2. Healthcare resource use variables (hospital data)

The health services performed to follow-up the patients will be measured by recording the number of assessments performed over the study observation period. These data represent the items necessary to determine the direct healthcare costs incurred by the healthcare system which will be included in the Cost Effectiveness Analysis (CEA). These data are normally traced by hospital records (e.g., eHRs, administrative data), and should be only transferred into the Register platform from treating clinicians. These data are not to be asked to patients. These variables will be measured throughout the patient's the hospital stay. In this study, the following data will be recorded by the doctors during the 6-month follow-up period.

Section 1. Hospitalizations

1.1 Reason for hospitalization

- Heart failure: yes/no/unknown + number
- Ictus ischemic: yes/no/unknown + number
- Ictus hemorrhagic: yes/no/unknown + number
- Bleeding: yes/no/unknown + number
- Renal failure: yes/no/unknown + number
- Respiratory failure: yes/no/unknown + number
- Arrhythmia: yes/no/unknown + number
- Other (please specify): _____ [maximum 5 reasons]

1.2 Number of bed-days in regular ward (e.g., cardiac care ward, other): n (units)

1.3 Number of days in ICU (i.e., intensive care unit): n (units)

1.4 Procedures performed (0 if no procedures are performed)

- Blood transfusion: yes/no/unknown + number
- Dialysis: yes/no/unknown + number
- Ventilatory support: yes/no/unknown + number
- Surgery: yes/no/unknown + number
- Type of surgery (qualitative comment)
- Local interventions: Gastroscopy: yes/no/unknown + number
- Local interventions: Thoracic drainage: yes/no/unknown + number
- Local interventions: Endoscopy: yes/no/unknown + number
- Local interventions: other (please specify name and units): _____
- Physiotherapy: yes/no; nr. of weekly cycles: n (units)
- Ambulatory visit: n (units)

1.5 Exams

- CT Scan: yes/no; n (units)
- MRI: yes/no; n (units)
- Angiography: yes/no; n (units)
- Other (please specify): _____

Section 2: Pharmaceutical consumption during hospitalization

2.1 Drugs used

- Antibiotics: yes/no; days on antibiotics (units)

2.2 Medical devices used

- Nr. of Impella devices used (units)
- Nr. of ECMO devices used (units)
- Dialysis: yes/no
- Extracorporeal purification: yes/no
  - (If yes) Cytosorb: yes/no
  - (If yes) Other (please specify): yes/no + name
- Other (please specify) _____

Section 3: Emergency department

- ER access for heart failure-related symptoms: yes/no
- ER access with no subsequent hospitalization: yes/no + number
- ER access leading to hospitalization: yes/no + number
- Use of the ambulance services: yes/no

Section 4: Other relevant information

- Recovery time needed to go back to work or to "normal life" (from clinician's perspective): 30 days/60 days/120 days/NA

Supplementary Material 3. Patient questionnaire to assess the societal impact of the disease

The following questionnaire will be answered by patients. It has been translated in Italian and will be administered to patients in Italian, however it will be inserted in the Register in English. Both Italian and English versions are provided hereafter. The questionnaire is comprised of two parts:

A. baseline questionnaire, to be administered at signature of informed consent/at ICU-discharge (typically in-person);
B. follow-up questionnaire, to be administered at 6 months, typically over the phone.

*****

A. Baseline questionnaire

1. Employment status:
1.1 What is your current employment status?
If employee:
- factory worker
- employee
- manager, director

If self-employed:
- businessman/woman, freelancer
- other self-employed

If non-professional status:
- retired
- student
- housewife
- other, not employed

1.2 If you are a worker, what is your employment status?
- Full time
- Part-time: 20 hours/week
- Part-time: 24 hours/week
- Part-time: 30 hours/week
- Part-time: 36 hours/week

2. Travel information:
2.1 How much do you spend on average to reach the hospital?
€ _____

2.2 How do you typically reach the hospital?
- By car
- By public transport
- By taxi

- Other (specify)

***

B. Follow-up questionnaire

1. Out-of-pocket (OOP) expenses information:
1.1 In the past 3 months, did you sustain any expense due to cardiogenic shock?
Yes
No
1.2 If yes, what where the healthcare expenses related to?
Medical care

- Specialty visits/exams (e.g., second opinion)
- Drugs (e.g., non-reimbursable drugs, supplements)
- Psychological support
- Other (specify)

1.3 If yes, how much did you spend for each health event?
€ _____
€ _____
€ _____

2. Hospitalizations outside the clinical site of study:
2.1 In the past 3 months, were you hospitalized in a different hospital from this one?

- Yes
- No

2.2 If yes, please indicate the reason: _____ and the hospitalization duration (days): _____

2.3 Did you use emergency services?

- Emergency department
- Ambulance
- None

2.4 Did you pay for any of these services?

- Yes
- No

2.5 If yes, how much did you spend?
€ _____

3. Informal or formal assistance:
3.1 Who gave you informal assistance following your episode of cardiogenic shock? If more than one person, please indicate the one who gives you the most help.

- No one
- Spouse/cohabitant/partner

- Child
- Parent
- Brother/Sister
- Friend
- Other

3.2 If you indicated that someone assists you, how many days does this person assist you, on average, each month, due to issues related to cardiogenic shock? If you want to indicate half a day, write 0,5.
_____ days

3.3 If you indicated that someone assists you, considering the total time you receive as informal assistance from this person, please indicate what percentage you are assisted in the following activities (the sum of the percentages must make 100%):

Activities	%
Nursing activities (eg. drugs administration) and personal care (eg. getting dressed, personal washing)	
Daily activities (eg. work, study, house works, family activities, entertainment, travel)	
Psychological support	

3.4 In the past 3 months, because of complications following your case of cardiogenic shock, have you turned to paid contractors/workers for household help (e.g., babysitter, domestic helper)? (1 answer only)
1. No
2. Yes; How much did you spend? ____ €

4. Limitations caused by the pathology:
4.1 In the past 3 months, approximately how many days of work (professional or home) have you lost due to problems related to cardiogenic shock (if half a day, indicate 0.5)? Exclude any days you have missed for visits, examinations or hospitalizations.
_____ days

4.2 In the past 3 months, how many days have you missed out on activities related to your personal and social life (e.g., going out with friends, hobbies, sports, family activities, etc.) due to problems related to cardiogenic shock (if half a day, indicate 0.5)? Exclude any days you have missed for visits, examinations or hospitalizations.

_____ days

Supplementary Material 4. Patient questionnaire to assess quality of life (EQ-5D-5L)

The EQ-5D-5L questionnaire will be administered to patients included prospectively in the study. The Italian validated version of the questionnaire will be employed. The questionnaire will be administered in a paper-based format, with the clinicians supporting the administration phase (e.g., reading out loud the questions to the patients and making their answers). The questionnaire will be administered to patients in Italian, and inputted in English in the Register. The questionnaire will be administered in three time points following Impella or ECMO implantation: i) after 7 days (i.e., while the patient is still in the hospital); ii) after 30 days; iii) after 6 months of follow-up.A formal request to use the EQ-5D-5L questionnaire has been submitted via the official website (ID: 48771).

Questionario sulla salute

Versione italiana per l'Italia

(Italian version for Italy)

VERSIONE PER LA SOMMINISTRAZIONE DA PARTE DELL'INTERVISTATORE/INTERVISTATRICE

Nota per l'intervistatore/intervistatrice: sebbene si debba tenere conto del particolare stile di conversazione dell'intervistatore/intervistatrice, il testo delle istruzioni del questionario dovrà essere seguito il più fedelmente possibile. Nel caso del sistema descrittivo EQ-5D-5L a pagina 2 del questionario, il testo deve essere seguito fedelmente.

Se l'intervistato/a ha difficoltà nello scegliere una risposta, o chiede chiarimenti, l'intervistatore/intervistatrice dovrà ripetere la domanda parola per parola e chiedere all'intervistato/a di rispondere in un modo che sia il più vicino ai suoi pensieri sulla sua salute oggi.

INTRODUZIONE

(Nota per l'intervistatore/intervistatrice: legga quanto segue all'intervistato/a.)

Desideriamo conoscere ciò che pensa della sua salute. Le spiegherò cosa fare man mano che procedo, ma mi interrompa pure nel caso in cui non dovesse comprendere qualcosa o ritenesse che qualcosa non le fosse chiaro. Non ci sono risposte giuste o sbagliate. Siamo interessati solo al suo personale punto di vista.

Per prima cosa, leggerò alcune domande. Ogni domanda ha una scelta di cinque risposte. Mi dica quale risposta descrive meglio la sua salute OGGI.

Non scelga più di una risposta per ogni gruppo di domande.

