**Title:** Innovative solutions to organ-substituting technologies in the treatment of heart and pulmonary failure

**NCT number**: Will be provided

**Date:** 15.04.2021

## 1. Abstract

In order to improve the results of ECMO and septic patients, various techniques used to reduce the systemic inflammatory response syndrome, immunocorrection, and others. Today, there are many ways to prevent the development of a systemic inflammatory response by removing leukocytes from the bloodstream by inserting a filter with a special screen into the perfusion circuit to remove leukocytes and prevent them from entering the systemic circulation.

The most effective method is the hemoadsorption, intended for additional therapy of patients with elevated levels of cytokines in the context of systemic inflammatory response syndrome. In-patient with acute respiratory distress syndrome and cardiogenic septic shock on the background of extracorporeal membrane oxygenation (ECMO) and mechanical support of the left ventricle, additionally installed a system for veno-venous hemofiltration, a system designed to eliminate a wide range of inflammatory mediators also various proteins and metabolites.

New methods developed to restore the function of affected organs after implantation of mechanical support devices and patients with sepsis will be a great importance both for Kazakhstan and for countries with similar category of patients, which will improve the efficiency of surgical treatment and reduce the level of complications and mortality.

Clinical research data will form the basis of practical protocols for extracorporeal membrane oxygenation (ECMO) and patients with sepsis, which will improve organ repair, reduce postoperative complications, improve quality of life and reduce mortality after surgery.

The goal of the program: Improvement of organ-substituting technologies in the treatment of heart and respiratory failure.

**Study Design**

Study Type: Interventional (Clinical Trial)

Estimated Enrollment: 90 Participants

Allocation: randomized

Interventional Model: Parallel assignment

Masking: None (Open Label)

The results of a clinical study will improve the effectiveness of surgical treatment and reduce the level of complications and mortality, improve the quality of life of patients undergoing cardiac surgery. The introduction of a clinical protocol for the use of an extracorporeal adsorbent in this category of patients will allow standardizing this technique in the Republic of Kazakhstan.

The data obtained on the treatment of patients with heart and lung failure and organ restoration through the use of innovative technologies will provide the necessary information to

improve the quality of tertiary care and the quality of life of patients in Kazakhstan and around the world. The developed methods can be used as new standards and recommendations both domestically and abroad through successful presentations at various conferences. If there are unique developments in the use of an extracorporeal adsorbent, patent applications will be filed.

In general, the expected effectiveness and efficiency of the proposed project will make a significant contribution to the development of transplantation, cardiac surgery and cardiology in Kazakhstan.

## 2. Explanatory note

### 1. General information

1.1. The title of the scientific and technical program (hereinafter - the program): “Innovative solutions to organ-substituting technologies in the treatment of heart and pulmonary failure”.

1.2. The name of the priority area for the development of science, according to which the application is submitted. The Science of Life and health.

1.3. Name of the specialized scientific field in which the application is submitted, type of research. Biotechnologies in medicine: New technologies and biologically active substances for solving anti, postnatal development aging, prolonging of human life problems.

1.4. Estimated project start date and duration. 2021-2023 years.

1.5 Requested amount of grant funding for the entire duration of the project for 2021 - 2023 – 63 083 thousand tenge, 2021 – 18 574 thousand tenge, 2022- 22 228 thousand tenge, 2023 – 22 280 thousand tenge.

1.6. Keywords that characterize the industry and the direction of the application for the selection of experts. Organ-substituting technologies. Heart failure. Pulmonary failure. Sepsis. Extracorporeal membrane oxygenation. Adsorber

### 2. General project concept

2.1. Introduction

Principal Investigator – Timur Lesbekov, MD, Chief of Cardiac Surgery Department of JSC “National Research Center for Cardiac Surgery” (hereinafter referred to as JSC NNCS).

