

UNRAVELLING HETEROGENEITY   
OF MULTI-MORBIDITIES   
USING MACHINE LEARNING IN INTENSIVE CARE PATIENTS

“Livet forstås baglæns, men må leves forlæns.”   
Life is understood backwards but must be lived forwards

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The proposal will be updated during the next weeks. Some parts need more work than others.

Please read and comment on everything you feel comfortable with. Please add information that fits both the overall text and the information in the WP. Please add information using track changes.

Furthermore, as WP descriptions should be no longer than 2 pages text from these WPs might be transferred to the overall text.

The lay-out of the WPs is made as uniform as possible.

In the text colours are added to guide members and collaborators to add crucial information (see below).

Members of WP1 will implement all changes if applicable.

Legends:

Figures list

Tables list

List of acronyms

Remaining questions

Open for check

# 1. Excellence

##### Why?

Imagine two critically ill patients (A and B) who arrive at the Intensive Care Unit (ICU). Patient A is a 65-year-old male who has diabetes, hypertension and benign prostate hyperplasia. He uses antihypertensive and anti-diabetic medication. Patient B is a 57-year-old female who recently underwent cholecystectomy for gallstones but has an otherwise insignificant medical history. Both patients are admitted to the ICU with acute respiratory insufficiency and bilateral pulmonary infiltrates detected by imaging techniques, with no apparent cardiac involvement, hence fulfilling the criteria for Acute Respiratory Distress Syndrome (ARDS) (a syndrome-based diagnosis). They receive current state-of-the-art treatment: microbial cultures are obtained, empiric antibiotic therapy is started (dose and type equal for all patients), vasopressors are administered for maintaining blood pressure (equal for all patients regardless of age, gender or medical history) and they are mechanically ventilated (with ‘optimal’ settings derived from large randomised trials). Families are told we, the caregivers, have no idea what their outcome will be. Patient A makes a quick recovery after a few days, while patient B deteriorates and despite maximum effort eventually dies.

Each day caregivers have to make decisions for patients like A and B, determine treatments and give information on outcome to patients and relatives, while frustrated by a lack of understanding of the complex patient conditions and causal mechanisms.

The sickest patients, i.e. critically ill patients, in the hospital converge in the ICU: 3 million patients are estimated to be admitted to European ICUs every year.1 As a consequence, and independently of their admission diagnosis, ICU patients have the highest multi-morbidity rate per patient, often with two or more diseases (chronic or acute) and medical conditions co-occurring at the same time. These patients suffer high rates of adverse outcomes, including a mortality rate of up to 60%, while those who survive have high rates of long-term mental (delirium up to 60%) and non-mental disorders (kidney failure 40%), and reduced quality-of-life.2 The ICU offers a unique window of opportunity to investigate causative mechanisms and improve their prognosis.3 Previous isolated research efforts failed to improve the ineffective treatment regimens used today in this highly heterogeneous patient population, primarily due to the lack of knowledge regarding the true underlying causes within individual patients.4

Intensivists frequently observe that patients with originally different reasons for ICU admittance may nonetheless evolve similarly, likely because these patients, despite presenting with different symptoms, are affected by the same causal mechanisms. Therefore, we urgently need to explore the potentially common pathophysiological causative mechanisms in different diseases and gain insight into how, and why, patients A and B present so differently.

#### Diagnostic challenge

Virtually all patients present with multimorbidity upon ICU admission. Of all interventions performed daily by intensivists, only very few have been proven to be beneficial, likely due to lack of knowledge on causal mechanism of diseases of the group of heterogeneous critically ill patients. This is illustrated by the use of many syndrome-based diagnoses. The first major challenge is to tackle the lack of knowledge on the causal mechanisms.

#### Short-term outcome challenge

Patients in the ICU suffer numerous life-threatening events, such as sudden massive bleedings or infections. Most will be in a highly unstable disease state, and at a high risk of sudden, new events likely to lead to negative outcomes which can substantially worsen their short-term prognosis. Given how quickly these potentially devastating events may occur, the second major challenge is to better predict and reduce the risk of patient deterioration during ICU stay.

#### Long-term outcome challenge

In addition to the high mortality rate among critically ill patients, the rates of long-term mental and non-mental disorders, as well as reduced quality-of-life for those who survive are also exorbitantly high. There is often insufficient attention given to patients’ preferences regarding their own outcomes, and caregivers are often not adequately equipped to predict and inform patients (and their families) of what outcome to expect. Therefore, the third challenge is to improve patient-centred-outcome evaluation and improve outcome prognostication.

#### Research infrastructure challenge

Data and expertise are oftentimes fragmented, with an obvious, easily accessible multinational infrastructure to support joint research clearly lacking. The last decades of isolated research efforts in critical care have insufficiently progressed in identifying causal disease mechanisms. The fourth major challenge is to set up this research infrastructure, not only for the current project, but also for continued use in the future.

##### How?

Our established network of ICUs will collaborate with both experts for outcome variables as well as experts from the field of machine learning. In contrast with previous isolated efforts, we will combine all types of variables and biomarkers gathered in contemporary databases following the European Union general data protection regulation. Together, these experts will analyse existing data from existing cohorts, and collaborate to create a large, multinational prospective cohort study focussing on the diagnostic and prognostic challenges. The prognostic cohort will use the results of the retrospective studies and studies of the existing literature to build on all available knowledge.

##### What?

**HEALICS** (unravelling HEterogeneity of multi-morbidities using mAchine Learning in Intensive Care patientS) will discover key physiologic, genetic, epigenetic, and biomarker variables suggesting associations with underlying causative mechanisms. Follow-up will allow testing for potentially causal relationships between multimorbidity, ICU-induced morbidities, long-term healthy recovery, and quality-of-life. In addition, we will improve the characterisation of patients and their complex disease state upon admittance. We will shift the current diagnostic process away from syndrome-based classifications towards one based on novel clustering of patients according to causal mechanisms. We will improve patients’ outcome by reducing adverse event rates through a new dynamic alert tool. We will also improve the prognostication of patients and improve their counselling by including an evaluation of their mental status and cognitive function. To optimally analyse such high-dimensional and complex data, we will apply and develop new machine learning algorithms, finally fulfilling the ICU’s long-time need for digitalization. Lastly, we will build an open, multinational data infrastructure connecting existing cohorts to facilitate retrospective data analysis and setting up future prospective studies.

Thanks to HEALICS, patients C and D ICU-stay will not be the same as that of patients A and B. Caregivers will be able to better estimate their outcomes, and the understanding gained into the individual disease mechanisms of these patients will lead to improved care and subsequent quality of life for patients and their families.

## Objectives

The overall objective of HEALICS is to identify causative mechanisms of multimorbidity in the heterogeneous, critically ill ICU patient population.

Our mission is to improve the characterisation of patients and discover common causal pathophysiological pathways of disease which have not been recognised up to now. Once this has been achieved, we will be able to better predict, and treat or prevent life-threatening and morbidity-causing events in ICU patients. Additionally, we need to improve the outcome estimation for individuals to inform treatment decisions and improve the patient-centred outcomes. Finally, we need to improve the research efforts in ICU to facilitate progress.

The overall objective of HEALICS is to identify common causal mechanisms and pathways in multimorbid disease in the highly heterogenous critically ill population. Achieving this rests on four pillars:

1. Improving the characterisation of patients and to identify causative mechanisms of multimorbidity.
2. Reducing the occurrence of new morbidities associated with events while patients are admitted to the ICU.
3. Improving the patient-centred long-term outcome estimation for individuals to inform treatment decisions.
4. Developing a sustainable, multinational and long-term infrastructure for critical care research.

The main overall objective can be divided into more specific objectives according to the four domains:

#### Diagnostic objectives

The main diagnostic objective to identify common causative mechanisms and to identify clusters of homogenous patients will be divided into specific objectives of:

* To improved characterisation of patients beyond the standard ICU admission variables (limited to risk scores such as the Acute Physiology and Chronic Health Evaluation), by including information regarding demographics, including socio-economic and lifestyle factors, chronic diseases, previous medication use, and clinical characteristics, as well as complex imaging data and functional assessments. This specific objective focuses on the design of a set of variables, informed by a layer structure according to the availability of data depending on either on details of the patient or resources of the participating centres. This should reflect realistic scenarios according to clinical need for additional diagnostic testing, resources of the participating centres, or logistic limitations (WP2 and WP3).
* To determine the value of specific biomarkers in combination with certain clinical variables for diagnosis, prediction of treatment response and prognosis, with a special focus on identifying markers with the highest (additional) value. We will focus on unravelling the interactions between multiple biomarkers and determining their added value towards obtaining a completer and more integral picture of the patient.
* To determine the value of genetic and epigenetic loci and profiles associated with multimorbid conditions and with different disease statuses.

#### Short-term outcome objective

The main short-term outcome objective *to reduce the occurrence of new morbidities associated with events while patients are admitted to the ICU* requires to get a grip on the instantaneous risk of deterioration of these critically ill patient (a short-term whether forecast) and to capture and measure patient's complexity in the context of co- and multi-morbidities. This main objective will be subdivided into:

* Creating machine learning-based prediction models for the prognostication of immediate or short-term (e.g. 6 hours) mortality risk of critically ill patients.
* To create a bedside automatically updated, visual early warning monitoring system. This may initially be a simple web-based option, which can later be transform into a tool integrated within the electronic health record system (EHRS) of the patient.

#### Long-term outcome objective

The main long-term outcome objective to improve patient-centred, long-term outcome estimation at an individual level to better inform treatment decisions can be divided into several specific objectives:

* To develop longer-term and more individualised mortality and outcome prognostication tools, which may inform patients, their families and the physicians who counsel them, as well as provide guidance for optimal treatment decisions.
* To develop broader evaluations of longer-term, patient-centred outcomes by including mental, non-mental, cognitive function and novel quality-of-life assessments. This specifically demands:
  + the development of quality of life (QoL) assessment tools suited for follow-up of ICU patients.
  + exploring and validating new cognitive function assessment tools.
  + the incorporation of non-mental disorders, including multi-morbidities and specifically their associations with mental and QoL outcomes.
  + the inclusion of cost-effectiveness evaluations.

#### Research infrastructure objective

The development of the research infrastructure to improve research efforts in ICU will be made possible by:

* Exploiting and connecting existing cohorts for retrospective analysis of potentially important variables. This requires the harmonisation and integration of data systems of multiple international cohorts of ICU patients.
* Connecting the electronic health record systems (EHRS) in four major hospitals participating in this consortium and automating the data capturing process from the electronic health record systems. By returning data to clinicians, collected e-information about healthcare services helps to inform caregivers. Once successful, we aim to expand this infrastructure to other data systems so as to cover as many partner institutions as possible.
* To facilitate a prospective cohort study with automated data capturing in a multinational, multicentre setting, including detailed patient characterisation (WP3) and long-term patient-centred follow-up (WP5).
* To develop a structure where the individual patient data in the local or national databases and only the aggregate data will be transferred to the central coordinating data centre.

#### The perspective of the caregivers

An additional domain is the perspective of the caregivers. Every day, we caregivers (intensivists and nurses, physiotherapists, dieticians and other team members) are faced with the hard reality that we are currently not providing the best possible care for patients with multimorbidity, thanks to a system based on syndrome-based diagnoses for which most causal mechanisms remain unknown. Every day, we carry out interventions targeted at improving signs and symptoms rather than at tackling the underlying causal mechanisms of disease, the effectiveness of which we cannot guarantee. While uncertainty will remain a part of medical care, it is taxing on caregivers and families to repeat and hear how we cannot reliably predict how the future will look like, and that *“... we are not sure, we have to wait and see …”*. It is our objective to improve this, and provide a new state-of-the-art standard for the care of critically ill, multimorbidity patients and … Please provide the most suitable information.

## 1.2 Relation to the work programme

HEALICS can improve this current abovementioned very frustrating state-of-the-art and will address many health challenges mentioned in the **H2020 Work Programme 2018–2020 on Health, Demographic Change and Well-being**. HEALICS will address the witnessed *rising healthcare costs caused by the increasing prevalence of chronic diseases, as reflected by multimorbidity, in an ageing population requiring increasingly complex care*. The scope of HEALICS ranges from diagnosis to prognosis with clear integration of *personalised approaches into healthcare services and systems to the benefit of patients and citizens*. By the identification of homogeneous clusters of patients, HEALICS will form the basis for the development of novel and repurposed therapeutic approaches. HEALICS’ priority is to *deliver healthcare solutions to benefit individual patients and their environment*, by generating and *translating knowledge on disease aetiology and technological innovation into personalised health and care solutions*. This priority targets a recognisably high-risk group: a general acutely critically ill population. More specifically, HEALICS will address the challenges of the call as shown in the table x below.

Table x. Challenges addressed in HEALICS

|  |  |
| --- | --- |
| ***Specific Challenge and Scope cited by the call*** | ***How HEALICS will address the challenges*** |
| The increasing number of individuals with **co- and multi-morbidities** poses an urgent need to improve management of patients with multiple co-existing diseases. | The patients with the highest burden of multi-morbidities converge in the ICU. We will identify common underlying pathophysiological pathways and mechanisms in this setting of highly dense prevalence, event rates and monitoring. |
| A better understanding of their causative mechanisms is needed to develop **early diagnosis, efficient prevention and monitoring, and better treatments** adapted to co- and multimorbid patients throughout their life course. | A stay in the ICU can be seen as a progeric process leading to accelerated ageing in a short period of time. We will characterise underlying mechanisms in ICU patients with multimorbidity. |
| There are many different aetiological models of co-morbid conditions (e.g. direct causation model or a consequence of treatment). In this context, **capturing and measuring patient's complexity** in the context of co- and multi-morbidities is crucial for adequate management of these conditions and requires innovative approaches | We will capture patient’s complexity at admission by unmodifiable variables and variables susceptible to interventions, by multi-morbidities, but also by treatment interactions with the disease and its complications, which is all highly dynamic in the ICU. To unravel causative mechanisms, we will involve machine learning, including automated feedback versus aetiology to account for the complexity. |
| Proposals should identify and validate causative mechanisms (e.g. molecular, genetic, correlative, drug-drug interaction) of co- and multi-morbidities **combining mental and any non-mental disorders** through the integration of basic, pre-clinical and/or clinical research. | We will evaluate conventional non-mental outcomes, mental disorders, cognitive impairment and patient-centred outcomes (including QoL) and validate observations in independent international cohorts and explore causal mechanisms by integrated approaches, including genome-wide genetic, epigenetic and biomarker research. |
| Applicants should prove the **relevance** of the identified mechanisms for co-morbid development. | We will identify causal mechanisms of multimorbidity by their impact on critically important patient-centred outcomes. |
| Where pertinent, development of **biomarkers and other technologies** for diagnosis and monitoring of comorbid conditions in patients is encouraged. | We include genetics, epigenetics and other biomarkers, as well as advanced monitoring in our patient characterisation during ICU stay. |
| A purposeful exploitation of **existing data,** biobanks, registries and cohorts is expected, but does not exclude **generation of new data**. | We will explore mechanisms in multiple international existing cohorts and registries and validate observations in new and enriched prospective cohorts by connecting electronic health record systems. |
| Sex and gender aspects, age, socio-economic, lifestyle and behavioural factors and any other **non-health related individual attributes** should be taken into consideration. | Sex and gender aspects are included in the patient characterisation. Further, biological age (risk profile, epigenetics) versus calendar age will be included. Socio-economic, lifestyle and behavioural factors will be evaluated as well. |
| **SME** participation is strongly encouraged. | SMEs are involved in data management, in machine learning, and in the communication and implementation of prognostic models, likely to be commercialised after the project. |

HEALICS will also contribute to:

1. Establishing Europe as a global leader in personalised medicine research.
2. Supporting the personalised medicine scientific base through a coordinated, collaborative approach to research.
3. Providing evidence to policy makers of the benefit of personalised medicine to citizens and healthcare systems.

We do know that unravelling the heterogeneity of the patients in the ICU is of utmost importance to take better care of the ‘sickest of the sick’. The diversity in admitting diagnosis, demographic characteristics, multi-morbidities, disease progression (patients), many interventions (process) and outcomes, creates this heterogeneity, hampering the understanding of the underlying disease and consequently the best treatment for a healthy recovery. We also know that the ICU with its high density of patients with multimorbidity as well as the highest density of monitoring, is the place where patients can be characterised most in depth by baseline variables and vital signs during their illnesses resulting in a large and varied amount of relevant data. While heterogeneity may drive for the lack of understanding, it is also a challenge and may be an opportunity to reveal common pathophysiological pathways in distinct diseases. This challenge of the heterogeneity of patients is at the same time *the opportunity* to discover common pathways in patients with various diseases and multi-morbidities. Therefore, the *ICU offers the ideal setting to evaluate causative mechanisms in multimorbidity*. We need to focus on unravelling heterogeneity before establishing the benefits of interventions. We need to take a step back before we can make many steps forward, *a step back to the individual patient*.

To take this step back to the individual patient HEALICS has gathered prominent basic and clinical research experts in the field, including the leaders of the critical care in Europe, patient characterisation including biomarkers and genetics, patient-centred outcome, data infrastructure and machine learning experts into one consortium (figure x – HEALICS overview). Involvement of the network of ICUs for data delivery and in return academic output and integrated electronic health record system tools guarantees implementation of results and impact in daily practice. Involvement of SMEs for data infrastructure and machine learning guarantees sustainable deliverables and impact beyond the duration of this project. HEALICS aims to maximise integration between existing consortia of clinical and non-clinical, between academia, non-academia, and SMEs, for effective utilization of available resources.

## 1.3 Concept and methodology

Key concepts and methods of this proposal are briefly presented in this section but described more in detail in the corresponding WPs and specific tasks.

The overall concept of HEALICS is:

1. Improving the characterisation of patients.
2. Improving the patient outcome evaluation.
3. Improving the machine learning analyses techniques.
4. Improving the data and research infrastructure.
5. Improving effective communication and dissemination.

### 1.3.1 Concepts

The key concept underpinning this entire enterprise is that critical illness can be regarded as an accelerated evolution of multimorbidity in life, evoked by the actual admission diagnosis. There are several major achievements and opportunities which meet in this challenging HEALICS project. It is not the individual approaches of improved patient characterisation (WP3), improved patient outcome evaluation (WP5), improved machine learning analyses techniques (WP4), a data infrastructure (WP2) or effective communication and dissemination (WP6), but rather the combination of all these approaches which is the key concept here. Analogue to what Søren Kierkegaard stated *“Livet forstås baglæns, men må leves forlæns.” (Life is understood backwards but must be lived forwards):* we must look back to learn and (re)cluster patients in homogenous groups in order to improve our understanding of what is happening, understand the patients’ outcomes and how to improve that.

New diagnostic concepts, prognostic models, genetics, biomarkers, machine learning methods, or a continued data registry platform in itself are not innovative, but it is all *these combined approaches* with *the opportunity and supported by the capacity* present in the current consortium which offer the unique window of opportunity for new insights and impact.

