Title: Development of innovative technologies for the treatment of pulmonary and heart failure to prolong human's life

NCT number: Will be provided

Date: 01.01.2021

1. Annotation

There are used multiple techniques to reduce the syndrome of systemic inflammatory response, immunocorrection, and others in order to improve the results of implantation of mechanical devices, patients on the extracorporeal life-sustaining system and septic patients before surgery. Today, there are many ways to prevent the development of a systemic inflammatory response by removing leukocytes from the bloodstream by integrating a filter with a special screen in the perfusion circuit to remove leukocytes and prevent the latter from entering the systemic circulation.

The most effective approach is the method of extracorporeal hemadsorption, intended for additional therapy of patients with an increased level of cytokines in conditions of the systemic inflammatory response syndrome, in which a patient with acute pulmonary distress syndrome and cardiogenic septic shock against the background of an extracorporeal hemofiltration, an extracorporeal cytokine adsorber system was installed, intended to eliminate a wide range of inflammatory mediators, as well as multiple proteins and metabolites.

The purpose of the program.

Formulation of new treatments for heart and pulmonary failure through using organ-replacing technologies.

Formulation of a clinical protocol and implementation of treatment methods into clinical practice heart and pulmonary failure using organ-replacing technologies.

Study design.

Study type: interventional (clinical study)

Set of participants: 100 participants

Distribution: randomized

Interventional model: parallel

Masking: no

Primary Goal: Treatment

New methods were created for rehabilitating the function of affected organs after implantation of the LVAD, a total artificial heart, an extracorporeal life-sustaining system will be of great importance, both for Kazakhstan and for states with similar problems of donor organ deficiency, will also improve the effectiveness of surgical treatment and reduce

the level of complications and mortality of patients on the extracorporeal life-sustaining system and septic patients.

Furthermore, the results will lead to modernization and an increase in the share of innovative organ-replacing technologies in the health care system.

2. Explanatory note

1. General information

1.1. Name of the topic of the scientific, scientific and technical program "Development of innovative technologies for the treatment of pulmonary and heart failure to prolong human's life".

1.3. Location of the program. ~The Republic of Kazakhstan, Nur-Sultan.

1.4. Estimated start and end date of the program, its duration in months. 2021 - 2023 years, 36 months.

1.5. Organization applying for the program. Non-profit JSC "National Research Center for Cardiac Surgery".

1.6. Executors of the program. Non-profit JSC «National Research Center for Cardiac Surgery».

1.7. The requested amount of targeted program financing for the entire duration of the program is 240 265 thousand tenge, 2021 - 84 107 thousand tenge, 2022 - 84 817 thousand tenge, 2023 - 71 340 thousand tenge.

1.8. Key words characterizing the sector and the direction of the program for the selection of independent experts. Anesthesiology. Cardiothoracic surgery. Nephrology. Perfusion. Efferentology.

2. The general concept of the program.

2.1. Introductory part.

Non-profit JSC «National Research Center for Cardiac Surgery» (hereinafter – Non-profit JSC "NRCCS") is a research center that implements a program for the treatment of patients with chronic heart failure (CHF) and pulmonary failure (PF) in the terminal stage, including orthotopic transplantation of the heart and lungs, mechanical support of blood circulation.

Scientific supervisor of the program - Yuriy Vladimirovich Pya - Director for Surgery and Science of the Non-profit JSC «NRCCS», Associate Professor, Doctor of Medical Sciences, cardiac surgeon of the highest category.

Scientific co-director of the program - Timur Dostaevich Lesbekov - Non-profit JSC «National Research Center for Cardiac Surgery», candidate of medical sciences, cardiac surgeon of the highest category.

The implementation of this program will improve organ recovery, reduce postoperative complications, reduce postoperative mortality and improve the quality of life of patients with pulmonary and heart failure.

2.2. The purpose of the program.

Development of new treatments heart and pulmonary failure using organ-replacing technologies.

Development of a clinical protocol and implementation of treatment methods into clinical practice heart and pulmonary failure using organ-replacing technologies.

2.3. Objectives of the program.

Task 1. Assessment the results of the use of extracorporeal life support systems in the treatment of pulmonary and / or heart failure.

Subtask 1.1. Assessment of the restoration of organ function during extracorporeal life support systems using extracorporeal hemocorrection.

Subtask 1.2. Assessment of the normalization of the body's immune response and restoration of organ function during extracorporeal life support systems using an extracorporeal cytokine adsorber.

Task 2. Studying the restoration of organ function during implantation of the left ventricular assist device as an organ-replacing aid in heart failure.

Subtask 2.1. Assessment of the restoration of organ function during implantation of the left ventricular assist device with the use of extracorporeal hemocorrection.

Subtask 2.2. Assessment of the normalization of the body's immune response and restoration of organ function upon implantation of the left ventricular assist device using an extracorporeal cytokine adsorber.

Task 3. Studying the restoration of organ function during the implantation of the total artificial heart as an organ-replacing aid in case of heart failure.

Task 3.1. Assessment of normalization of organ function restoration during implantation of the total artificial heart with the use of extracorporeal hemocorrection.

Task 4. Studying the restoration of organ function during operations in conditions of the long-term cardiopulmonary bypass.

Task 4.1. Assessment of the restoration of organ function during operations with long-term cardiopulmonary bypass, hypothermia and circulatory arrest, with the use of extracorporeal hemocorrection.

Task 4.2. Assessment of the restoration of organ function during operations with long-term cardiopulmonary bypass, hypothermia and circulatory arrest using an extracorporeal cytokine adsorber.

Task 5. Improvement of the method of implantation of organ-replacing technologies to reduce complications in the treatment of heart and pulmonary failure.

3. Scientific innovativeness and significance of the program.

Organ replacement technologies are increasingly being used in the treatment of end-stage pulmonary and heart failure to prolong human life. Severe refractory cardiogenic shock, refractory ventricular arrhythmia, active cardiopulmonary resuscitation in cardiac arrest and acute or decompensated right heart failure, sepsis, pulmonary and multiple organ failure.

Careful patient selection and consideration of possible complications are key factors in optimizing the treatment of patients in this category. Well-defined pathways for medical care to centers capable of delivering heart and lung support replacement therapy (e.g., durable ventricular assist device or heart transplant) is essential to provide high-level patient care, stabilized with extracorporeal life support, and the ability to wean from the device. Ultimately, the concentration of the most complex care in large centers of our country with developed cardiac surgery and anesthetic capabilities can be a way to significantly improve the care of this group of patients.

