Part B "Project Description"

Project Title: "Multiparametric optical technique for fluid resuscitation and vasopressor therapy guidance in critically ill COVID-19 patients"

1. Scientific Excellence

The global spread of different SARS-CoV-2 variants causes major public health burden in the world reaching 200 million cases. Approximately 5% of them develop to severe lung damage requiring hospital admission. The global economic crisis is related to the load of intensive care unit, where mortality rate varies 8-38%. Critically ill covid-19 patients require aggressive fluid and vasopressor therapy to maintain systemic hemodynamic, however guidance of such therapies are adopted from septic patient care and is based on monitoring of systemic hemodynamic and lactate level, which is insufficient. This multidisciplinary project aims at development of optical multimodal technique for guidance of fluid resuscitation and vasopressor therapy in intensive care unit of critically ill COVID-19 patients by monitoring macrohemodynamic and microvascular parameters. A set of therapy guidance recommendations will be developed.

Keywords: COVID-19, fluid resuscitation therapy, vasopressor therapy, microcriculation, imaging photoplethysmography

Project applicant and research team.

The project applicant is research group of cardiovascular physiologists and physicists from the University of Latvia (UL) Inst. of Atomic Physics and Spectroscopy Dept. of Biophotonics and Faculty of Biology, in close collaboration with a group of national level frontline COVID-19 experts of the Dept. of Human Physiology Riga Stradins University (RSU) Dept. of Intensive Care Unit (ICU). Research team has multi-project R&D experience in patient examination and monitoring technique in ICU bedside environment. **The aim of the project** is to develop multimodal technique for guidance of fluid and vasopressor therapy of critically ill COVID-10 ICU patients.

Burden of COVID-19 disease.

In late 2019, a new coronavirus was identified in Wuhan, China [1-6] SARS-CoV-2 symptomatic ranges from asymptomatic to severe symptoms requiring mechanical lung ventilation [6] According to the World Health Organization, coronavirus disease -COVID-19, records more than 200 million cases and more than 4 million deaths [1-6]. About 5% of cases develop severe lung damage with possible multi-organ dysfunction (MODS). [3,4]. Mortality range in the ICU is fluctuates 8-38%. [1-6] currently causing major public health burden worldwide. The economic/social restrictions and lockdown is related to the **ICU capacity depletion**. Experts suggest that appearance of new virus variants diminish efficiency of existing vaccines, and in the foreseeable future patient admission to the ICU could significantly increase [7].

Current management of critically ill COVID-19 patients.

After the virus enters into host cells, immune system and damaged cells produce cytokines to coordinate immune response. Excessive cytokine concentration disrupts the normal functioning of the immune system increasing micro vascular permeability and inducing intravascular coagulation with micro thrombi formation which may result in shock and tissue damage, leading to multiple organ dysfunction (MOD) [4-6]. Clinical manifestation of COVID-19 ranges from mild to critical. The moderate infection symptoms are shortness of breath while severe form is associated with respiratory distress, hypoxia as well as respiratory failure, septic shock and MOD thus requiring admission to the ICU. [3,4] In the most severe forms, COVID-19 manifestation with lung damage requiring ventilation support which may vary from a nasal cannula oxygen supplementation to invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) in cases of severe acute respiratory distress syndrome. [6-11]. Such critically ill patients are likely to undergo aggressive fluid and vasopressor administration to maintain systemic hemodynamic.

Fluid resuscitation therapy

Fluid management in the severe COVID-19 pneumonia/ARDS is challenging, due to life-threatening risk of fluid overload, while hypovolemia is associated to reduced tissue perfusion requiring higher vasopressor dosage; therefore optimal fluid management is essential to optimize tissue perfusion. The goal of fluid resuscitation (FR)

is to achieve cardiac output preload independent (i.e. reaching the plateau portion of the Frank-Starling curve), that proves to be a difficult task in clinical routine. Once plateau portion is reached, yet fluid administration continues, it can lead to a shift of fluid into the interstitial space, further disturbing capillary blood flow and oxygen diffusion. Hypovolemia is associated with hypotension, low tissue perfusion and MOD as well as higher doses of vasopressor to maintain systemic hemodynamic. Aim of FR is to restore effective tissue perfusion. COVID-19 guidelines [6] suggests using dynamic parameters, e.g. capillary refilling time (CRT) and/or lactate level and passive leg raising test to assess fluid responsiveness. FR is the first-line therapy for shock, but there is considerable uncertainty regarding optimal strategy in case of COVID-19, though it is recommended to apply conservative fluid management i.e to administer 30ml/kg isotonic crystalloid fluid in the first 3 hours.

Vasopressor therapy

Patients with hemodynamic instability require FR and vasopressor therapy, guided by hemodynamic monitoring. Thus, vasopressor agents must be titrated in order to maintain mean arterial pressure (MAP) >65. Initial dose of vasopressor is often high, especially in hypovolemic patients. For adults with COVID-19 and shock, norepinephrine is the first-choice which increases MAP due to peripheral vasoconstriction with subsequent increase of peripheral resistance, with negligible effect on heart rate, while dopamine increases MAP and cardiac output, primarily due to an increase of the heart rate. Nevertheless, norepinephrine is more potent than dopamine and may be more effective reversing hypotension in patients with septic shock. However high-dose of vasopressor in prolonged time causes peripheral ischemia and necrosis [9] which could lead to limb amputation.