The achievements, experience (check right and uniform use of names of collaborators) and capacity include:

* An established network of (30 or 40) European ICUs, highly experienced and capable in running well-designed large pragmatic randomised clinical trials (RCTs) (CRIC, CPH, DK). While RCTs are clearly out of the scope of this call, we are capable of conducting studies on a large continent scale (CPH, DK). At the same time the deliverables and impact feed back into this same network of ICUs.
* A national registry of ICU data (Aarhus, DK).
* Cohort studies and biomarker evaluations (Helsinki, F; Aarhus, DK; LUH, Sweden; Groningen, NL).
* A large network of machine learning with complementary expertise and experiences that are essential; experience include representation learning, supervised and unsupervised schemes for feedforward neural networks and prototype-based systems, as well as methods of feature selection, relevance learning and visualization (RUG, Groningen, NL); dimensionality reduction in general, recurrent and deep neural networks, and transfer learning (…., Bielefeld, G); statistical inference, risk prediction and the machine learning based analysis of omics-, genetic and phenotypic data in translational research (Rutgers, USA); design of decision support systems, interpretable systems and the detection of causal relations in complex data sets (Liverpool, GB); data management, including e-health systems and artificial intelligence based decision support systems (…, Cyprus); big data infrastructure and deep learning (Target, Groningen, NL).

Opportunities:

* There is no other medical specialty area where the prevalence of multimorbidity is near 100%. If we wish to discover pathophysiological causal mechanism or new find targets for interventions in multimorbidity and if we wish to address the increasing numbers of individuals with co- and multi-morbidities, we need to focus at where the prevalence is highest: *it is at the ICU*.
* The enormous high event rates of mortality and serious adverse events are associated with unfavourable outcome. This makes the ICU setting extremely powerful for discovery and validation of diagnostic and prognostic models.
* The four largest ICUs in this consortium all have recently implemented EPIC as electronic health record system in their hospitals. This is therefore the ideal momentum to embark on this ambitious project with chances for success.

#### Diagnostic concept

##### Two aspects of multimorbidity

There are two overarching categories of research questions involving co- and multimorbidity. The first category includes multimorbidity at admission as risk factor for critical illness and adverse outcomes (WP3). The second includes the development of additional new morbidities such as kidney dysfunction, new-onset diabetes, or mental disorders, and their tremendous impact on quality-of-life, as outcome for ICU survivors (WP5). So, chronic multi-morbidities contribute to disease states, but new morbidities also evolve into part of the outcome states. We are currently uninformed about the complex interplay between risk factors (at entrance) and effect-modifiers (during ICU stay) which underpin the vast majority of diseases (as outcomes). As such, the ICU is the ideal research setting for evaluating the effects of existing multimorbidity on disease states and investigating the pathways of new morbidities originating from critical illness. The ICU setting with all its interventions and the dynamic interaction of the continuously improved diagnosis and prognosis of the patient as well as the high-density complex data (including continuously measured hemodynamic and pulmonary function as well as imaging data) cannot be analysed using simple conventional methods. In HEALICS, healthcare professionals and computer scientists will use machine learning tools to uncover hidden associations and identify homogeneous clusters of patients within the multi-factorial data modalities and heterogeneous patient populations.1

##### The ICU syndromes

The lack of knowledge of disease mechanisms is reflected by the widespread use of syndromes for patient grouping for diagnosis and prognosis in the ICU. The use of systemic inflammatory response syndrome (SIRS) as admission criterion is one example.2 Similarly, the use of terms like acute kidney injury (AKI) and post-intensive care syndrome (PICS) to describe clinical outcomes reflects not only the lack of knowledge of disease mechanisms but has also prevented the development of effective treatment strategies. Categorising patients by syndromes inevitably leads to grouping of patients with different disease mechanisms, different risk profiles, different responses to interventions, and with varying outcomes, which increases heterogeneity of patient groups and often translates as non-significant average intervention effects in large randomised trials. The conventional syndrome-based way of thinking needs to be replaced by clinical reasoning which is based on pathophysiological substrates. To achieve this, patient characterisation must be improved by incorporating a wide view on variables rather than only focusing on e.g., one biomarker, primarily by focusing on causal mechanisms, and interventions must be targeted on what is known about the underlying causes of disease. Only clustering of patients into sub-phenotypes based on underlying pathophysiological mechanisms will allow for better therapeutic approaches, and for healthier recovery in terms of patient-centred outcomes. As is the case with syndromes, we hypothesise that the admitting diagnosis is merely the ‘tip of the iceberg’ in patients suffering multi-morbidities, and that using the admission diagnosis as the basis for patient characterisation and clustering increases the risk of error in prognostication and diagnosis. Patients with similar symptom-based diagnoses often have divergent outcomes, probably due to as-of-yet unidentified differences in underlying disease mechanisms. Similarly, two patients with different diagnoses at presentation and expected to progress differently based solely on incidental observations, frequently end up progressing similarly because they may share some unidentified, underlying pathophysiological mechanism.

Evidence is evolving for clusters in syndromes such as ARDS[[1]](#footnote-2) and sepsis. Please provide the most suitable information.

##### The personalised medicine paradox

Personalise medicine attempts to integrate clinical phenotype with patient data on clinical characteristics, laboratory measures and (epi)genetics to define a subgroup of patients that may benefit from a particular treatment and therewith tailor the treatment for individual patients. However, evidence-based medicine principles require evidence from groups before interventions can be accepted. Therefore, in personalised or precision medicine we individualise treatment based on evidence from sufficiently large clusters of similar patients. This suggests that the individualised approach should actually be cluster-derived. Only then can personalised or stratified medicine become a reality in the ICU; and the identified optimal interventions can be extended or adapted to other areas of medicine with similar multimorbid patients. Thus, there is an urgent need to identify clusters of common causal pathways in the wide heterogeneous group of critically ill patients, irrespective of admission diagnoses, in order to personalise and improve treatments. Furthermore, for an individual patient the identification of a cluster to which the patient fits to has to be established within hours as short-term outcome is determined by the underlying pathophysiologic mechanism and the course of disease can evolve quickly. It might even be that identifying a cluster fits the patients at that time-point while the course of disease and interventions by caregivers might lead to fitting into a different cluster later.

#### Short-term outcome concept

The downfall events

The course of patients admitted to the ICU frequently experience sudden unexpected deterioration (figure x – course of disease and outcome). At each moment there is a certain risk of each patient to become highly unstable (hemodynamically, respiratory, neurological, infectious, or other) and they may experience serious adverse events which lead to a downfall in their physical condition, or worse even death may suddenly occur. After such a downfall it frequently takes a long time to recover and only rarely patients make it to full recovery up to pre-ICU admission states. Modification or prevention of the general bad outcomes of critically ill patients may best be accomplished by preventing such serious adverse events. If we forecast the occurrence of instability of patients (on the short term, that is within 6 hours or so), at least in a proportion of all the cases, then we could potentially intervene and either prevent such events from occurrence or reduce the impact on causing a bad outcome. Up to now there are some static prognostic models which only in general conclude on risks of mortality of critically ill patients. Instead we would need a highly dynamic model which could be updated, at least several times a day in order to become useful in practice. For such dynamic models nourished by highly complex ICU data we need involvement of machine learning techniques.

#### Long-term outcome concept

##### Dynamic prognostication

There are several prognostic models predicting mortality for ICU patients. None however is frequently used in clinical practice and certainly not for individual patient decision making. Most models stem from the time when data had to be registered by hand, while the data infrastructure and information technology facilities in 2019 have improved considerably. Also, analyses techniques have improved from classical statistical methods to machine learning algorithms. Models have up to now been static while currently we need dynamic models capturing the patient’s improvements or deteriorations. The variables included into the models are less limited in the modern era and prognostication can result from all variables from traditional baseline demographic and clinical characteristics to newly identified biomarkers and (epi)genetic markers. In respect to biomarkers it should be emphasised that biomarkers could show a relation to prognosis as well as predict whether a patient will respond to treatment. It might be that different variables, including biomarkers, predict short-term outcome, response to interventions and long-term outcome.

##### Patient-centred approach

Outcome evaluation of critically ill patients has largely been limited to mortality status and length of ICU stay. The patient perspective including patient preferences and health-related quality of life issues have largely been ignored. Part of this can be explained by loss to follow-up, competing events and cognitive dysfunction which may prevent reliable assessments, and logistic problems associated with lack follow-up of such a heterogeneous group of patients. Some evaluations of the patients’ subjective health status can be obtained from the patient while for other (i.e. elderly and/or the cognitive severely disabled) can only be obtained from their families or next of kin. We urgently need to shift away from limited outcome evaluations (mortality) to patient-preferences, including personalised follow-up: this may include app-based techniques for those who are cognitive capable to home visiting of those who are severely disabled (either somatic or mentally).

#### Research infrastructure concept

There have been various cohorts of studies including critically ill patients for various research questions. The reported observations frequently contrast with previous findings and seldom these were replicated or validated in external (international) cohorts. This can only be done in a European collaboration.

Separate isolated efforts have shown the potential of targeting heterogeneity by measuring genetic and epigenetic markers with machine learning-based techniques, in single-centre cohorts. However, none of these efforts were designed to be scalable to multiple centres, nor did they combine two or more of our concepts of detailed patient characterisation, machine learning, and improved patient outcome evaluation. HEALICS intends to connect the isolated efforts into *one international cohort network* and pioneer new concepts of *patient characterisation, machine learning, and outcome evaluation*.

##### Design and positioning of the project

HEALICS is situated early in the spectrum from ‘idea to application’. We will set up the research infrastructure for an on-going multicentre, multinational prospective cohort study of ICU patients with long-term (1-year) follow-up. This cohort study is intended to evolve into a registry (coordinated by the partners from WP1 and WP2) after this project with automatic data capture from among others electronic health record systems, for continued future scientific inquiry allowing updating of dynamic machine learning models and addressing new research questions.

##### Linked national or international research and innovation activities

HEALICS will build on knowledge and evidence acquired in past European international and national projects: the H2020 project IMPACT focusing on decision support for cardiovascular diseases; the FP7 project BioCog on the development of biomarkers in postoperative cognitive dysfunction; MechML, funded by the Federal Ministry of education and research, Germany, aiming to blend machine learning technology to address current medical challenges in microbiological data analysis; BigTempHealth, a big data project funded by the Innovation Foundation Denmark, focusing on improved prediction from deep phenotyping using full registry and electronic health record data from ICU patients from half of Denmark. Please provide the most suitable information.

### 1.3.2 Methodology

In the ICU the amount of available data on patients and even individual patients is tremendous. By connecting all variables obtained through the electronic health record systems obtains data from patient monitoring systems, bedside apparatus (e.g. pumps, organ support systems such as ventilators, dialysis machines and mechanical circulatory support). This data should serve for diagnosis, prediction models and benchmarking. However, the state of critically ill patients can be represented as a complex balance of interactions between various variables and effect modifiers such as clinical interventions (figure x – iceberg). This state should be continuously updated to allow for diagnostic and prognostic evaluations, both processes occur simultaneously. To this end, we will connect data from existing international cohorts of critically ill patients, enriching existing and prospective databases and biobanks with high density data and genetic and epigenetic biomarkers. We need to associate variables and causative mechanisms with patient-centred outcomes of prognosis, such as long-term mortality, serious adverse events, improved measures of quality-of-life, mental health including mild cognitive impairment, chronic kidney disease, and endocrine function. Findings need to be externally validated in independent international cohorts of ICU patients.

The methodology used in HEALICS is:

1. to systematically review the existing literature to establish key variables.
2. to combine and analyse existing cohort data to identify and validate key variables using the knowledge of experts on intensive care, outcome measures, data management and machine learning with the academia and in small and medium enterprises.
3. to build a prospective cohort study to validate existing and discover new key variables, as biomarkers and ….

To achieve its ambitious goals, HEALICS will use mixed methods to gather qualitative and quantitative data. Data collection and data storage must be harmonisedacross participating centres and countries. To this end, modern data storage and high-end analytic techniques will be used to process the vast amounts of baseline clinical, genetic, epigenetic, biomarker, quality-of-life- and mental status-related and somatic variables collected during and after ICU stay. To ensure uniformity of data in this process, a standard data collection, process, and analysis protocol will be established to be used in all centres, covering all steps from variable collection methods to data entering into data management systems, such as the publicly available **Virtual Research Workspace** provided by the Center of Information Technology at the University of Groningen(Please provide the most suitable information **DASH**) and …. Please provide the most suitable information (**Aarhus and Enversion**). We estimate that the entire duration of the HEALICS project will take five years.

The HEALICS project will start with a systematic review of current available literature (A), followed by analyses of data derived from several existing cohorts (B), and finally a large international prospective study (C). Results from phase A and B will be used for guidance of phase C. Before commencing phase C, a Steering Committee meeting involving partners (see 3.2.1 Management structure) and patient representatives. will take place to discuss results from phase A and B and to decide on future perspectives and directions for phase C.

#### Systematic reviews (A)

The first step in HEALICS is to obtain a comprehensive overview of literature by conducting systematic reviews in order to summarize and synthesize the current state-of-the-art on:

* Current risk scores in the ICU.
* Genetic and epigenetic markers and biomarkers and their relation to clinical outcomes in ICU patients.
* Long-term non-mental and mental outcomes.
* Data sets and data structures as well as algorithms already applied in research settings in the field.

The systematic reviews will provide a comprehensive set of variables suggested to be of importance both during and after ICU stay, and which should therefore be considered in a new prospective cohort study. The reviews will be conducted according set standards and the protocols will be published on PROSPERO (<https://www.crd.york.ac.uk/prospero/>) prior to publication.

#### Combining and analysing existing cohort data (B)

An important aspect of HEALICS is the availability of well-defined sample / clinical data repositories from cohort studies as well as large randomized controlled trials at individual beneficiary sites (Figure X). Available collections are described in table X.The existing cohorts are derived from research collaborations by the Centre for Research in Intensive Care (CRIC; Denmark, www.cric.nu), the FINNAKI study group (Finland) and the Simple Intensive Care Studies (SICS) group (the Netherlands). Members of these groups are active in the Scandinavian Critical Care Trials Group (SCCTG, www.ssai.info/research).

##### Data infrastructure

A uniform common data model for both existing data (phase B) and the prospective study (phase C) will be developed. This common data model can be applied locally within each partner of the distributed data network and will provide uniform data management, validation, visualization and aggregation of results. Two studies describing the prevalence and prognosis of multimorbidity will serve as use cases to test the model. Aggregated results can be uploaded and merged within the HEALICS common data platform, which also allows uploading of raw data and cleaned individual-level data after appropriate deidentification. The data platform and sharing process is illustrated in figure x.

Three steps are envisioned to be essential:

1. Profiling of the existing cohorts. There will be uniform gathering of information from the relevant HEALICS consortium partners with existing cohorts in Denmark, Finland, and the Netherlands. We will collect metadata describing the cohorts, their data items and mappings between data across the cohorts, as basis for integrated analysis (using MOLGENIS data catalogue developed by UMCG).
2. The development and application of a common data model. Based on core variables identified in task 2.1, a common data model will be developed and described to form a distributed data network. Scripts will be developed in existing software or in an open-source language for implementation within each site and tested by two use cases with the aim to describe the heterogeneity of multimorbidity within and between included cohorts.
3. The establishment of a common HEALICS data platform (Enversion), alike the Virtual Research Workspace provided by the Center of Information Technology at the University of Groningen. The HEALICS common data platform will allow all HEALICS consortium partners to share and work on aggregated and/or anonymized individual-level data.
   1. The platform will be developed in accordance with the Finable, Accessible, Interoperable, Reusable (FAIR) data principals. Please provide the most suitable information (**CMB – Braun**).
   2. Furthermore, the platform will be developed in accordance with the General Data Protection Regulation (GDPR). The research workspace of the UMGG, on which the platform will be based, is conforming to the privacy by design and by default principle, thus enabling a technically secure setup of the platform. Furthermore, the research workspace environment provides the software tools required such as dedicated research data collection environments for i.e. imaging data (XNAT) and Trusted Third Party for de-identification of data (TTP). Please provide the most suitable information (**DASH**).
   3. The platform will be able to receive structured data from electronic health record system (EHRS), such as the EPIC. These connections between the research environment and the EHRs will be based on standards such as Fast Healthcare Interoperability Resources (FHIR). Please provide the most suitable information (**DASH**).

ICUs participating in the cohorts will be the core for the prospective cohort in which data will be harmonised and enriched. There are several existing cohorts, established by the partners of this consortium and available for this project (table x): critically ill patients in Copenhagen (n = 11,000 patients), the registry of critically ill of Denmark (The Danish Intensive Care Database; each year n = 32,000 patients)1, the cohort of critically ill patients with acute kidney injury in Helsinki (FINNAKI; n = 2,901 patients)2, and two cohorts of critically ill patients in Groningen (SICS-I with n = 1,075 patients and SICS-II, with n = 400 patients and ongoing inclusion)3. These cohorts will serve as the basis for the international infrastructure of prospective cohorts of critically ill patients that we will build in phase C. In addition, Lifelines, a very large cohort and biobank of the general population in Groningen (the Netherlands, n = 167,000) will provide healthy controls. Data from these cohorts will be analysed with machine learning techniques, to replicate and validate the observations from the systematic reviews. These cohorts will also be used in the discovery and testing phase, providing the basis for the identification of patient clusters and key variables which support the development of machine learning-based diagnostic and prognostic algorithms.

Table x. Existing cohorts from partners in the project

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Participants | Located | n | Clinical data | Biomaterial | Follow-up |
| CPH | critically ill | DK, CPH | 11,000 | Y | ? | ? |
| DICD | critically ill | DK, Aarhus | each year 32,000 | Y | N | ? |
| FINNAKI | critically ill with acute kidney injury | F, Helsinki | 2,901 | Y | Y | 1-year |
| SICS-I | critically ill | NL, Groningen | 1,075 | Y | N | 90-day |
| SICS-II | critically ill | NL, Groningen | 300 | Y | N | 90-day |
| Lifelines | general population | NL, Groningen | 167,000 | N | Y | ? |

Abbreviations:

#### Prospective cohort study (C)

We will conduct a prospective observational multicentre cohort study with in-depth characterisation of the ICU patients and their diseases and multi-morbidities upon admission, during their ICU stay and evaluate long-term follow-up of patient important outcomes (figure x - cohorts). For the duration of the HEALICS project, the expansion of the network to other international centres will allow for an increasingly large number of patients to be included in this unique cohort of patients for whom uniform, validated multimodal data is collected. Given the number of partner institutions, this prospective cohort is expected to reach thousands of patients, as the consortium expands from at least 30 collaborating ICUs (in six European countries). The prospective cohort study can be divided in two conceptually distinct parts (one part focused on diagnosis and prognosis, and the other focused on cost-effectiveness) as outlined below.

##### Selection criteria

All acutely admitted critically ill patients will be included in the prospective cohort study. Selection criteria will not involve admitting diagnoses due to our hypotheses on admitting diagnoses, especially concerning syndrome-based diagnoses there will be no.