Despite advances in mechanical ventilation, severe acute pulmonary distress syndrome (APDS) is associated with high morbidity and mortality rates ranging from 26% to 58%. Extracorporeal life sustaining system is a procedure for long-term cardiopulmonary bypass and oxygen saturation of the blood outside the body, used in patients with acutely developed and potentially reversible pulmonary and / or heart failure, whose treatment does not respond to maximum standard therapy. The Heart-Lung Sustaining System is a complex network that provides oxygenation and ventilation and allows the lungs to rest and recover from pulmonary failure while minimizing the iatrogenic lung damage caused by the ventilator. In intensive care in the conditions of an extracorporeal life support system. In 2011, the National Research Center for Cardiac Surgery Non-profit JSC launched a program to provide extracorporeal life support system in Kazakhstan, and in 2016 Non-profit JSC «NRCCS» has entered to the global ELSO register (Extracorporeal Life Support Organization).

The constant increase in the number of patients with CHF is associated with both an increase in the life expectancy of patients and a decrease in mortality among patients with a complicated course of acute myocardial infarction, heart defects, etc. The most common causes leading to the development of CHF are arterial hypertension, coronary heart disease and myocardial infarction. The gold standard for treatment of patients with end-stage heart failure, tolerant to drug therapy is heart transplantation.

Deficiency of donor organs remains the most important factor holding back the development of lung and heart transplantation all over the world and in our country. Left ventricular assist device (LVAD) implantation is a bridge to heart transplantation, which improves the quality and duration of life by improving blood circulation in most patients with chronic heart failure [1]. In recent studies, it was shown that the 1-year survival rate of patients after implantation of mechanical blood circulation support devices as a "bridge to transplantation" (BTT - bridge to transplantation) was 85%, and the 2-year survival rate in patients with ventricular assist device as " final treatment "(" DT - destination therapy ") - 76% [2]. It was also noted that patients with LVAD support improve functional status and quality of life [2].

A Total Artificial Heart is a form of mechanical circulatory support in which the patient's ventricles and valves are removed and replaced with an artificial heart. Currently, a fully artificial heart is implanted in the terminal stage of biventricular heart failure as a "bridge" to heart transplantation. However, given the increasing global burden of cardiovascular disease and congenital heart disease with heart failure, the number of end-stage heart failure patients awaiting heart transplants now far outnumbers the available hearts. As a result, the use of mechanical circulatory support, including a fully artificial heart, is growing exponentially.

Sepsis, septic shock, and systemic inflammatory response syndrome are life-threatening conditions resulting from a systemic response. Dysregulation can lead to multiple organ dysfunctions [30-36].

While sepsis and septic shock are infectious in origin, systemic inflammatory response syndrome (SIRS) can also have noninfectious triggers such as open heart bypass surgery, ex vivo heart / lung perfusion, extracorporeal life support, and mechanical circulatory support. It should be noted that mortality in SIRS, septic shock and sepsis reaches 7, 16, and 40%, accordingly [37-45]. According to Sepsis-3 2016, the new definition has two categories: sepsis and septic shock [46-49]. Previous definitions of sepsis, published in 1992, have

highlighted the role of systemic inflammatory response syndrome (SIRS) as a key element in the definition of sepsis.

In order to improve the results of implantation of mechanical devices, patients on the extracorporeal life support system and septic patients before surgery, various techniques are used to reduce the syndrome of systemic inflammatory response, immunocorrection, and others. To date, there are many ways to prevent the development of a systemic inflammatory response by removing leukocytes from the bloodstream by including a filter with a special screen in the perfusion circuit to remove leukocytes and prevent the latter from entering the systemic circulation [9].

The most effective is the method of extracorporeal hemadsorption, intended for additional therapy of patients with an increased level of cytokines in conditions of the systemic inflammatory response syndrome, in which a patient with acute pulmonary distress syndrome and cardiogenic septic shock against the background of an extracorporeal system has additional life support in the circuit of the apparatus for the veno-venous hemofiltration, an extracorporeal cytokine adsorber system was installed, designed to eliminate a wide range of inflammatory mediators, as well as various proteins and metabolites [55-61].

There are some new data showing that the use of an extracorporeal cytokine adsorber for long periods of cardiopulmonary bypass surgery (> 120 minutes) may be useful for preventing SIRS and reducing cytokine levels in patients have overcome by elective heart surgery [62-68].

In this study, methods will be developed to restore the function of affected organs before and / or after mechanical support of blood circulation (implantation of a completely artificial heart, implantation of an artificial left ventricle, an extracorporeal life support system) in combination with the use of an extracorporeal cytokine adsorber, which will improve the results of surgical treatment of patients with terminal heart and pulmonary failure.

New methods developed for restoring the function of affected organs after implantation of an artificial left ventricle, a completely artificial heart, an extracorporeal life support system will be of high importance, both for Kazakhstan and for states with similar problems of donor organ deficiency, will also improve the effectiveness of surgical treatment and reduce the level of complications and mortality of patients on the extracorporeal life support system and septic patients.

The clinical study data will form the basis of practical protocols for the implantation of an artificial left ventricle, a fully artificial heart, an extracorporeal life support system,

following which will improve organ recovery, reduce postoperative complications, improve the quality of life and reduce mortality after surgery.

4. Research methods and ethical issues.

All patients admitted to Non-profit JSC "NRCCS" who meet the study criteria (patients on an extracorporeal life support system, mechanical circulatory support, surgery on the aortic arch) will be included in the study after obtaining a signed informed consent. Participants will be randomized into 2 groups in a 1: 1 division.

Intervention team # 1 using an extracorporeal hemoperfusion device Jafron (Zhuhai Jafron Biomedical, China) (50 patients) in subgroups: A (n = 10) - patients on extracorporeal life support systems with heart failure; B (n = 10) - patients on extracorporeal life support systems with pulmonary failure; C (n = 5) - patients with implantation of a left ventricular accessory device; D (n = 25) - during operations with prolonged artificial circulation, hypothermia and circulatory arrest.

Intervention team # 2 using extracorporeal cytokine, CytoSorb (CytoSorbents Corporation, Monmouth Junction, NJ, USA) (50 patients) in subgroups: A (n = 10) - patients on extracorporeal life support systems in heart failure; B (n = 10) - patients on extracorporeal life support systems with pulmonary failure; C (n = 5) - patients with implantation of a left ventricular accessory device; D (n = 25) - during operations with prolonged artificial circulation, hypothermia and circulatory arrest.