JSC “National Research Center for Cardiac Surgery” is a research center that implements a program for treating patients with chronic heart failure (CHF) and pulmonary failure (PF) at the terminal stage, including orthotopic transplantation of the heart and lungs, mechanical support of the blood circulation.

The implementation of this project will improve the effectiveness of surgical treatment and reduce the level of complications and mortality among patients with heart failure and heart failure in the terminal stage.

2.2. The goal of the program.

Improvement of organ-substituting technologies in the treatment of heart and respiratory failure.

2.3. Objectives of the program.

**Objective 1. To study the restoration of organ function during implantation of extracorporeal membrane oxygenation (ECMO), as an organ replacement, in cardiac and / or respiratory failure.**

**Subtask 1.1.** Evaluation of the recovery of organ function during ECMO using extracorporal hemocorrection procedure.

**Subtask 1.2**. Evaluation of the normalization of the organism immune response and restoration of organ function when conducting ECMO using the extracorporeal cytokine adsorber.

**Subtask 1.3**. Evaluation of the normalization of the organism immune response and restoration of organ function when conducting ECMO using the extracorporeal hemoperfusion cartridge.

**Objective 2. To study the results of applying organ-substituting technologies in the treatment of sepsis.**

**Subtask 2.1**. Assessment of the recovery of organ function in the application of extracorporal hemocorrection in septic patients.

**Subtask 2.2**. Evaluation of the normalization of the organism immune response and restoration of organ function when using the extracorporeal cytokine adsorber in septic patients.

**Subtask 2.3**. Evaluation of the normalization of the organism immune response and restoration of organ function when using the extracorporeal hemoperfusion cartridge.

**3. Scientific novelty and significance of the program**

According to statistics, CHF is an increasingly widespread condition in most countries of the world. In the general population within adults, CHF is revealed annually in 1-2% of the population [1]. With increasing age, the incidence of CHF is increasing exponentially. The incidence of CHF reveals its multiple increase in each subsequent age group: in 25-34 years old - 0.02 per 1000 population, in 55-64 - 3.0-4.0 per 1000, 75-84 years - 13.0- 14.0 per 1000 population [2-5]. 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 of CHF are arterial

hypertension, coronary heart disease and myocardial infarction. The gold standard for treating patients with terminal heart failure, tolerance to drug therapy is heart transplantation.

In 2012 the JSC "National Research Center for Cardiac Surgery" developed the heart transplantation program in Kazakhstan. Considering the geographical features of our country (donor hearts are transported from regions remote from the Center> 1000 km.), remote delivery and heart preservation has been developed using an organ preservation system. The Center has been performed 81 heart transplants for 8 years. The survival rate by 12 months was 80%. According to data, for 2018, more than 200 people need heart transplants every year in Kazakhstan.

The lack of donor organs remains the most important factor hindering the development of lung and heart transplants throughout the world and in our country.

Extracorporeal membrane oxygenation (ECMO) is a procedure for prolonged cardiopulmonary bypass and oxygenation of the blood outside the body, used in patients with acutely frisky and potentially reversible respiratory and / or heart failure, whose treatment is not amenable to the maximum standard therapy. In 2011, the JSC "National Research Center for Cardiac Surgery" launched a program to provide ECMO in Kazakhstan, and in 2016 the Center entered to the World Register ELSO (Extracorporeal Life Support Organization) [6-14].

Sepsis, septic shock and SIRS are life-threatening conditions associated with an overreacting immune response. The deregulated response can lead to multiple organ dysfunction [15-21].

While sepsis and septic shock have an infectious origin, SIRS may also have non-infectious triggers such as cardiac surgery using the Cardiopulmonary Bypass (CPB), ex vivo heart/lung perfusion device, ECMO, and Mechanical circulatory Support. This is of particular interest for this report. SIRS, sepsis and septic shock have a mortality of an estimated 7, 16 and 40% respectively [22-30]. The new 2016 Sepsis-3 definition has two grades: sepsis and septic shock [31-34]. The previous sepsis definitions published in 1992 emphasized on the role of systemic inflammatory response syndrome (SIRS) as a key element of the sepsis definition.