##### Patient characterisation

We target to include a large cohort of patients in the study, who will be characterised in depth and in novel ways, by taking patient-centred mental and non-mental outcomes and quality-of-life into account. Patients will be characterised uniformly according to the variables selected by WP3. There will be site-specific stratification, i.e., sites may vary according to the types of variables which they can register. All sites are able to characterise patients according to a basic set of variables. Some sites however may be able to facilitate more advanced clinical characterisation, e.g., specific biomarkers or imaging or cardiac output measurements. Finally, four sites (Groningen, NL; Helsinki, F; Copenhagen, DK; Cambridge, UK) are planned to conduct genetic and epigenetic analyses.

##### Outcome data

The outcomes of patients will be registered, including mortality but also health outcomes in terms of health-related quality of life will be registered and to estimate costs of the treatments for ICU patients using (patient-centred) preference-based health outcome measures and standardized cost estimation methodology. The health outcomes will be defined in a comprehensive and generalizable way and will be collected via innovative application for easy administration and possible applicability throughout Europe.

##### Derivation and validation

Both derivation and validation are necessary in cohort studies. The identified clusters through (epi)genomic, proteomic and metabolic biomarkers are prone to confounding. The validation in a separate cohort is mandatory. The electronic health record systems can be leveraged to efficiently identify such cluster. Please provide the most suitable information.

##### Sample size estimation

There are no previous examples with such a large-scale enterprise available so as to derive estimates for the assumptions needed for the sample size estimation. Machine learning techniques with such number of variables may risk type I and type II errors.

##### Informed consent

National legal informed consent procedures will be followed, usually according to deferred consent. Please provide the most suitable information.

##### Data infrastructure

HEALICS will develop or adapt tools for a) data capture, b) data standardisation and harmonisation, and c) data integration. The Department of Epidemiology in Aarhus experience in data management will be used in the project.

The data infrastructure for the prospective study (phase C) is highlighted under section B. This data platform is aimed to serve for the prospective data collection including automated data capturing from electronic medical record systems, to start at least with EPIC which is used in the majority of the sites. We target to share and work on anonymized individual-level data across centres. If problematic for technical or legal reasons, there will be the option of aggregated data as a back-up plan.

##### Data analyses

General text on data analysis.

#### Diagnostic analyses

As described before, the lack of knowledge of disease mechanisms is reflected by the widespread use of syndromes for patient grouping for diagnosis and prognosis in the ICU. The purpose of a medical diagnosis is to inform patient and caregiver on natural disease prognosis, and more importantly, on ways to influence this prognosis, for example by installing medical treatment. The aim of the ‘diagnosis study’ is to identify a subset of patients or clustering of patients based on new characterizations that could replace the conventional syndrome-based ICU diagnoses. These characterizations will be composed of a combination of physiologic, genetic, epigenetic, biomarker, and imaging data and may or may not overlap with conventional diagnosis. To assess the associations between different phenotypes and outcomes, machine learning techniques will be applied. The relevance of a certain characterization will be determined by its ability to correctly predict outcome (prognostic study). In the ‘prognosis study’ we will use physiologic, (epi)genetic and biomarker data in combination with patient-centred outcomes to create clusters of patients with similar prognosis using modern machine learning techniques. For machine learning on large datasets harmonisation of data across multiple sites and validation of clusters in multiple data sets is needed. Please provide the most suitable information on machine learning for this: latent class analysis and principal components analysis. Ultimately with the characterizations will be used to form more homogeneous clusters of patients with similar disease characteristics that may provide new targets for therapy.

#### Short-term outcome analyses

There have been several early warning systems developed for warning of deterioration of patients on a short-term. WP4 text on machine learning techniques for developing and validating early warning systems. Please provide the most suitable information.

#### Long-term outcome analyses

Prognostic modelling with machine learning. Please provide the most suitable information.

##### Dynamic updating of machine learning models and algorithms

We hypothesize that prognostic models are dynamic; i.e., prognostic models need updating when time moves on. Also, populations in hospitals may change due to changes in policy or with evolving techniques. Also, prognostic models may be different according to different locations, i.e., one model may perfectly predict outcomes in hospital 1 while a totally different model might perform best in another hospital. We emphasize this dynamic aspect of prognostic models and acknowledge the need for updating in time and place.

##### Cost-effectiveness analysis

##### The consortium distinguishes between cost-utility and cost-effectiveness. Please provide the most suitable information.

* Cost-utility measures will be a focus in the evaluation of …. As health outcomes for the cost-utility measures, we will measure quality of life adjusted years (QALYs; elicited using surveys or based on literature review), disability- adjusted life year (DALYs, available from WHO and the Global Burden of Diseases project) and healthy year equivalents (HYEs). The effect on health outcomes are calculated together with the costs of the programme to obtain the two measures for cost-utility.
* Cost-effectiveness measures are primarily computed for the initial evaluation of the …. Since HEALICS targets …., it is important to evaluate the interventions based on improved outcomes in these areas. Thus, we compute a series of cost- effectiveness measures, including prevalence of healthy recovery outcome measures.

Notably, below we use the term cost-effectiveness analysis referring to both cost-effectiveness and cost-utility.

HEALICS will, where possible, follow the so-called generalized cost-effectiveness analysis, according to the WHO Guide to Cost-Effectiveness Analysis, which describes how to evaluate and compare different interventions based on costs and health effects, by estimating costs, savings and health gains as far as possible. By employing this methodology, the consortium aims to enhance comparability of evaluations for each intervention (for the retrospective as well as prospective analyses of interventions; see below) and for each country separately. We will use different methodologies that allow ...

##### Incentives for participation

*Compensation:* The cohort study participating sites will not be given any financial compensation or case money for each patient. Instead we plan to provide the participating sites with monitoring software to be developed for short-term-outcome warning system, either in a rather basic version available for them as on-line access system, or in a matured version immediately accessible on the patient monitor.

*Publication and authorship:* The steering committee will grant authorship depending on personal input according to the Vancouver definitions. If a study site investigator is to gain authorship, the site has to include 50 patients or more, with full data entry including 1-year follow-up. We aim for additional site authorships for each additional 50 patients included with the author names registered and listed in PubMed as minimum. The investigators not qualifying for authorship will be acknowledged with their names under the ‘HEALICS-consortium investigators’ in an *appendix* to the final manuscript.

##### Gender dimension

Available data suggests that survival after ICU admission is similar between male and female, so no sex selection criteria will be applied in the patient populations of the retro- and prospective cohort studies. However, sex and gender aspects are included in the patient characterisation and may be one of the major drivers for identifying subgroups, understanding underlying mechanism of disease and understanding longer-term patient-centred outcomes. All acutely ill patients will be included, irrespective their sex. The gender balance as to the lead of work packages is 50% each.

We will strive for equal rate of male/female when hiring new personnel.

## 1.4 Ambition

Remember patient A and patient B. HEALICS has the ambition that these two patients who are admitted to the ICU, both with the same admitting symptoms and signs, will soon be treated very differently from current practice. HEALICS has the ambition that based on key variables identified upon initial analysis, the caregivers will identify underlying mechanisms of disease associated with their multi-morbidities and that treatments differ based on targeted mechanisms. Short-term events can be foreseen, and their prognoses vary but can be predicted accurately. The two patients will be treated with different interventions. Individual treatment, individual targets and personalised follow-up will allow for their highest chances of healthy recovery according to the patients’ perspective.

The overall ambition of HEALICS is to identify causative mechanisms of multimorbidity in the heterogeneous, critically ill ICU patient population distinguishes four domains of:

1. to ….
2. to ….
3. to ….
4. to ….

HEALICS has the ambition to generate, in an innovative and patient-centred way, new knowledge on underlying mechanisms for critically ill patients, with the ultimate goal to unravel heterogeneity and find novel personalized or improved quantifiers for prognostication on outcome and diagnostics for interventions. To reach these goals HEALICS will exploit available resources and additionally create a new ongoing multicentre, multinational observational study bio and (epi)genetic marker and patient datasets.

The prospective study will allow growing sample repositories, comprehensive (global) coverage of scientific excellence, unprecedented access to tissue biopsies, extracellular vesicles and advanced model systems and imaging platforms, which jointly will lift this HEALICS project into a HEALICS platform of research infrastructure approaches to biomarker discovery beyond the state-of-the-art for critically ill patients.

#### Diagnostic ambition

Shift from traditional syndrome-based diagnosis to clustering of patients based on common causal pathways (for targeting interventions). Identifying variables that are indicative of causal mechanisms behind diagnoses. Capturing variables that are proxies for underlying morbidities that interact with the main underlying cause of disease. The symptoms-based diagnoses have largely been replaced by clustering of pts based on causal mechanisms. These improvements have managed to master the increasing needs and scarce of ICU resources by reducing ICU stay and by improved decision making

* Reduce the number of variables monitored in the ICU that do not contribute to diagnosis, first-time-right intervention, and prognosis, and that preclude precise patient characterisation of critically ill patients with multi-morbidity.

#### Short-term outcome ambition

We envision an improved estimation of the instantaneous risk for adverse events (early warning systems) which may prevent the development of new morbidities. Monitoring of critically ill patients will change risk for emergency downfalls will be estimated to assist intensivists for early interventions and as such prevent sudden deterioration of patients.

* Change and modernise daily ICU practice, by implementing the use of dynamic models for short-term outcome prognostication in patients with multimorbidity to assist clinicians in providing rapid responses to emergency instability and treatment decisions.

#### Long-term outcome ambition

Precise individual outcome prediction including patient-centred outcomes. Development of survival analysis models based on competing risks, which account for the occurrence of events related to co-morbidities that preclude the event of interest and are not independent, thereby reducing the bias in survival estimate. Increase the interpretability of prognostic models by developing interactive, “user-in-the-loop” machine learning studies that include clinicians and expert knowledge in the model development process

* Shift outcome evaluation towards patient-centred outcomes, including increased attention to longer-term mental disorders and quality-of-life in the ICU and beyond.
* Improve counselling and information of patients and families regarding their prognosis, subsequently increasing the main stakeholders’ involvement in the decision-making process regarding treatment continuation and/or cessation.
* Change and modernise daily ICU practice, by implementing the use of dynamic models for long-term outcome prognostication in patients with multimorbidity to assist clinicians in treatment decisions.

#### Research infrastructure ambition

The societal changes including demography, social issues, way of life, ageing, new behaviours, increasing comorbidities and the societal needs for health care resources urge to create an infrastructure for research that is dynamic and adaptive. We cannot foresee changes needed to optimise research and therefore we want to create a structure that is lasting. Some main characteristics of the infrastructure have been identified.

##### Dynamic in- and exclusion of variables

The infrastructure should allow to add variables that showed to be promising in other cohorts or from basic research and variables that showed to be redundant. Both adding and retracting variables allows for focussed data retrieval and makes participation as feasible as possible. For this purpose, rapid identification and validation using established multinational collaborative ICU research infrastructure is considered necessary. Structured variable pre-processing protocols for all different types of data collected before, in, and after ICU so as to increase the predictive performance of diagnostic and prognostic algorithms.

##### Dynamic inclusion of SMEs

Research fields can progress and change rapidly, the scientific questions most likely will change during the course of this 5-year project and there is no doubt that new or better analysis techniques will become available. Involving small innovating (biotech) companies will both promote such new initiatives as well as create a flexible research environment. HEALICS will utilize such dynamic SMEs relevant to specific field of expertise (including those for the genetic, epigenetic, biomarker, data management, ….). This inclusion of selected SMEs, whenever appropriate as decided in the Executive & Management Board, is to be implemented in full agreement with the Intellectual Property agreement of HEALICS and, especially in cases where the expertise is not covered by members in the consortium. Several … partners have reserved part of their budgets to be able to react swiftly on upcoming research demands. This is in line with the goal that the funding mechanism for any additional SMEs can be covered in annual budget updates. The consortium has a wide contact network with SMEs from collaborations close by academia and through the ESICM network.

By the end of the project, there will be a research platform in which all data and algorithms are integrated, and new data and analyses can be added after the project has been finished; in other words, there will be a sustainable solution.

* HEALICS will establish an EU platform for shared cohort/registry of data, with data open for analyses and future research on critically ill patients providing timely answers to various research questions by machine learning techniques.
* The results of HEALICS and other observational studies can be used to optimise the design of clinical trials.
  + By identifying multiple clusters trials should enrol and randomise patients across multiple clusters, i.e. stratification. As different groups of patients progress through the trial, their response to interventions in different biomarker-defined groups triggers, via pre-specified Bayesian models, adaptations in the randomisation scheme (response-adaptive randomisation). These rules allow the trial to reduce exposure of patient subgroups that may be harmed by the treatment and improve trial efficiency.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table x.   |  |  |  | | --- | --- | --- | |  | ***Current state*** | ***Envisioned future*** | | ***Clinical practice*** | | | | Numbers of variables | Large amount of all variables available | Reduced number of key-variables | | Clinical interpretation | Clinical judgment of all variables | Emphasise relevant variables | | Patient characterisation | Based on symptoms, signs and syndromes | Based on causal mechanisms | | Biomarker patient characterisation | Not used in clinical practice | Each patient | | Treatments | Usually ineffective; treatment based on expert opinion | Treatment based on causal mechanisms | | Counselling of patients/ families | Average prognosis of ICU patients | Individual prognosis including mental outcome and QoL | | Intensivists early warning system | Clinician expertise | Dynamic tool for early warning | | Treatment decisions | Based on clinicians’ expert opinions | Informed by patient-centred outcomes prognoses | | ***Research*** | | | | Evaluated outcomes | (Short-term) mortality, length-of-stay, mechanical ventilation days, surrogate endpoints | Long-term (1-year) non-mental, mental disorders (cognitive function), and QoL | | Research efforts | Separate isolated efforts | New international infrastructure | | Data analysis | Univariate and multivariate modelling | Machine learning techniques | | From research question to answers | Slow, due to lack of infrastructure | Quick, due to living research structure | | ICU data connection | None existing | Multinational | | Future randomised trials | Pragmatic approach, including all patients, usually not informed by causal mechanisms | Interventions targeted at causal mechanisms in ’characterised’ subpopulations | |

# 2. Impact

## 2.1 Expected impacts

HEALICS will impact **all stakeholders** involved in the care for critically ill patients with multimorbidity, including the patients and their families, caregivers, policy makers, and the SMEs involved.

The expected impacts of HEALICS is to identify causative mechanisms of multimorbidity in the heterogeneous, critically ill ICU patient population are:

1. to identify key variables for diagnostics, guide interventions and prognostication.
2. to identify biomarkers and (epi)genetic markers for more accurate and earlier diagnosis and prognosis.
3. to create an *infrastructure that facilitates rapid answers and immediate validation in independent partner cohorts and serve a platform for randomised trials*

HEALICS will address the expected impact from the call ‘identifying biomarkers and epigenetic markers for more accurate and earlier diagnosis, prognosis as well as monitoring of patients' condition’, which will mainly affect patients and their families. By creating a dataset and platform for new directions for clinical research, outcomes for patients will improve. The focus of patient outcomes will shift from simple survival measures to estimates of health and well-being. The information on their prognosis will be more precise. Their prognoses will include longer-term estimates of their mental disorders and quality-of-life. The families of patients will receive improved counselling for treatment decisions, informed by more precise prognoses of patient-relevant outcomes.

Major impacts are also expected on health care professionals: **clinicians**, **nurses** and **other caregivers**. Patients’ characterisation upon admission and during ICU stay will change from registration of all available variables towards emphasis on a reduced number of key variables. Further, identified biomarkers and (epi)genetic markers for more accurate and earlier diagnosis, prognosis as well as monitoring of patients’ condition will become standard for patients’ characterisation. Treatments will be applied depending on stratification of patients based on key variables associated with causal mechanisms. The caregivers will be able to better counsel patients and their families on the expected long-term prognosis, which will guide decisions on treatment limitations.

HEALICS will address the expected impact from the call *‘****new directions for clinical research to improve prevention, diagnosis, prognosis, therapy development, and management of co- and multi-morbidities’,*** which will have major impact on **scientists*.*** Through sophisticated machine learning techniques applied to in-depth collections of patient data, HEALICS will uncover causal mechanisms underlying multimorbidity. The design of future randomised trials will change from testing non-causal interventions in all patients to testing interventions targeted at causal mechanisms in stratified subgroups. Research will shift from short-term convenient measures to long-term patient-relevant outcomes including (mental) health and quality-of-life. Our new infrastructure will facilitate rapid answers and immediate validation in independent partner cohorts. Concluding, there will be a major **diagnostic impact, as the** paradigm shifts towards personalized clustering of causal pathophysiology resulting in appropriate treatment. On short term the major impact will be the improved outcome, seen from fewer events and a decrease in adverse event due to the increase of appropriate treatment. Long term impact entails the shift towards patient-centred outcomes while improving prognostic models, providing opportunities to improve counselling of patients and their relatives. In terms of research infrastructure, the impact will be large, as data collection can both be executed quick but sophisticated in multiple settings. With the combined expertise, prespecified protocols and interaction between SMEs and skilful researchers and physicians, results can be described and debated efficiently in open access journals.

#### Diagnostic impact

Paradigm shift in diagnoses at the ICU and probably also in other specialty.

New targets for treatment.

#### Short-term outcome impact

Fewer events.

Improved patient outcome by …

#### Long-term outcome impact

Shift towards patient-centred outcome evaluation.

Improved prognostication.

Improved counselling.

Improved long-term patient outcome.

#### Research infrastructure impact

##### Structure for ongoing research with uniformly collected data impact

* Redirect the focus of future randomised clinical trials, targeting the discovery of causal mechanistic pathways, and using improved patient stratification based on validated key variables to unravel differential intervention effect estimates;
* Improve outcome and prognosis of critically ill patients with multimorbidity during and after ICU stay, by using the knowledge on causal mechanisms to optimise interventions;
* Build an adaptive platform that in the long run facilitates the translation and adoption of the HEALICS methodology in other areas of medicine with a lower prevalence of patients with multimorbidity.

##### Market opportunities

The establishment of the HEALICS consortium provides many opportunities for collaborations with various types of companies. As the infrastructure created within HEALICS is built to answer research questions in a structured manner, companies with similar ambitions are welcome to collaborate. For example, Biomarker SME’s connect to the HEALICS consortium infrastructure (established between 2019-2024) for evaluation of new biomarkers. The additional diagnostic and/or prognostic value can immediately be explored and internationally validated in sufficiently large cohorts of critically ill patients.

The HEALICS consortium has established a cooperation with **TARGET** (<https://www.target-holding.nl>)…. Please provide the most suitable information (**TARGET**).

The HEALICS consortium has built a cooperation with **Enversion**(<http://enversion.health/en/>)for data management and is expanding with other SMEs for connections to other clinical areas and similar consortia. Please provide the most suitable information (**Enversion**).