Retrospective analysis of patients who received a fully artificial heart.

The duration of the intervention in each group will be 72 hours. Each Jafron / CytoSorb Removal Column can be used within 24 hours, so all patients in 2 groups use 3 filters during the study.

Researchers will collect demographic, clinical and laboratory data from patients before, during and after surgery.

The incidence of early cellular or humoral rejection, the duration of ventilation, intensive care and hospital stay, the use of vasopressors and inotropes in the perioperative period, and the incidence of perioperative complications and survivals will be documented.

The level of cytokines (IL-1, IL-6, IL-8, IL-10, tumor necrosis factor alpha) and complements will be determined before, during and after the use of the extracorporeal life support system for heart and pulmonary failure; surgery on the aortic arch, patients on mechanical circulatory support, if investigators find a corresponding difference between the two groups in terms of clinical variables.

Study design.

Study type: interventional (clinical study)

Set of participants: 100 participants

Distribution: randomized

Interventional model: parallel

Masking: no

Primary Goal: Treatment

Intervention team (1 group)	**Intervention / treatment (device)**
Extracorporeal hemoperfusion device will be installed in the device of the extracorporeal life support system for heart failure... (10 patients)	HA330 - Jafron Biomedical Co., Ltd., China - extracorporeal hemocorrection, which is based on the removal of cytokines from whole blood by sorption on a special hemoadsorbent due to the peculiarities of its porous structure and inner surface, which is indicated in conditions where cytokine levels are extremely elevated.
Extracorporeal hemoperfusion device will be installed in the device of the extracorporeal life support system for pulmonary failure (10 patients).	HA330 - Jafron Biomedical Co., Ltd., China - extracorporeal hemocorrection, which is based on the removal of cytokines from whole blood by sorption on a special hemabsorbent due to the peculiarities of its porous structure and inner surface, which is indicated in conditions where cytokine levels are extremely elevated.
An extracorporeal hemoperfusion device will be installed in patients before / during the implantation of a left ventricular assist device (5 patients).	HA330 - Jafron Biomedical Co., Ltd., China - extracorporeal hemocorrection, which is based on the removal of cytokines from whole blood by sorption on a special hemoadsorbent due to the peculiarities of its porous structure and inner surface, which is indicated in conditions where cytokine levels are extremely elevated.
An extracorporeal hemoperfusion device will	HA330 - Jafron Biomedical Co., Ltd., China

be installed in patients during operations with prolonged cardiopulmonary bypass, hypothermia and circulatory arrest. (25 patients).	- extracorporeal hemocorrection, which is based on the removal of cytokines from whole blood by sorption on a special hemoadsorbent due to the peculiarities of its porous structure and inner surface, which is indicated in conditions where cytokine levels are extremely elevated.
Intervention team (2 groups)	
Extracorporeal hemoperfusion device will be installed in the device of the extracorporeal life support system for heart failure. (10 patients)	CytoSorb (CytoSorbents Corp., USA) - an extracorporeal cytokine adsorber is a biocompatible polymer with high adsorption capacity, which is indicated in conditions where cytokine levels are extremely elevated.
Extracorporeal hemoperfusion device will be installed in the device of the extracorporeal life support system for pulmonary failure. (10 patients)	CytoSorb (CytoSorbents Corp., USA) - an extracorporeal cytokine adsorber is a biocompatible polymer with high adsorption capacity, which is indicated in conditions where cytokine levels are extremely elevated.
An extracorporeal hemoperfusion device will be installed in patients before / during the implantation of a left ventricular assist device (5 patients)	CytoSorb (CytoSorbents Corp., USA) - an extracorporeal cytokine adsorber is a biocompatible polymer with high adsorption capacity, which is indicated in conditions where cytokine levels are extremely elevated.
An extracorporeal hemoperfusion device will be installed in patients during operations with prolonged cardiopulmonary bypass, hypothermia and circulatory arrest. (25 patients)	CytoSorb (CytoSorbents Corp., USA) - an extracorporeal cytokine adsorber is a biocompatible polymer with high adsorption capacity, which is indicated in conditions where cytokine levels are extremely elevated.

Performance evaluation criterias

Extracorporeal life support system with pulmonary and / or heart failure
Primary results

1	Cytokine response [Time: 24-48 hours] The level of pro- and anti-inflammatory cytokines (IL-1, IL-6, IL-8, IL-10, tumor alpha-factor) before the implantation, 2 hours after the start of ECMO support, explantation of ECMO, 24 hours after explantation of ECMO.
2	SOFA-Score [Time Frame: 24, 48, 72 hours] Sequential Organ Failure Assessment Score at 24, 48, 72 h (values from 6 to 24, where the higher values explain higher disease severity)
3	Difference of mean arterial pressure [Time Frame: 24, 48, 72 hours] Comparison of mean arterial pressure at 24, 48, 72 hours between between two interventions (CytoSorb and Jafron)
4	Difference of CVP [Time Frame: 24, 48, 72 hours] Comparison of CVP at 24, 48, 72 hours between between two interventions (CytoSorb and Jafron)
5	Serum lactate [Time Frame: 24, 48, 72 hours] Level of serum lactate at 24, 48, 72 h
6	• Days on ventilator, vasopressor and renal replacement therapy [Time Frame: until day 30 post-surgery] Total days on ventilator, vasopressor and renal replacement therapy within 30 days post-surgery will be assessed
7	Doses of vasopressors and / or inotropes (µg / h / kg bodyweight) [Time: first 72 hours]
Secondary results	
1	Inflammatory response - The level of C-reactive protein (CRP) [Time: 24-48 hours] The level of C-reactive protein (CRP) before the start of ECMO, 2 hours after the implantation of ECMO, during ECMO, 24 hours after ECMO explantation.
2	Inflammatory response - The level of leukocytes [Time: 24-48 hours] The level of leukocytes before the start of ECMO, 2 hours after the implantation of ECMO, during ECMO, 24 hours after ECMO explantation.
3	Inflammatory response - The level of procalcitonin [Time: 24-48 hours] The level of procalcitonin before the start of ECMO, 2 hours after the implantation of ECMO, during ECMO, 24 hours after ECMO explantation.
4	Level of leukocyte [Time: 24-48 hours] Level of leukocyte cells in the bloodstream at 24, 48 hours.