However, evidence showed that SIRS criteria are non-specific and insensitive as predictor for sepsis related mortality, thus are not included in the most recent international sepsis definitions. The members of the Sepsis-3 taskforce suggested that sepsis should be considered in the event of an infectious process associated with an increase in SOFA score of two points or more. Patients with septic shock would be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater, and serum lactate level greater than 2 mmol/l (>18 mg/dl) in the absence of hypovolemia. SIRS patients identified by fulfilling two or more of the four SIRS criteria. The two main therapeutic priorities include early identification of a potential infectious origin and hemodynamic stabilization of the patient. Other than the control of the primary site of infection, there is no causal treatment for sepsis, septic shock or SIRS [35-39].

In order to improve the results of ECMO and septic patients, various techniques used to reduce the systemic inflammatory response syndrome, immunocorrection, and others. Today, there are many ways to prevent the development of a systemic inflammatory response by removing leukocytes from the bloodstream by inserting a filter with a special screen into the perfusion circuit to remove leukocytes and prevent them from entering the systemic circulation [9].

The most effective method is the hemoadsorption, intended for additional therapy of patients with elevated levels of cytokines in the context of systemic inflammatory response syndrome. In-patient with acute respiratory distress syndrome and cardiogenic septic shock on the background of extracorporeal membrane oxygenation (ECMO) and mechanical support of the left ventricle, additionally installed a system for veno-venous hemofiltration, a system designed to eliminate a wide range of inflammatory mediators also various proteins and metabolites [40-46].

There are some new data showing that the use of extracorporeal cytokine adsorber and hemoperfusion cartridge for a long time cardiopulmonary shunting (> 120 minutes) may be useful in preventing CVS and reducing cytokine levels in patients undergoing heart surgery [47-53].

In this study, will be developed methods to restore the function of affected organs after implantation of ECMO and patients with sepsis in combination with extracorporeal hemocorrection, which will improve the results of surgical treatment of patients with end-cardiac and respiratory failure.

New methods developed to restore the function of affected organs after implantation of mechanical support devices and patients with sepsis will be a great importance both for Kazakhstan and for countries with similar category of patients, which will improve the efficiency of surgical treatment and reduce the level of complications and mortality.

Clinical research data will form the basis of practical protocols for extracorporeal membrane oxygenation (ECMO) and patients with sepsis, which will improve organ repair, reduce postoperative complications, improve quality of life and reduce mortality after surgery.

## 4. Research methods and ethical issues

Patients before implantation of ECMO and/or patients with sepsis will enrolled in the study after giving a written, signed informed consent.

The participants will randomized into 3 groups:

- **Intervention group #1** a cytokine adsorber will be used (30 patients): patients on ECMO – subgroup A; septic patients – subgroup B.
- **Intervention group #2** an extracorporeal hemoperfusion cartridge will be used (30 patients): patients on ECMO – subgroup C, septic patients – subgroup D.

- **Control group #3** without using extracorporeal adsorber (30 patients): patients on ECMO subgroup - E, septic patients - subgroup F.

The investigators will collect demographic, clinical and laboratory data about patients before, during and after the operation

The incidence of early cellular or humoral rejection, length of ventilation, ICU and hospital stay, the use of vasopressors and inotropes in the perioperative period and incidence of perioperative complications and survival will documented.

The level of cytokines (IL-1, IL-6, IL-8, IL-10, tumor necrosis factor-alfa) and complements before, during and after the use of ECMO, patients with sepsis will be determined if the investigators find relevant difference between the two groups in clinical variables.