(Nota per l'intervistatore/intervistatrice: per prima cosa, legga tutte e cinque le opzioni per ogni domanda. Quindi, chieda all'intervistato/a di scegliere quella che pensa si applichi a se stesso/a. Ripeta la domanda e le opzioni se necessario. Contrassegni la casella appropriata sotto ciascun titolo. Potrebbe essere necessario ricordare regolarmente all'intervistato/a che l'intervallo di tempo è OGGI.)

SISTEMA DESCRITTIVO EQ-5D

Per prima cosa, vorremmo chiederle della CAPACITÀ DI MOVIMENTO. Direbbe che:

1. Non ha difficoltà nel camminare ❑
2. Ha lievi difficoltà nel camminare ❑
3. Ha moderate difficoltà nel camminare ❑
4. Ha gravi difficoltà nel camminare ❑
5. Non è in grado di camminare ❑

Quindi, vorremmo chiederle della CURA DELLA PERSONA. Direbbe che:

1. Non ha difficoltà nel lavarsi o vestirsi ❑
2. Ha lievi difficoltà nel lavarsi o vestirsi ❑
3. Ha moderate difficoltà nel lavarsi o vestirsi ❑
4. Ha gravi difficoltà nel lavarsi o vestirsi ❑
5. Non è in grado di lavarsi o vestirsi ❑

Quindi, vorremmo chiederle delle ATTIVITÀ ABITUALI, per es. lavoro, studio, lavori domestici, attività familiari o di svago. Direbbe che:

1. Non ha difficoltà nello svolgimento delle attività abituali ❑
2. Ha lievi difficoltà nello svolgimento delle attività abituali ❑
3. Ha moderate difficoltà nello svolgimento delle attività abituali ❑
4. Ha gravi difficoltà nello svolgimento delle attività abituali ❑
5. Non è in grado di svolgere le attività abituali ❑

Quindi, vorremmo chiederle quanto DOLORE O FASTIDIO prova. Direbbe che:

1. Non prova alcun dolore o fastidio ❑
2. Prova lieve dolore o fastidio ❑
3. Prova moderato dolore o fastidio ❑
4. Prova grave dolore o fastidio ❑
5. Prova estremo dolore o fastidio ❑

Infine, vorremmo chiederle dell'ANSIA O DEPRESSIONE. Direbbe che:

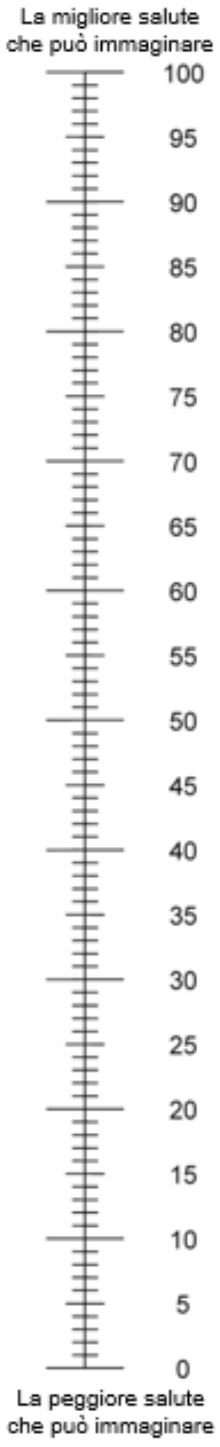
1. Non è ansioso/a o depresso/a ❑
2. È lievemente ansioso/a o depresso/a ❑
3. È moderatamente ansioso/a o depresso/a ❑
4. È gravemente ansioso/a o depresso/a ❑
5. È estremamente ansioso/a o depresso/a ❑

EQ-5D VAS

- **Adesso, vorremmo sapere quanto è buona o cattiva la sua salute OGGI.**
- **Vorremmo che immaginasse una linea verticale numerata da 0 a 100.**
  (Nota per l'intervistatore/intervistatrice: in caso di intervista faccia a faccia, mostrare all'intervistato/a la linea VAS.)
- **100 in cima alla linea rappresenta la migliore salute che può immaginare.**

  0 in fondo alla linea rappresenta la peggiore salute che può immaginare.
- **Vorrei che ora mi indicasse un punto sulla linea per indicare com'è la sua salute OGGI.**
  (Nota per l'intervistatore/intervistatrice: contrassegni la linea nel punto che indica la salute dell'intervistato/a OGGI. Ora, scriva il numero indicato sulla linea nella casella sottostante.)

LA SALUTE DELL'INTERVISTATO/A OGGI = ☐



Grazie per il tempo dedicato a rispondere a queste domande.

SPIROS (Standardized Protocol Items: Recommendations for Observational Studies) checklist

Section and topic	Description / sub-categories	Addressed in the manuscript (Paragraph name)
i) General information		
Title	Descriptive title identifying study design	Title page
Protocol version	Version or amendment number and date and summary of changes	NA
Protocol summary	Brief summary of protocol research	Abstract
Sponsor and partner institute name	Name of sponsor and participating institutes (if applicable)	Title page; Funding
Investigators name	Name of principal and co investigators.	Title page
Affiliations of investigators	Affiliated institutions of investigators	Title page
Principal researcher contact detail	Name, email address, affiliation of Principal researcher for correspondence	Title page
Table of content	Table of content	NA
Page number	Page number on each page of protocol	Yes
List of abbreviations	A detailed List of all abbreviations used in protocol with full form.	List of abbreviations
ii) Introduction		
Background of study	Scientific background of study	Background
Review of prior research	Summary of all previous relevant research	Background
Rationale of study	Justification for conducting the study	Background
Aim	Broader aims and specific objectives of the study	Study objectives
Objective of study	Primary and secondry objectives of study	Study objectives
Prespecified hypothesis	Prespecified null or alternative hypothesis	NA
iii) Methods		
Study design	Description of type/design of study	Study design
Study setting	Description of setting, locations, relevant dates, including periods of recruitment/survey, exposure, follow-up, and data collection. Schedule of study procedure – Figure or table	The Impella Network
Sample size	Estimated number, calculation and assumptions Power calculation	Sample size
Sampling procedure	Description of sampling strategy to ensure representativeness and control of potential bias	Study population
Participants	**Cohort study**—eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. For matched studies, give matching criteria and number of exposed and unexposed	Study population

	Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case **Cross-sectional study**—Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	• All outcomes • Exposures- definition of exposure of interest, • Predictors • Potential confounders • Effect modifiers	Outcomes of interest (Clinical parameters; Healthcare resource use and cost; Quality of life)
Data Sources/Measurement	• For each variable of interest, give sources of data and details of methods of assessment (measurement). • Describe comparability of assessment methods if there is more than one group • Data collection points table • Blinding procedure	Supplementary material
Bias	Describe any efforts to address potential sources of bias. More specifically: • Information bias • Selection Bias • Control for confounding	NA
Statistical analysis plan	• Method of primary / secondary outcomes and additional analysis • Handling of missing data • Post-hoc analysis	Data analysis (Statistical analysis; Cost-effectiveness analysis; Budget impact analysis)
Handling of withdrawals and lost to follow up	Describe the procedures to be followed when a participant ceases participation in the study prematurely or is lost to follow up	NA
Replacements	Provide information on whether or not participants who discontinue the study will be replaced via additional recruitment to maintain the required sample size.	NA
Outcome	Define and describe all primary and secondary outcome or lost to follow up	Outcomes of interest (Clinical parameters; Healthcare resource use and cost; Quality of life)
Database management	Detail plan of database management including: • Data collection (electronic or paper based), • Source data • Data entry • Data editing • Coding • Data storage	Data collection and management

	• Record retention • Data confidentiality	
Validation of instrument	Reliability / validity of instrument or plan to establish validation	NA
Follow up	Plan of follow up and addressing lost to follow up	Study design
Quality control	• Method of quality control • Monitoring (internal and external) • Training of surveyors	NA
Quality assurance	Plan of quality assurance	NA
Expected outcome / results	A brief description of expected outcome or results	NA
iv) Ethical consideration		
Ethical approval	Weather it has been obtained and name of ethical committees. If approval not sought , Reason	Ethics and dissemination
Agreement and consent	Method of taking consent. Reason if consent not sought	Patient and public involvement; Ethics and dissemination
Risk / Harm to participants	Any potential risk or harm to study participants	NA
Adverse event and Severe adverse event reporting	Outline how Adverse Event and Severe adverse event information will be collected.	NA
v) Reporting and dissemination		
Protocol amendments	Methods of communicating to investigators/IRBs and documenting	Study design
Dissemination	How results will be disseminated to participants, practitioners, public	Ethics and dissemination
Publication Plan	Who has right to publish; restrictions; authorship guidelines Open Access	Ethics and dissemination
Reporting of early stopping	Dissemination of results if trial is stopped early (for any reason)	NA
vi) Others		
Limitations	Limitations of proposed study, including risk of bias	Strengths and limitations of this study
Strength of study	Highlight strengths of proposed study	Strengths and limitations of this study
References	List of references cited in protocol	References
Data collection forms	Summary table of all forms used for data collection at each point of study	Supplementary materials
Inform consent forms	Sample of informed consent form, translated into local language	NA
Funding	Source of funding and the role of the funders for the present study	Funding
Acknowledgement for protocol development	Acknowledgement of persons involved in protocol preparation	Acknowledgements
Data sharing policy	To describe how data will be made available in public domain.	
Contributions of authors to protocol	Listed authors should have participated sufficiently in preparation of protocol with details of their contribution.	Authors contribution
Trial registry	For observational studies also registered as trial	NA
Annexures	Data collection form /instruments	Supplementary materials