Perspectives of fluid resuscitation and vasopressor therapy guidance in critically ill COVID-19 patients

Traditionally, FR and vasopressor therapy is conducted at the ICU by monitoring vital signs and lactate, among other parameters. While these parameters may reflect systemic cardiovascular response, they do not necessarily indicate therapeutic effect on microvasculature due to different pathological conditions, where so called coherence between these circulatory levels is disturbed. The guiding of these therapies (FR and vasopressor) in critically ill COVID-19 patients is relatively recent issue, and there is a sparse knowledge in this field. Up to date, the majority of recommendations are adopted from conventional septic patient management. However pathophysiology of conventional septic and severe covid-19 are somewhat different, for instance, venous thromboembolism and arterial thrombosis occur more frequently in COVID-19 induced coagulopathy compared to non-SARS-CoV-2 induced coagulopathy. Cytokine storm is the major risk in sepsis unlike immunosuppression in COVID-19. Sepsis is characterized by systemic hypercoagulation and suppressed fibrinolysis while severe COVID-19 induced coagulopathy promotes local thrombus formation, permeability of lung capillaries and ARDS is dominant in COVID-19 patients. Several studies pinpoints to drawbacks of conventional FR application that alone doesn't reflect the feedback on adequate infused fluid amount, thus threatening fluid non-responsive patients with ARDS that are susceptible for fluid infiltration and edema. Here a more comprehensive approach could be additional monitoring of microcirculation, however in spite of urgent need, currently there are no well-established ICU bedside techniques for FR response assessment microcirculatory level. To date the most promising approach is CRT assessment that is supported by recent studies of Castro et al., comparing CRT vs. lactate targeted FR protocol. Author observed that a FR strategy based on achieving an index finger CRT>3 seconds during the first 24 hours achieves more often the predefned perfusion target compared to a strategy aiming to reduce lactate below<2 mmol/l or a decrease>20% every 2 h, which indicate that CRT is more sensitive marker than lactate changes. Similar evidence came from Andromeda-Schok Trial, suggesting that microcirculation guided strategy based on CRT might reduce organ failure and patient mortality compared to a lactate-targeted one.

Another measure of microcirculation with the high potential in critically ill COVID-19 patient FR and vasopressor therapy guidance is microvascular perfusion assessment and its spatial distribution analysis (perfusion maps), which is supported by the evidence that inadequate resuscitation produces substantial derangements of microcirculatory function manifesting as heterogeneous skin patches and locally decreased cutaneous perfusion[12], as a result of local vasoconstriction and coagulopathy, being is very common sign of critically ill COVID-19 patients. Similarly, supporting evidence is gathered from intravital capilaroscopy studies, revealing decreased functional capillary density in fluid non responsive critically-ill septic patients. Moreover microcirculation monitoring in critically ill COVID-19 patients could be crucially important, during relatively long stay at the ICU (days to months) to identify peripheral tissue local hypo perfusion regions with subsequent ischemia, as FR is often combined to vasopressors, in particularly for fluid non responsive patients, which over

the time may develop peripheral tissue hypo perfusion resulting in ischemia and even gangrene, which leads to amputation of limbs. The potential of proposed technology has been successfully evaluated by our team in a pilot study and presented to public on the 2021. International Baltic Congress of Anaesthesiology, Intensive Care and Pain Management, and an abstract published in the e-Supplement of the European Journal of Anaesthesiology Volume 38, Supplement 59, December 2021.
Prior this project, the potential of the offered microcirculation monitoring during FR is proved by our recent pilot study, executed by COVID-19 frontline ICU clinicians prof. Sabelnikovs, and prof. Vanags. Taken together these findings suggest that targeted microcirculation assessment in addition to routine macro vascular systemic hemodynamic monitoring substantially improve fluid and vasopressor therapy guidance avoiding both over and under resuscitation and eliminating potential issues of inadequate vasopressor use, thereby substantially reducing patient ICU stay, thus optimising ICU workload which is crucially important during coronavirus pandemics.

Proposed technique

Ample evidence suggests potential of multimodal approach comprising macro-circulatory and microcirculatory variables for fluid and vasopressor therapy guidance in critically ill COVID-19 patients, targeting CRT and perfusion index measurements as supplementary, yet crucially important modalities such as:

Monitoring of systemic hemodynamics

Intra-arterial systemic hemodynamic monitoring is a mandatory part of ICU setup. Fluid responsiveness will be assessed using existing guidelines. Common targets are MAP>65mmHg (MAP=[(2 x diastolic pressure) + Systolic]/3) and, following fluid bolus (usually 10ml/kg) over 60 min time. These measures will be combined with other modalities to make decision on fluid therapy.

Monitoring of lactate level in arterial blood

Lactate level in ICU is reflecting tissue hypoxia and is mostly used in ressucutation therapies as a goal directing marker. The measurement of lactate in ICU is performed by laboratory or point-of-care blood gas analysers, hand-held devices. Most devices used at the bedside have acceptable limits of agreement compared to the laboratory devices and the sampling site of the blood (arterial, venous, capillary, etc.) has negligible affect to the results. The lactate level before and after FR therapy will be utilized as a marker by adopting existing ICU guidelines, and along other 3 modalities of the offered technique will be incorporated in recommendations.