5	Application and dosage of vasopressors [Deadline: first 48 hours] Incidence of application and level of dosage of vasopressors on days 2 and 3 after surgery;
6	Application and dosage of inotropes [Deadline: first 48 hours] Incidence of application and level of dosage of inotropes on days 2 and 3 after surgery;
Long-term results	
1	Length of stay in the intensive care unit [Duration: first 48 hours]
2	Length of hospital stay [Term: up to 1 month];
3	30 day survival rate.

Patients with left ventricular assist device implantation	
Primary results	
1	Difference of Cytokine response [Time: 24-48 hours] Level of pro- and anti-inflammatory cytokines (IL-1, IL-6, IL-8, IL-10, tumor necrosis factor-alfa, procalcitonin)
2	Doses of vasopressors and / or inotropes (μg / h / kg bodyweight) [Deadline: first 72 hours]
3	Renal function [Time: first 72 hours] creatinine level
4	Lactate level [Time: first 72 hours]
Secondary results	
1	Inflammatory response - The level of C-reactive protein (CRP) [Time: 24-48 hours] The level of C-reactive protein (CRP) before the start of the operation, 2 hours after the start of the operation, when the operation is turned off, 24 hours after the shutdown of the operation
2	Inflammatory response - The level of leukocytes [Time: 24-48 hours] The level of leukocytes before the start of the operation, 2 hours after the start of the operation, when the operation is turned off, 24 hours after the shutdown of the operation
3	Inflammatory response - The level of procalcitonin [Time: 24-48 hours] The level of procalcitonin before the start of the operation, 2 hours after the start of the operation, when the operation is turned off, 24 hours after the shutdown of the operation

4	Application and dosage of vasopressors [Deadline: first 48 hours] Incidence of application and level of dosage of vasopressors on days 2 and 3 after surgery;
5	Application and dosage of inotropes [Deadline: first 48 hours] Incidence of application and level of dosage of inotropes on days 2 and 3 after surgery;
Long-term results	
1	Length of stay in the intensive care unit [Duration: first 48 hours]
2	Length of hospital stay [Term: up to 1 month];
3	30 day survival rate.

For operations with prolonged cardio pulmonary bypass, hypothermia and circulatory arrest	
Primary results	
1	Cytokine response [Time: 24-48 hours] Difference of Cytokine response [Time: 24-48 hours] Level of pro- and anti-inflammatory cytokines (IL-1, IL-6, IL-8, IL-10, tumor necrosis factor-alfa, procalcitonin, C-reactive protein)
2	SOFA-Score [Time Frame: 24, 48, 72 hours] Sequential Organ Failure Assessment Score at 24, 48, 72 h (values from 6 to 24, where the higher values explain higher disease severity)
3	Difference of mean arterial pressure [Time Frame: 24, 48, 72 hours] Comparison of mean arterial pressure at 24, 48, 72 hours between between two interventions (CytoSorb and Jafron)
4	Difference of CVP [Time Frame: 24, 48, 72 hours] Comparison of mean arterial pressure at 24, 48, 72 hours between between two interventions (CytoSorb and Jafron)
5	Level of Serum lactate [Time Frame: 24, 48, 72 hours] Comparison of mean arterial pressure at 24, 48, 72 hours between between two interventions (CytoSorb and Jafron)
Secondary results	
1	Inflammatory response - The level of C-reactive protein (CRP) [Time: 24-48 hours] The level of C-reactive protein (CRP) before the cardiopulmonary bypass 2 hours

	after the cardiopulmonary bypass, when the cardiopulmonary bypass is turned off, 24 hours after the cardiopulmonary bypass.
2	Inflammatory response - The level of leukocytes [Time: 24-48 hours] The level of leukocytes before the cardiopulmonary bypass 2 hours after the cardiopulmonary bypass, when the cardiopulmonary bypass is turned off, 24 hours after the cardiopulmonary bypass.
3	Inflammatory response - The level of procalcitonin [Time: 24-48 hours] The level of procalcitonin before the cardiopulmonary bypass 2 hours after the cardiopulmonary bypass, when the cardiopulmonary bypass is turned off, 24 hours after the cardiopulmonary bypass.
4	Application and dosage of vasopressors [Deadline: first 48 hours] Incidence of application and level of dosage of vasopressors on days 2 and 3 after surgery;
5	Application and dosage of inotropes [Deadline: first 48 hours] Incidence of application and level of dosage of inotropes on days 2 and 3 after surgery;
Long-term results	
1	Length of stay in the intensive care unit [Duration: first 48 hours]
2	Length of hospital stay [Term: up to 1 month];
3	30 day survival rate.

Statistical research

1) statistical data processing

2) comparison and analysis of initial data

After data acquisition, statistical analysis will be performed using SPSS Statistics version 22. For quantitative data, the nonparametric Mann-Whitney Yu test and parametric t-test will be performed, and for qualitative studies, the nonparametric Fisher's exact test and the parametric χ^2 test will be performed. Also, logistic regression for categorical outcomes and survival analyzes (non-parametric Kaplan-Meyer and parametric Cox regression) will be performed.

Age: 18 years and older

Gender: All

Inclusion of healthy volunteers: Not

Groups	Inclusion criteria	Exclusion criteria
Patients on an extracorporeal life support system with heart failure	• Implantation of intravenous ECMO • Hemodynamic support with vasopressors and / or tonics; • Procalcitonin level ≥ 1 ng / ml; • Invasive hemodynamic monitoring; • Written informed consent.	• Age less than 18 years old • Terminal hepatic or renal failure just before the procedure • Patient's written refusal to participate in the study
Patients on an extracorporeal life support system with pulmonary failure	• IV ECMO implantation • High levels of venous and arterial CO2 (CO2> 50 mmHg), • Low paO2, SvO2, SpO2. • Invasive hemodynamic monitoring; • Written informed consent.	• Age less than 18 years old • Terminal hepatic or renal failure just before the procedure • Patient's written refusal to participate in the study
Patients with left ventricular assistive device implantation	• LVAD implantation • Biventricular heart failure IV • INTERMACS I-III • Hemodynamic support with vasopressors and / or tonics; • Procalcitonin level ≥ 0.1 ng / ml; • Invasive hemodynamic monitoring; • Written informed consent.	• Age less than 18 years old • Acute hepatic or renal failure just before the procedure • Patient's written refusal to participate in the study
Patients in operations with prolonged artificial circulation, hypothermia and circulatory arrest	• Hemodynamic support with vasopressors and / or tonics; • Bypass duration> 120 minutes • Hypothermia ≤ 25 0C • Circulatory arrest	• Age less than 18 years old • Terminal hepatic or renal failure just before the procedure • Patient's written refusal to