	Informed consent form Standard operating procedures (SOPs) Detailed Statistical analysis plan (SAP)	

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Impella vs. VA-ECMO for the treatment of Patients with Cardiogenic Shock. The Impella Network project: Observational Study Protocol for Cost-effectiveness and Budget Impact Analyses

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Impella vs. VA-ECMO for the treatment of Patients with Cardiogenic Shock. The Impella Network project: Observational Study Protocol for Cost-effectiveness and Budget Impact Analyses

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Note: first and last author names go to the two PIs (Bocconi and San Raffaele), whereas the names of the other clinical centers are ordered alphabetically by surname.

Abstract

Introduction. The treatment of patients with cardiogenic shock (CS), encompasses several health technologies including Impella pumps and veno-arterial extra-corporeal membrane oxygenation (VA-ECMO). However, while they are widely used in clinical practice, information on resource use and quality of life (QoL) associated to these devices is scarce. The aim of this study is therefore to collect and comparatively assess clinical and socio-economic data of Impella versus VA-ECMO for the treatment of patients with severe CS, to ultimately conduct both a cost-effectiveness (CEA) and budget impact (BIA) analyses.

Methods and analysis. This is a prospective plus retrospective, multicenter study conducted under the scientific coordination of the Center for Research on Health and Social Care Management (CERGAS) of SDA Bocconi School of Management and clinical coordination of IRCCS San Raffaele Scientific Institute in Milan. The Impella Network stemmed for the purposes of this study and comprises seventeen Italian clinical centers from Northern to Southern Regions in Italy. The Italian network qualifies as a subgroup of the international Impella Cardiac Surgery (ImCarS) Registry. Patients with CS treated with Impella pumps (CP, 5.0 or 5.5) will be prospectively recruited, and information on clinical outcomes, resource use and QoL collected. Economic data will be retrospectively matched with data from comparable patients treated with VA-ECMO. Both CEA and BIA will be conducted adopting the societal perspective in Italy. This study will contribute to generate new socio-economic evidence to inform future coverage decisions.

Ethics and dissemination. As of May 2024, most of the clinical centers submitted the documentation to their Ethical Committee (N=13; 76%), six centers received ethical approval, and two centers started to enroll patients. Study results will be published in peer-reviewed publications and disseminated through conference presentations.

Strengths and limitations of this study

- This is an observational multicenter study that will evaluate the cost-effectiveness and budget impact associated to use of Impella against VA-ECMO in the treatment of patients with cardiogenic shock;

- The analyses will be performed with the two-fold perspective of the national health system and the larger society in Italy;
- Data collection will leverage the existing infrastructure of the Impella Cardiac Surgery (ImCarS) Registry;
- The outcomes of interests that will be collected are both clinical parameters and socio-economic data, including healthcare resource use and costs, and quality of life;
- This study does not consider alternative therapeutic courses for the treatment of patients with cardiogenic shock (e.g., intra-aortic balloon pump, pharmacological therapy alone), nor the combination of devices (e.g., ECPELLA), as primary therapeutic strategy.

Introduction

Background

Mechanical circulatory support (MCS) has gained wide application for the treatment of cardiogenic shock (CS) and received a class IIA recommendation by the most recent European Society of Cardiology guidelines on heart failure [1]. In recent years, transcatheter systems have brought great innovation in this field since they enable mechanical left ventricle (LV) unloading, through a lower invasive approach compared to previous generation extracorporeal support devices, equally providing high anterograde flow to reverse the shock status and end-organ damage. They have also the potential to overcome some typical limitations of MCS providing full support up to prolonged period of time and promote patients' recovery at the same time [2–6].

Although both devices are widely used in daily practice, evidence on their uptake and clinical efficacy is constantly evolving. Several meta-analyses evaluated MCS devices for the management of patients with CS [7–9], yet only a few were comparative studies on Impella versus VA-ECMO [10–13]. In this context, conducting comparative studies like randomized controlled trials (RCTs) has proven to be complex, with 5 out of seven RCTs on Impella being discontinued due to inadequate patients' enrollment [14]. Comparative effectiveness studies have become increasingly pivotal since the new Health Technology Assessment Regulation (HTAR 2021/2282) was approved in December 2021 by the EU Parliament [15]. With this regulation, high-risk, life-saving technologies would need to be comparatively assessed at the European level, in line also with the national guidelines of several countries in Europe. However, a prior review by Ardito et al. highlighted that to date virtually no study investigates comparatively socio-economic variables in association to the use of Impella versus VA-ECMO [10]. In light of the new regulatory provisions, the lack of comparative robust clinical and socio-economic evidence might be paralyzing for Member State who are called to take informed coverage and reimbursement decisions [16–18]. As a matter of fact, the limited healthcare resources need to be allocated considering not only the health impact on patient outcomes, but also the financial burden for government budgets. In this context, performing not only economic evaluations (e.g., cost-effectiveness analysis or cost-utility analysis) but also health technology assessments at large, accounting for social, organizational, legal, ethical, or environmental aspects of health technologies, will thus become increasingly pivotal for the uptake of new health technologies and their coverage under national health

services. To date, there are only a few studies investigating the cost effectiveness of MCS devices in the literature. For instance, in a study from 2013 by Roos et al., the cost-effectiveness of Impella was compared to the intra-aortic balloon pump (IABP) in the European perspective, by considering only direct costs [19]. In 2015, the clinical and economic impact of percutaneous ventricular assist devices (pVAD) were compared with IABP for high-risk patients undergoing percutaneous coronary intervention (PCI) by means of conducting a retrospective analysis of published evidence [20]. More recently, another study examined the benefits, harms, cost-effectiveness, and budget impact of the Impella percutaneous ventricular assist device (pVAD) in high-risk PCI and CS [21]. This work builds on the need to conduct more comparative studies in the field of MCS health technologies for the treatment of cardiogenic shock, and to expand the knowledge from existing studies in the Italian framework, which report clinical but not economic data [22–25].

Study objectives

The aim of this study is to generate comparative evidence on the use of Impella versus VA-ECMO for the treatment of patients with severe CS, with the goal to ultimately perform a cost-effectiveness (CEA) and budget impact (BIA) analyses from the national health system (NHS) and societal perspectives in Italy. Both prospective and retrospective data on clinical endpoints and healthcare resource consumption will be collected in Italian heart failure referral centers reunited in what has been named the Impella Network.

The Impella Network

The Impella Network has been created with the purpose of conducting this study. It is a national scientific and medical entity which connects all the Italian institutions within MCS programs and referral for heart failure treatment in which Impella is already used in the clinical practice. All the centers involved in the Impella Network currently run MCS programs and treat patients with CS.

The creation of the Impella Network is promoted under the joint scientific coordination of the Center for Research on Health and Social Care Management (CERGAS) of SDA Bocconi School of Management and IRCCS San Raffaele Scientific Institute in Milan. To answer its specific research question (i.e., assessing the cost-effectiveness and budget impact of Impella versus VA-ECMO for patients with CS), the Impella Network

will leverage the infrastructure of the existing Impella Cardiac Surgery (ImCarS) Registry, therefore qualifying as an ImCarS subgroup analysis of the Italian scenario.

Italian centers were eligible to join the Impella Network if all the following requirements were fulfilled: i) level 2 or 3 center status (with onsite heart failure and mechanical circulatory support program); ii) implantation of Impella 5.0 or Impella CP as standard of care per site; iii) at least one Impella 5.0 or 20 Impella CP implants in the last 3 years (from 2020 to present). The centers meeting the inclusion criteria have been asked to join the Impella Network through a formal invitation from CERGAS SDA Bocconi and IRCCS San Raffaele Scientific Institute as principal clinical center. Table 1 presents the list of clinical centers who agreed to be part of this study.