**Study Design**

Study Type: Interventional (Clinical Trial)

Estimated Enrollment: 90 Participants

Allocation: randomized

Interventional Model: Parallel assignment

Masking: None (Open Label)

| **Experimental (subgroups)** | **Intervention / treatment (device)** |
|---|---|
| Cytokine adsorber filter will be installed into the (hemodialysis or cardiopulmonary bypass (CPB) (15 patients on ECMO) | Cytokine adsorber is a biocompatible, high adsorptive polymer indicated in conditions where cytokine levels are extremely elevated. |
| Cytokine adsorber filter will be installed into the (hemodialysis or cardiopulmonary bypass (CPB) (15 patients with sepsis) | Cytokine adsorber is a biocompatible, high adsorptive polymer indicated in conditions where cytokine levels are extremely elevated. |
| Extracorporeal hemoperfusion cartridge will be installed into the (hemodialysis or cardiopulmonary bypass (CPB) (15 patients on ECMO) | Extracorporeal hemoperfusion cartridge is a biocompatible, high adsorptive polymer indicated in conditions where cytokine levels are extremely elevated. |
| Extracorporeal hemoperfusion cartridge will be installed into the (hemodialysis or cardiopulmonary bypass (CPB) (15 patients with sepsis) | Extracorporeal hemoperfusion cartridge is a biocompatible, high adsorptive polymer indicated in conditions where cytokine levels are extremely elevated. |
| **Control (subgroups)** | |
| No filter will be installed into the ECMO in | |

| | |
|---|---|
| this study group (15 patients) | |
| No filter will be installed into the patient with sepsis (15 patients) | |

**Outcome Measures**

**Primary Outcome Measures**

*ECMO patients*

1. Difference of Cytokine response [ Time Frame: 6-24 hours ]

Level of pro- and anti-inflammatory cytokines (IL-1, IL-6, IL-8, IL-10, tumor necrosis factor-alfa) before initiation of ECMO, 2 hours after initiation ECMO support, at explantation of ECMO support, 6-12-24 hours after explantation of ECMO support.

**Secondary outcomes**

1. Ventilator free days (VFD) [Time Frame: 30 days]

Ventilator free days (VFD) in the first 30 days after randomization, where invasive mechanical ventilation (IMV), non-invasive ventilation (NIV) and ECMO are defined as ventilator days. VFD=0, if the patient dies in the first 30 days after randomization

2. Time to extubation from ventilation and explantation from ECMO [ Time Frame: 30 days ]

Time to extubation from ventilation and explantation from ECMO. Death under ventilation and/or ECMO will be analyzed as a competing event. The time will be censored at the time of last visit for surviving patients under ventilation and/or ECMO.

3. Difference of d-dimers [Time Frame: 24, 48, 72 hours]

Comparison to enrollment or between 3 groups at 24, 48, 72 h

4. Difference of Serum lactate [Time Frame: 24, 48, 72 hours]

Comparison to enrollment or between 3 groups at 24, 48, 72 h

5. 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)

6. Serious adverse device effects [Time Frame: 30 days]

   Serious complications or malfunctions related to the CytoSorb device

7. Adverse event of special interest: air in the ECMO system [Time Frame: 30 days]

Unintended air in the ECMO system during operation of the device

8. Adverse event of special interest: blood-clotting in the ECMO system [Time Frame: 30 days]

   Unintended blood-clotting in the ECMO system during operation of the device

9. Adverse event of special interest: bleeding complications [Time Frame: 30 days]

   Major bleeding events

*Patient with septic shock*

1. Difference of Cytokine response [ Time Frame: 24-48 hours of septic shock ]

Cytokine response: Level of procalcitonin, Level of C-reactive protein, Level of interleukin-1, Level of interleukin-6, Level of interleukin-8, Level of interleukin-10, Level of Tumor Necrosis Factor- α at 24, 48 hours.

**Secondary Outcome Measures:**

1. Inflammatory reaction [Time Frame: 6 - 24 hours]

Level of C reactive protein (CRP), white blood cells and procalcitonin immediately after induction of anesthesia, before initiation of adsorber, 2 hours after initiation of adsorber, at termination of adsorber, 6-12-24 hours after wean of adsorber.