The HEALICS consortium and **Evidencio** (<https://www.evidencio.com>) have introduced new standards for prognostication of critically ill patients, including dynamic continuously updated prognostic scores for both short and long-term estimations of prognosis. These may inform clinical ICU practice. Please provide the most suitable information (**Evidencio**).

Future collaboration between HEALICS and ***health care centred enterprises*** could improve the collaboration between private and public research. For example, companies aimed at improving care for the critically ill can get coaching or advice from HEALICS experts so they can integrate relevant clinical and research expertise with their specific ambition. Large companies such as GE Healthcare can share their expertise about imaging or data analyses within HEALICS focus groups in which the latest developments in ICU will be debated. This will not only allow for brainstorming about next steps or discussing challenges faced in ICU, but also for companies and research in critical care to align and complement each other’s developments as opposed to doing similar projects without collaboration.

**Health management stakeholders** will experience impact as well. Costs will decrease as efficiency increases by spot-on treatment decisions through better diagnosis. Improved outcomes and healthy recovery after ICU stay will translate in reduced costs associated with fewer newly developed comorbidities. Improved diagnosis and prognosis will inevitably lead to better decisions, less complications, shorter ICU and hospital stays, and increased capacity for planning. Furthermore, as the amount of unnecessary care will be reduced, there can be more time personalized palliative care and for saying goodbye, a sometimes-inevitable situation but important for patients, relatives and health care providers.

The **society** will experience higher economic production as patients recover faster and experience improved health outcomes. ICU length of stay will be shortened by days, which saves tremendous expenses as one day in the ICU can cost up to one thousand euros.[[2]](#footnote-3) Moreover, the patients who survive require less support as they are healthier, and provide more value to society, partly due to accelerated return to societal activities and work.

HEALICS will stimulate growth of the **SMEs** involved in this project, which will create a breeding ground for innovative products and services in personalised care.

In conclusion, with new insights obtained within HEALICS, sophistication of diagnosis and prognosis will be taken to a higher level. Fostering traditional outcomes with a set of patient-centred outcome measures for healthy recovery will improve counselling of **patients** and **their families** and increase shared decision making. HEALICS’ impact will constitute no less than a quantum leap in ICU cure and care.

The principal goals of HEALICS encompass enhancing the diagnostic accuracy to unravel mechanisms that clusters patients with similar underlying pathophysiological mechanisms. These in turn can guide prognostics and treatments and provide a basis for future cost savings for the public healthcare systems. It is envisioned that HEALICS will build on the successes and lessons learnt from previous large cohorts and randomized trials in critically ill patients and expand the knowledge by close collaboration with a network of various? experts. The research, SMEs and societal sectors involved in HEALICS will benefit from the cooperation and knowledge sharing which will occur in these projects.

##### Clinical impact

Personalising the care of critically ill patients will primarily bring benefits to patients and their families. As the amount of non-informative variables that need to be obtained will decrease, the time spent by the health care providers in obtaining and interpreting these tests will also decrease. The time that becomes available can benefit patient interaction and allows health care providers to spend more time explaining the value and impact of informative tests to their patients and relatives. Moreover, as health care providers will be able to better characterize patients using epigenetics and informative variables, they benefit from personalised care leading to more precise estimations on patient centred outcomes. With more tailored treatments and better understanding of risk estimations per subgroup, counselling patients and their families through this difficult time in their lives will improve. The focus will move towards the patient and all his or her facets, as opposed to person X with diagnosis Y.

For health care providers, all aspects mentioned above allow for a rearrangement of tasks throughout a regular ICU shift. Instead of spending about 30% of time administrating unnecessary variables, time can be allocated to counselling patients at the bedside or discussing with colleagues about complex cases. Moreover, as HEALICS will develop dynamic early warning tools, physicians can estimate which patients require extra attention and which patients have a very low risk of developing complications. This all together will provide a healthier work environment, which increases time available for teaching new physicians, enhanced team communication and healthier physicians themselves. Not only will this attract health care providers to come work in the ICU, but improving physician health also positively influences patient outcomes, and can prevent burnout among dedicated staff.[[3]](#footnote-4)

Personalising the care of critically ill patients will bring benefits to patients, their families and health care providers by:

* Improving characterisation of patients, by reducing numbers of non-informative variables and increasing informative variables.
* Shift away from current diagnosis into reclustering of patients into subphenotypes according to causal mechanisms of disease.
* Introduce epigenetic characterisation into clinical practice.
* Inform ….
* Improved counselling of patients by more accurate prognosis.
* More patient-centred outcome assessment.
* Provide caregivers at the Intensive Care Unit with dynamic early warning tools.

##### Innovation impact

Data from HEALICS will generate new insights into mechanisms of disease in critically ill patients, resulting in important new opportunities for both academia and industry

* New causal mechanisms extrapolated to areas of medicine outside critical care.
* Possibilities for SMEs.
* Infrastructure for research opportunities including biomarker (and epigenetics) validation.
* Providing new targets for pre-clinical research.
* Generating new hypotheses, targets and stratifications for interventions.

##### Societal impact

General line on societal impact

* Improved diagnosis and more accurate prognosis have the potential to decrease patient suffering, both from pre-existing morbidities, new co-morbidities emerging from adverse events originating from ICU treatment.
* Improving diagnosis can allow for targeting interventions of existing and newly developed interventions, e.g. the right intervention to the right patient.
* Preventing or alleviating complications which result from new co-morbidities.
* Interaction with patients. Please provide existing examples from different (your) country here.
* Reduced societal costs due to improved knowledge of prognosis (informing treatment limitations) and more effective interventions resulting from knowledge on causal mechanisms.
* We will have direct contact with patients and indirect through social media (including a website, Twitter, etc) and thereby will educate and empower the patient and network, which is expected to contribute to patient empowerment (QoL).

HEALICS will have direct contact with patients throughout all collaborating centres and indirect contact through social media. The aim of these outreach campaigns is to increase valorisation of research projects and their results, but also to offer patients and their relatives to be able to connect with peers. Building a network of all those involved during ICU stay, especially the patients, may aid in helping others before or after ICU stay to improve their (mental) well-being.

##### Academic impact

General line on academic impact

* FAIR catalogue of available cohorts and their contents to promote reusability for research and health.
* Connecting of key players from academia, paving for new innovative research
* Due to involvement of experts from various areas, including, machine learning, data scientists, genetic experts and cognitive function and QoL experts will probably raise academic discussions to a next level
* Creating a consortium which may provide access to a wealth of data inspiring future research projects, according to conditions of open access (Open structure of data (see MIMIC))
* The findings from HEALICS will inspire future testing of new interventions in large-scale randomised clinical trials, with improved stratification/enrichment based on newly identified variables and markers indicating common causal pathways of multimorbidity in an a priori heterogeneous patient population.

##### Educational impact

Although it appears that HEALICS has no specific educational objectives, the educational impact will be large, as education is integrated throughout this entire proposal. First, young researchers are invited to collaborate in HEALICS, and those becoming future researchers will build their career learning from the HEALICS consortium, being a well-structured, collaborative research initiative. The principles of collaborating across borders, working in teams, aiming for open access and valorisation of research will allow young physicians or researchers to learn and achieve scientific integrity. This may seem of inferior importance, but all these factors influence the infrastructure created within HEALICS, which will be extremely beneficial if established continuously for a longer period of time, thus requiring the current HEALICS consortium to involve and teach their future successors.

Second, the intense collaboration between academic and SME partners, the planned information exchanges between ICU experts and people with specific expertise from outside the ICU will create opportunities for not only scientists or physicians but also younger scientists and trainees to build their research portfolio which will make them extremely suitable to become our future academic intellect

While HEALICS has no specific educational objectives, the intense collaboration between academic and SME partners, the planned information exchanges between ICU experts and people with specific expertise from outside the ICU will create opportunities for younger scientists and trainees to build their research portfolio which will make them extremely suitable to become our future academic intellect.

HEALICS results will be translated into training material, distance learning tools and a Learning Management System (WP6). Updated training manuals and training tools will be used for pre-service and in- service training (especially using e-learning and mobile technology). The project will reach … health workers for training and capacity building. Revised nationally used training instruments will have a wider reach.

Moreover, as time allocation by health care providers will become more efficient, more attention can be directed towards those in training throughout all layers of ICU staff.

##### EU as a leading partner

HEALICS will strengthen the EU role as a leading partner in the promotion of health for the critically ill and establishing a platform for research on complex illnesses, comorbidities and common causal pathways in distinct diseases.

## 2.2 Measures to maximise impact

### 2.2.1 Dissemination and exploitation of results

The coordinators will implement methods for fluent communication and reporting, building on experience from earlier consortia. Face-to-face meetings, Skype and telephone conferences, public seminars, newsletters, the consortium website and a proactive interaction with a stakeholder audience will be presented. The partners’ continued dissemination of their work in highest profile scientific journals and meetings, following EC’s Open Access principles, ensuring the widest accessibility to the project outcomes possible. Media contacts (press releases, interviews) and popular scientific publications and presentations will make HEALICS visible to a wide general public. Partner X and X (ESICM), …., will be involved in optimizing the ways to convey the HEALICS message to the target audience dissemination including the ESICM.

The key issue in dissemination is that the primary audience for results are the intensivist. And this is the same network of ICU which participate in providing the data, which makes dissemination part the two-way deal of this project. Their incentive for participation is in fact the results which they will receive in return.

HEALICS will adopt a multi-channel, multi-target strategy to establish efficient dissemination and exploitation of knowledge and results. The partners have an established network of research centres, regulatory bodies, patient federations and SMEs for sharing knowledge. A detailed dissemination and exploitation plan will be currently implemented to create a project head start; this will be the reference document and guideline for all partners with respect to the HEALICS dissemination and exploitation strategy. The dissemination plan will be further evolved as the project progresses and be regularly updated to meet the requirements for timely, reliable and comprehensive dissemination of results and knowledge. HEALICS intends to arrange joint thematic seminars, web-based seminars and workshops with partners from all partner sites, promoting exchange of results and knowledge between partner and across the WPs.

To underline the importance of dissemination we targeted a WPX on communication. This WP is dedicated to communication among participating centres for data acquisition and on communication with colleagues *(dissemination to the scientific community)* and patients *(dissemination to the non-specialist public)* through a well-established European network (ESICM). Moreover, new media will be exploited as considered important by patients, their network and care-givers. Furthermore, the open structure of HEALICS will allow for communication with researchers currently not involved in HEALICS.

The HEALICS website will also play an important role in the dissemination of novel discoveries in the diagnosis and prognosis of critically ill patients to a lay public. Content will be presented in a method suitable for the target audience, for example informative short videos about project results or interactive quizzes and promotional material. For this the consortium can make use of the services of communicators and journalists at both …… with a long track record as scientific writers in the field of Intensive Care. Through a highly appreciated webpage (……) the general public in the …. countries are informed about research progress in the field of Intensive Care. Press releases, both in English and the appropriate language are published by the university communicators and through them on …., worldwide business-to-business science news service (…. www.alphagalileo.org), supplying media with breaking research news. HEALICS will urge their partners to seek the interaction with the public and will involve the …. and its representatives where possible for widening its reach.

##### Dissemination to the scientific community

All partners will disseminate their research results to the widest extent possible. Already now the consortium partners have impressive track records in scientific publications in high profile journals, with a large readership and visibility, and they will continue to do so. Publications will indicate the source of the work (HEALICS). In parallel, results will be presented at scientific conferences, e.g. the annual ESICM and machine learning meetings (such as Datathon), and other relevant national and international meetings.

* Research published in peer-reviewed journals Open source papers of research conducted throughout this project will be published in peer-reviewed journals ensuring dissemination of the research results.
* Each of the Consortium members is also part of other networks such as academic networks, alliances and broad networks. Through these networks nearly all countries will be reached: Consortium members will share professional contacts to populate the mailing list for disseminating e.g. the HEALICS policy briefs and will disseminate key findings on relevant list servers. Research findings will be shared at academic and other conferences and workshops attended by members as well.

We will communicate and disseminate findings in strategic cooperation with stakeholders (healthcare providers, patients, their families, patients’ organizations, health care professionals, researchers, policy makers), and small and medium-sized enterprises (SMEs), so that the key variables, novel personalised risk scores and diagnostic strategies can be made readily available.

##### Dissemination to the non-specialist public/popular publications

Dissemination will be laid out to maximize HEALICS’ impact on the non-specialist audiences. A key criterion in all dissemination activities targeted to the non-scientific public will be the translation of HEALICS’ complex scientific work and output into comprehensible messages adequately applicable for the respective target group using a variety of channels. We aim at both, the dissemination of novel discoveries in a better diagnosis of underlying mechanisms and possible implications for prognosis and improved treatment, and at increasing the general understanding of the indication behind HEALICS research and its international, collaborative nature.

Policy briefs and journal or newspaper publications will be used for dispersing information directly and flagging links to other sources of communication and dissemination (journal publications, case studies illustrating best practices and project outputs such as guidelines and tools). Communication team will support dissemination of journal publications through press releases, mailing lists, social media and the website.

Insert table with timing of WP, deliverables and milestones

### 2.2.2 Communication activities

##### Stakeholder meetings, advisory boards and consultations

Translating research findings into recommended policy is a long process which requires regular and repeated contact with policy makers. Consortium members of this project have connections with the Ministries of Health and other relevant ministries (e.g. Ministry of Planning), societies of Intensive Care Medicine (ESICM and in each participating country) ……. The positions and strategies of these organisations ensure integration of the project into the health systems, as through societies implementation in protocols and guidelines is endorsed. The project will also share results with …. Furthermore, the composition of the HEALICS consortium and the integration in European and National Boards ensure that research gets directed towards the needs of all stakeholders and that its results will get used.

The development and adaptation of guidelines and tools in line with international best practice will be used within participating countries and also made available for use in other countries. We will connect with the ESICM and other societies to ensure that these tools are strong, relevant and useful. Education materials will be made available on several platforms.

Include a business plan where relevant.

* Management structure
  + The HEALICS management structure foresees in clear lines of communication between all consortium members and with all stakeholders.
* Websites
  + HEALICS will develop a website for sharing information on the project.
* Social media
  + The project will develop comprehensive social media packages, including graphics and infographics. Social media pages will be created to share information, and social media graphics and infographics will be used to share any existing information. Through the combined networks of the Consortium, the platforms would reach nearly xxx users.
* Public awareness
  + HEALICS will raise awareness using a toolkit including flyers, video, posters, banners and infographics.
* Project updates
  + All involved parties will be regularly updated by mailings, reports, and policy briefs.

# 3. Implementation

## 3.1 Work plan — Work packages, deliverables

To reach our goals HEALICS is organised in six work packages (WP1-6). The combined efforts lead to the deliverables on the four domains of diagnostic, short-term-outcome, long-term outcome, and research infrastructure. While the research infrastructure deliverable largely follows from WP2, all other domain deliverables of diagnostic, short-term and long-term outcome require intensive and close collaboration between clinicians and the science experts represented in all the WPs.

##### Work package committees

HEALICS involves 6 WPs. One member of each team contributing to a particular WP is member of the WP committee. One member of this group of teams is assigned as the work package leader. The WP committee shall assure that the tasks assigned to a WP are efficiently processed and deliverables and milestones are provided in time. The WP leader shall regularly communicate with the Steering committee (SC) as well as the Project coordinator (PC) regarding all duties assigned to a WP.

##### Timing of the HEALICS project

The HEALICS project is planned for a period of five years. The project will start soon after signing the Grant Agreement. For convenience, the start of the project is now set on January 1st, 2020 but will start earlier if appropriate. The systematic reviews and retrospective study of existing cohorts are tentatively set on 18 months in total. The prospective study will be estimated to take two years. The last 18 months are planned for analyses and exploitation of deliverables. The timing of the project is shown in the Gantt chart below in table x.

Table x. Gantt chart of HEALICS project with details on the WPs

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 20 |  |  |  | 21 |  |  |  | 22 |  |  |  | 23 |  |  |  | 24 |  |  |  |
| Quarter | 1st | 2nd | 3rd | 4th | 1st | 2nd | 3rd | 4th | 1st | 2nd | 3rd | 4th | 1st | 2nd | 3rd | 4th | 1st | 2nd | 3rd | 4th |
| WP1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| WP2 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| WP3 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| WP4 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| WP5 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| WP6 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

INSERT HERE: timing of the different WPs and their components (Gantt chart or similar)

INSERT: list of WPs

Table 3.1a: list of work packages

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| WP no | WP title | Lead participant no | Lead participant short name | Person-months | Start month | End month |
| 1 | Overall project management |  | UMCG |  | 1 | 60 |
| 2 | Data management |  | AU |  | 1 | 60 |
| 3 | Patient characterisation |  | LUH |  | 1 | 60 |
| 4 | Machine learning |  | Bielefeld |  | 1 | 60 |
| 5 | Outcome evaluation |  | IER |  | 1 | 60 |
| 6 | Dissemination, exploitation and communication |  | CPH |  | 1 | 60 |
| total |  |  |  | ?? |  |  |

Table 3.1b: Description of each work package

|  |  |  |
| --- | --- | --- |
| WP no | WP title | Description |
| 1 | Overall project management |  |
| 2 | Data management |  |
| 3 | Patient characterisation |  |
| 4 | Machine learning |  |
| 5 | Outcome evaluation |  |
| 6 | Dissemination, exploitation and communication |  |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Work package number** | 01 | | **Lead beneficiary** | | | UMCG, NL | | | | |
| **Work package title** | Project management | | | | | | | | | |
| **Participant number** | 1 | Fill in | | Fill in | Fill in | | Fill in | Fill in | Fill in | Fill in |
| **Short name of participant** | UMCG |  | |  |  | |  |  |  |  |
| **Person/months per participants** | Fill in | Fill in | | Fill in | Fill in | | Fill in | Fill in | Fill in | Fill in |
| **Start month** | 0 | | | | End month | | 60 | | | |

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| **Objectives**  This WP work will ensure the overall technical, administrative, financial and legal management of the consortium and project activities, as well as appropriate communication with the EC officer. In particular, it will ensure achievement of the objectives of the project with efficient management and financial control of the project by:   * Establishing and coordinating a well-functioning research consortium of scientists from different disciplines and locations; * Managing the consortium and represent it in all external relations; * Making sure results from the different WPs and from the different disciplines and commercial partners are integrated; * Preparing official reports of the project. |