Table 1 List of clinical centers involved in the data collection

ID	Clinical Center	Location
1	IRCCS Ospedale San Raffaele (PI)	Milano
2	ASST Grande Ospedale Metropolitano Niguarda	Milano
3	San Giovanni Bosco Hospital	Torino
4	Azienda Ospedaliera Universitaria di Padova	Padova
5	Policlinico di Sant'Orsola	Bologna
6	Ospedale Careggi	Firenze
7	Azienda Ospedaliera Universitaria Città della Salute e della Scienza di Torino	Torino
8	Mater Dei Hospital	Bari
9	Azienda Ospedaliera Sant'Anna e San Sebastiano	Caserta
10	Fondazione IRCCS San Gerardo dei Tintori	Monza
11	Mediterranea Cardiocentro	Napoli
12	IRCCS Ospedale Policlinico San Martino	Genova
13	Azienda Ospedaliera S.Camillo Forlanini	Roma
14	Azienda Ospedaliero-Universitaria delle Marche	Ancona
15	IRCCS Humanitas Research Hospital	Rozzano
16	Azienda Ospedaliera-Universitaria Siena	Siena
17	Ospedale Monaldi, Azienda dei Colli	Napoli

Interestingly, as the field of MCS evolves at high speed and scientific evidence is pivotal to improve clinical practice, the Impella Network might also become a facilitator for prospective analyses of future technologies, and be considered eligible for inclusion in international projects on MCS.

Methods and Analysis

Study design

This will be an observational multicenter study. Patients with severe CS treated either with Impella (CP, 5.0 or 5.5) or with VA-ECMO will represent the study population in the prospective arm. This study population will be compared with a similar population of retrospective patients treated with VA-ECMO for severe CS, which will represent the control group. There is no randomization procedure and all patients will be treated according to the standard of care per site. This protocol has been written following the SPIROS (Standardized Protocol Items: Recommendations for Observational Studies) guidelines [26].

The prospective study foresees a period of six months of follow-up for each patient. Investigators are requested to enroll all patients with CS in their units, according to the inclusion criteria. Data will be collected on a strictly observational basis. The investigators will carry out their usual activity, without any constraints due to the study, both in terms of diagnosis but also regarding patients' management, and the choice of possible treatments. Medical and mechanical circulatory support treatment will be initiated at the discretion of each investigator, according to routine practice. Overall study duration might be variable depending on the time needed for patient enrollment and follow-up in each site, but is estimated to be approximately around 18 months.

Information of comparable patients will be retrieved by retrospectively reviewing the clinical records of patients treated for CS in the Impella Network (retrospective study arm). This information will be retrieved by the clinicians in each participating center and will be inputted within the Impella Cardiac Surgery (ImCarS) Registry, and will ultimately populate the study database together with the information from the prospective study arm. All patients who meet inclusion and exclusion criteria in the appropriate time periods (see "Study population" paragraph) will be included, both for the patients treated with Impella (study arm) and for the patients treated with VA-ECMO (control arm).

It is anticipated that the study protocol might be subject to minor amendments depending on how the data collection unfolds (e.g. fewer patients treated with the technologies in scope to be enrolled in the study, or fewer centers participating in the study).

Study population

Patients treated with Impella

The study population will include all patients suffering from CS, according to clinically relevant classifications (Interagency Registry for mechanically assisted circulatory support (INTERMACS) and International Society for Cardiovascular Angiography and Interventions (SCAI)) treated with Impella 5.5, Impella 5.0 or Impella CP at the Impella Network institutions. To be included in the study group (i.e. Impella Intention To Treat group), patients must meet all the following inclusion criteria:

- CS at presentation (as defined by INTERMACS Class 1-2-3 or SCAI Class C-D-E);
- Support as single device strategy;
- Impella support duration of at least 24 hours;
- Patients treated in the last 3 years (2020-2022) (for retrospective data collection);
- Onset of CS from less than 12 hours.

Different primary diseases and etiologies of heart failure are expected: patients will be further stratified according to the cause of heart failure and phenotype of presentation to account for potential bias in the analysis. Patients' shock degree will also be objectified through clinical risk score calculation. Furthermore, patients meeting any of the following exclusion criteria will not be included in the study:

- Impella implantation for elective protected PCI;
- Impella implantation for post-cardiotomy CS;
- Impella support duration for less than 24 hours;

Patients treated with VA-ECMO

The control group will include all patients treated at the Impella Network institutions for severe left ventricular failure with VA-ECMO. To be included in the control group (i.e. VA-ECMO intention to treat group), patients must fulfill ALL the following inclusion criteria:

- CS at presentation (as defined by INTERMACS Class 1-2-3 or SCAI Class C-D-E);
- VA-ECMO support as single device strategy;
- VA-ECMO support duration of at least 24 hours;

- Onset of CS from less than 12 hours.

Different primary diseases and etiologies of heart failure are expected: patients will be further stratified according to the cause of heart failure and phenotype of presentation to account for potential bias in the analysis. Patients' shock degree will also be objectified through clinical risk score calculation. Furthermore, patients meeting any of the following exclusion criteria will not be included in the study:

- VA-ECMO support for post-cardiotomy CS;
- VA-ECMO support duration for less than 24 hours;
- VA-ECMO for refractory prolonged cardiac arrest (ECPR);
- Presence of biventricular failure;
- Onset of CS from more than 12 hours.

In the era of Impella 5.0/5.5, patients with CS treated with VA-ECMO may be indicative of a more severe population compared to the study group counterpart. In order to prevent potential bias, only VA-ECMO patients with isolated LV failure will be included in the study and patients with CS severity profile comparable to the Impella counterpart at baseline will be analyzed.

Sample size

For the prospective arms, any patient treated with Impella or VA-ECMO technologies that meets the inclusion criteria will be recruited and considered for the analyses. Therefore, the sample size cannot be estimated ex-ante. For the retrospective arm, based on previous data from the Italian clinical experience, it is expected that data from approximately 200 VA-ECMO patients will be retrieved and included in the analyses.

Outcomes of interest

Clinical parameters

Data related to medical history, shock related hospitalization, mechanical circulatory support characteristics (for Impella or VA-ECMO), clinical and hospital outcomes will be collected from each center and included in a pre-specified structured data set. Short term MCS related adverse events will be defined according to most recent recommendations [27]. In addition to data registered at specific time points (for example, at baseline)

and outcome measures, several hemodynamic, laboratory and clinical data will be assessed regularly during the treatment with Impella or VA ECMO to assess the evolution of the condition of shock during support. The detailed list of clinical parameters to be collected through the study is outlined in the Supplementary Material 1.

Healthcare resource use and costs

Direct healthcare resource use will be identified through the analysis of collected clinical data (e.g., number of visits, device implanted, possible management of adverse events, etc.). Monetary quantification will be performed by applying official reimbursement rates (e.g., DRGs for hospitalizations or tariffs for outpatient services).

The collection of "societal costs" will be performed through the administration to patients of a socio-economic questionnaire, developed ad hoc by CERGAS researchers, and it will include information on out-of-pocket (OOP) expenses (e.g. transport costs for carrying out visits or exams), productivity losses and cost of informal care (provided by relatives). The questionnaire will be administered by the clinicians involved in the study to patients before the intervention (at baseline) and during the follow-up visits (e.g., at 30 days).

Direct healthcare resource use will be measured both for prospective and retrospective patients, while information on "societal costs" will only be available for the group of prospective patients as it is collected through patient questionnaires (not available retrospectively). The detailed list of healthcare resource use variables and the questionnaire to assess the societal impact are reported in the Supplementary Material 2 and Supplementary Material 3, respectively.

Quality of life

Only for the patients prospectively enrolled in the study, the patient's quality of life will be measured through the EuroQol 5D-5L questionnaires. EuroQol 5D-5L is a questionnaire capable of providing a generic and synthetic measure of the quality of life (QoL) in relation to health. The questionnaire consists of two parts: the first includes five items that refer to different health aspects: mobility, personal care, usual activities, pain or discomfort, anxiety or depression. For each item there are five levels of response which indicate, for that area, the absence or presence of mild, moderate, severe or extreme problems. The second part of the questionnaire consists of a graduated visual analogue scale (VAS) from 0 to 100 on which the subject indicates his/her

perceived state of health. The questionnaire will be administered by the clinicians involved in the study to patients before the intervention (at baseline) if possible and during the follow-up visits (e.g., at 7 days, 30 days) using a paper-based format. The clinicians will choose an appropriate timing to fill in the questionnaire, namely when patients are awake, conscious and willing to respond. However, should the patients be too weak to respond, or should they fail to recover from the shock, they will be excluded from the QoL analyses.

The questionnaire has been requested for non-commercial use via the EuroQol website (registration ID 48771), and is reported in its integral version in the Supplementary Material 4.