Automated determination of capillary refill time and related parameters

Physicians are referring to CRT as a marker of microcirculation, however examination is performed manually is rather subjective. To the best of our knowledge, no clinically accepted CRT measurement devices available, which substantially compromise reliability of this valuable marker of microcirculation. The automated CRT measurement is the third modality of our proposed technique, and its reliability and potential for therapy guidance is confirmed by our previous pilot studies. Custom made prototype has been developed by a collaborating spin-of company and is based on embedded optoelectronic system, comprising adjustable ckin contact patch supporting frame, moving optical actuator and contactless temperature sensor. The CRT measurement is performed by applying and removing load of ≈ 1 kg on ≈ 0,8 cm2 skin area, while recording signal intensity at 525nm illumination. Time parameters characterizing capillary refill, and skin temperature data is exported. The CRT related parameters will be adjusted to the patient skin temperature, and together with Imaging Photoplethysmography (PPGI) will deliver multimodal clinical evidence used for therapy guidance.

Determination of cutaneous perfusion

Skin is the largest organ, with its neuro-immune-endocrine system, is easy accessible for optical examination that can provide information of microcirculatory state. Considering reliability, cost effectiveness and our group experience, contactless IPPG technique will serve as the fourth modality of the offered system. In addition to its non-intrusiveness and low cost, IPPG can provide information regarding cutaneous microperfusion and its heterogeneity, the latter is often drastic in case of COVID-19 due to the coagulopathy and deranged micro perfusion and could serve as an marker for shock state which requires urgent FR. During present project dedicated IPPG system will be developed for operation in ICU environment at the bedside.

Scientific approach and developments of the project

The main goal of project is to develop a multimodal technique for fluid and vasopressor therapy guidance for ICU COVID-19 patients. This will be achieved in close collaboration of experts from three different fields: clinicians-frontline COVID-19 ICU experts, experts in cardiovascular physiology and biophotonics. The project R&D team has previous experience in development of ICU equipment for risk stratification of septic patients and neuropathic patient diagnostics which raises success of present project.
The proposed technique will include: COVID-19 patient examination protocols for multimodal fluid/vasopressor therapy guidance and rules for interpretation of examination results (guidelines will be developed by clinicians). Prototype - demonstrator of IPPG/CRT technology, for microcirculation assessment and acquisition of perfusion signal with subsequent skin microcirculation spatial mapping which will be computed using real-time data analyses software (will be developed by physicists).
In order to provide comprehensive interpretation of multi modal data (four aforementioned modalities) clinical protocols and guidelines will be developed. This task requires high level of experience of COVID-19 patient management at ICU, therefore will be provided by our team lead ICU clinicians. The guidelines will comprise recommendation for decision making on whether patient is fluid responsive, and already applied amount of fluid is sufficient for optimal resecution and targeted goal – normalized arterial pressure and insure adequate organ micro perfusion, in parallel minimizing risk of peripheral hypoperfuzion, with subsequent ischemia due to administration of vasopressors considering length of ICU stay.

Multimodal assessment of fluid responsiveness

In order to provide optimal resuscitation of patient before further volume therapy fluid responsiveness will be evaluated using modified "passive leg raising test" protocol, which can predict whether cardiac output will increase with volume expansion, by transferring approximately 300ml volume of venous blood from lower body towards the right heart by tilting patient head down flat and feet up at 45 angle. During the test multimodal measurement will be accomplished, including monitoring of systemic hemodynamics, and microcirculation. According to our preliminary guidelines, the patient is considered to be fluid responsive if certain criteria during passive leg rising test is met: MAP increased by 5% or more, Cardiac output (CO) >10%, IPPG perfusion index acquired from skin increased by 10% and CRT related parameters T90 decreased by 20% and Tst by 17%.

Fluid resuscitation guidance

The efficiency of FR will be evaluated using following protocol: multimodal signals will be acquired before and after fluid bolus infusion (10ml/kg over 60min) and after 30ml/kg in 3h and at 6h, 12h, 24h each time interval. Macrohemodynamics variables- MAP continuously acquired reaching target ≥65mmHg, lactate level sampled from arterial blood and decrease of lactate level at each time interval > 10% until stabilization has reached. Continuous monitoring of IPPG cutaneous perfusion index (reaching target >18 % from baseline) and its heterogeneity coefficient (<10%) , to insure effect of positive effect of resuscitation on microcirculation, The sufficient volume is reached if T90 decreases for 10%, Tst at least 17% from the baseline. The described protocol and guidelines are preliminary and are based on our previous pilot studies which were executed in the beginning of 2022 and results were presented in "RSU COVID-19 International Conference", on mid-2022. Riga, Latvia and "Euroanaesthesia 2022" , Milano, Italy, 2022. The abstract was published in the e-Supplement of the European Journal of Anaesthesiology (Volume 39, Supplement 60, June 2022),, however more extensive elaboration of protocols and guidelines will be the deliverable of the present project.

Guidance of vasopressor therapy

Usually vasopressor therapy is administered in parallel to fluid therapy; therefore the purpose of its guiding is to minimize use of pressors as they can cause peripheral ischemia in the limbs. The protocol is similar to fluid resuscitation collecting systemic and microcirculatory variables during vasopressor titration reaching the aim as MAP>65mmHg, Lact <2mmol/L, IPPG perfusion index >10% above baseline, T90 decreases for 10% and TST decrease for 17%.The sign of vasopressors overdose will be considered positive heterogeneity gradient at least 25%, towards distal parts of extremities.
Hereby, at the current level, the proposed techniques and therapy guidance approach is based on several preliminary investigation study results by our research group:

1. M. Klibus, Z. Marcinkevics, U. Rubins, A. Grabovskis, I. Vanags, O. Sabelnikovs "**Multimodal assessment of peripheral perfusion in COVID-19 patients**. A pilot study", ESAIC 2022, Milan. Italy.
2. M. Klibus, Z. Marcinkevics , U. Rubins , A. Grabovskis , I. Vanags, O. Sabelnikovs "**Evaluation of peripheral perfusion using remote photoplethysmography and automated capillary refill time technique in severe COVID-19 ARDS patients**" RSU international COVID-19 conference "Impact, innovation and planning". 2022. Riga. Latvia.
3. Klibus M., Marcinkevics Z., Rubins U., Laksa E., Sabelnikovs O. "**Evaluation of perpheral perfusion to fluid response using remote photoplethysmography imaging and automatized Capillary refill time technique in COVID - 19 patients. A Pilot study**". ESAIC congress 2021.
4. Māra Klibus, Zbigņevs Marcinkevičs, Uldis Rubins, Edgars Ļaksa , Oļegs Sabeļņikovs " **Evaluation of microcirculation using imaging photoplethysmography and automated capillary refill time measurement in COVID-19 ARDS patients**", Baltanest 2021.

The demonstrator of imaging photoplethysmography system. In addition to biomedical activities (development of diagnostic guidelines and protocols) the microcirculatory imaging photoplethysmography IPPG module as a microcirculatory technique of multimodal system will be developed comprising hardware and software components. The proposed technology is non-contact and sterile, and will be easily applicable to the real-time assessment of hemodynamic parameters in clinical environment. The prototype will be designed and developed for patient and control group data acquisition during examination protocols. The system hardware comprise the following modules: 1) green light LED emitter for skin illumination with linear-polarized light; 2) high-speed monochrome video camera for acquisition of the diffuse reflected radiation from skin; 3) a narrow-band optical filter (CW = 540 nm) and a polarizer attached to the camera lens to amplify the signal which is related to blood volume changes; 4) computational module for PPGI signal processing and haemodynamic parameter calculation in real-time; 5) touch screen display for real-time monitoring and controlling. The most sophisticated and computationally extensive functions will be implement in Matlab based software on microcomputer, and comprise video acquisition, temporal filtering of PPGI signal and signal waveform analysis in order to calculate set of haemodynamic parameters in real time. Measurement data will be saved in computer memory and will be later transferred using wireless link to computer.

2. Impact

2.1. Project's scientific results and technological knowledge, the dissemination plan

The scientific results of the project are: patient examination **device prototype** (technology demonstrator) as a part of multimodal system containing PPGI and CRT modules with control software and data processing algorithms; technologic **know-how** – a set of engineering and methodological knowledge and clinical therapy guidance recommendations, being partly used for disseminated as scientific publications and conference proceedings, while some aspects will be subject of non-disclosure due to following protection of intellectual property during the lifetime of the project. Hereby during the project **three scientific publications** in journals with citation impact factor at least 50% of the average citation index in the sector, **three reports** at the international conference with **three** relevant **conference proceedings** indexed at the scientific databases SCOPUS and Web of Science will be published. Furthermore throughout the project 6 secondments are planed visiting the symposiums and conferences of ICU and reanimatology thus according to the form of physician meeting events also **6 short abstracts** will be submitted to the meeting organizers.
The **continuation of the project research** will be achieved by preparing **scientific project proposal** at the international i.e. EU ERDF or National/Bilateral Programmes or other calls during the project life cycle. In line with the development of this project, further direction of this research will be laid either in the direction towards commercialization and application or by joining an international/multicentric clinical study towards development of clinical guidelines of critically ill COVID-19 patient therapy.
At least **two theses** in the interdisciplinary fields will be prepared and defended in the frame of this project: one **Master thesis** in Biology and one **Doctoral thesis** in clinical medicine. Every sub-division of the researcher's group of the project that executes each work package will be formed by enrolling a student participant in order to promote the transfer of knowledge within the scientific staff, and during each task execution student participants will gain experience in cross-discipline environment.

Project results will undergo **sustainable dissemination plan**– each of three attended international conferences of Biophotonics will result a **proceeding manuscript indexed** in the scientific databases (WoS, SCOPUS), while three scientific papers submitted to the journals with citation **impact factor** will be published for **open access** thus providing wide spread of the project results and recognition of the project research that is crucial for successive development of project consortium and technology commercialization. The dissemination plan addresses both **professionals, policy makers, stakeholders and general public**:

- reports on the achieved tech and clinical R&D results will be submitted in open-access manner to highly ranked journals e.g. Physiological Measurements, Critical Care and Annals of Intensive Care, and will be presented at institutional seminars and international conferences (provisionally: SPIE Photonics Europe, SPIE European Conferences on Biomedical Optics, Annual World Congress of Anaesthesiologists, Euroanaesthesia and European Society of Intensive Care Medicine Congress or other). Target groups: professionals, policy makers, researchers,
- addressing the **general public** via unauthorized part of the project website in the portal of the University of Latvia: www.lu.lv including brief reports on recent achievements and current tasks. Target groups: all interested parties – students, researchers, clinical personnel, policy makers, stakeholders.
- **press releases** or interviews to the mass media will be presented upon request (newspapers, TV, radio, internet portals). Target groups: general public.
- demonstration of the developed proof-of-concept prototype and imaging technology in general at the **specialized exhibition**(s) or **public events** (European Researchers' Night, Knowledge Agora etc). Target groups: general public, cross-disciplinary students.

Other project result is an anonymised patient examination database according to **Open Data** principles, to be created and maintained in order to accumulate the patient and control group examination data. The metadata will be uploaded as the journal supplements to reach the FAIR principles.

Collaboration to the local and government institutions

The state university hospital and its general ICU department that admits COVID patients during the pandemic play the main role granting access to the patients and clinical infrastructure. Project's Principal investigator is the head of both the academic and clinical departments and also an adviser to the government's COVID-19 taskforce. This will allow rapid changes to the research strategy depending on government decisions and the dynamics of the pandemic.