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| **Description of work**  The management and organisation of all activities by the consortium will be led by the project coordinator (UMCG). Details of the management structure and its members are outlined in *Section 3.2.1* and figure x.  **Task 1.1: Management plan, administrative and financial coordination, and communication with the EC**  **Subtasks 1.1.1:** …  **Subtask 1.1.2:** …  **Subtask 1.1.3:** …  **Approach:** The coordinator will be responsible for achieving the objectives of the project in line with the grant agreement and project proposal. Together with the project manager, the coordinator will liaise with the EC on behalf of the HEALICS project consortium, ensuring that reports are transferred, and that the EC is kept informed of any major issues or modifications to the work plan. The coordinator will be supported by a Project Support Team to deliver effective project management. The project manager will take care of the day-to-day management of the project, will provide an administrative link with the EC officer and the leads at partner institutions, will oversee reports throughout the project (administrative, legal, and financial) and will drive effective and efficient project implementation.  **Task 1.2: Monitoring of the work plan**  **Subtasks 1.2.1:** …  **Subtask 1.2.2:** …  **Subtask 1.2.3:** …  **Approach:** The Supervisory Board will set the annual scientific objectives, policy and strategic orientations of the project in accordance with the project program, the consortium agreement and the rules of the grant agreement, thereby coordinating workflow. The project manager and coordinator will ensure compliance of the project with the technical annex and, if necessary, propose modifications. The project manager will also prepare progress reports.  **Task 1.3: Communication among the partners to exchange internal information and handle risk and contingencies**  **Subtasks 1.3.1:** …  **Subtask 1.3.2:** …  **Subtask 1.3.3:** …  **Approach:** HEALICS is a particularly large consortium. The project manager and coordinator will organise a dedicated meeting schedule to facilitate information exchange and risk identification among partners. Monthly video conferences among the work package leaders and co-leaders will serve as the main forum for formal discussions of progress and for identifying and resolving issues. However, *ad hoc* meetings will be organised to address unexpected events whenever needed. The coordinator and project manager will share responsibility for organising annual consortium meetings.  **Task 1.4: Coordination of data communication outside the consortium**  **Subtasks 1.4.1:** …  **Subtask 1.4.2:** …  **Subtask 1.4.3:** …  **Approach:** We will ensure that data are accessible for further research by publishing results in open access journals. If questions cannot be answered using these databases after the study period, researchers outside of the HEALICS consortium will be granted access to project-specific data upon request. The Supervisory Board will evaluate if the proposed research question falls within the scope of the informed consent provided by participants. |

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| **Deliverables** (brief description and month of delivery)  **D1.1** Consortium agreement (M1)  **D1.2** Data management plan (M3)  **D1.3** Mid-term report (M26)  **D1.4** Final progress and financial reports to the EC (M49) |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Del. no.** | **Deliverable name** | **WP no** | **Short name of lead participant** | **Type1** | **Dissemination level2** | **Start Date** | **Delivery date 3** |
| D1.1 | Consortium agreement | WP1 | UMCG () | R | PU | M0 | M1 |
| D1.2 | Data management plan | WP1 | UMCG () | R+OTHER | PU | M0 | M3 |
| D1.3 | Mid-term report | WP1 | UMCG () | OTHER | CO | M0 | M26 |
| D1.4 | Final progress and financial reports to the EC | WP1 | UMCG () |  |  | M0 | M49 |

**Critical risks for implementation**

|  |  |  |
| --- | --- | --- |
| **Description of risk (indicate level of likelihood: Low/Medium/High)** | **Work package(s) involved** | **Proposed risk-mitigation measures** |
| Fill in. *(level of likelihood: low)* | WP1, WP2, WP6 | Fill in |
| Fill in. *(level of likelihood: low)* | WP1, WP2, WP6 | Fill in |
| Fill in. *(level of likelihood: low)* | WP2, WP6 | Fill in |
| Fill in. *(level of likelihood: low)* | WP2 | Fill in |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Work package number** | 2 | | **Lead beneficiary** | | | AU, Denmark | | | | |
| **Work package title** | Data management | | | | | | | | | |
| **Participant number** | Fill in | Fill in | | Fill in | Fill in | | Fill in | Fill in | Fill in | Fill in |
| **Short name of participant** | UMCG |  | |  |  | |  |  |  |  |
| **Person/months per participants** | Fill in | Fill in | | Fill in | Fill in | | Fill in | Fill in | Fill in | Fill in |
| **Start month** | 0 | | | | **End month** | | 60 | | | |

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| **Objectives**  This WP will provide an understanding of multimorbidity in existing ICU cohorts through the development of a common data model and data infrastructure for the HEALICS project in close collaboration with the other WPs. The specific objectives are:   * To provide detailed information of each participating cohort (data located in Denmark, Finland, the Netherlands) with respect to the population included, the data available, the local data model, the mechanism generating the data, and the ability to address specific re-use issues (such as ability to contact the patients or inclusion of patients in clinical trials). * To develop and apply a common data model with scripts for data validation, description of data, data visualization and data analyses for two studies focusing on the characterization of heterogeneity of ICU patients within and between cohorts. These scripts allow similar data handling and analyses to be performed at multiple sites and results (aggregated data) to be merged when individual-level data cannot be transferred to the data repository for legally or technically reasons. * To establish a common HEALICS data platform including a data repository for aggregated and anonymized individual-level data for the existing data and the prospective cohort study. |

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| **Description of work**  The WP2 team will build upon experience from previous EU funded projects and existing data sources to conduct studies describing the heterogeneity of ICU patients through development of a uniform, common data model for both existing data and prospective studies. This common data model can be applied locally within each partner of the distributed data network and will provide uniform data management, validation, visualization and aggregation of results. Two studies describing the prevalence and prognosis of multimorbidity will serve as use cases to test the model. Aggregated results can be uploaded and merged within the HEALICS common data platform, which also allows uploading of raw data and cleaned individual-level data after appropriate deidentification. The data platform and sharing process is illustrated in the figure x.  **Task 2.1: Profiling of existing cohorts (AU)**  **Subtasks 2.1.1:** Obtain information about existing cohorts located in Denmark, Finland, and the Netherlands.  **Subtasks 2.1.2:** Examine the ability to enrich data by linking data to local/national registries and biobanks and to re-use data to contact the patients or to include patients in clinical trials.  **Subtask 2.1.3:** Report the description of the HEALICS cohort of existing data.  **Approach:** A survey will be used to secure uniform gathering of information from the relevant HEALICS consortium partners with existing cohorts in Denmark, Finland, and the Netherlands. Information will include study period, context (type of ICU), the detail in the data available, the local data model, the coding scheme, the availability of free text records, and internal data quality standards and verification. The ability to re-use data will be examined. Each partner will be asked to provide a full description of the data.  **Task 2.2: Development and application of common data model (AU)**  **Subtasks 2.2.1:** To develop a common data model to be used throughout the HEALICS Platform architecture to represent queries and result sets for aggregate and patient-level data based on core variables identified in task 2.1.  **Subtasks 2.2.2:** Development of scripts for local data cleaning, mapping, validation, as well as data description, visualization, and analysis.  **Subtasks 2.2.3:** Implementation of the scripts in local data to generate aggregated data, which are merged at the HEALICS common data platform (Task 2.3).  **Subtasks 2.2.4:** Test of the common data model by use cases including two studies examining the heterogeneity of prevalence and prognosis of multimorbidity.  **Approach:** Based on core variables identified in task 2.1, a common data model will be developed and described to form a distributed data network. Scripts will be developed in existing software or in an open-source language for implementation within each site and tested by two use cases with the aim to describe the heterogeneity of multimorbidity within and between included cohorts.  **Task 2.3: Establishment of common HEALICS data platform (Enversion)**  **Subtasks 2.3.1:** Development of the HEALICS common data platform providing the technical infrastructure for secure, cross-project data exchange across up to 30 ICUs in 6 countries.  **Subtask 2.3.2:** Development and implementation of scripts for deidentification of individual-level data.  **Subtask 2.3.3:** To define the different types of users of the HEALICS Platform, the levels of access for each type of user, and the procedures and safeguards to handle permissions.  **Subtask 2.3.4:** To create a development environment for the Platform ecosystem, enabling the creation of software such as the clinical information browser, the evolving biomedical knowledge bases and the Private Remote Research Environments.  **Approach:** The HEALICS common data platform will allow all HEALICS consortium partners to share and work on aggregated and/or anonymized individual-level data. The platform will be developed in accordance with the Finable, Accessible, Interoperable, Reusable (FAIR) data principal and in accordance with the General Data Protection Regulation. The platform will be able to receive structured data from electronic medical record systems, such as the EPIC. |

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| **Deliverables** (brief description and month of delivery)  **D2.1** Profiling of existing cohorts(M12)  **D2.2** Common data model (M24)  **D2.2.4** Final application in use cases (M60)  **D2.3** HEALICS common data platform (M36) |

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Del. no.** | **Deliverable name** | **WP no.** | **Short name of lead participant** | **Type1** | **Dissemination level2** | **Start Date** | **Delivery date 3** |
| D2.1 | Profiling of existing cohorts | WP2 | AU (CFC) | R | PU | M0 | M12 |
| D2.2 | Common data model | WP2 | AU (LP) | R+OTHER | PU | M0 | M24 |
| D2.3 | HEALICS common data platform | WP2 | Enversion (JHB) | OTHER | CO | M0 | M36 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Milestone number** | **Milestone name** | **Related work package(s)** | **Estimated date** | **Means of Verification** |
| M2.1.1 | Delivery of information from existing cohorts | WP1, WP3, WP4 | M6 | Information delivered |
| M2.2.2 | Common data model with scripts | WP3, WP5 | M20 | Data analyses possible |
| M2.3.3 | Common data platform established and accessible | WP1, WP3, WP4, WP5, WP6 | M24 | Data available for other WPs |

**Critical risks for implementation**

|  |  |  |
| --- | --- | --- |
| **Description of risk (indicate level of likelihood: Low/Medium/High)** | **Work package(s) involved** | **Proposed risk-mitigation measures** |
| Data from existing cohorts not available for the common data model *(level of likelihood: low)* | WP1, WP2, WP6 | Information to participants about the study including the fact that analyses will be performed locally without data leaving the centre/country. |
| Lack of local data management skills to prepare the data and run scripts locally. *(level of likelihood: low)* | WP1, WP2, WP6 | Provide a thorough description of the task to participating centres. Use of open-access software. |
| Local data from electronic medical record systems not available for the prospective study. *(level of likelihood: medium)* | WP2, WP6 | Collaboration with partners (Cambridge) with experience in using specific electronic health record systems for research, e.g. the EPIC. |
| Individual-level data cannot be delivered from sites due to legal issues. *(level of likelihood: high)* | WP2 | The common data model can be applied locally by the developed scripts and results can be merged without need for individual-level data. |

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| **Work package number** | 3 | | **Lead beneficiary** | | | LUH, Sweden | | | | |
|  |  | | **Deputy leads** | | | UH, Fin; UMCG, NL | | | | |
| **Work package title** | Patient characterisation | | | | | | | | | |
| **Participant number** | Fill in | Fill in | | Fill in | Fill in | | Fill in | Fill in | Fill in | Fill in |
| **Short name of participant** | LUH | UH | | UMCG |  | |  |  |  |  |
| **Person/months per participants** | 60 | 60 | | 60 | Fill in | | Fill in | Fill in | Fill in | Fill in |
| **Start month** | 0 | | | | **End month** | | 60 | | | |

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| **Objectives**  This WP work will identify key variables through analyses of existing data and by the new developed prospective cohort study. The specific objectives are:   * To scrutinize genetic markers and genetic risk scores based on genome-wide association studies (GWAS) combined with new epigenetic and metabolomic markers for development of 1-3 test panels in observational cohort data of critically ill patients with different combinations of co-morbidities for:   + differentiation of more homogeneous sub-phenotypes in common clinical syndromes (SIRS, sepsis, AKI, ARDS)   + prediction of treatment effects in the above-mentioned clinical populations to improve patient-related outcomes with a precision medicine approach * To test novel biomarkers in observational cohort data of critically ill patients with different combinations of co-morbidities to:   + illuminate endothelial damage/leak as a causal mechanism of organ dysfunction in experimental models   + detect time-dependent treatment effects (in combination with abovementioned genetic, epigenetic and metabolomics markers)   + detect the development of organ dysfunction in clinical settings * To create and validate in close collaboration with WP4 (machine learning), the:   + diagnostic ability of a combined panel of clinical variables, genetic, epigenetic, metabolomic and biomarker data in a large observational cohort of critically ill patients   + prognostic ability of a combined panel of clinical variables, genetic, epigenetic, metabolomic and biomarker data on short- and long-term outcomes including health-related quality of life and mild cognitive dysfunction in a large observational cohort of critically ill patients |

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| **Description of work**  The main goal of HEALICS and WP3 is to unravel heterogeneity by identifying common genotypic, epigenetic, biomarker and clinical characteristics that may be amenable to therapeutic targets and explore variables that may contribute to better diagnosis and prognosis of clusters.  We will validate the predictive power of a comprehensive set of variables including clinical, genetic, epigenetic, metabolomic, and biomarker data that may account for differential treatment effects.  This WP will also investigate suggested pathophysiologic mechanisms (such as endothelial damage/leakage) that may be amenable to therapeutic interventions and explore new mechanisms that may contribute to heterogeneity in treatment effects.  **Task 3.1. (Epi)genetics and metabolomics (UMCG, UH, contribution LUH)**  To coordinate and perform the uniform laboratory and statistical analysis of genetics, epigenetics and metabolomics from samples obtained from collaborating sites upon admission.  This task focuses on the coordination of international collection of samples and conducting laboratory and statistical analysis of genetic, epigenetic and metabolomic in existing data and new prospective cohorts.  **Subtasks 3.1.1:** To coordinate transport and perform genetic and epigenetic laboratory analyses.  **Subtasks 3.1.2:** To perform laboratory analysis of metabolomics.  **Subtasks 3.1.3:** To perform uniform quality control analyses across cohorts.  **Subtasks 3.1.4:** To perform genome-wide genetic and epigenetic (meta) analysis of cohort data.  **Approach:** Epigenetic and genetic markers will be measured using the latest generation of arrays covering the whole genome. For epigenetics, we will use the EPIC array from Illumina interrogating 850,000 methylation markers (CpG sites), and for genetics we will use Illumina’s global screening array including ~700,000 genetic markers. For metabolomics we will use an established panel of >60 metabolites.  We will perform a GWAS meta-analysis in the total HEALICS sample size of at least 20,000 individuals. Assuming an outcome rate of 25% (e.g., mortality, AKI, etc.) this will yield a detectable effect size of odds ratios between 1.16 and 1.38 per risk allele for minor allele frequencies between 5% and 50% with 80% power and a type 1 error rate of 5x10-8 (generally accepted GWAS significance level). Additionally, polygenic risk scores for a range of common complex diseases will be calculated based on the most recent GWAS evidence (Khera et al., 2018).  We will initially perform a nested matched case-control epigenome-wide association study (EWAS) for mortality in the existing FINNAKI cohort with replication and subsequent meta-analysis across multiple cohorts. A total sample size of 1000/1500 cases and 1000/15000 controls at 80% power and a type 1 error rate of 5x10-7 (Bonferroni corrected EWAS significance level for the 850K chip) will give us detectable effect sizes of methylation differences between 2% and 6%. Additionally, we will explore predictive value of different established methylation scores of biological age (Horvath et al., 2018).  Metabolomics…Please provide the most suitable information.  **Task 3.2. Biomarkers (LUH, UH and contribution of UMCG)**  To coordinate the selection, uniform measurement and analysis of biomarkers across the collaborating sites upon admission and during ICU stay.  **Subtasks 3.2.1:** To perform systematic reviews of biomarkers related to sub-phenotypes of common clinical syndromes, different treatment effect and outcomes.  **Subtasks 3.2.2:** To identify and select additional potentially important new biomarkers.  **Subtasks 3.2.3:** To explore and validate biomarkers in existing and newly recruited international prospective cohort studies of the HEALICS consortium.  **Approach:** We will initiate a list of all potentially relevant biomarkers. This will include a panel of 15 to 20 of both established and novel promising biomarkers, e.g. hsTnT, NT-pro-BNP, MR-proADM, bioADM, CT-pro-ET1, Copeptin, FABP, NGR-1, GDF-15.  In close collaboration with WP2 we explore and validate these variables in data of existing cohorts (table x). Public data repositories will also be used. We will reduce the numbers of currently collected variables by excluding the variables which are not contributing information (with WP4).  **Task 3.3. Clinical variables and outcome models (UH, UMCG)**  To coordinate the selection and uniform measurement of clinical variables across the collaborating sites upon admission and during ICU stay. Combine these clinical variables with (epi)genetic, metabolomics and biomarker data for delivery to WP4, to create and validate diagnostic and prognostic models.  **Subtasks 3.3.1:** To perform a systematic review of clinically available data related to subphenotypes of common clinical syndromes, different treatment effects and outcomes.  **Subtasks 3.3.2:** To explore and validate clinical variables in our existing international cohorts.  **Subtasks 3.3.3:** To define a common set of clinical variables for inclusion in the prospective cohort study.  **Subtasks 3.3.4:** To validate relevance of clinical variables in the prospective cohort study.  **Subtasks 3.3.5:** To deliver a dataset consisting of high-density complex clinical data including continuously measured hemodynamic and pulmonary function, epigenetic, genetic, metabolomic, biomarker and imaging data as input for diagnostic and prognostic machine learning modelling (WP4).  **Approach:** We are conducting a systematic review on all prognostic models used for critically ill patients. This will deliver a list of clinical variables with additional value for prognosis. These clinical variables can be tested using machine learning (in collaboration with WP4) in existing cohorts of ICU patients. Next to the widely known and accepted prognostic variables there may be other variables with potentially additional value also to be tested. Initial testing in retrospective cohorts will also reduce the number of variables currently used in daily practice.  The variables which seem relevant based on the result from subtask 3.3.1 and 3.3.2 will be externally validated in the new prospective international cohort study. We will work in close collaboration with partners from WP4 in delivering input variables and interpreting results of diagnostic and prognostic machine learning models. |

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| **Deliverables** (brief description and month of delivery)  **D3.1** Large-scale genetic (n=20,0000) and epigenetic (n=3,000) database in critically ill patients (Mx)  **D3.2** A developed and validated set of biomarkers with additional value in diagnostic models and prediction of treatment effect (Mx)  **D3.3** A new validated dynamic prognostic model comprising clinical variables, (epi)genetic, metabolomic and biomarker data (Mx)  **D3.4** Set of high-density complex clinical data including continuously measured hemodynamic and pulmonary function, epigenetic, genetic, metabolomic, biomarker and imaging data for exploration within WP4 (Mx) |

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| **Del. no.** | **Deliverable name** | **WP no.** | **Short name of lead participant** | **Type1** | **Dissemination level2** | **Start Date** | **Delivery date 3** |
| D3.1 | Large scale database | WP3 | UH (VP) | R | PU | M0 | Mx |
| D3.2 | Biomarkers | WP3 | LUH (MC) | R+OTHER | PU | M0 | Mx |
| D3.3 | Prognostication | WP3 | UH (VP) | OTHER | CO | M0 | Mx |
| D3.4 | High-complex data | WP3 | UMCG (HS) |  |  | Mx | Mx |

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| **Milestone number** | **Milestone name** | **Related work package(s)** | **Estimated date** | **Means of Verification** |
| M3.1 | Large-scale genetic and epigenetic database | WP1, WP3, WP4 | M36 | Information delivered |
| M3.2 | Validated diagnostic (more homogeneous patient groups), predictive (treatment) and prognostic (patient-related outcomes) hypotheses for further testing in RCTs | WP3, WP5 | Mx | Data analyses possible |
| M3.3 | The new dynamic and validated prognostic models | WP1, WP3, WP4, WP5, WP6 | M60 | Data available for other WPs |