Data collection and management

Data will be collected through the infrastructure of the existing ImCarS Registry. While this study qualifies as an independent study answering a specific research question (i.e., assessing the cost-effectiveness and budget impact of Impella vs. VA-ECMO for patients with CS), it will leverage the ImCarS Registry (i.e., eCRF, IT platform, capabilities) as a facilitator for the data collection phase [28], therefore qualifying as an ImCarS subgroup analysis of the Italian scenario. More in details, each center belonging to Impella Network will join the ImCarS registry and the current project will benefit from the employment of an electronic Case Report Form (eCRF), that will support any activities related to data collection. The company that will handle the eCRF and will ensure data protection is KKS Gießen Marburg. A per-patient fee of approximately 300€ for Impella cases and 100€ for VA-ECMO cases will be provided by the ImCarS Registry to each participating center. Possibly a clinical research organization (CRO) could be involved upon request of the clinical centers for the management of periodic quality controls to ensure completeness and consistency according to a specific plan agreed among the participating centers. Each clinical center will maintain the ownership of the data points of their own patients.

Patient data recorded in each participating clinical center (hospital medical records) as well as responses to quality of life and socio-economic questionnaires will be anonymized and entered by the clinicians in the eCRF of ImCarS Registry. At the end of the applicable operations and checks, the anonymized data set will be transferred to CERGAS researchers in order to perform the cost-effectiveness analysis (CEA) and budget impact analysis (BIA).

Data analysis

Statistical analysis

The data obtained will be analyzed in a descriptive and inferential way using the most suitable statistical model for each variable. Continuous variables with a symmetrical distribution (e.g., age, questionnaire scores) will be expressed as means and standard deviations (SD). As regards the asymmetrically distributed continuous variables (such as, for example, hospital stay) they will be expressed as median and range. The categorical variables (gender, intra and postoperative complications) will be expressed as frequencies and percentages. Sub-group analyses may be performed depending on the type of data collected, to have consistent results. Possible missing data for the retrospective group of patients will be treated case by case, depending on the quality of the data themselves.

Cost-Effectiveness Analysis (CEA)

The implementation of a CEA model [29] will aim to compare the management of patients with CS with Impella versus VA-ECMO from both NHS and societal perspectives in Italy. The analysis will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [30, 31].

The model will project costs, life years (LYs) and quality adjusted life years (QALYs) on a lifetime horizon in order to evaluate the incremental cost-effectiveness ratio (ICER) and the incremental cost-utility ratio (ICUR). They will be calculated as the difference in the mean expected costs divided by the difference in the mean expected health outcomes (LYs or QALYs) of the considered management strategies. It has to be specified that QoL will be measured as long as patients stay alive. Interpolation techniques might be used to manage missing data (e.g., to carry forward QoL measurements occurred prior to death); however, patients who never completed QoL measurements will be excluded from QALYs analyses.

The CEA model will be developed based on the following phases: 1) Identification of clinical pathways and healthcare resources consumption for the considered strategies; 2) Inclusion of patients' clinical outcomes and possibly quality of life for the considered strategies (available from data collection phase); 3) Monetary quantification of the healthcare resource consumption from both NHS and societal perspectives (e.g., DRG charges/tariffs, productivity losses and out-of-pocket costs reported by the patients); 4) Analysis and

interpretation of model results; 5) Sensitivity analyses. In addition, if collected data will allow it, centers will be clustered based on the number of implanted Impella devices and patients treated, to investigate if there is a relationship between cost-effectiveness and the volumes of device use in each center. The definition of the clusters and conduct of sub-group analyses will depend on the data that will be actually collected.

Budget Impact Analysis (BIA)

A BIA model will be developed starting from the CEA model to evaluate the impact on the hospital healthcare expenditure in Italy of the adoption of Impella, possibly differentiating by the type of Impella pumps, over a period of 3 or 5 years, according to the following steps: 1) Identification of patients' pathways and healthcare resources consumption for the considered strategies; 2) Monetary quantification of the healthcare resource consumption from the hospital perspective through a micro-costing analysis; 3) Definition of the current scenario of distribution of patients among the two considered options: Impella 5.0 and VA-ECMO; 4) Definition of future scenarios in which appropriate increased uses of Impella according to different annual penetration rates are considered. The forecasted increased use of Impella may be estimated on the basis of the evidence available in the literature and/or by clinical opinions collected by an ad-hoc e-survey and by observing market trends in other jurisdictions (e.g., Germany, USA); 5) Analysis and interpretation of model results; 6) Sensitivity analyses (e.g., Impella 5.5).

As a final note, it has to be highlighted that the BIA will be conducted from an Italian perspective, based on the cost framework observed within Italian facilities. Therefore, extending the study results to other geographical contexts should be done with caution, and marginal adjustments might be needed to account for country-specific differences in the costs sustained at the local level.

Patient and public involvement

Being an observational study, patients will be enrolled as part of the research activities. Informed consent will be provided to, and signed by, patients to ensure the purposes of the study are well understood, and the patients' interests protected. We plan on involving relevant patient associations when disseminating the study results.

Ethics and dissemination

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Clinical Practices. No specific risks related to the enrolment in the study are expected for patients, since the study is observational and patients will receive best available treatment. Informed consent collection will be performed according to the ImCarS registry protocol and eventually further disciplined according to specific guidelines and/or best practices of the Ethical Committees of each clinical center. Similarly, collection of data at each participating site will be performed according to the policies of the local institutional review board/ethics committee.

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures.

SDA Bocconi received approval of this protocol from Bocconi University's Ethical Committee (EC). IRCCS San Raffaele Hospital Institute also received ethical approval of the ImCarS protocol from its EC. In parallel, each clinical center had to present the documentation to join the ImCarS Registry to their own ECs for approval. As of May 2024, among the participating centers, the majority (N=13, 76%) already presented the relevant documentation, while six of them – Azienda Ospedaliera San Camillo Forlanini (Rome), Clinica Mediterranea (Naples), San Giovanni Bosco (Turin), Città della Salute e della Scienza (Turin), and Humanitas (Rozzano) – already received the EC approval.

The study results will be disseminated through peer-reviewed scientific publications and presentation in international conferences. The economic analyses, namely the results of the CEA and BIA analyses, will be published in one or more scientific publications on top-tier, peer-reviewed journals. The exact publication pipeline depends from the actual start of the data collection. After the end of the data collection, it will take approximately 9 months for the research team to process the evidence and prepare the aforementioned manuscripts.

List of abbreviations

BIA: Budget impact analysis

CEA: Cost-effectiveness analysis

CERGAS: Center for Research on Health and Social Care Management

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

CRO: Clinical research organization

CS: Cardiogenic shock

DRG: Diagnosis related groups

EC: Ethical Committee

eCFR: electronic Case Report Form

HTAR: Health Technology Assessment Regulation

IABP: Intra-aortic balloon pump

ICER: Incremental cost-effectiveness ratio

ImCarS: Impella Cardiac Surgery

IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico (research hospital)

LV: Left ventricle

LYs: Life years

MCS: Mechanical circulatory support

NHS: National Health System

OOP: Out-of-pocket

PCI: Percutaneous coronary intervention

pVAD: Percutaneous ventricular assist devices

QALYs: Quality adjusted life years

QoL: Quality of life

RCTs: Randomized controlled trials

SD: Standard deviation

SPIROS: Standardized Protocol Items: Recommendations for Observational Studies

VA-ECMO: Veno-arterial extra-corporeal membrane oxygenation

VAS: Visual analogue scale

Footnotes

Authors contributions

RT and AMS developed the initial study concept. VA, CR and MP devised the study design, including methodology, and wrote the original draft of the protocol. AB, CB, EC, GG, MI, AL, MM, AM, JO, DP, MP, VP, IP, PS, GT, SV, PV contributed to critical revisions of the manuscript. RT and AMS are the Scientific Coordinators of the study and take overall responsibility for all aspects of study design, the protocol and the study conduct. RT acquired funding for the study. All authors VA, CR, MP, AB, CB, EC, GG, MI, AL, MM, AM, JO, DP, MP, VP, IP, PS, GT, SV, PV, RT and AMS contributed to review and editing of the protocol and have read and approved this manuscript.

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Conflict of interest

None to declare.

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Supplementary Materials

Supplementary Materials 1. Clinical parameters

Table 1 reports the comprehensive list of clinical variables to be collected for both prospective and retrospective patients. Specifically, the relevant variables for the Impella and ECMO groups are specified, along with the timing for measurements during the observation period.