2.2. Socio-economic impact and publicity of the results

The **principal impact** of this project will be improved technique for critically ill COVID-19 patient stabilization right after admission to the ICU: improved fluid resuscitation and vasopressor therapy guidance. Clinical pilot studies with PPGI and CRT executed by our group at the ICU environment (results accepted for publishing) indicate effective compliance of the offered technique to the intended application. Our proposed therapy guidance approach will allow more precise fluid and vasopressor dosage, thus improving clinical outcome and potentially reduce the load to ICU. Both these factors are invaluable and crucially important both from economic and social perspective. This clearly evidences contribution of this project for **public benefit**.

The **associated impact** of the project is directly related to the contribution of resolution of the problem/-s defined in the Latvia's Smart Specialization RIS3 strategy.

The **project goal** is **compliant** to the national economy transformation axis as defined in **RIS3**. This project provides considerable **horizontal impact** on the society due to the high expenditures of patient being admitted to the ICU. At the same time this project contributes to the **transformation of the national economy** by generating new, innovation-based comparative advantages in healthcare sector, by increasing the share of technology development and innovation induced clinical applications.

Interdisciplinary project will be developed in the fields of medical physics, biology and clinical medicine, which are mentioned in **RIS3 6th Growth priority** as relevant to the transformation process of Latvia's national economy as corresponding to the needs of knowledge intensive healthcare sector development. The diagnostic method developed is based on the **biophotonics – key-enabling technology identified by European Commission**, implementing an innovative optical imaging of severity of disease in the form of non-invasive contactless testing which serves as an example for smart technologies application in healthcare, promoting activity in the **framework of 1st Growth priority**.

2.3. Contribution to the capacity building of the project research team, including students, as well as to the improvement of the study environment

The **transfer of knowledge** within the different scientific sector project group (student) participants will be accomplished through significant involvement in cross-disciplinary tasks and work packages and project execution. The project research will be executed **side-by-side with the academic work** e.g. student laboratory workshops and thesis research investigation tasks thus ensuring that knowledge is acquired and transferred to young scientists, residents and PhD candidates who will inherit the knowledge and experience gained in the project.

The skills accumulated during the R&D of the prototype device and performed laboratory/clinical examinations and transferred to the student participants and interdisciplinary researchers will significantly increase their **scientific capacity** promoting obtaining scientific degree, new skills and networking. At least three students of Biology and one residential physician will conduct and defend the thesis in frame of this project, obtaining scientific degrees. Both physiological and clinical methodology and imaging technique demonstrations will be utilized as visual aids in student classes thus completing the trainee techniques.

3. Implementation

3.1. Project applicant and scientific team

The project is applied and coordinated by the researchers group from the University of Latvia (UL) **Biophotonics Lab.** at the Inst. of Atomic Physics and Spectroscopy (IAPS) and **Dept. of Human Physiology** at the Faculty of Biology (FB) closely collaborating in a joint research with partner institution **Dept. of Anaesthesiology and Intensive Care** at the Riga Stradins University (RSU) and Pauls Stradins Clinical University Hospital (CUH) general **Intensive Care unit** (ICU), providing clinical pilot study – patient access and examinations as well as clinical data analysis. The project core staff – Biophotonic and Physiology researchers are supported by the ICU physicians hereby building experienced **multidisciplinary team** of clinical medicine, biophotonics and human physiology experts.

Project applicant scientific institution's team of physicists and biologists are experts in development of optical/thermal diagnostic technology for **early sepsis diagnostics** particularly used in **ICU at patient bedside**, with extensive experience of conducting critically ill patient and control group examination and microcirculatory impairment assessment [17-19]. IAPS researchers are specialized in development of key-enabling technologies of optical diagnostic and patient monitoring (biomedical) techniques in Latvia. In the Innovation System Review and Research Assessment Exercise Report, prepared by the European Union auditors, the Institute researchers were evaluated in the same group of 150 Latvian scientific institutions and were rated among 8% of highest quality scientific organizations[20] proving long-term capacity of highly qualified personnel, excellence in science and infrastructure facility, as well as high development potential.

Both the partner's RSU and CUH ICU departments are run by the same staff - the clinicians being experts at COVID-19 therapy, with experience of routine critically ill patient stabilization and treatment. Both lead clinical researchers of the scientific team as anaesthesiologists-reanimatogists are between **key policy makers** in national level of COVID-19 therapy guidelines and recommendations. They are co-authors of the published research "Life with

COVID-19: Evaluation of overcoming the coronavirus crisis in Latvia and recommendations for societal resilience in the future."

The Project Principal Investigator Andris Grabovskis, PhD in physics, lead researcher in the Biophotonics Laboratory at Institute of Atomic Physics and Spectroscopy, University of Latvia, experienced in the establishment of national and international scientific/business consortium and research teams e.g. the FP7-ICT-2011-8 STREP and ESF/ERDF calls as well as private funding investment. In the recent eight-years has been a project principal investigator in three full scale scientific projects and team lead in previous three EU ESF/ERDF research projects, focusing on the development of optical diagnostic techniques (contact/imaging photoplethysmography) and clinical measurements and methodology standardization. **WP1 and WP4 teamlead**. Development supervisor of the contact-less patient examination device prototype and technique.