2. Difference of serum interleukin-6 level [Time Frame: 48, 72 hours]

Comparison to enrollment or between 3 groups at 48, 72 h

3. Difference of serum interleukin-1β level [Time Frame: 24, 48, 72 hours]

Comparison to enrollment or between 3 groups at 24, 48, 72 h

4. Difference of serum interleukin-10 level [Time Frame: 24, 48, 72 hours]

Comparison to enrollment or between 3 groups at 24, 48, 72 h

5. Difference of serum procalcitonin level [Time Frame: 24, 48, 72 hours]

Comparison to enrollment or between 3 groups at 24, 48, 72 h

**Other Pre-specified Outcomes:**

1. •Overall survival time [ Time Frame: 30 days ]

Overall survival time, defined as time from randomization to death. The time will be censored at the time of last visit for surviving patients

2. •Days on intensive care unit (ICU) [ Time Frame: 30 days ]

Days on intensive care unit (ICU)

3. •Vasopressor dosage [ Time Frame: 24, 48, 72 hours ]

Vasopressor dosage of adrenaline, noradrenaline, vasopressin, and dobutamine at 24, 48,72 h

4. Fluid substitution and fluid balance [ Time Frame: 24, 48, 72 hours ]

Total fluid[ml] substitution and fluid balance [ml] at 24, 48, 72 h

3. Length of hospital stay [Time Frame: up to 1 months]

Days at hospital

4. Mortality [Time Frame: First 72 hours]

The period of occurrence of mortality

**Statistical studies**

1) Statistical data processing
2) Comparison and analysis of source data

After data receiving, statistical analysis will be performed using SPSS Statistics software version 22. For quantitative data, the Mann-Whitney Yu non-parametric test and parametric t-test will be performed, and Fisher's non-parametric exact test and $\chi 2$ parametric test will be performed for qualitative studies. Also, a logistic regression for categorical outcomes and a survival analysis (non-parametric Kaplan-Meier and parametric Cox regression) will be performed.

**Ages**:18 Years and older

**Sex**: All

**Accepts healthy volunteers**: No

| **Groups** | **Inclusion criteria** | **Exclusion Criteria:** |
|---|---|---|
| ICU patients with ECMO | • Hemodynamic support with vasopressors<br>• Procalcitonin level ≥ 1 ng/ml<br>• Invasive hemodynamic monitoring<br>• Written informed content | • age < 18 years<br>• acute liver or kidney failure straight before transplantation<br>• the patient declines participating in the study |
| ICU patients with septic shock of medical origin | • Signs of hypoperfusion: serum lactate >2 mmol/L, low central venous oxygen saturation (ScvO2) (<70%) or high ScvO2 (>85%), metabolic acidosis, oligo-anuria, | • Patients under 18 years<br>• Pregnancy (bHCG test positivity)<br>• Surgical intervention in context with the septic insult |

| | | |
|---|---|---|
| | high venous-to-arterial CO2-gap (dCO2 >6 mm Hg)<br>• Hemodynamic support with vasopressors<br>• Procalcitonin level ≥ 1 ng/ml<br>• Invasive hemodynamic monitoring<br>• Written informed content | New York Heart Association IV heart failure<br>• Acute coronary syndrome<br>• Acute haematological malignancies<br>• Immunosuppression, systemic steroid therapy (>10mg prednisolon/day)<br>• Human immunodeficiency virus infection (HIV) and active AIDS<br>• Patients with donated organs<br>• Thrombocytopenia (<20.000/ml)<br>• More than 10%-of body surface area with third degree burn |

Study will be conducted in accordance with international standards of Good Clinical Practice, Joint Commission International, Scientific Ethics (Helsinki Declaration), as well as the Order of the Minister of Health of the Republic of Kazakhstan April 2, 2018 No. 142 "On approval of the Rules for conducting biomedical experiments, preclinical (nonclinical) and clinical studies, as well as requirements for preclinical and clinical bases". It will also take place according to the recommendations of the Local Ethical Commission at the NSCC. All patients will receive voluntary informed consent of the established sample with permission to use clinical data for scientific purposes. In addition, the study will be strictly controlled by researchers for the absence of plagiarism, falsification and fabrication of data in order to achieve the most ethical conduct of the study. The obtained patient data will be kept strictly confidential, ensuring privacy by strictly limited access to data, de-identification of data and destruction after the end of the study.