	Target patients		Timing of measurement			
Patients' characteristics	Impella group	ECMO group	T0 (Baseline)			
Age (years)	X	X	X			
Sex (male/female)	X	X	X			
BMI (kg/m2)	X	X	X			
Arterial Hypertension (yes/no)	X	X	X			
Diabetes Mellitus (yes/no)	X	X	X			
Chronic kidney disease (yes/no)	X	X	X			
Peripheral artery disease(yes/no)	X	X	X			
ICD/CRT (yes/no)	X	X	X			
Previous PTCA (yes/no)	X	X	X			
Previous CABG (yes/no)	X	X	X			
Chronic heart failure (yes/no)	X	X	X			
Cause of acute heart failure:						
*Acute coronary syndrome (yes/no)	X	X	X			
*Myocarditis (yes/no)	X	X	X			
*End stage dilatative cardiomyopathy (yes/no)	X	X	X			
*Arrhythmia/ arrhythmic storm(yes/no)	X	X	X			
*Other (specify)	X	X	X			
Phenotype of cardiogenic shock:						
* LV dominant (yes/no)	X	X	X			
*RV isolated (yes/no)	X	X	X			
* Biventricular failure(yes/no)	X	X	X			
Onset of shock (hours)	X	X	X			
Hemodynamic presentation of shock:						
* Wet and cold (classic CS) (yes/no)	X	X	X			

* Wet and warm (vasodilatory CS) (yes/no)	X	X	X			
* Dry and cold (euvolemic CS) (yes/no)	X	X	X			
Revascularization procedure with stent implantation (yes/no)	X	X	X			
Cardiac arrest(yes/no)	X	X	X			
eGFR (ml/min/m2)	X	X	X			
AKI requiring CRRT yes/no)	X	X	X			
Mechanical ventilation yes/no)	X	X	X			
Days of mechanical ventilation yes/no)	X	X	X			
Mortality risk score	Impella group	ECMO group	T0 (Baseline)			
NYHA	X	X	X			
INTERMACS score	X	X	X			
SCAI class	X	X	X			
CARDshock score (see below)	X	X	X			
RESCUE SCORE	X	X	X			
SAVE score	X	X	X			
MCS strategy and data	Impella group	ECMO group	Event (Y/N)			
Implantation pathway:						
* MCS escalation (yes/no)	X	X	X			
* MCS de-escalation (yes/no)	X	X	X			
* First support (yes/no)	X	X	X			
Device implantation pre PCI (yes/no)	X	X	X			
Device implantation post PCI (yes/no)	X	X	X			
Implantation strategy[1]*:*						
* Bridge to recovery (yes/no)	X	X	X			
* Bridge to LVAD (yes/no)	X	X	X			
* Bridge to transplant (yes/no)	X	X	X			
* Bridge to candidacy (yes/no)	X	X	X			
Implantation route:						
*Axillar (yes/no)	X	X	X			
* Femoral (yes/no)	X	X	X			
Successful implantation (yes/no)	X	X	X			

[1] Typically reassessed also at the end of the patient journey, as it might be subject to changes from the original plan

Need for surgical implant (yes/no)	X	X	X			
Duration of implantation (min)	X	X	Y, minutes			
Hemodinamic and Lab Parameters Trend	Impella group	ECMO group	T0 (Baseline)	24 h post implantation	48-72 h post implantation	First measurement after device removal
Mean arterial pressure (mmHg)	X	X	X	X	X	X
Systolic arterial pressure (mmHg)	X	X	X	X	X	X
Heart rate (bpm)	X	X	X	X	X	X
CVP (mmHg)	X	X	X	X	X	X
CI (l/min/mq)	X	X	X	X	X	X
PCWP (mmHg)	X	X	X	X	X	X
SvO2 (%)	X	X	X	X	X	X
RVSWI (g/m/beat/m^2)	X	X	X	X	X	X
Creatinine (mg/dl)	X	X	X	X	X	X
Lactates (mmol/L)	X	X	X	X	X	X
Troponin (pg/ml)	X	X	X	X	X	X
Inotropic score	X	X	X	X	X	X
NT-proBNP (ng/L)	X	X	X	X	X	X
Platelets (per microliter)	X	X	X	X	X	X
D-dimers (µg/mL)	X	X	X	X	X	X
Bilirubin (mg/dl)	X	X	X	X	X	X
LV EF (%)	X	X	X	X	X	X
RV EF (%)	X	X	X	X	X	X
Mechanical ventilation (yes/no)	X	X	X	X	X	X
Safety in-hosp complications	Impella group	ECMO group	Event during support(yes/no)	Eventual comments/event description		
Bleeding (and site):						
*Major (yes/no)	X	X				
*Moderate (yes/no)	X	X				
*Minor (yes/no)	X	X				
Bleeding requiring surgery (yes/no)	X	X				
Bleeding from Impella (ECMO insertion site (yes/no)	X	X				
Limb ischemia (yes/no)	X	X				
Vascular complication requiring intervention/surgery (yes/no)	X	X				
Ischemic stroke (yes/no)	X	X				
Device malfunction(yes/no)	X	X				
LV perforation (yes/no)	X					

Aortic valve injury (yes/no)	X			
Mitral valve injury (yes/no)	X			
Lesion to other intracardiac structure (yes/no)	X	X		
aortic dissection (yes/no)	X	X		
Other device related injury (yes/no)	X	X		
Major Hemolysis (yes/no)	X	X		
Minor Hemolysis (yes/no)	X	X		
AKI requiring CRRT (yes/no)	X	X		
Sepsis (yes/no)	X	X		
Extracorporeal purification (i.e. Cytosorb) (yes/no)				
EC transfusion, numbers of unit	X	X		
FFP transfusion, numbers of unit	X	X		
PLT transfusion, numbers of unit	X	X		
Device related outcomes	Impella group	ECMO group	Variable	Eventual comments/event description
Duration of MCS support (days)	X	X		
mobilization (chair) with MCS and physiotherapy (yes/no)	X	X		
mobilization (walk) with MCS and physiotherapy (yes/no)	X	X		
Major device malfunction (yes/no)	X	X		
Device exchange (yes/no)	X	X		
Reason for device exchange	X	X		
Survival and cardiac outcomes	Impella group	ECMO group	Event (yes/no)	Eventual comments/event description
30-day mortality (yes/no)	X	X		
ICU mortality (yes/no)	X	X		
Hospital mortality (yes/no)	X	X		
Survival to next therapy (yes/no)	X	X		
Weaning from MCS (yes/no)	X	X		
Myocardial recovery (yes/no)	X	X		
Bridge to LVAD (yes/no)	X	X		
Bridge to Transplant (yes/no)	X	X		
Cause of death	X	X		
Duration of ICU stay, days	X	X		
Duration of hospital stay, days	X	X		
Sequelae of hospital complication at discharge (yes/no)	X	X		

Details of sequelae	X	X		
Duration of mechanical ventilation(days)	X	X		
Tracheostomy (yes/no)	X	X		
Able to perform self-care at discharge (yes/no)	X	X		
Able to return to work at discharge (yes/no)	X	X		

CARDshock score calculation:

Age > 75 years (yes/no)

Confusion at presentation (yes/no)

Prior myocardial infarction of CABG (yes/no)

Acute coronary syndrome ethology (yes/no)

Blood lactate level (<2/2-4/>4)

eGRF (>60/30-60/<30 ml/min/m2)

To the eCRF section dedicated to DTI, it should be added bivalirudin.

It should be added a section that recaps the types of antibiotics use and the duration of therapy (to estimate costs):

Antibiotic class	**Use (yes/no)**	**Duration of therapy (days)**
Cephalosporines (yes/no)		
Pennicillins (yes/no)		
Penicillins (yes/no)		
Glycopeptides (yes/no)		
Fluoroquinolones (yes/no)		
Macrolides (yes/no)		
Carbapenems (yes/no)		
Lyncosamids (yes/no)		
Aminoglicosides (yes/no)		
Tetracyclins (yes/no)		
Sulfonamides (yes/no)		
Oxazolidinones (yes/no)		
Polypeptides (yes/no)		
Other (yes/no) – specify class		
Second line antibiotic therapy needed (yes/no)		

Supplementary Material 2. Healthcare resource use variables (hospital data)

The health services performed to follow-up the patients will be measured by recording the number of assessments performed over the study observation period. These data represent the items necessary to determine the direct healthcare costs incurred by the healthcare system which will be included in the Cost Effectiveness Analysis (CEA). These data are normally traced by hospital records (e.g., eHRs, administrative data), and should be only transferred into the Register platform from treating clinicians. These data are not to be asked to patients. These variables will be measured throughout the patient's the hospital stay. In this study, the following data will be recorded by the doctors during the 6-month follow-up period.