**Critical risks for implementation**

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| **Description of risk (indicate level of likelihood: Low/Medium/High)** | **Work package(s) involved** | **Proposed risk-mitigation measures** |
| Data from existing cohorts not available for the common data model *(level of likelihood: low)* | WP1, WP2, WP6 | Fill in |
| Lack of local data management skills to prepare the data and run scripts locally. *(level of likelihood: low)* | WP1, WP2, WP6 | Fill in |
| Local data from electronic medical record systems not available for the prospective study. *(level of likelihood: low)* | WP2, WP6 | Fill in |
| Individual-level data cannot be delivered from sites due to legal issues. *(level of likelihood: low)* | WP2 | Fill in |

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| **Work package number** | 4 | | **Lead beneficiary** | | RUG, Bernoulli Institute | | | | |
| **Work package title** | Machine Learning | | | | | | | | |
| **Participant number** | Fill in | Fill in | | Fill in | Fill in | Fill in | 8 | Fill in | Fill in |
| **Short name of participant** | MB  RUG | BH  UNIBI | | GB  Rutgers | PL  Liverpool | CS  Cyprus | TGHO  (Target) | Fill in | Fill in |
| **Person months per participants** | 108=  4yr.PhD  +5yr.Postd. |  | | 5  (visits) | 12+PhD student | Fill in | 48 | Fill in | Fill in |
| **Start month** | 1 | | | | **End month** | 60 | | | |

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| **Objectives**  This WP work will develop and apply machine learning algorithms suitable for the analysis of existing and new, prospectively-obtained data. The specific objectives are:   * The development and implementation of an integrated homogeneous treatment of electronic health record systems, bedside monitoring, imaging, omics-, genetic, epigenetic and other ICU data, such that the quality demands of data analytics algorithms are met (tasks 4.1) * The design and implementation of tools which identify relevant characteristics and biomarkers able to discriminate subgroups of individuals within the ICU population, and which will help uncover causal relations and develop differential, personalized treatment strategies (tasks 4.2 and 4.3) * The development of early warning and long-term decision support systems based on the data driven predictive models, which allow for the efficient visualization and analysis of patient-specific multi-modal, multi-source clinical ICU data (tasks 4.3 and 4.4) |

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| **Description of work**  his WP is central to the project, taking data from WP2 and designing predictive models for integration into clinical decision support for use in WP3, whose outcomes will be evaluated in WP5. The tasks start with data integration across measurement modalities as well as domain adaptation between clinical centres, to provide a strong evidence base for knowledge extraction and biomarker discovery, with specific reference to the identified use cases. This will enable predictive models to be made and initially validated with retrospective data e.g. (…) . The models will be designed so that, at any point in the time during (and after?) ICU stay, a) both the short-term impact of interventions and the long-term prognosis can be predicted; b) as time progresses, the short-term predictions based on causal models will be validated and used as feedback for learning; and c) predictions will be adjusted for the effect of co-morbidities in individual patients. The resulting models will be integrated into decision support systems aligned with the clinical protocols for patient management, which will use visualisation and model interpretation to verify consistency of the models with clinical expertise.  **Task 4.1 Data: integration and analysis of heterogeneous, multi-modal, multicentre data**  **Subtasks 4.1.1:** To … data management and communication between WP2 and WP4 (Cyprus, Target).  **Subtasks 4.1.2:** To … pre-processing of incomplete and noisy information, missing data and privileged information (Cyprus, RUG, Bielefeld).  **Subtasks 4.1.3:** To … learning techniques for domain adaptation of multicentre data sets with diverging data availability and target distributions (RUG, Bielefeld, Liverpool, Target).  **Subtasks 4.1.4:** To … techniques for representing, aligning and fusing multi-modal datasets into a homogeneous integrated format that is suitable input for both clustering techniques and decision support systems (RUG, Target).  **Approach:** ……  **Task 4.2 Biomarkers: features for classification, clustering and causality analysis**  **Subtasks 4.2.1:** To communicate between WP3 and WP4 to identify state of the art therapeutic and prognostic models and biomarkers from existing databases to be used in novel decision support systems (Rutgers, Liverpool).  **Subtasks 4.2.2:** identification of new key markers for the detection and discrimination of patient subgroups/clusters by means of feature relevance learning, saliency maps, and interpretable models (RUG, Bielefeld, Rutgers).  **Subtasks 4.2.3:** To … causal analysis and counterfactual models derived with Bayesian networks for disentangling heterogeneous causes of co-morbidity and complex risk factor (Liverpool, Bielefeld).  **Approach:** ……  **Task 4.3 Early warning systems predicting short- term patient progression and developing interfaces to ICU personnel**  **Subtasks 4.3.1:** To … development, implementation and validation of transparent, predictive models for short term detection of deterioration (Liverpool, Cyprus, Bielefeld, RUG, Target).  **Subtasks 4.3.2:** To … dimension reduction and visualization of real time data, aiming at model robustness: visualisation in latent spaces/model interpretation/ deep learning (Bielefeld, RUG, Target, Cyprus).  **Subtasks 4.3.3:** To … identification of dynamic markers, which characterize individual short-term patient progression and can trigger an early warning (Bielefeld, RUG).  **Approach:** ……  **Task 4.4 Long-term patient prognosis: decision support systems to inform treatment decisions**  **Subtasks 4.4.1:** To … development, implementation and validation of transparent, predictive models for medium/long term QoL prognosis in close collaboration with WP5 (Liverpool, Cyprus, Bielefeld, RUG, Target).  **Subtasks 4.4.2:** To … development and implementation of real-time patient cluster identification system based on key biomarkers, enabling ICU personnel to compare current patient to previous cases and treatment strategies (RUG, Bielefeld).  **Subtasks 4.4.3:** To … design of an explainable AI decision making module, towards optimal patient management and treatment planning. The explainable AI module will be based on machine learning and deep learning (including decision trees and recurrent neural networks (RNN)) and other expert knowledge analysed (Cyprus, Liverpool).  **Subtasks 4.4.4:** To … hypothesis identification for prospective cohort study, as proof-of-concept ([...]).  **Approach:** …… |

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| **Deliverables** (brief description and month of delivery)  **D4.1** Pre-processed data sets in standard, uniform formats for sharing and modelling (M6?)  **D4.2** Set of novel biomarkers for predicting prognosis of multimorbid ICU patients (M12?)  **D4.3** Short-term prediction tools of disease progression / patient status (M24?)  **D4.4** Long-term prognostic models with respect to quality of life (QoL) (M36?)  **D4.5** Decision support system for three use cases: to be completed (please provide input) |

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| **Del. no.** | **Deliverable name** | **WP no.** | **Short name of lead participant** | **Type1** | **Dissemination level2** | **Start Date** | **Delivery date 3** |
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| **Milestone number** | **Milestone name** | **Related work package(s)** | **Estimated date** | **Means of Verification** |
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|  | Fill in | Fill in | Fill in | Fill in |
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**Critical risks for implementation**

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| **Description of risk (indicate level of likelihood: Low/Medium/High)** | **Work package(s) involved** | **Proposed risk-mitigation measures** |
| Fill in *(level of likelihood: low)* | Fill in | Fill in |
| Fill in *(level of likelihood: low)* | Fill in | Fill in |
| Fill in *(level of likelihood: low)* | Fill in | Fill in |
| Fill in *(level of likelihood: low)* | Fill in | Fill in |

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| **Work package number** | 5 | | **Lead beneficiary** | | | IER | | | | |
| **Work package title** | Outcome evaluation | | | | | | | | | |
| **Participant number** | Fill in | Fill in | | Fill in | Fill in | | Fill in | Fill in | Fill in | Fill in |
| **Short name of participant** | IER | HRAH | | DIC | .. | |  |  |  |  |
| **Person/months per participants** | 70 | 2 | | 2 | Fill in | | Fill in | Fill in | Fill in | Fill in |
| **Start month** | 0 | | | | End month | | 60 | | | |

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| **Objectives**  To unravel the heterogeneity of ICU patients and identify variables with prognostic value, relevant and accurate (long-term) outcome measures are required. The specific objectives are:   * To create a user-friendly, easily administered mobile tool for online collection of the health outcomes. * To design and apply a patient-centred and preference-based health outcome measure for the overall health condition of ICU patients based on a modern measurement framework. * To measure the short- and long-term outcomes of (non)-mental disorders of ICU patients. * To measure/estimate the overall costs of treatment of ICU patients using standard costing methodology. * To provide relevant data input into WP2 in order to optimize the clinical course of patients so as to maximise outcomes, minimise costs, and increase cost-effectiveness. |

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| **Description of work**  The goal of the WP5 is to measure health outcomes in terms of health status and quality-of-life, and to estimate costs of the treatments for ICU patients. The health outcomes will be defined in a comprehensive and generalisable way and will be collected via innovative, easy-to-use applications which can be applied throughout Europe.  **Task 5.1. Definition of health outcomes (IER, HRAR, DIC)**  **Subtasks 5.1.1:** To … (IER, HRAR, DIC).  **Subtasks 5.1.2:** To … (…).  **Subtasks 5.1.3:** To … (…).  **Subtasks 5.1.4:** To … (…).  **Approach:** To measure the utility of the health condition of ICU patients, the EQ-5D-5L will be used as a validated and standardized instrument for measuring generic health status (five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Using EQ-5D, preference weights for health conditions are estimated, and can be translated into health gains. Other outcome measures will be delirium, cognitive deficits, and psychological outcomes. The health outcomes of the ICU patients will not only be collected during ICU stay, but also at multiple time points after discharge.  **Task 5.2. Creation of a modern, user-friendly software tool for online collection of the health outcomes (IER)**  **Subtasks 5.2.1:** To … (IER, HRAR, DIC).  **Subtasks 5.2.2:** To … (…).  **Subtasks 5.2.3:** To … (…).  **Subtasks 5.2.4:** To … (…).  **Approach:** In order to assure their participation, a user-friendly online software tool will be created that will include the outcome measures as defined in Task 5.1. The tool will be easily accessible, not time-consuming, attractive, user-friendly, and compliant to current software and safety standards. For this a recently developed mobile app will be used: HealthSnApp©. This as a ‘smart’ data collection technology in combination with a central server ([www.healthsnapp.info](http://www.healthsnapp.info)). This technology platform will be extended to include all other health outcomes used in this study (See Task 5.3, 5.4, 5.5). ICU patients will be encouraged to response on the health outcomes as often as possible, e.g. at every change in their health condition. ICU patients may be less competent to assess their own health condition or to complete the tasks on a smartphone or computer. Therefore, assessment by proxies (e.g., caregivers, spouse, research nurse) is considered.  **Task 5.3. To develop and apply a patient-centred, preference-based tool to measure the health-related quality-of-life of ICU patients (IER)**  **Subtasks 5.3.1:** To … (IER, HRAR, DIC).  **Subtasks 5.3.2:** To … (…).  **Subtasks 5.3.3:** To … (…).  **Subtasks 5.3.4:** To … (…).  **Approach:** To develop a robust health-outcome instrument especially for ICU patients, careful selection of health items is paramount. For this, the existing HealthFan methodology will be used, in which ICU patients (or proxies) will provide the health-outcome items they perceive as most important (step 1). The selected set of items will then constitute the content of the actual patient-reported ICU outcome measure (PROM). The ICU PROM will differ from conventional PROMs because it is patient-centred (item selection and assessment done by patients) and preference-based (all items and their levels are weighted based on the information obtained from patients or proxies). Responses will be collected each month during the first year after discharge from ICU.  **Task 5.4. To measure the short- and long-term outcomes of (non)-mental disorders of ICU patients (HRAH, DIC)**  **Subtasks 5.4.1:** To … (IER, HRAR, DIC).  **Subtasks 5.4.2:** To … (…).  **Subtasks 5.4.3:** To … (…).  **Subtasks 5.4.4:** To … (…).  **Approach:** Patient-centred outcomes including delirium, cognitive deficit after critical illness and psychological outcomes in the short and longer term will be studied. Validated instruments will be used to measure at discharge from ICU and during a 1-year period follow-up. For delirium the CAM-ICU (Confusion Assessment Method ICU: 4 items) will be used, for identifying cognitive impairment the MoCA (Montreal Cognitive Assessment: 30 items, cut-point score ≤26). Acute stress response and post-traumatic stress disorder symptoms will be assessed with the PCL-5 (20 items, cut-point score ≥33). For assessing anxiety and depression the HADS (Hospital Anxiety and Depression Scale: 14 items) will be used.  **Task 5.5. Cost estimation/simulation (IER)**  **Subtasks 5.5.1:** To … (IER, HRAR, DIC).  **Subtasks 5.5.2:** To … (…).  **Subtasks 5.5.3:** To … (…).  **Subtasks 5.5.4:** To … (…).  **Approach:** As the collection of the data on clinical procedures and outcomes will be automated for each event during the patients’ clinical course, the costs of these events can be simulated/estimated and adapted according to purchasing power parity of different countries. The costs will be measured in EUR, and discount rate as well as exchange rates will be applied as necessary. The estimation of costs will serve as input into WP2 for clinical pathway optimization during ICU admission, so as to promote cost minimization and maximum cost-effectiveness. |

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| **Deliverables** (brief description and month of delivery)  **D5.1** Definition of health outcomes (M10)  **D5.2** Data collection software (M16)  **D5.3** Novel ‘smart’ ICU PROM (M24)  **D5.4** Cost-estimation (M54) |

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| **Del. no.** | **Deliverable name** | **WP no.** | **Short name of lead participant** | **Type1** | **Dissemination level2** | **Start Date** | **Delivery date 3** |
| D5.1 | Definition of health outcomes | WP5 | IER (RU) | R | PU | M0 | M10 |
| D5.2 | Data collection software | WP5 | IER (PK) | R+OTHER | PU | M0 | M16 |
| D5.3 | Novel ‘smart’ ICU PROM | WP5 | HRAH (KP) | OTHER | CO | M0 | M24 |
| D5.4 | Cost-estimation | WP5 | IER (RU) | R | PU | Mx | M54 |

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| **Description of risk (indicate level of likelihood: Low/Medium/High)** | **Work package(s) involved** | **Proposed risk-mitigation measures** |
| For the development of the ‘smart PROM’ we need assess to ICU patients after discharge of the hospital. *(level of likelihood: low)* | WP1, WP2, WP3 | None |
| Development software tool to collect patient responses for the health outcome measures. *(level of likelihood: low)* | WP3 | Restrict the use of the software tool to administer the ICU PROM to be developed (software already available for this type of PROM) and use conventional administer modes (paper-pencil, research nurse) for the other existing health outcomes. |
| HADS (Hospital Anxiety and Depression Scale) will be used. This is the preferred tool for measuring these types of psychological symptoms, but a per patient copyright cost seems applicable. *(level of likelihood: low)* | WP5 | An alternative PROM instrument to measure anxiety and depression may be considered. |

**Milestones**

M5.1 Costing methodology framework defined (M10)

M5.2 Outcome measures framework defined (M10)

M5.3 Health content (items) of the ‘smart’ ICU PROM determined (M18)

M5.4 Databases with health outcomes and costs for current treatment pathways prepared (M54)

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| **Milestone number** | **Milestone name** | **Related work package(s)** | **Estimated date** | **Means of Verification** |
| M5.1 | Costing methodology framework defined | WP1, WP3, WP4 | M10 | Check |
| M5.2 | Outcome measures framework defined | WP3, WP5 | M10 | Check |
| M5.3 | Health content (items) of the ‘smart’ ICU PROM determined | WP1, WP3, WP4, WP5, WP6 | M18 | Check |
| M5.4 | Databases with health outcomes and costs for current treatment pathways prepared | WP1, WP3, WP4, WP5, WP6 | M54 | Check |

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| **Work package number** | 06 | | **Lead beneficiary** | | | UMCG | | | | |
| **Work package title** | Dissemination and implementation | | | | | | | | | |
| **Participant number** | Fill in | Fill in | | Fill in | Fill in | | Fill in | Fill in | Fill in | Fill in |
| **Short name of participant** | UMCG | Perner | | Petilla | Christiansen | | Wong | Evidencio |  |  |
| **Person/months per participants** | Fill in | Fill in | | Fill in | Fill in | | Fill in | Fill in | Fill in | Fill in |
| **Start month** | 1 | | | | **End month** | | 60 | | | |

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| **Objectives**  The main goal of WP6 is to disseminate and implement sophisticated machine learning algorithms for ICU patients in a responsible, transparent and durable manner. This way, impact for patients and their families, caregivers, researchers, and policy makers is maximized. The main objectives for WP6 are:   1. Disseminating and implementing machine learning algorithms for patient diagnostics and prognostics, decision support, and patient/family counselling to improve care and outcome.   This is achieved through the development of user-friendly, explainable web-based tools or apps to unravel patient heterogeneity and facilitate clustering of individual ICU patients based on relevant clinical variables. Evidencio (SME) will be responsible for developing and ensuring the functioning of the online platform which will allow for direct communication of these tools with the electronic health record system, an essential step in facilitating their integration into the ICU workflow.   1. Promoting transparency and interpretability of sophisticated machine learning algorithms.   This is achieved by publishing all contributing variables, their relative weights, and outcomes regarding model performance in highest profile scientific journals and meetings, following EC’s Open Access principles, and ensuring the widest accessibility to the project outcomes possible.   1. Ensuring durable application of prediction models by facilitating local validation and continuous update of the algorithms in different ICU populations throughout the European Union. We expect this methodology to provide the patient diversity needed to make our models truly generalisable.   This is achieved through the use of a dedicated module for semi-automated external validation of developed machine learning algorithms using existing international cohorts of ICU patients. Evidencio (SME) will provide a digital platform for bilateral information transfer and centralized pooling of data for high-throughput external validation as well as continuous model improvement through recalibration of diagnostic and prognostic prediction models. |