Leading participant professor Oļegs Sabeļņikovs, PhD in Medicine and Healthcare, Clinical medicine, asoc. prof. at the Dpt. Of Anaesthesiology and Reanimatology RSU, is the COVID-19 frontline intensive care expert and patient management and admission guideline author. In this project the **teamlead of the WP3 and WP4**.

Project medical research supervisor, will develop the set of recommendations for here developed optical technique applications in COVID-19 therapy guidance.

Leading participant, asoc. professor Zbigņevs Marcinkevičs, PhD in Cardiovascular Physiology, lead researcher and Associate professor in Department of Human and Animal Physiology at the University of Latvia, focuses on control mechanisms of skin microcirculation and tissue optical measurements (diffuse optics). **WP2 teamlead,** he will design the control group examination protocol – physiological measurement conditions and provocations and validate technology by performing the optical measurements on healthy volunteers.

Project participant Uldis Rubīns, lead researcher in Biophotonics Laboratory at Institute of Atomic Physics and Spectroscopy, University of Latvia, has expert skills in Matlab GUI programming and vast experience in Photoplethysmography Imaging signal processing. **WP1 and WP4 participant**, he will design enhanced optical data processing algorithms and diagnostically valuable PPG signal waveform parameters.

Student participant M.D. Anaesthesiologist-reanimatogist, Māra Klibus during COVID-19 pandemic works as Anaesthesiologist-reanimatogist at the Pauls Stradins CUH ICU, will be a **WP3 and WP4 participant** by conducting the patient examination series and preparing publishing papers and presentations.

Student participant Alise Aglinska, B.Sc. in Biology, scientific assistant in Department of Human and Animal Physiology at the University of Latvia, has extensive experience conducting physiological measurements in laboratory environment and patient examination in clinics. **WP2 participant**; her research topic is within the project scope and the microcirculatory response of control group volunteers assessed with the developed technology will be included in her Master thesis in Biology.

Project synergy

During the development of the proof-of-concept patient examination prototype components, this project will cooperate with the high-tech R&D company "TechLab Ltd" providing 3D design and prototyping solutions. This synergy will bring together professionals of electronic engineering and rapid prototyping thus enabling the development of above the state-of-art technology demonstrator for ICU bedside patient examination needs. Results of the performed clinical trial of optical capillary refill time measurements will be used for licencing the currently patent pending technology developed, owned and offered to this project by the start-up "Blazar Ltd".

3.2. Work plan

The strategy of the work plan defines the work packages (WP) which are based on the concept that each WP focuses on a particular challenge and environs respective research and clinical infrastructure and professionals with related foreruns and the matching experience. According to the project aim, **four main objectives** are formulated in step with the respective WP for their implementation:

- clinically evaluate the concept of optical PPGI and CRT technique application for critically ill patient skin microperfusion assessment, and develop the roadmap (recommendations) for their use in ICU in case of COVID-19;
- develop the technological demonstrator of PPGI technique, supplemented with optical CRT measurement and other clinical routine techniques for conducting critically ill ICU patient bedside examinations;
- develop the physiological provocation manoeuvres e.g. partial tissue occlusion and passive leg rising tests mimicking altered states of the peripheral vascular resistance adapting them for use in combination with the developed non-invasive in-vivo optical technique;
- perform the necessary tasks for dissemination of the project results through the participation of scientific conferences and open access scientific reports, and ensure the enhancement and sustainability of research through preparing project proposal at national or EU research project Programme calls.

Each Work Package focuses on a single objective and is implemented by the principal investigator or lead participant and is divided in consecutive tasks (WP/Task launch and finish project months), Institution in charge: involved participants:

WP1: Development of the proof-of-concept prototype for ICU patient examinations for therapy guidance (1^{st}-36^{th}), UL IAPS: principal investigator PhD A. Grabovskis and lead researcher U. Rubīns, also student participant (physics-biophotonics);

T1.1. Adaptation and customisation of the PPGI and clinically available equipment in early stage setup for pilot patient bedside examination (1^{st} month).

Immediately after project launch, the initial early stage patient examination PPGI platform will be assembled by customising the existing PPGI modules and adapting the clinically available vital sign monitors for use in ICU patient bedside micro-perfusion assessment.;

T1.2. Collection of the physiology lab reports and clinical feedback, compiled as technical requirements for final stage patient examination device prototype development (2^{nd}-5^{th}).

During this task technical staff (mostly student participants – resident physicians) will be enrolled in clinical/laboratory trials by collecting the reports from clinicians and biologists regarding prototype properties and features thus shaping the technical specification – the **Milestone M1** for the complete system prototype development;

T1.3. R&D of the complete system prototype for patient examinations for ICU critically ill patients (6^{th}-10^{th}).

Technical and scientific staff will design and construct the technologic demonstrator suitable for use in ICU environment as a routine examination technique. Task includes device hardware (camera, light source), control software and MPPGI signal processing algorithm development. Task will also formulate the technical know-how, partially presented in conference events and scientific papers. The developed hardware and its control software is a **milestone M2**, reached at the end of 10^{th} project month;

T1.4. Technical support and patient examination data processing (11^{th}-36^{th}).

Further physiological measurements and patient examination will be followed by this task of upgrading the data processing algorithms and performing the optically obtained patient data processing with an outcome of patient/control group microperfusion parameter database.

WP2: Development and validation of the physiological provocation manoeuvres and examination protocols (1^{st}-5^{th} and 11^{th}-36^{th}), UL FB: lead researcher Z. Marcinkevičs PhD. Biol. and student participant.

T2.1. Development of the ethical protocol (1^{st} month).

The research actions at the physiological laboratory will be launched by preparing the ethical protocol.