## 5. Planning and program management

| № | Name | Position | Directions of work in the project | % of project involvement |
|---|---|---|---|---|
| 1 | Timur Lesbekov | Principal investigator | Principal investigator 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 | 50% |
| 2 | Rymbay Kaliyev | Senior researcher | Definition of the vision and direction of the project, participation in the analysis of results, participation in the preparation of publications. | 50% |
| 3 | Zhuldyz Nurmykhametova | Middle researcher | Patient selection, analysis of clinical data, development of a questionnaire of quality of life. Participation in the analysis of results and preparation of publications, methods, including methods of prevention. | 50% |
| 4 | Ainel Iskakova | Junior researcher | Participation in the analysis of results and preparation of publications, methods, including methods of prevention. | 50% |
| 5 | Roza Ayapbergenova | Junior researcher | Selection of patients, conducting clinical studies, filling out the cards of project participants, obtaining informed consent, analysis of clinical data, participation in the preparation of publications. | 50% |
| 6 | Aydyn Kuanyshbek | Junior researcher | Selection of patients, conducting clinical studies, filling out the cards of project participants, obtaining informed consent, analysis of clinical data, participation in the preparation of publications. | 50% |

Project involves 6 specialists in the field of cardiac surgery, perfusion, cardiology, anesthesiology, efferentology, and public health.

Principal Investigato - Timur Dostaevich Lesbekov, Candidate of Medical Sciences, Head of the Department of Cardiac Surgery, JSC National Scientific Cardiac Surgery Center. According to Scopus, the Hirsch index is 2, the Author ID in Scopus is 6505523476.

Kaliev Rymbay Bolatovich - Head of the Operations Department with the Laboratory of Assisted Circulation of the National Scientific Cardiac Surgery Center JSC. According to Scopus, the Hirsch index is 2, the Author ID in Scopus is 57053326800.

Nurmykhametova Zhuldyz Askarovna - doctor perfusionist of the operating department with the laboratory of auxiliary circulation of the JSC "National Scientific Cardiac Surgery Center". According to Scopus, the Hirsch index is 2, the Author ID in Scopus is 57194187404.

**International publications:**

1 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), c. 969-975

2 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, c. 319-320

3 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

4 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

5 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 Kaliyev, R., Kapyshev, T., Goncharov, A., Lesbekov, T., Pya, Y.
Maternal and fetal recovery after severe respiratory failure: A case report of air transportation of a pregnant woman on ECMO using the CentriMag transporter system//ASAIO Journal, 2015, 61(5), c. e33-e35

7 Shneĭder, I.A., Lesbekov, T.D., Kuznetsov, K.V.,Rogacheva, N.M., Iuferov, A.P.
Coronary endarterectomy during off-pump coronary artery bypass surgery// Angiologiia i sosudistaia khirurgiia = Angiology and vascular surgery, 2008, 14(3), c. 101-106

8 Shneĭder, I.A., Lesbekov, T.D., Kuznetsov, K.V.,Aleshin, N.G., Tsoĭ, M.D.
Coronary artery of the heart reconstructions after endarterectomy//Vestnik khirurgii imeni I. I. Grekova, 2006, 165(5), c. 17-20