Section 1. Hospitalizations

1.1 Reason for hospitalization

- Heart failure: yes/no/unknown + number
- Ictus ischemic: yes/no/unknown + number
- Ictus hemorrhagic: yes/no/unknown + number
- Bleeding: yes/no/unknown + number
- Renal failure: yes/no/unknown + number
- Respiratory failure: yes/no/unknown + number
- Arrhythmia: yes/no/unknown + number
- Other (please specify): _____ [maximum 5 reasons]

1.2 Number of bed-days in regular ward (e.g., cardiac care ward, other): n (units)

1.3 Number of days in ICU (i.e., intensive care unit): n (units)

1.4 Procedures performed (0 if no procedures are performed)

- Blood transfusion: yes/no/unknown + number
- Dialysis: yes/no/unknown + number
- Ventilatory support: yes/no/unknown + number
- Surgery: yes/no/unknown + number
- Type of surgery (qualitative comment)
- Local interventions: Gastroscopy: yes/no/unknown + number
- Local interventions: Thoracic drainage: yes/no/unknown + number
- Local interventions: Endoscopy: yes/no/unknown + number
- Local interventions: other (please specify name and units): _____
- Physiotherapy: yes/no; nr. of weekly cycles: n (units)
- Ambulatory visit: n (units)

1.5 Exams

- CT Scan: yes/no; n (units)
- MRI: yes/no; n (units)
- Angiography: yes/no; n (units)
- Other (please specify): _____

Section 2: Pharmaceutical consumption during hospitalization

2.1 Drugs used

- Antibiotics: yes/no; days on antibiotics (units)

2.2 Medical devices used

- Nr. of Impella devices used (units)
- Nr. of ECMO devices used (units)
- Dialysis: yes/no
- Extracorporeal purification: yes/no
  - (If yes) Cytosorb: yes/no
  - (If yes) Other (please specify): yes/no + name
- Other (please specify) _____

Section 3: Emergency department

- ER access for heart failure-related symptoms: yes/no
- ER access with no subsequent hospitalization: yes/no + number
- ER access leading to hospitalization: yes/no + number
- Use of the ambulance services: yes/no

Section 4: Other relevant information

- Recovery time needed to go back to work or to "normal life" (from clinician's perspective): 30 days/60 days/120 days/NA

Supplementary Material 3. Patient questionnaire to assess the societal impact of the disease

The following questionnaire will be answered by patients. It has been translated in Italian and will be administered to patients in Italian, however it will be inserted in the Register in English. Both Italian and English versions are provided hereafter. The questionnaire is comprised of two parts:

A. baseline questionnaire, to be administered at signature of informed consent/at ICU-discharge (typically in-person);
B. follow-up questionnaire, to be administered at 6 months, typically over the phone.

*****

A. Baseline questionnaire

1. Employment status:
1.1 What is your current employment status?
If employee:
- factory worker
- employee
- manager, director

If self-employed:
- businessman/woman, freelancer
- other self-employed

If non-professional status:
- retired
- student
- housewife
- other, not employed

1.2 If you are a worker, what is your employment status?
- Full time
- Part-time: 20 hours/week
- Part-time: 24 hours/week
- Part-time: 30 hours/week
- Part-time: 36 hours/week

2. Travel information:
2.1 How much do you spend on average to reach the hospital?
€ _____

2.2 How do you typically reach the hospital?
- By car
- By public transport
- By taxi

- Other (specify)

***

B. Follow-up questionnaire

1. Out-of-pocket (OOP) expenses information:
1.1 In the past 3 months, did you sustain any expense due to cardiogenic shock?
Yes
No
1.2 If yes, what where the healthcare expenses related to?
Medical care

- Specialty visits/exams (e.g., second opinion)
- Drugs (e.g., non-reimbursable drugs, supplements)
- Psychological support
- Other (specify)

1.3 If yes, how much did you spend for each health event?
€ _____
€ _____
€ _____

2. Hospitalizations outside the clinical site of study:
2.1 In the past 3 months, were you hospitalized in a different hospital from this one?

- Yes
- No

2.2 If yes, please indicate the reason: _____ and the hospitalization duration (days): _____

2.3 Did you use emergency services?

- Emergency department
- Ambulance
- None

2.4 Did you pay for any of these services?

- Yes
- No

2.5 If yes, how much did you spend?
€ _____

3. Informal or formal assistance:
3.1 Who gave you informal assistance following your episode of cardiogenic shock? If more than one person, please indicate the one who gives you the most help.

- No one
- Spouse/cohabitant/partner

- Child
- Parent
- Brother/Sister
- Friend
- Other

3.2 If you indicated that someone assists you, how many days does this person assist you, on average, each month, due to issues related to cardiogenic shock? If you want to indicate half a day, write 0,5.
_____ days

3.3 If you indicated that someone assists you, considering the total time you receive as informal assistance from this person, please indicate what percentage you are assisted in the following activities (the sum of the percentages must make 100%):

Activities	%
Nursing activities (eg. drugs administration) and personal care (eg. getting dressed, personal washing)	
Daily activities (eg. work, study, house works, family activities, entertainment, travel)	
Psychological support	

3.4 In the past 3 months, because of complications following your case of cardiogenic shock, have you turned to paid contractors/workers for household help (e.g., babysitter, domestic helper)? (1 answer only)
1. No
2. Yes; How much did you spend? ____ €

4. Limitations caused by the pathology:
4.1 In the past 3 months, approximately how many days of work (professional or home) have you lost due to problems related to cardiogenic shock (if half a day, indicate 0.5)? Exclude any days you have missed for visits, examinations or hospitalizations.
_____ days

4.2 In the past 3 months, how many days have you missed out on activities related to your personal and social life (e.g., going out with friends, hobbies, sports, family activities, etc.) due to problems related to cardiogenic shock (if half a day, indicate 0.5)? Exclude any days you have missed for visits, examinations or hospitalizations.

_____ days

Supplementary Material 4. Patient questionnaire to assess quality of life (EQ-5D-5L)

The EQ-5D-5L questionnaire will be administered to patients included prospectively in the study. The Italian validated version of the questionnaire will be employed. The questionnaire will be administered in a paper-based format, with the clinicians supporting the administration phase (e.g., reading out loud the questions to the patients and making their answers). The questionnaire will be administered to patients in Italian, and inputted in English in the Register. The questionnaire will be administered in three time points following Impella or ECMO implantation: i) after 7 days (i.e., while the patient is still in the hospital); ii) after 30 days; iii) after 6 months of follow-up.A formal request to use the EQ-5D-5L questionnaire has been submitted via the official website (ID: 48771).

Questionario sulla salute

Versione italiana per l'Italia

(Italian version for Italy)

VERSIONE PER LA SOMMINISTRAZIONE DA PARTE DELL'INTERVISTATORE/INTERVISTATRICE

Nota per l'intervistatore/intervistatrice: sebbene si debba tenere conto del particolare stile di conversazione dell'intervistatore/intervistatrice, il testo delle istruzioni del questionario dovrà essere seguito il più fedelmente possibile. Nel caso del sistema descrittivo EQ-5D-5L a pagina 2 del questionario, il testo deve essere seguito fedelmente.

Se l'intervistato/a ha difficoltà nello scegliere una risposta, o chiede chiarimenti, l'intervistatore/intervistatrice dovrà ripetere la domanda parola per parola e chiedere all'intervistato/a di rispondere in un modo che sia il più vicino ai suoi pensieri sulla sua salute oggi.

INTRODUZIONE

(Nota per l'intervistatore/intervistatrice: legga quanto segue all'intervistato/a.)

Desideriamo conoscere ciò che pensa della sua salute. Le spiegherò cosa fare man mano che procedo, ma mi interrompa pure nel caso in cui non dovesse comprendere qualcosa o ritenesse che qualcosa non le fosse chiaro. Non ci sono risposte giuste o sbagliate. Siamo interessati solo al suo personale punto di vista.

Per prima cosa, leggerò alcune domande. Ogni domanda ha una scelta di cinque risposte. Mi dica quale risposta descrive meglio la sua salute OGGI.

Non scelga più di una risposta per ogni gruppo di domande.

(Nota per l'intervistatore/intervistatrice: per prima cosa, legga tutte e cinque le opzioni per ogni domanda. Quindi, chieda all'intervistato/a di scegliere quella che pensa si applichi a se stesso/a. Ripeta la domanda e le opzioni se necessario. Contrassegni la casella appropriata sotto ciascun titolo. Potrebbe essere necessario ricordare regolarmente all'intervistato/a che l'intervallo di tempo è OGGI.)