T2.2. Development of the control group examination protocol (2^{nd}-5th)

Based on the review of recent literature and the forerun of executed pilot studies, a protocol of physiological manoeuvres will be designed for provoking the altered response of microcirculatory bed. The developed protocol, as a part of **milestone M1**, will be approved by the Ethical Committee and used in combination with the device prototype;

T2.3. Validation of the prototype and methodology in laboratory environment, control group data acquisition (11^{th}-28^{th}).

The developed set of technology demonstrator and physiologic manoeuvres protocol will be validated on control group of healthy volunteers during physiological measurement trial;

WP3: Evaluation of the optical multimodal proof-of-concept system in ICU environment (1st-5^{th} and 11^{th}-36^{th}) RSU Intensive care clinicians: lead researcher Prof. O. Sabeļņikovs and student participant (resident ICU physician) MD Māra Klibus;

T3.1. Development of the ethical and preliminary patient examination protocol (1^{st} month).

During this task the involved physicians will at first develop the patient examination ethical protocol and inclusion criteria.

T3.2. Patient examination pilot study (2^{nd}-5^{th})

By receiving the early stage prototype system, ICU clinicians will conduct critically ill patient examination during the expected patient admission peak (February-May) and produce the description of parameters of the proof-of-concept technology demonstrator for use in the ICU environment as a part of **Milestone M1**. Physicians will support the R&D team of electronic engineers and physicists, by guiding the development and prototyping process and reviewing the prototype accordance to their needs;

T3.3. Validation of the prototype system and methodology in ICU environment, formulation of the therapy guidance recommendations (clinical know-how) (11^{th}-36^{nd}).

During the extended validation study, physicians will accumulate critically ill COVID-19 patient examination data by conducting longitudinal observation study regarding vasopressor dosage effects on peripheral microcirculatory bed and by acquiring optically derived microperfusion parameters during fluid resuscitation.

This task will produce clinical data (outcome) and optically derived parameter comparison that will be used for formulating the therapy guidance recommendations **milestone M3** and publishing in clinical medicine periodical;

WP4: Research sustainability and project result dissemination (1st – 36th), Both participant institutions: principal investigator A. Grabovskis, lead researchers Prof. O. Sabeļņikovs, Z. Marcinkevičs, U. Rubīns, and student participants;

T4.1. Research sustainability management through project/grant proposal (application) submission (6th - 36th).

During the lifetime of the project, proposals at the national or EU work programmes will be prepared and submitted in order to increase the technologic readiness level of the offered technique. The question of intellectual property shares between participants and their potential transfer to start-up or SME will be addressed. Group members will collaborate with the National Contact Point experts throughout the project to possibly establish or join to the network of international research groups for preparing research project proposal. In frame of ERDF programmes governed by national institutions, a commercialization plan of the offered technique will be considered;

T4.2. Project result dissemination to public and professionals (4th-36th).

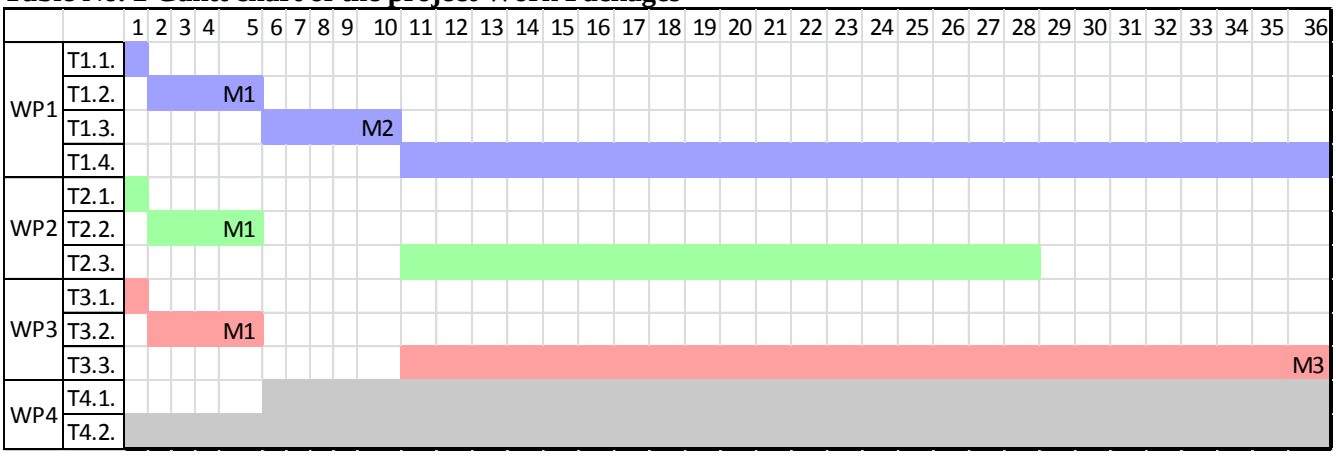
During the project, alongside to the aforementioned WP's, project group will prepare the project results and participate at the international scientific conferences, such as SPIE Photonics Europe 2024, SPIE European Conferences on Biomedical Optics 2023, Annual World Congress of Anaesthesiologists, Euroanaesthesia and ESICM by **submitting relevant proceedings and abstracts**, indexed in the SCOPUS and WoS databases. Additionally **two scientific papers** in journals such as Critical Care, European journal of Anaesthesiology, Physiological Measurements and Biosensors with citation index at least 50 percent of the average citation index in the sector will be prepared and submitted describing the clinical and technologic results of the pilot study.