	• Procalcitonin level ≥ 1 ng / ml; • Invasive hemodynamic monitoring; • Written informed consent.	participate in the study

The study will be conducted in accordance with the international standards Good Clinical Practice, Joint Commission International, scientific ethics (Declaration of Helsinki), as well as the Order of the Minister of Health of the Republic of Kazakhstan dated December 11, 2020 No. 248 “On approval of the rules for conducting clinical trials of drugs and medical devices, clinical laboratory testing of medical devices for diagnostics outside of a living organism (in vitro) and requirements for clinical bases and provision of public services. Issuance of a permit for conducting a clinical trial and (or) testing of pharmacological and medicinal products, medical devices. " The study will also take place in accordance with the recommendations of the Local Ethics Commission at Non-profit JSC «NRCCS». All patients will receive a voluntary informed consent of the established form with permission to use clinical data for scientific purposes. In addition, the research will be strictly monitored by the researchers to ensure that it is free from plagiarism, falsification and fabrication of data in order to achieve the highest ethical conduct of the research. The resulting patient data will be strictly confidential with ensuring privacy through strictly limited access to data, de-identification of data and destruction after the end of the study.

5. Research team and program management

No.	Full name (degree, academic title)	Main place of work, position	Role in the program	Employment	Project work period (months)		
					1st year	2nd year	3rd year
1	Pya Yuri Vladimirovich	Non-profit JSC "NRCCS" Director of Science and Surgery	Leader Scientific supervisor of the project. General project management, definition of the vision and direction of the project, participation in the analysis of results, participation in the preparation of publications	Part-time	12	12	12
2	Lesbekov Timur Dostaevich	Non-profit JSC "NRCCS" Head of the Department of Cardiac Surgery	Co-leader General project management, definition of the vision and direction of the project, participation in the analysis of results, participation in the preparation of publications	Part-time	12	12	12
3	Kaliev	Non-profit JSC	Leading researcher	Part-time			

	Rymbay Bolatovich	"NRCCS" Head of the operating department with a laboratory for circulatory support	Selection of patients, analysis of clinical data, development of a quality of life questionnaire. Participation in the analysis of results and preparation of publications, methods, including methods of prevention.		12	12	12
4	Nurmykhametova Zhuldyz Askarovna	Non-profit JSC "NRCCS" Physician perfusionist of the operating department with a laboratory for circulatory support	Secondary researcher Selection of patients, analysis of clinical data, development of a quality of life questionnaire. Participation in the analysis of results and preparation of publications, methods, including methods of prevention	Part-time	12	12	12
5	Kuanyshbek Aydin Sayatovich	Non-profit JSC "NRCCS" Head of the Department of Anesthesiology,	Secondary researcher Selection of patients, analysis of clinical data, development of a quality of life questionnaire. Participation in the analysis of results and preparation of	Part-time	12	12	12

		Reanimation and Intensive Care	publications, methods, including methods of prevention				
6	Dzhabaeva Nilufar Amirbekovna	Non-profit JSC "NRCCS" Doctor nephrologist Extracorporeal hemocorrection laboratories	SNS Selection of patients, analysis of clinical data, development of a quality of life questionnaire. Participation in the analysis of results and preparation of publications, methods, including methods of prevention	Part-time	12	12	12
7	Faizov Linar Renatovich	Non-profit JSC "NRCCS" Physician perfusionist of the operating department with a laboratory for circulatory support	SNS Selection of patients, analysis of clinical data, development of a quality of life questionnaire. Participation in the analysis of results and preparation of publications, methods, including methods of prevention	Part-time	12	12	12
8	Position		Economic calculations, preparation of interim and annual reports	Part-time			

					12	12	12
9	Iskakova Ainel Talgatovna	Non-profit JSC "NRCCS" Chief Specialist Department of Science	Organizational project management, preparation of semi-annual acts, reports.	Part-time	12	12	12
10	Position		Statistical processing of the obtained research data	Part-time			
11	Position		Statistical processing of the obtained research data	Part-time			

In total, 11 specialists in the field of cardiac surgery, perfusion, cardiology, anesthesiology, efferentology, and public health are involved in the project.

Principal Investigator - Yuriy Vladimirovich Pya - Director for Surgery and Science of the National Research Center for Cardiac Surgery, a graduate of the 2nd Moscow State Medical Institute named after V.I. NI Pirogova, international cardiac surgeon, associate professor, doctor of medical sciences. Winner of a number of state awards, including the Order of the Republic of Kazakhstan "Parasat", "Doctor of the Year 2012", the honorary title "Kazakhstan Enbek Eri". The supervisor will be involved throughout the entire research period. According to Scopus, the Hirsch index - 10, Author ID in Scopus - 7801690331. Proncipal Investigator of the projects:

1. Scientific project Committee of Science of the Ministry of education and science of Republic of Kazakhstan 2018-2020 on the topic "Study of the effectiveness of a new method of conditioning for the preservation of the donor heart";
2. Scientific program Targeted program financing of the Ministry of Health of the Republic of Kazakhstan 2017-2019 on the topic "New molecular genetic methods of pre-symptomatic diagnostics and methods of treatment of a number of significant diseases", Surgical treatment of CHF;
3. Y. Pya, A. Medressova, S. Bekbobysynov, dated August 25, 2020, No. US 10,751,456 B2, METHOD OF IMPLANTATION OF LEFT VENTRICULAR MECHANICAL ASSIST DEVICE HEARTMATE III (US Patent Office);
4. Y. Pya, A. Medressova, S. Bekbossynov, dated November 16, 2020, No. 201800238 Method of implantation of a device for mechanical support of the left ventricle HEARTMATE 3 (Eurasian Patent Office).

Co-head of the program - Timur Dostaevich Lesbekov, Candidate of Medical Sciences, Head of the Department of Cardiac Surgery, Non-profit JSC «NRCCS». According to Scopus, the Hirsch index - 2, the Author ID in Scopus - 6505523476.

Kaliev Rymbay Bolatovich - head of the operating department with the laboratory of auxiliary blood circulation, Non-profit JSC «NRCCS». According to Scopus, Hirsch index is 3, Author ID in Scopus - 57053326800.

Kuanyshbek Aydin Sayatovich - Head of the Department of Anesthesiology, Reanimation and Intensive Care of the Non-profit JSC «NRCCS». According to Scopus, Hirsch index - 1, Author ID in Scopus -57221294150.