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| **Description of work**  WP6 elaborates on WP4 and WP5 through ensuring the dissemination and implementation of developed machine learning algorithms to healthcare professionals (intensivists) throughout the European Union. Hereto, intuitive tools for diagnosis and prognosis will be made available on an easily accessible online platform to improve healthcare outcomes of ICU patients. In addition, it’s our ambition to make this tools also available for health care professionals in other discipline. We, therefore, propose a three-stage approach.  First of all, the implementation of our tools should comply with the rules and regulations set forward by the GDPR. We will warrant that the personal data of each patient that is entered into the system is processed lawfully, fairly and in a transparent manner. The subjects entered into the system will have the right to consent, to information, to access, to rectification, to erase, to restrict processing, to data portability, and to object.  Secondly, to put this into practice, we will make use of the recently introduced secure, online Virtual Research Workspace of the University of Groningen and the UMCG (also see <https://youtu.be/YZL1X-1AzHg>). This workspace will offer a secure way to form partnerships with researchers and/or institutions worldwide. Logging in is done through, secure multi-factor authentication and it is possible to work on multiple studies simultaneously in a secure manner. Researchers will have full control over their data and results with minimal risks of data breaches. Each research project has its own closed system, which makes it impossible to exchange data. Working in this environment guarantees that the data is safe, even in the event of loss or theft of a laptop, the data does not end up on the street.  In the final stage, we want to ensure that the tools developed and implemented also become available for (health care) professionals in other discipline. To warrant this we will….  This WP team builds on the well-established European network of clinical trial programs in which both observational studies and randomised trials already are being done (www.cric.nu). Partners within the network will get full access to developed machine learning algorithms while simultaneously contributing through harvesting clinical data for continuous model improvement through validation and recalibration.  In addition to scientific dissemination through open peer-reviewed journals, (social) media contacts, leaflets, and a dedicated website will make HEALICS visible to a wide general public. A HEALICS Dissemination and Implementation Group will be installed which will be responsible for coordination of the overall activities.  **Initial dissemination:**   1. Design HEALICS website and information leaflet, and other promotional material for distribution to potential stakeholders (infographics, explanimations). 2. Create mailing list of potential stakeholders to include intensivists, patient support groups, policy makers, and special interest groups in addition to existing European networks such as the established European Society of Intensive Care Medicine (ESICM, www.esicm.org).   **Continued dissemination:**   1. Update website, information leaflet, and other promotional material to ensure that early results (such as the performance of developed machine learning algorithms) are visible and comprehensible. 2. Developed machine learning algorithms made accessible as intuitive, interactive web-based tools implemented in a way that optimizes the HMI experience and stimulates trust. 3. Integrate interactive web-based tools into electronic health record system (EHRS) through an application programming interface (API) to facilitate their use in the ICU and maximize impact. 4. Regular project updates through social media platforms as LinkedIn, Facebook, and Twitter.   **Dissemination at end of project:**   1. Provide a durable digital platform for bilateral information transfer and centralized pooling of data to facilitate local external validation as well as continuous model improvement through recalibration of machine learning algorithms. 2. Disseminate the project’s findings with Public Health Institutes and existing networks across Europe regarding the added value of machine learning algorithms to unravel heterogeneity in ICU patients. 3. Ensure lay summaries are available for all major results of the project. 4. Publish the project’s findings in open peer-reviewed scientific journals relevant to the field. |
| **Task 6.1. Make dedicated machine learning algorithms accessible as intuitive user-friendly tools on a web-based platform (UMCG, RHCPH, AU, Hunimed, Evidencio)**  **Subtasks 6.1.1:** To … (CPH, Evidencio).  **Subtasks 6.1.2:** To … (…).  **Subtasks 6.1.3:** To … (…).  **Subtasks 6.1.4:** To … (…).  **Approach:** Machine learning algorithms developed in WP4 and WP5 will be converted into easy-to-use tools for everyday use in the ICU setting. These functional tools consist of simple buttons and sliders with which categorical and continuous input variables can be inserted, respectively, facilitating the clustering of individual patients into different (risk) groups.  **Task 6.2:** **Integrate machine learning algorithms in the electronic health records system workspace (UMCG, RHCPH, Evidencio)**  **Subtasks 6.2.1:** To … (CPH, Evidencio).  **Subtasks 6.2.2:** To … (…).  **Subtasks 6.2.3:** To … (…).  **Subtasks 6.2.4:** To … (…).  **Approach:** In order for decision-support tools to have true impact on medical decision-making, these tools should be integrated into the everyday workspace as much as possible. In addition, conditional outcome text fragments will be created to provide additional context information for clinicians’ dependent on patient-specific characteristics. To establish this, a standards based application programming interface (API) will be developed that allows for direct communication with the electronic health records (EHR) system. Because all ICUs participating in the project use Epic as their EHR, the primary focus will be integration with Epic. The same approach, however, is also extendable to different EHR vendors in the future.  **Task 3: Create validation module for local external validation and continuous updating of machine learning algorithms using site-specific datasets from international partners (UMCG, RHCPH, UH, AU, Hunimed, Evidencio)**  **Subtasks 6.3.1:** To … (CPH, Evidencio).  **Subtasks 6.3.2:** To … (…).  **Subtasks 6.3.3:** To … (…).  **Subtasks 6.3.4:** To … (…).  **Approach:** External validation is of utmost importance to ensure robustness, generalizability, and validity of machine learning algorithms and *must* be performed prior to widespread clinical implementation. Ideally, multiple external validations are performed using independent datasets containing data from ICU populations of different sites within the European Union. International partners collaborating within this project will deliver data for this purpose. To facilitate local external validation and model updating, a semi-automated validation module will be developed by Evidencio (SME). |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Del. no.** | **Deliverable name** | **WP no.** | **Short name of lead participant** | **Type1** | **Dissemination level2** | **Start Date** | **Delivery date 3** |
| 1 | HEALICS website, mailing list, information leaflets | WP6 | UMCG, Wong, Cecconi | DEC | PU | M1 | M12 |
| 3 | Scientific papers based on project output | WP6 | Perner, Christiansen | R | PU | M12 | M24 |
| 4 | Web-based tools made available online | WP6 | Evidencio | DEC | PU | M24 | M36 |
| 5 | API for communication with EHR system *(focus on Epic EHR)* | WP6 | Evidencio | OTHER | PU | M36 | M48 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Milestone number** | **Milestone name** | **Related work package(s)** | **Estimated date** | **Means of Verification** |
| M6.1 | Validity of machine learning algorithms evaluated in multiple international local datasets. | WP6 | M24 | Model performance assessment based on external validation |
| M6.2 | Machine learning algorithms converted into user-friendly interactive web-based tools | WP6 | M36 | Testing web-based tools by dedicated user group |
| M6.3 | Implementation of machine learning algorithms in EHR system (Epic) completed | WP6 | M48 | Testing API for direct communication with Epic EHR system |

**Critical risks for implementation**

|  |  |  |
| --- | --- | --- |
| **Description of risk (indicate level of likelihood: Low/Medium/High)** | **Work package(s) involved** | **Proposed risk-mitigation measures** |
| Errors may occur when converting machine learning algorithms into functional tools on a web-based platform.  *(level of likelihood: low)* | WP6 | External validation is always performed prior to clinical application of machine learning algorithms. This way, errors that impair model performance will prevent the algorithm from being applied in medical practice. |
| The machine learning algorithms might not perform well upon external validation in different cohorts throughout the EU.  *(level of likelihood: medium)* | WP6 | Methods for updating machine learning algorithms will be applied for recalibration of algorithms in different populations. |
| External validation of machine learning algorithms in unselected patient cohorts may lead to over- or underestimation of predicted risks in specific subgroups.  *(level of likelihood: medium)* | WP6 | Subgroup analyses will be performed to identify patient categories in which specific machine learning algorithms perform best. |
| Full integration of machine learning algorithms into one or more electronic health record systems might not be reached within the timeframe of the project.  *(level of likelihood: medium)* | WP6 | Machine learning algorithms are hosted on an external web-based platform, ensuring direct accessibility to ICU’s throughout the EU. |

**Budget estimation**

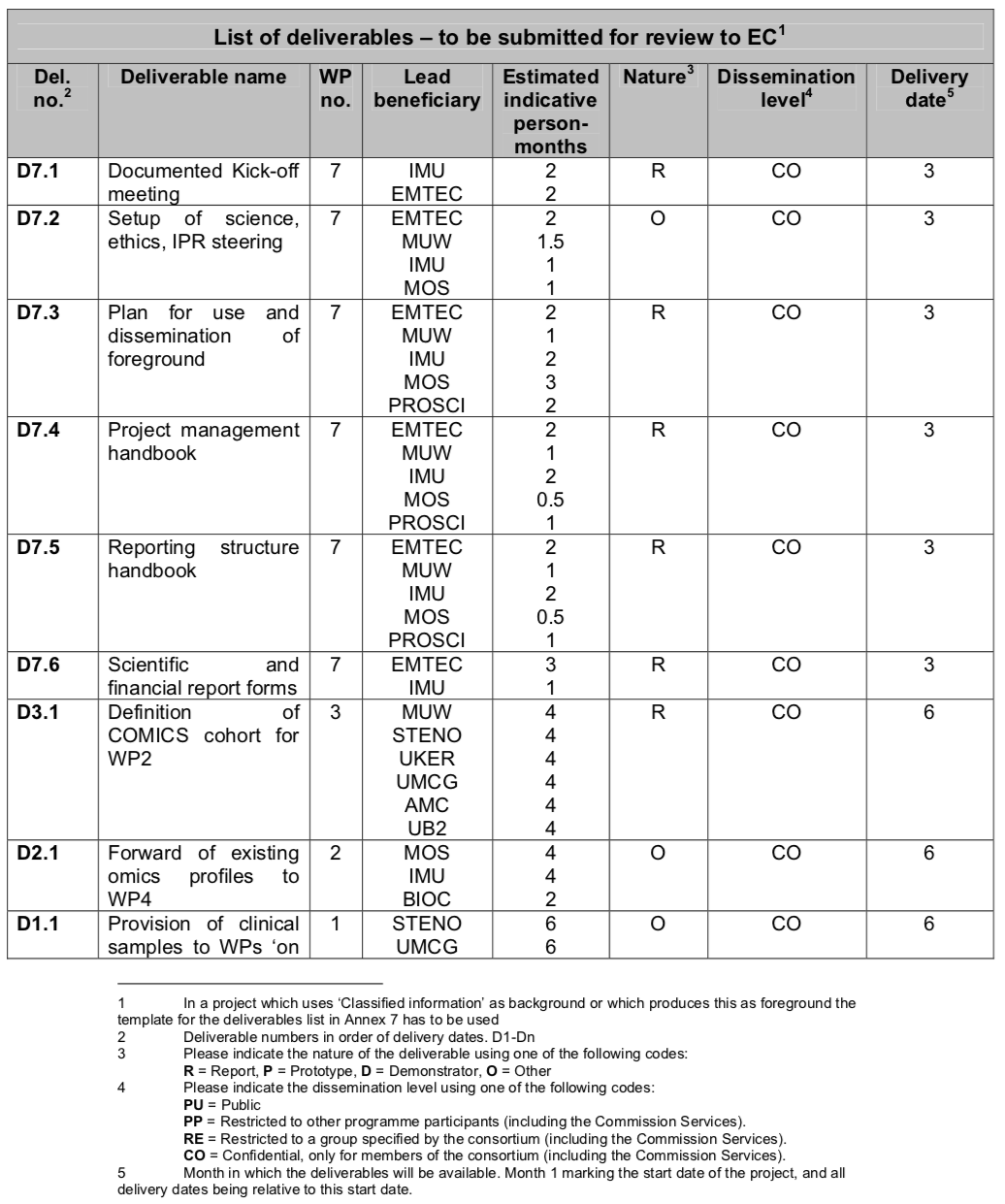
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Deliverables** | **Work package(s) involved** | **Short name of lead participant** | **Estimated budget** |
| 1 | HEALICS website, mailing list, information leaflets, organize symposia | WP6 | UMCG, Wong, Cecconi | 90.000 euro |
| 3 | Scientific papers based on project output | WP6 | Perner, Christiansen | 340.000 euro |
| 4 | Web-based tools made available online | WP6 | Evidencio | 190.000 euro |
| 5 | API for communication with EHR system | WP6 | Evidencio | 170.000 euro |
| *Total for WP6* | | | | 790.000 euro |

INSERT: Table 3.1c: List of major deliverables

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Deliverable no | Deliverable name | WP no | Lead participant | Type | Dissemination level | Delivery date |
| D4.2 | Consortium agreement | 1 | UMCG | R | CO | M1 |
| D5.2 |  |  |  |  |  |  |
| … | … | … | … | … | … | … |

INSERT HERE: graphical presentation of the components showing how they inter-relate (Pert chart or similar)

List of deliverables (summarise all WP … more of the same)



## 3.2 Management structure, milestones and procedures

For all critical aspects of the methodology of HEALICS, experts are involved as reflected by the Work packages (WP1–6; figure x). The collaborating network of ICUs across Europe is responsible for providing all the data of the critically ill patients, including both existing cohort data and data of a new prospective cohort study. This network is built on the Scandinavian Critical Care Trial Group, initiated by A. Perner, and for this project and thereafter extended to other participating sites in non-Scandinavian European countries to represent Europe. Therewith, our network of collaborating ICUs will entail at least 30 in six European countries. This network will collect clinical patient data during ICU stay as well as biomarker (blood, genetic, epigenetic, metabolomic) and long-term survival data (WP3; LIU, Sweden; HUS, Finland; UMCG, the Netherlands). Experts in health economics and mental disorders (outside the field of Intensive Care Medicine) will design and analyse long-term *quality-of-life*, *mental disorders* and *cognitive outcomes* (WP5; IER, Slovenia; CUH, United Kingdom; UOM, Australia); experts in *data management* will build the infrastructure for data collection (WP2; AU, Denmark; Enversion, SME, Denmark); and experts in *computer science* will apply machine learning and artificial intelligence for identification of key variables and create homogenous clusters of patients (WP4; RUG, the Netherlands; UNIBI, Germany; UCY, Cyprus; LJMU, United Kingdom; Rutgers, USA; Target Holding, SME, the Netherlands). Finally, optimal dissemination and implementation of the results of HEALICS will be achieved through the involvement of leaders and key players within the ICU community and with experts from outside the ICU for communication (WP6; REGIONH, Denmark; HUNIMED, Italy; Evidencio, SME, the Netherlands). Optimal interactions among all WPs are key for a successful project, but especially the overall management and coordination (WP1) needs to interact effectively with all partners and facilitate all kinds of internal cooperation. Further, the data management partners (WP2) need to interact closely with the partners of the patient characterisation (WP3), outcome evaluation (WP5) and machine learning (WP4) for optimal handling of all data. Scientific consortium partners not only hail from across all parts of Europe but also from Australia (unique expertise on mild cognitive impairment) and the USA (unique expertise on computational bioinformatics, statistical inference, survival analysis and translational research) facilitating global dissemination of HEALICS findings. Furthermore, three SMEs are already involved in this project for machine learning, safe collection, storage, and linkage of data, and automated risk scoring within electronic patient records in Denmark (Enversion) and the Netherlands (Target holding and Evidencio).

### 3.2.1 Management structure

The management structure is built to support and lead the consortium. The HEALICS consortium consists of 17 partners and 2 associate partners (see the commitment letters of each institute in section 4), all considered consortium members. The consortium composition ensures that research institutes in Europe are strongly linked and that ICU experts and non-ICU science experts are not only well represented in WPs, as WP leaders and committees, but also need to interact and work together closely in order to obtain clinically relevant deliverables.

HEALICS will have a governance structure that ensures a balanced representation of all participants. Day-to-day management of the project will be achieved through the formation of a dedicated **Executive and Management Team (EMT)** that includes a team of scientists and project managers ensuring the scientific/strategic, administrative and financial coordination of the project. The **Steering Committee (SC)** will take care of the project achieving its milestones in an appropriate and timely manner. Having the permanent oversight on the project progress and the interactions in the consortium it will regularly conduct gap analyses of project tasks and develop alternative scenarios for implementation or approval by the **General Assembly (GA)**, if required.

#### Lead partner (LP) and coordinator (LC)

The lead partner is the UMCG and the lead coordinator Harold Snieder.

##### Members

The members of the LP consist of the LC and the other members of the coordination team Frederik Keus and Iwan van der Horst. The LP shall be a central point of contact between the SC and WP leaders. The LP is supported by all other partners in the project. The coordinator will be assisted by a Project Management Team (PMT) and the grant support office of the UMCG (incl. LEAR, TTO, finance & legal support).

**Responsibilities**

Overall management of the HEALICS consortium will be the responsibility of the lead investigator supported by the coordinating team, which is accountable to the General Assembly through the Executive Board. Management and decision-making are based on democratic principles and on direct and open communication, participation, mediation and consensus building. Manage internal affairs and participate in the consortium following the rules and regulations of the Consortium Agreement. All partners are responsible for the management of their own tasks and work and for communication with the LP.

The LP will perform certain duties as laid out in the Grant Agreement. In particular, the LC shall be responsible for:

* Grant coordination and management.
* Submission of deliverables to the …. after approval by the EMT.
* Coordination of the preparation of the period report and submission to …
* Preparation of amendments to the HEALICS Grant Agreement and submission to …
* Monitoring the compliance by Beneficiaries with their obligations under the Grant Agreement.
* Transmitting any documents and information connected with the Project to and between the Beneficiaries concerned.
* Overseeing the contractually agreed audit regime that enables the … to proceed to audits.

#### Executive and Management Team (EMT)

**Members**

The EMT will consist of the coordinator, the vice-coordinators …. For decisions, each member will have one vote except for the vice-coordinators that will have half a vote each. Furthermore, the EMT will include the **Project Management Team (PMT)** that is experienced in managing public-private partnerships as well as legal, IP and communication procedures within the IMI framework. Members of the PMT are … The PMT will be an integral part of the EMT, however without a vote on its decisions.

##### Responsibilities

The EMT will be supported by an FTE Project Manager performing general administrative tasks and further Assistants for the steering committee chairs. For further taking care of the complexity of the project a SC is implemented, and for each WP a WP leader is established. The distinct responsibility profiles of their functions in the EMT will be clearly communicated to each of the participating beneficiaries at the HEALICS kick-off meeting. Major impact for successfully guiding HEALICS will also come from our Advisory Board keeping science, application, and medical/patient needs in focus. The EMT will review and approve the project deliverables before submission to the … by the coordinator. It will be responsible for initial mediation in any disputes between the Beneficiaries relating to the execution of the project and which cannot be handled within the WP. It will prepare decisions to be taken by the SC and/or the GA regarding budget reallocations or major changes to WP tasks and deliverables or to project research questions. In order to ensure the smooth operation of the Action and guarantee that all efforts are focused towards the objectives, the EMB will instruct the Beneficiaries of the due date for deliverables. Focusing on the goals of the HEALICS project, the EMT will evaluate new external opportunities for collaboration that are of interest and considered as supplementary to the research questions of the Action.

Overview of responsibilities:

* Advising the coordinator on allocation and distribution of the … Financial Contribution among Beneficiaries, in accordance with the Grant Agreement and the Consortium Agreement.
* Jointly with coordinator monitoring activities and take appropriate measures to ensure the compliance by beneficiaries with their obligations under the Grant Agreement.
* Overseeing the contractually agreed audit regime that enables the … to proceed to audits.
* Coordinating the negotiation of the Consortium Agreement jointly with the coordinator.
* Working with Beneficiaries to prepare and negotiate any non-disclosure agreements that may be required.

#### Steering committee (SC)

##### Members

The SC shall be made up of all WP leaders and the EMT. For decisions, each member will have one vote. In addition, the coordinator, the project leader and co-leader, have one vote, each, and the vice-coordinators have half a vote each, as long as they are not acting as representative of a WP.