In parallel, project results will be disseminated to the public for example by attending the HORIZON-MSCA-2022-CITIZENS-01-01 European Researchers' Night 2023-2024 and annually throughout the project lifetime. Also the students enrolled in the project will be endorsed participating in the international scientific conferences – annual conference of the UL and ResearchWeek at the RSU, and local student conferences in medicine, pharmacy and other Natural sciences. Project progress will be published in the project coordinator's Web page.

Project **implementation progress** will be evaluated by following achievement of **three milestones**:

M1	T1.2. T2.2. T3.2.	Technological report – final stage device prototype technical requirements and description prepared at the task T1.2. containing both the outcome of physiological laboratory task T2.2. (recommendations) and clinical task T3.2. (bedside clinical feedback). Milestone M1 sets the ground for development of the final stage patient examination prototype at the task T1.3.	5th project month
M2	T4.3.	Final stage prototype – technology demonstrator for contactless in-vivo patient microcirculation (micro-perfusion) assessment, being fine-tuned for bedside use at the Intensive Care Unit. Achievement of the M2 allows launching extended patient and control group examination series.	10th project month
M3	T3.3.	Methodologic guidelines for use of the new-developed multimodal optical technique for fluid resuscitation and vasopressor therapy guidance in critically ill COVID-19 patients	36th project month

Table No. 2 Gantt chart of the project Work Packages



3.3. Project management and risk management

Project implementation will be guided and inspected during the monthly project research team fullscale meetings involving institutional administrators and enrolled student participants, while the work package teamleads will assign the current tasks and anticipate deadlines in weekly on-line meetings.

Project monitoring at the RSU and the UL is carried out by the Project Council in accordance with the scientific institution's internal law (Rules of monitoring and implementation of national and European Union structural and other foreign funds projects).

Project Council will be nominated by the Chief Executives of the participating departments, and will ensure the interests of the scientific partner institutions to monitor scientific and administrative leadership of the project, and the cooperation among the partners. Moreover both institution departments are involved contributing in successful project implementation. Project Council's role is to monitor project activities, follow the R&D progress of the results according to project's general targets and outputs, as well as be advisers for project management guidance. The Project Council consists of one representative from each of the partner institutions. Present or online meetings of the Project Council are arranged once in three months by the Administrative Project Leader or Senior/Main researcher.

Project Scientific and Administrative leaders are responsible for full project implementation according to grant contract and scientific institution's inner law, as well as for cooperation with responsible departments and external institutions to ensure successful project implementation and achievement of project results.

Project administrative supervision and project implementation according to grant contract and internal and external legislation is ensured by Research and Projects Department's Project planning and monitoring unit from both partner institutions. The cash flow and expenditures according to project budget and grant contract is monitored by the Finance and accounting departments. Employment of staff and maintenance of personnel files will be carried out by Human Resources Departments according to internal and external legislation. The organization of public procurement procedures is ensured by Legal Department's Units of Procurement. Quality Management Departments on a random basis carries out inner control of general requirements of grant contract, document flow, finances, leadership, etc.

The project's technical **implementation will be also overseen** by the head of the Biophotonics Laboratory at Institute of Atomic Physics and Spectroscopy **Professor Janis Spigulis**; the **project management and administration will be governed** by the Chief Executive of the Institute of Atomic Physics and Spectroscopy and the expert of National Contact Point of the H2020 programme Inga Šīrante and the research project coordinator Dace Šantare at the Dept of Research of the Riga Stradins University.

The Ethical aspects of any project modifications and the performed patient or healthy subject examinations will be coordinated with the corresponding Ethics Committee at the Institute of Experimental and Clinical Medicine at the University of Latvia led by the **Prof. Alfreds Janis Sipols**, the Ethics Committee at the Riga Stradins University led by the **Prof. Jānis Vētra,** and the Ethics Committee of the Pauls Stradins Clinical University Hospital.

Table No. 3 Risk assessment

No.	Risk type	Risk description	Assessment		Risk prevention/reduction measures
			Probability	Impact	
1.	Technological	Technological bottlenecks – flaw of the scientific approach	Low	High	The scientific approach and each technological solution has been proved in previously conducted pilot studies
2.	Technological	Prototype unsuitability to the clinical needs, limited functionality	Low	High	Enrolled physicians will support prototype design and R&D actions during the task T3.2.
3.	Implementation	Ethics committee(s) rejects the proposed in-vivo validation protocol	Low	High	Careful examination of the requirements and decision record of the Committee will be performed in advance.
4.	Implementation	Delays of the procurement	Low	Average	Required supplies and components will be ordered through direct purchase and later refunded through the regression process. Project applicant has available short-term prepayments.

5.	Personnel	Key investigator(s) may leave the research group	Average	High	Multidisciplinary team and Institute staff allows short term redeployment, meanwhile leaving person will be substituted with expert having relevant skills
6.	Administrative	Absence of a management team member due to vacancies, business trips, illness, etc.	Average	Low	Project manager will be replaced by administrative secretary, and opposite; accountant will be replaced by the administrative secretary, and vice versa.
7.	Knowledge transfer risk	Peer-reviewers reject submitted manuscript(s)	Average	Low	Each study will be conducted by obtaining large amount of supplementary data, thus submission(s) will be revised and improved upon the reviewer request
8.	Socioeconomic	Cost limitations (e.g. too expensive component prices)	Low	High	The difference of the procurement costs will be funded from institutional backup funds.
9.	Socioeconomic	Unexpected inflation	Low	Average	According revision of proposed purchases will be taken by management. The expenses will remain as planned.

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