Nurmykhametova Zhuldyz Askarovna - doctor perfusionist of the operating department with a laboratory for auxiliary circulation of the Non-profit JSC «NRCCS». According to Scopus, Hirsch index - 1, Author ID in Scopus -57221292855.

Faizov Linar Renatovich - doctor perfusionist of the operating department with the laboratory of auxiliary circulation of the Non-profit JSC «NRCCS». According to Scopus, Hirsch index - 2, Author ID in Scopus - 57194181173.

List of international publications (last):

1	Medressova, A., Faizov, L., Kuanyshbek, A., Kaliyev, R., Myrzakhmetova, G., la Fleur, P., Pya, Y. Successful heart transplantation after 17 h ex vivo time using the Organ Care System—3 years follow-up//Journal of Cardiac Surgery, 2021 (in press) (52 percentile, Scopus)
2	Zimpfer, D., Gustafsson, F., Potapov, E., Pya, Y., Schmitto, J., Berchtold-Herz, M., Garbade, J. (2020). Two-year outcome after implantation of a full magnetically levitated left ventricular assist device: Results from the ELEVATE registry. European Heart Journal, 41(39), 3801-3809. doi:10.1093/eurheartj/ehaa639 (99 percentile, Scopus)
3	Pya, Y., Netuka, I., Latremouille, C., Bekbossynova, M., Medressova, A., Bekbossynov, S., Salov, R., & Hetzer, R. (2020). CARMAT total artificial heart implantation: report on the first successful clinical experience as bridge to heart transplantation. Cardiovascular Diagnosis And Therapy, 0. doi:10.21037/cdt-20-353 (63 percentile, Scopus)
4	Mirza, Kiran & Gustafsson, F. & Pya, Y. & Shaw, S. & Diegeler, A. & Netuka, I. & Lavee, Jacob & Garbade, Jens & Morshuis, M. & Heatley, J. & Saeed, Diyar & Potapov, Evgenij & Schmitto, Jan & Zimpfer, Daniel. (2019). Atrial Fibrillation is a Predictor of Poor Physical Capacity 6 Months after Implantation of a Full Magnetically Levitated Left Ventricular Assist Device: An Analysis from ELEVATE. The Journal of Heart and Lung Transplantation. 38. S45. 10.1016/j.healun.2019.01.095. (99 percentile, Scopus)
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	Transplantation. 39. S184. 10.1016/j.healun.2020.01.768. (99 percentile, Scopus)
6	Loforte, Antonio & Gliozzi, G. & Potapov, E. & Mariani, Carlo & Schoenrath, Felix & Netuka, I. & Pya, Y. & Gummert, Jan & Meyns, B. & Pacini, Doreen & By, T.M.M.H.. (2020). Concomitant Cardiac Procedures during Implantation of Long-Term Continuous-Flow LVADs: A European Registry for Patients with Mechanical Circulatory Support (EUROMACS) Analysis. The Journal of Heart and Lung Transplantation. 39. S122-S123. 10.1016/j.healun.2020.01.1009. (99 percentile, Scopus)
7	Kaliyev, R., Lesbekov, T., Bekbossynov, S. Samalavicius, R., Pya, Y. Comparison of Custodiol vs warm blood cardioplegia and conditioning of donor hearts during transportation with the organ care system//Journal of Cardiac Surgery, 2019, 34(10), с. 969-975 (52 процентиль, Scopus)
8	R. Kaliyev, S. Bekbossynov, Zh. Nurmykhametova. Sixteen-Hour Ex Vivo Donor Heart Perfusion During Long-Distance Transportation for Heart Transplantation//Artificial organs – 43(3), 2019, с. 319-320 (60 percentile, Scopus)
9	Пя Ю.В., Калиев Р.Б., Лесбеков Т.Д., Бекбосынов С.Т., Капышев Т.С., Нурмыхаметова Ж.А., Смагулов Н.К., Аширов Ж.З., Фаизов Л.Р. Программа экстракорпоральной мембранной оксигенаций в Казахстане: ближайшие результаты // «Журнал им. акад. Б.В. Петровского Клиническая и экспериментальная хирургия» - №1-2017 г. С. 41-45 (6 percentile, Scopus)
10	Пя Ю.В., Калиев Р.Б., Бекбосынов С.Т., Лесбеков Т.Д., Нурмыхаметова Ж.А., Смагулов Н.К., Новикова С.П., Аширов Ж.З., Фаизов Л.Р., Медресова А.Т., Мурзагалиева М.О. Новый метод сохранения донорского сердца с использованием кровяной кардиоплегии и кондиционирования // «Журнал им. акад. Б.В. Петровского Клиническая и экспериментальная хирургия» - №3-2017 г. С. 54-60 (6 percentile, Scopus)
	Пя Ю.В., Бекбосынов С.Т., Бекбосынова М.С., Куатбаев Е.М.,Лесбеков Т.Д., Калиев Р.Б., Джетыбаева С.К., Медресова А.Т., Нурмыхаметова Ж.А., Мурзагалиев М.У., Новикова С.П., Капышев Т.С.,Смагулов Н.К., Фаизов Л.Р., Вахрушев И.А., Андосова С.А.,Мырзахметова Г.Ш., Надирбекова Г.Е., Шайсултанова С.Т., Дюсенбина Ж.С. Программа трансплантации сердца в эпоху механической поддержки кровообращения: опыт Республики

	Казахстан // «Журнал им. акад. Б.В. Петровского Клиническая и экспериментальная хирургия» - №3-2017 г. С. 49-54(6 percentile, Scopus)

8. Plan for the implementation of the program.

P / p No.	Name of tasks and measures for their implementation	Start of execution (dd / mm / yy)	Duration, months	Expected results of the program implementation (in the context of tasks and activities), completion form		
				1st year	2nd year	3rd year
1	2	4	5	6	7	8
1	Literature review on organ replacement technology in the treatment of patients with heart and pulmonary insufficiency	2021	9	A literature review on organ replacement technology in the treatment of patients with heart and lung failure will be obtained.		
1.1	A review of the literature on the restoration of organ function when using extracorporeal life support systems as an organ-substituting aid for heart and pulmonary	2021	3	A review of the literature on the restoration of organ function using extracorporeal life support systems as an organ-substituting aid for heart and pulmonary failure will be obtained.		