SISTEMA DESCRITTIVO EQ-5D

Per prima cosa, vorremmo chiederle della CAPACITÀ DI MOVIMENTO. Direbbe che:

1. Non ha difficoltà nel camminare ❑
2. Ha lievi difficoltà nel camminare ❑
3. Ha moderate difficoltà nel camminare ❑
4. Ha gravi difficoltà nel camminare ❑
5. Non è in grado di camminare ❑

Quindi, vorremmo chiederle della CURA DELLA PERSONA. Direbbe che:

1. Non ha difficoltà nel lavarsi o vestirsi ❑
2. Ha lievi difficoltà nel lavarsi o vestirsi ❑
3. Ha moderate difficoltà nel lavarsi o vestirsi ❑
4. Ha gravi difficoltà nel lavarsi o vestirsi ❑
5. Non è in grado di lavarsi o vestirsi ❑

Quindi, vorremmo chiederle delle ATTIVITÀ ABITUALI, per es. lavoro, studio, lavori domestici, attività familiari o di svago. Direbbe che:

1. Non ha difficoltà nello svolgimento delle attività abituali ❑
2. Ha lievi difficoltà nello svolgimento delle attività abituali ❑
3. Ha moderate difficoltà nello svolgimento delle attività abituali ❑
4. Ha gravi difficoltà nello svolgimento delle attività abituali ❑
5. Non è in grado di svolgere le attività abituali ❑

Quindi, vorremmo chiederle quanto DOLORE O FASTIDIO prova. Direbbe che:

1. Non prova alcun dolore o fastidio ❑
2. Prova lieve dolore o fastidio ❑
3. Prova moderato dolore o fastidio ❑
4. Prova grave dolore o fastidio ❑
5. Prova estremo dolore o fastidio ❑

Infine, vorremmo chiederle dell'ANSIA O DEPRESSIONE. Direbbe che:

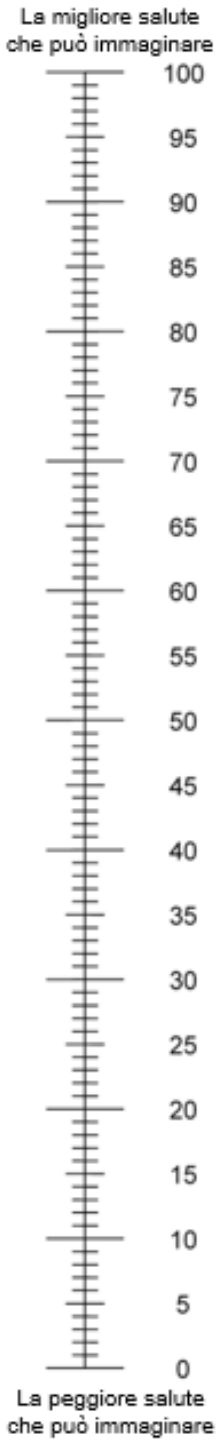
1. Non è ansioso/a o depresso/a ❑
2. È lievemente ansioso/a o depresso/a ❑
3. È moderatamente ansioso/a o depresso/a ❑
4. È gravemente ansioso/a o depresso/a ❑
5. È estremamente ansioso/a o depresso/a ❑

EQ-5D VAS

- **Adesso, vorremmo sapere quanto è buona o cattiva la sua salute OGGI.**
- **Vorremmo che immaginasse una linea verticale numerata da 0 a 100.**
  (Nota per l'intervistatore/intervistatrice: in caso di intervista faccia a faccia, mostrare all'intervistato/a la linea VAS.)
- **100 in cima alla linea rappresenta la migliore salute che può immaginare.**

  0 in fondo alla linea rappresenta la peggiore salute che può immaginare.
- **Vorrei che ora mi indicasse un punto sulla linea per indicare com'è la sua salute OGGI.**
  (Nota per l'intervistatore/intervistatrice: contrassegni la linea nel punto che indica la salute dell'intervistato/a OGGI. Ora, scriva il numero indicato sulla linea nella casella sottostante.)

LA SALUTE DELL'INTERVISTATO/A OGGI = ☐



Grazie per il tempo dedicato a rispondere a queste domande.

SPIROS (Standardized Protocol Items: Recommendations for Observational Studies) checklist

Section and topic	Description / sub-categories	Addressed in the manuscript (Paragraph name)
i) General information		
Title	Descriptive title identifying study design	Title page
Protocol version	Version or amendment number and date and summary of changes	NA
Protocol summary	Brief summary of protocol research	Abstract
Sponsor and partner institute name	Name of sponsor and participating institutes (if applicable)	Title page; Funding
Investigators name	Name of principal and co investigators.	Title page
Affiliations of investigators	Affiliated institutions of investigators	Title page
Principal researcher contact detail	Name, email address, affiliation of Principal researcher for correspondence	Title page
Table of content	Table of content	NA
Page number	Page number on each page of protocol	Yes
List of abbreviations	A detailed List of all abbreviations used in protocol with full form.	List of abbreviations
ii) Introduction		
Background of study	Scientific background of study	Background
Review of prior research	Summary of all previous relevant research	Background
Rationale of study	Justification for conducting the study	Background
Aim	Broader aims and specific objectives of the study	Study objectives
Objective of study	Primary and secondry objectives of study	Study objectives
Prespecified hypothesis	Prespecified null or alternative hypothesis	NA
iii) Methods		
Study design	Description of type/design of study	Study design
Study setting	Description of setting, locations, relevant dates, including periods of recruitment/survey, exposure, follow-up, and data collection. Schedule of study procedure – Figure or table	The Impella Network
Sample size	Estimated number, calculation and assumptions Power calculation	Sample size
Sampling procedure	Description of sampling strategy to ensure representativeness and control of potential bias	Study population
Participants	**Cohort study**—eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. For matched studies, give matching criteria and number of exposed and unexposed	Study population

	Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case **Cross-sectional study**—Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	• All outcomes • Exposures- definition of exposure of interest, • Predictors • Potential confounders • Effect modifiers	Outcomes of interest (Clinical parameters; Healthcare resource use and cost; Quality of life)
Data Sources/Measurement	• For each variable of interest, give sources of data and details of methods of assessment (measurement). • Describe comparability of assessment methods if there is more than one group • Data collection points table • Blinding procedure	Supplementary material
Bias	Describe any efforts to address potential sources of bias. More specifically: • Information bias • Selection Bias • Control for confounding	NA
Statistical analysis plan	• Method of primary / secondary outcomes and additional analysis • Handling of missing data • Post-hoc analysis	Data analysis (Statistical analysis; Cost-effectiveness analysis; Budget impact analysis)
Handling of withdrawals and lost to follow up	Describe the procedures to be followed when a participant ceases participation in the study prematurely or is lost to follow up	NA
Replacements	Provide information on whether or not participants who discontinue the study will be replaced via additional recruitment to maintain the required sample size.	NA
Outcome	Define and describe all primary and secondary outcome or lost to follow up	Outcomes of interest (Clinical parameters; Healthcare resource use and cost; Quality of life)
Database management	Detail plan of database management including: • Data collection (electronic or paper based), • Source data • Data entry • Data editing • Coding • Data storage	Data collection and management

	• Record retention • Data confidentiality	
Validation of instrument	Reliability / validity of instrument or plan to establish validation	NA
Follow up	Plan of follow up and addressing lost to follow up	Study design
Quality control	• Method of quality control • Monitoring (internal and external) • Training of surveyors	NA
Quality assurance	Plan of quality assurance	NA
Expected outcome / results	A brief description of expected outcome or results	NA
iv) Ethical consideration		
Ethical approval	Weather it has been obtained and name of ethical committees. If approval not sought , Reason	Ethics and dissemination
Agreement and consent	Method of taking consent. Reason if consent not sought	Patient and public involvement; Ethics and dissemination
Risk / Harm to participants	Any potential risk or harm to study participants	NA
Adverse event and Severe adverse event reporting	Outline how Adverse Event and Severe adverse event information will be collected.	NA
v) Reporting and dissemination		
Protocol amendments	Methods of communicating to investigators/IRBs and documenting	Study design
Dissemination	How results will be disseminated to participants, practitioners, public	Ethics and dissemination
Publication Plan	Who has right to publish; restrictions; authorship guidelines Open Access	Ethics and dissemination
Reporting of early stopping	Dissemination of results if trial is stopped early (for any reason)	NA
vi) Others		
Limitations	Limitations of proposed study, including risk of bias	Strengths and limitations of this study
Strength of study	Highlight strengths of proposed study	Strengths and limitations of this study
References	List of references cited in protocol	References
Data collection forms	Summary table of all forms used for data collection at each point of study	Supplementary materials
Inform consent forms	Sample of informed consent form, translated into local language	NA
Funding	Source of funding and the role of the funders for the present study	Funding
Acknowledgement for protocol development	Acknowledgement of persons involved in protocol preparation	Acknowledgements
Data sharing policy	To describe how data will be made available in public domain.	
Contributions of authors to protocol	Listed authors should have participated sufficiently in preparation of protocol with details of their contribution.	Authors contribution
Trial registry	For observational studies also registered as trial	NA
Annexures	Data collection form /instruments	Supplementary materials

	Informed consent form Standard operating procedures (SOPs) Detailed Statistical analysis plan (SAP)	