## 6. Project implementation plan

| № i/n | Name of task, activities for implementation of project tasks | Duration (in months) | Start and end date of work * (dd / mm / yy). | Years of project implementation, expected project results (in terms of tasks and activities) | | |
|---|---|---|---|---|---|---|
| | | | | 2021 | 2021 | 2022 |
| 1. | Literature review on treatment of patients with failure of heart and lung within innovation technolog | 6 months | 01.01.2021-01.06.2021 | | | |
| 1.1 | Literature review of patients on ECMO with using extracorporeal cytokine adsorber or hemoperfusion cartridge | | | Literature review for ECMO patients using an extracorporeal cytokine adsorber and an extracorporeal | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | hemoperfusion cartridge. Obtaining the results of the literary review. | | |
| 1.2 | Literature review of septic patients with using extracorporeal cytokine adsorber or hemoperfusion cartridge | | | Literature review for septic patients using an extracorporeal cytokine adsorber and an extracorporeal hemoperfusion cartridge will be conducted. Obtaining the results of the literary review. | | |
| 2. | Recruiting patients on ECMO / septic patients with using extracorporeal cytokine adsorber or hemoperfusion cartridge depend of diagnosis | 36 months | 01.01.2021-31.12.2023 | Initial patient condition will be studied | Initial patient condition will be studied | Initial patient condition will be studied |
| 2.1 | Examination of patients, verification of diagnosis and other procedure | | | | | |
| 2.2 | Study of directly clinical results of after using extracorporeal adsorbent on ECMO patients | | | | | |
| 2.3 | Study of directly clinical results of after using extracorporeal adsorbent on patients with sepsis. | | | | | |
| 3. | Clinical and laboratory data will be analyzed on basis of clinical research | 12 months | 01.01.2023-31.12.2023 | | | A protocol will be developed and optimized for the implementation of |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | extracorporeal adsorber technologies for this category of patients |
| 3.1 | A protocol for optimization of introduction novel technology will be developed and implemented | | | | | |
| 3.2. | Protocol implementation | | | | | |
| 4. | Preparation of publications, reports, development of methodological guidelines | 24 months | 2022-2023 | | Article in international and local journals | Article in international and local journals |
| 5. | Creation of intermediate and final reports | annually | 2021-2023 | Interim and final reports will be generated | Interim and final reports will be generated. | Interim and final reports will be generated. |

## 8. Expected results

The data of the Ministry of Health of the Republic of Kazakhstan show that annually in the country of terminal cardiac and pulmonary insufficiency is detected in 110-120 thousand people a year.

The clinical trial data will form the basis of practical protocols for extracorporeal membrane oxygenation (ECMO) and septic patients, the follow-up of which will improve organ repair, reduce postoperative complications, reduce mortality after surgery and improve quality of life.

The research results will be published in at least 3 (three) articles and (or) reviews in peer-reviewed scientific journals indexed in the Science Citation Index Expanded of the Web of Science database and (or) having a CiteScore percentile in the Scopus database of at least 35 (thirty five) , as well as in at least 1 (one) article or review in a peer-reviewed foreign or domestic edition recommended by the Committee for Monitoring in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan.

The results of a clinical study will improve the effectiveness of surgical treatment and reduce the level of complications and mortality, improve the quality of life of patients undergoing cardiac surgery. The introduction of a clinical protocol for the use of an extracorporeal adsorbent in this category of patients will allow standardizing this technique in the Republic of Kazakhstan.

The data obtained on the treatment of patients with heart and lung failure and organ restoration through the use of innovative technologies will provide the necessary information to improve the quality of tertiary care and the quality of life of patients in Kazakhstan and around the world. The developed methods can be used as new standards and recommendations both domestically and abroad through successful presentations at various conferences. If there are unique developments in the use of an extracorporeal adsorbent, patent applications will be filed.

In general, the expected effectiveness and efficiency of the proposed project will make a significant contribution to the development of transplantation, cardiac surgery and cardiology in Kazakhstan. In addition, the effective distribution of budgetary funds in accordance with the articles and amounts of expenditures will allow maximally concentrating the expenditure side of the implementation of this project to achieve the stated goals and objectives.

## 9. Bibliography


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