	failure.					
1.2	Literature review on implantation of mechanical circulatory devices using an extracorporeal cytokine adsorber	2021	3	A literature review on the implantation of mechanical circulatory devices using an extracorporeal cytokine adsorber will be obtained.		
1.3	Literature review on the use of an extracorporeal cytokine adsorber in operations with prolonged artificial circulation, hypothermia and circulatory arrest	2021	3	A literature review will be obtained on the use of an extracorporeal cytokine adsorber in operations for reconstructing the aortic arch with hypothermia and cardiopulmonary bypass.		
2	Based on the literature review, conduct a comparative assessment of the application of methods of extracorporeal hemoadsorption in	2021	9	Comparative evaluation will be carried out on the application of methods of extracorporeal hemoadsorption in pulmonary and heart failure		

	pulmonary and heart failure					
3	Patient recruitment	2021		Patient recruitment for the study will begin	Patient recruitment will continue	Patient recruitment will continue
3.1	Recruiting of patients using extracorporeal life support systems as an organ-substituting aid for heart and pulmonary failure.	2021	36	Recruiting of patients using extracorporeal life support systems as an organ-substituting aid for heart and pulmonary failure.	Recruiting of patients when using extracorporeal life support systems, as an organ-substituting aid, with heart and pulmonary failure will continue	Recruiting of patients when using extracorporeal life support systems, as an organ-substituting aid, with heart and pulmonary failure will continue
3.2	Recruiting of patients for implantation of mechanical circulatory devices using an extracorporeal cytokine adsorber	2021	36	Recruiting will begin patients with implantation of mechanical circulatory devices using an extracorporeal cytokine adsorber	Recruiting patients for implantation of mechanical circulatory devices using an extracorporeal cytokine adsorber will continue	Recruiting patients for implantation of mechanical circulatory devices using an extracorporeal cytokine adsorber will continue
3.3	Recruiting of patients for hypothermia and cardiopulmonary bypass reconstruction with an extracorporeal cytokine	2021	36	Will be started recruiting of patients for reconstructions of the aortic arch with hypothermia and cardiopulmonary bypass	Recruiting of patients for hypothermia and cardiopulmonary bypass reconstruction with an extracorporeal cytokine	Recruiting of patients for hypothermia and cardiopulmonary bypass reconstruction with an extracorporeal cytokine

	adsorber			using an extracorporeal cytokine adsorber	adsorber will continue	adsorber will continue
4	Collection of laboratory and clinical data	2021	36	There will be a collection laboratory and clinical data	There will be a collection laboratory and clinical data	There will be a collection laboratory and clinical data
4.1	Collection of laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, dose of vasopressors after implantation of extracorporeal life support systems as an organ-substituting aid for pulmonary failure	2021	36	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, dose of vasopressors after implantation of extracorporeal life support systems as an organ-substituting aid for pulmonary failure	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, dose of vasopressors after implantation of extracorporeal life support systems as an organ-substituting aid for pulmonary failure	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, dose of vasopressors after implantation of extracorporeal life support systems as an organ-substituting aid for pulmonary failure
4.2	Collection of data on the inflammatory response, leukocyte function, doses of inotropic support after implantation of	2021	36	There will be a collection data on inflammatory response, leukocyte function, doses of inotropic support after implantation of	There will be a collection data on inflammatory response, leukocyte function, doses of inotropic support after implantation of	There will be a collection data on inflammatory response, leukocyte function, doses of inotropic support after implantation of extracorporeal

	extracorporeal life support systems as an organ-substituting aid for pulmonary failure			extracorporeal life support systems as an organ-substituting aid for pulmonary failure	extracorporeal life support systems as an organ-substituting aid for pulmonary failure	life support systems as an organ-substituting aid for pulmonary failure
4.3	Long-term results collection: length of stay in the intensive care unit, 30 day survival after implantation of extracorporeal life support systems as an organ-substituting aid for pulmonary failure	2021	36	Long-term results will be collected: length of stay in the intensive care unit, 30 day survival after implantation of extracorporeal life support systems as an organ-substituting aid for pulmonary failure	Long-term results will be collected: length of stay in the intensive care unit, 30 day survival after implantation of extracorporeal life support systems as an organ-substituting aid for pulmonary failure	Long-term results will be collected: length of stay in the intensive care unit, 30 day survival after implantation of extracorporeal life support systems as an organ-substituting aid for pulmonary failure
4.4	Collection of laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, dose of vasopressors after	2021	36	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, doses of vasopressors after	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, doses of vasopressors after	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, doses of vasopressors after

	implantation of extracorporeal life support systems as an organ-substituting aid in heart failure			implantation of extracorporeal life support systems as an organ-substituting aid in heart failure	implantation of extracorporeal life support systems as an organ-substituting aid in heart failure	implantation of extracorporeal life support systems as an organ-substituting aid in heart failure
4.5	Collection of data on inflammatory response, leukocyte function, doses of inotropic support after implantation of extracorporeal life support systems as an organ-substituting aid in heart failure	2021	36	There will be a collection data on inflammatory response, leukocyte function, doses of inotropic support after implantation of extracorporeal life support systems as organ-substituting benefits for heart failure	There will be a collection data on inflammatory response, leukocyte function, doses of inotropic support after implantation of extracorporeal life support systems as organ-substituting benefits for heart failure	There will be a collection data on inflammatory response, leukocyte function, doses of inotropic support after implantation of extracorporeal life support systems as organ-substituting benefits for heart failure
4.6	Long-term results collection: length of stay in the intensive care unit, 30 day survival after implantation of extracorporeal life support systems as an	2021	36	There will be a collection long-term results: length of stay in the intensive care unit, 30 day survival after implantation of extracorporeal life support systems as an organ-	There will be a collection long-term results: length of stay in the intensive care unit, 30 day survival after implantation of extracorporeal life support systems as an organ-	There will be a collection long-term results: length of stay in the intensive care unit, 30 day survival after implantation of extracorporeal life support systems as an organ-substituting aid for

	organ-substituting aid for heart failure			substituting aid for heart failure	substituting aid for heart failure	heart failure
4.7	Collection of laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, dose of vasopressors after implantation of an auxiliary device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure.	2021	36	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, dose of vasopressors after implantation of an auxiliary device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, dose of vasopressors after implantation of an auxiliary device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines, assessment of organ dysfunction, dose of vasopressors after implantation of an auxiliary device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure
4.8	Data collection of inflammatory response, leukocyte function, inotropic support doses after implantation of an	2021	36	There will be a collection inflammatory response data, leukocyte function, inotropic support doses after implantation of an auxiliary	There will be a collection inflammatory response data, leukocyte function, inotropic support doses after implantation of an auxiliary	There will be a collection inflammatory response data, leukocyte function, inotropic support doses after implantation of an auxiliary

	auxiliary device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure.			device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure.	device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure.	device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure.
4.9	Long-term data collection: length of stay in the intensive care unit, 30 day survival after implantation of an auxiliary device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure.	2021	36	There will be a collection long-term results: length of stay in the intensive care unit, 30 day survival after implantation of an auxiliary device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure.	There will be a collection long-term results: length of stay in the intensive care unit, 30 day survival after implantation of an auxiliary device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure.	There will be a collection long-term results: length of stay in the intensive care unit, 30 day survival after implantation of an auxiliary device of the left ventricle and implantation of a completely artificial heart as an organ-replacing aid in case of heart failure.
4.10	Collection of laboratory and clinical data, blood sampling for pro- and anti-inflammatory	2021	36	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines,	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines,	There will be a collection laboratory and clinical data, blood sampling for pro- and anti-inflammatory cytokines,

	cytokines, assessment of organ dysfunction, dose of vasopressors during operations with prolonged artificial circulation, hypothermia and circulatory arrest, as an organ-substituting aid			assessment of organ dysfunction, dose of vasopressors after reconstruction of the aortic arch with long-term artificial circulation and hypothermia, as an organ-replacing aid	assessment of organ dysfunction, dose of vasopressors after reconstruction of the aortic arch with long-term artificial circulation and hypothermia, as an organ-replacing aid	assessment of organ dysfunction, dose of vasopressors after reconstruction of the aortic arch with long-term artificial circulation and hypothermia, as an organ-replacing aid
4.11	Collection of data on inflammatory response, leukocyte function, inotropic support doses during operations with prolonged artificial circulation, hypothermia and circulatory arrest, as an organ-substituting aid	2021	36	There will be a collection inflammatory response data, leukocyte function, inotropic support doses after reconstruction of the aortic arch with long-term artificial circulation and hypothermia, as an organ-replacing aid	There will be a collection inflammatory response data, leukocyte function, inotropic support doses after reconstruction of the aortic arch with long-term artificial circulation and hypothermia, as an organ-replacing aid	There will be a collection inflammatory response data, leukocyte function, inotropic support doses after reconstruction of the aortic arch with long-term artificial circulation and hypothermia, as an organ-replacing aid
4.12	Long-term data collection: length of stay in the intensive care unit, 30 day survival after	2021	36	There will be a collection long-term results: length of stay in the intensive care unit, 30 day survival after	There will be a collection long-term results: length of stay in the intensive care unit, 30 day survival after	There will be a collection long-term results: length of stay in the intensive care unit, 30 day survival after

	operations with long-term artificial circulation, hypothermia and circulatory arrest, as an organ-substituting aid			reconstruction of the aortic arch with long-term artificial circulation and hypothermia, as an organ-replacing aid	reconstruction of the aortic arch with long-term artificial circulation and hypothermia, as an organ-replacing aid	reconstruction of the aortic arch with long-term artificial circulation and hypothermia, as an organ-replacing aid
5	Analysis of clinical and laboratory data on the restoration of organ function using innovative technologies	2022	24		An analysis of clinical and laboratory data on the restoration of organ function will be carried out using innovative technologies	An analysis of clinical and laboratory data on the restoration of organ function will be carried out using innovative technologies
6	Statistical processing and analysis of the obtained data	2022	24		Statistical processing of the obtained research results will be carried out	Statistical processing of the obtained research results will be carried out
7	Determination of an effective method of treating heart and pulmonary failure using organ replacement technologies.	2023	12			An effective method will be determined of the treatment of heart and pulmonary failure using organ replacement technologies
8	Development of innovative methods of	2022	24		Innovative methods of treating patients using	Innovative methods of treating patients using organ-

	treating patients using organ-replacing technologies				organ-replacing technologies will be developed	replacing technologies will be developed
9	Development of practical protocols for the restoration of organ function	2022	24		Practical protocols to restore organ function will be developed	Practical protocols to restore organ function will be developed
10	Implementation of patient treatment protocols using organ-replacing technologies	2023	12			Patient treatment protocols using organ-replacing technologies will be introduced
11	Writing and submission of interim and final reports	2021	36	Interim report will be prepared	Interim report will be prepared	Final report will be prepared
12	Preparation of publications, reports	2022	24		Publications will be prepared	Publications will be prepared

9. Expected results of the program.

Direct results:

The obtained results of the study will form the basis for practical protocols for the use of extracorporeal life support systems, operations for the implantation of left ventricular assistive devices and a completely artificial heart.

The obtained protocols will be implemented in the treatment of patients using organ-replacing technologies and will be documented.

As part of the study, innovative methods of treating patients using organ-replacing technologies will be developed:

- with the implantation of a completely artificial heart, as an organ-replacing aid, in case of heart failure;
- with implantation of an auxiliary device of the left ventricle, as an organ-replacing aid, in case of heart failure;
- when using extracorporeal life support systems in the treatment of pulmonary and / or heart failure.

The developed methods will be used as new standards and recommendations for the treatment of heart and pulmonary failure.

The developed recommendations will form the basis for a number of educational events within the framework of the ECMO School with the involvement of specialists from all regions of the country.

Will be published at least 2 (two) articles and (or) reviews in peer-reviewed scientific journals in the scientific direction of the program included in the 1 (first), 2 (second) or 3 (third) quartiles in the Web of Science database and (or) having a percentile CiteScore in the Scopus database is at least 50 (fifty).

The results of the study can help to reduce the rate of postoperative mortality in critically ill patients with pulmonary and / or heart failure by 30%.

To popularize science, a separate website will be created, which will provide complete information on the progress of the program. For each scientific publication within the framework of the program, information will be published on the website and / or in social networks.

End results:

In general, the expected efficiency and effectiveness of the proposed project will make a significant contribution to the development of the health care system in Kazakhstan, namely, to improve organ recovery, reduce postoperative complications, reduce postoperative mortality and improve the quality of life of patients.

The data obtained on the treatment of patients with heart and pulmonary failure through the use of innovative technologies will provide the necessary information to improve the quality of tertiary medical care and the quality of life of patients in Kazakhstan and around the world.

This project is aimed at achieving the indicators of the State Program for Healthcare Development 2020-2025. An increase in the average life expectancy of population up to 75 years and a decrease in the risk of premature mortality from 30 to 70 years from cardiovascular diseases.

In addition, the results will lead to modernization and an increase in the share of innovative organ-replacing technologies in the health care system.

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