##### Responsibilities

The SC shall act as a supervisor of the overall progress of the research. It will ensure that all Beneficiaries are regularly updated on the scientific progress. In particular, it will:

* Ensure the scientific progress of the work with respect to the collaboration and exchanges across WPs
* Monitor and evaluate overall progress and timely submission of deliverables and milestones
* Contribute to the gap analysis of project tasks and develop alternative scenarios to ensure the achievement of the WP deliverables
* Take corrective action in order to ensure project progress and quality
* Review, propose and approve budget reallocations to the parties, both within and across WPs.
* Ensure adherence to ethical regulations
* Evaluate new external collaborations that support the research questions of the Action

#### General assembly (GA)

The GA will be made up of the scientific representatives of each partner, as indicated in the IMI SOFIA on-line tool.

##### Members

The General Assembly will be chaired by the coordinator and co-chaired by the project leader.

##### Responsibilities

The General Assembly shall decide on the following matters:

* Agreeing on the inclusion of a new partner in the project.
* Agreeing on the exclusion of a project partner from the project.
* Approve major changes in the project research strategy including new external collaborations that have been prepared by the SC.

All participants of HEALICS and the national principal investigators from the ICU network (one vote for each institute/each national PI).

The general assembly includes all participants contributing in any way to this project, including all clinicians and experts. The GA will be held on an annual basis and will be coordinated and chaired by the PC, supported by the steering committee chairs. Purpose of this instrument is to facilitate regular communication and networking between all consortium beneficiaries, to provide all beneficiaries a comprehensive overview of project efforts and to clearly communicate project objectives for the next period.

Decisions will be taken by the general assembly. Specifically, the general assembly will be responsible for proposals for changes to the Grant Agreement, changes of the consortium plan, or changes of the Consortium Agreement, as well as issues arising in the course of consortium evolution.

#### WP leads

Operational, day-to day decisions in the WPs will be the responsibility of WP leaders. To facilitate the management of the entire project, the tasks have been divided into WPs. The national principle investigators will manage the logistics and practical issues in each country.

**Members**

Each WP has two WP leads (WPL) who will act as empowered WP leaders. WP leads can delegate part of their responsibilities to designated WP members. The WPLs are responsible for the execution of the work plan in their respective WP, the support of interactions between the different WPs and the reporting of the progress or any delay of WP tasks or any other WP issue at the SC.

**Responsibilities**

Further, on a day-to-day basis, they will be responsible for:

* Coordination and day-to-day management of their WPs in line with the project plan, ensuring that all team members comply with the agreed project plan and study protocols.
* Ensuring that WP participants are aware of due dates for Project Deliverables and Milestones.
* Overviewing the overall WP budget and the individual partner budgets.
* Monitoring and reporting the progress of WP activities.
* Ensuring effective communication within WPs.
* Aligning with the other WPs and providing information regarding the progress of their work.
* If necessary, consulting the SC regarding any potential risks, hurdles and difficulties.
* Consulting the EMT in case of conflicts arising among members of their WPs.
* Ensuring that their WP is appropriately represented at all relevant Consortium meetings including the SC.
* Providing appropriate support to Consortium communication and dissemination activities.

#### Clinical committee (CC)

The clinical committee of this collaborating European ICU network consists of the national principal investigators of the participating countries.

##### Members

Each country will have a national principle investigator responsible for recruiting sites and national study coordination. The following national principal investigators will participate Denmark: A. Perner; Finland: V. Pettila; Italy: M. Cecconi; Netherlands: I.C.C. van der Horst; Sweden: M. Chew; UK: K. Preller.

##### Responsibilities

### 3.2.2 Meeting structure and communications

A well-balanced meeting structure has been designed to efficiently manage the complexity of the project. A kick-off meeting involving all beneficiaries will serve as the instrument to communicate and implement rules and guidelines for efficient project initiation and maintenance. Voting rights for the Steering Committees and General Assembly and approval procedures for external communications will be regulated in the consortium agreement.

Primary meeting body is the GA, planned for project months 1, 12, 24, 36, 48, and 60. The final meeting will be held in conjunction with a HEALICS conference planned on an international level to present the overall outcome of HEALICS and to discuss outlook and further results implementation with the scientific community. Additional general assembly meetings will be installed if demanded by the PC and at least one member of SC. Minutes of the general assembly meetings as well as of all steering committee meetings will be communicated to the EC. The SC will meet at minimum twice a year either on a personal basis or by teleconferences, and the minutes of these meetings will be communicated to the PC and distributed to all participants.

For decision making on a day to day operative level the following structure will be implemented: If more than one participant from an institution contributes to an activity, team leaders (TL) will be responsible for decisions on the beneficiary level and for managing the local team. TLs will be responsible for carrying out all scientific, administrative and financial tasks at the individual beneficiary level, communicating progress and results to work package leaders. At the same time TLs have to coordinate their tasks with a work package leader (WPL).

Each consortium member will communicate scientific progress on the level of milestones and deliverables to the SC. Deliverable documents will be reviewed and forwarded to the PL, who will then communicate to the commission. Additionally, quarterly scientific reporting will be demanded by the SC. All financial reports (also involving quarterly updates) and non-scientific deliverables will be demanded by the PL. Each beneficiary’s status and issues with respect to samples, data and ethics will be communicated to the ethics chair.

All dissemination (i.e. all communication involving third parties next to the consortium and the commission) has to undergo evaluation in the SC. After clarification of IPR, ownership and patenting strategy dissemination will be continued either on the scientific level by the involved beneficiaries, or as HEALICS communication driven by ... As additional information exchange platform our HEALICS website will hold a secured internal area with forum capabilities.

In order to ensure the best communication and exchange of knowledge, data and results in the consortium, and in and across work packages, the following frequency of meetings will be implemented:

**Table 3.2.2: Meeting frequencies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **EMT** | **SC** | **GA** | **WP** |
| **Face-to-face** | 1/month | 1/year | 1/year | 2/year |
| **Phone/web** | n.a. | 2/year | As needed; decisions can be  considered &  taken via e-mail | As needed |

We are exploring different options for mobile performance metrics (e.g. ….) for effective management, which will be tested on a smaller scale before a decision to implement it throughout HEALICS can be taken. It will not replace other reporting documents but may be a valuable tool to improve internal communication and to know what’s happening on a regular basis and thus, timely identify underperforming partners, pro-actively apply corrective measures and take actions.

#### Ethics Board (EB)

##### Members

The EB will be composed of experts with detailed knowledge of ethical policies. Experts who make up the committee shall represent the various interests involved, including clinical studies, data protection, biobanks and database specialties. The Executive and Management Board will ensure that the composition of the EB is appropriate to provide the guidance required.

##### Responsibilities

The EB will advise the GA, the SC and the EMT. The EMT will organise the meetings of the EB. Confidentiality rules will be agreed with the EB members.

The EB will be responsible for:

* monitoring the proper application of the ethical rules by Beneficiaries.
* providing advice to Beneficiaries and the SC.
* providing advice on the compliance with European ethical laws and regulations and with different guidelines, laws and regulations of countries where studies are being performed.

#### Advisory Board (AB)

HEALICS shall be supported by an AB. The representatives, the concept and the involvement of the AB will be laid out in a policy at the start of the project, aligning the needs for advice in strategy and operation and by that maximizing the value and impact of the AB for the project. The following persons have been contacted and agreed to be part of …... The AB will advise the GA, the SC and the EMT. The PM Team will organize the meetings of the AB. Confidentiality rules will be agreed with the AB members.

### 3.2.3 Milestones

Table 3.2a: List of milestones

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Milestone number** | **Milestone name** | **Related work package(s)** | **Due date (in month)** | **Means of verification** |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

### 3.2.4 Risks and mitigation

HEALICS is an ambitious project in terms of the numbers of participants, but also in the numbers and sizes of the selected ambitious goals.

One major risk is the numbers of participants involved in this project. This may make the entire coordination of the project complex and difficult to control and manage. However, during the development of this proposal we have experienced the dedication of all partners, motivated to contribute to this challenge. Due to the large numbers of tasks and also the high chances for additional opportunities we expect that there is plenty of opportunity for each participant to benefit and/or exploit from the deliverables of this project. To tackle this risk of many participants we have structured the totality of tasks into rather distinct but clear-cut pieces for each participant. This reduces the risks for lack of control and mismanagement.

The second major risk is that there are too main ambitious goals. While one may perceive that the numbers of task are rather high, this will increase the incentives of the ICUs participating in this project for delivering their data. Many tasks mean many deliverables, and this increases their incentives to participate.

The third major risk of this project are the expected impacts of this project. One may perceive the impact as paradigm shift in ICU in specific and care for the patients with multimorbidity in general. However, we have introduced risk mitigation measures is in this project. One example is the early warning system: The ambition is to develop and introduce an automatic dynamic integrated early warning system in the health record system to inform daily practice of ICU pts. The back-up plan, if failing by unforeseen logistic or other barriers, includes an online simple version which can be guaranteed based on what we know already. One other example of a risk-mitigation measure is to harmonise at least the sites which all use EPIC as patient health record system. Most sites use EPIC, which makes introduction of these goals much easier.

Table 3.2d Critical risk for implementation

|  |  |  |  |
| --- | --- | --- | --- |
| **Description of risk** | **Level of Risk** | **Work package(s) involved** | **Proposed risk-mitigation measures** |
| … |  |  |  |
|  |  |  |  |

## 3.3 Consortium as a whole

The **HEALICS** consortium is an aggregate of diverse expertise and leading institutions from all across the Europe, with connections to Australia and USA. Gender is equally distributed among the WP lead (3 females/3 males). The partners’ mutual interests in unravelling heterogeneity of the critically ill patients with multimorbidity make the consortium ideally placed to tackle the challenges posed within HEALICS. **Section 1.2** describes how the structure of the consortium matches the project’s objectives and how the partners complement one another. In **section 3.1** we have indicated how exactly each of the partners will contribute to the work plan, both to specific tasks and within which WPs. **Section 3.2** describes the management structure that will provide a frame for partners to work together. **Section 2.2a** describe mechanisms in HEALICSfor exploitation of results. Finally, **section 4** provides a more detailed description of each partner. Apart from what has already been stated in these sections, we would like to emphasise that partners in HEALICShave collectively demonstrated a long-standing commitment to research in critically ill patients, (epi)genetics, cognitive function, quality of life and machine learning.

Above all the sense that we urgently need to improve our care for the most critically ill is what has led to this whole enterprise. The bottom line is that the intensivist standing at the bedside of the patients A and B and taking to their families trying to explain them the lack of current knowledge on causal mechanisms at the core the multi-morbidities and critical illness and telling that we don’t know, and we have to wait and see what happens. This feeling of urgency is at the heart of this proposal. Also, a sense of privilege of being part of this ambitious enterprise and a strong belief that HEALICS will make a difference for critically ill patients has grown among partners during the preparation of this proposal.

## 3.4 Resources to be committed

 Please make sure the information in this section matches the costs as stated in the budget table in section 3 of the administrative proposal forms, and the number of person months, shown in the detailed work package descriptions.

Please provide the following:

a table showing number of person months required (table 3.4a)

a table showing ‘other direct costs’ (table 3.4b) for participants where those costs exceed 15% of the personnel costs (according to the budget table in section 3 of the administrative proposal forms)

|  |  |
| --- | --- |
| Remember to **plan and allocate resources** not only for “**personnel costs**” specifically for exploitation and dissemination activities, but also allocate “other direct costs” related to the exploitation and dissemination  activities. These costs can be necessary in case:  **•** you need to purchase data for market analysis | **•** you plan to file patents  **•** you need to publish  **•** you need to participate to InternationalCongresses  or technology market places/brokerage events or investors forums  **•** … Carefully evaluate what you will need in advance! |

Table 3.4a: Summary of staff effort

Please indicate the number of person/months over the whole duration of the planned work, for each work package, for each participant. Identify the work-package leader for each WP by showing the relevant person-month figure in bold.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | WPn | WPn+1 | WPn+2 | Total person-  months per Participant |
| Participant number/ Short name |  |  |  |  |
| Participant number/  Short name |  |  |  |  |
| Participant number/  Short name |  |  |  |  |
| Total person months |  |  |  |  |

Table 3.4b: ‘Other direct cost’ items (travel, equipment, other goods and services, large research infrastructure)

Please complete the table below for each participant if the sum of the costs for’ travel’, ‘equipment’, and ‘goods and services’ exceeds 15% of the personnel costs for that participant (according to the budget table in section 3 of the proposal administrative forms).

|  |  |  |
| --- | --- | --- |
| Participant number/ Short name | Cost (€) | Justification |
| Travel |  |  |
| Equipment |  |  |
| Other goods and services |  |  |
| Total |  |  |

Please complete the table below for all participants that would like to declare costs of large research infrastructure under Article 6.2 of the General Model Agreement[[4]](#footnote-5), irrespective of the percentage of personnel costs. Please indicate (in the justification) if the beneficiary’s methodology for declaring the costs for large research infrastructure has already been positively assessed by the Commission.

|  |  |  |
| --- | --- | --- |
| Participant number/ Short name | Cost (€) | Justification |
| Large research infrastructure |  |  |

STOP PAGE COUNT – MAX 70 PAGES (SECTIONS 1-3)

# 4. Members of the consortium

 This section is not covered by the page limit.

 The information provided here will be used to judge the operational capacity. Please make sure that you do not include information here that relates to the headings under sections 1 to 3. Experts will be instructed to ignore any information here which appears to have been included to circumvent page limits applying to those sections.

## 4.1. Participants (applicants)



Please provide, for each participant, the following (if available):

* a description of the legal entity and its main tasks, with an explanation of how its profile matches the tasks in the proposal;
* a curriculum vitae or description of the profile of the persons, including their gender, who will be primarily responsible for carrying out the proposed research and/or innovation activities;
* a list of up to 5 relevant publications, and/or products, services (including widely-used datasets or software), or other achievements relevant to the call content;
* a list of up to 5 relevant previous projects or activities, connected to the subject of this proposal;
* a description of any significant infrastructure and/or any major items of technical equipment, relevant to the proposed work;

if operational capacity cannot be demonstrated at the time of submitting the proposal, describe the concrete measures that will be taken to obtain it by the time of the implementation of the task*.[[5]](#footnote-6)*

## 4.2. Third parties involved in the project (including use of third-party resources)

Please complete, for each participant, the following table (or simply state "No third parties involved", if applicable):

|  |  |
| --- | --- |
| Does the participant plan to subcontract certain tasks (please note that core tasks of the project should not be sub-contracted) | Y/N |
| If yes, please describe and justify the tasks to be subcontracted | |
| Does the participant envisage that part of its work is performed by linked third parties[[6]](#footnote-7) | Y/N |
| If yes, please describe the third party, the link of the participant to the third party, and describe and justify the foreseen tasks to be performed by the third party | |
| Does the participant envisage the use of contributions in kind provided by third parties (Articles 11 and 12 of the General Model Grant Agreement) | Y/N |
| If yes, please describe the third party and their contributions | |
| Does the participant envisage that part of the work is performed by International Partners[[7]](#footnote-8) (Article 14a of the General Model Grant Agreement)? | Y/N |
| If yes, please describe the International Partner(s) and their contributions | |

## 4.3. Financial support to third parties

 For detailed specific info on terms and conditions: see General Annex K of the Horizon 2020 Work Programme published in the reference documents section of the H2020 Participants Portal ([*http://ec.europa.eu/research/participants/portal/desktop/en/funding/reference\_docs.html*](http://ec.europa.eu/research/participants/portal/desktop/en/funding/reference_docs.html))

Financial support in the form of a grant awarded after a call for proposals

Where this possibility is indicated under the relevant topic in the Work Programme and in the relevant calls for proposals, proposals which foresee a financial support to third parties, shall:

* clearly detail the objectives and the results to be obtained and
* contain the following specifications (as a minimum):
* a closed list of activities that qualify for financial support; please check in the Work Programme and call for proposals for the list of activities for which financial support to third party is allowed;
* the definition of persons or categories of persons that may receive financial support;
* the criteria for awarding financial support;
* the criteria for calculating the exact amount of the financial support;
* the maximum amount of financial support per third party, which must not exceed EUR 60 000, unless a higher amount is necessary to achieve the objectives of the action, and the criteria for determining it.

Please check in the Work Programme and call for proposals if there are other conditions that apply and, if so, include them in the specifications or in any other element of the proposal as appropriate.

Financial support in the form of a prize

Where this possibility is indicated under the relevant topic in the Work Programme, proposals which foresee a financial support in the form of a prize, shall:

* clearly detail the objectives and the results to be obtained and
* contain the following specifications (as a minimum):
* the conditions for participation;
* the award criteria;
* the amount of the prize;
* the arrangements for payment.

Please check in the Work Programme and the call for proposals if the are other conditions that apply and, if so, include them in the specifications or in any other element of the proposal as appropriate.

# 5. Ethics and Security

 This section is not covered by the page limit.

## 5.1 Ethics

 *For more guidance, see the* [*document "How to complete your ethics self-assessment"*](http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/ethics/h2020_hi_ethics-self-assess_en.pdf)*.*

If you have entered any ethics issues in the ethical issue table in the administrative proposal forms, you must:

* submit an ethics self-assessment, which:
  + describes how the proposal meets the national legal and ethical requirements of the country or countries where the tasks raising ethical issues are to be carried out;
  + explains in detail how you intend to address the issues in the ethical issues table, in particular as regards:
    - research objectives (e.g. study of vulnerable populations, dual use, etc.)
    - research methodology (e.g. clinical trials, involvement of children and related consent procedures, protection of any data collected, etc.)
    - the potential impact of the research (e.g. dual use issues, environmental damage, stigmatisation of particular social groups, political or financial retaliation, benefit-sharing, misuse, etc.).
* provide the documents that you need under national law (if you already have them), e.g.:
  + an ethics committee opinion;
  + the document notifying activities raising ethical issues or authorising such activities

 If these documents are not in English, you must also submit an English summary of them (containing, if available, the conclusions of the committee or authority concerned).

If you plan to request these documents specifically for the project you are proposing, your request must contain an explicit reference to the project title.

## 5.2 Security[[8]](#footnote-9)

Please indicate if your project will involve:

* activities or results raising security issues: (YES/NO)
* 'EU-classified information' as background or results: (YES/NO)

1. Calfee CS et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Med 2014;2(8):611–20. [↑](#footnote-ref-2)
2. Tan SS et al. Microcosting study of ICU costs in three European countries. Crit Care. 2008; 12(Suppl 2): P526. [↑](#footnote-ref-3)
3. Pastores SM et al. Academic Leaders in Critical Care Medicine (ALCCM) Task Force of the Society of the Critical Care Medicine. Workforce, Workload, and Burnout Among Intensivists and Advanced Practice Providers: A Narrative Review. Crit Care Med. 2019 Jan 24. [↑](#footnote-ref-4)
4. Large research infrastructure means research infrastructure of a total value of at least EUR 20 million, for a beneficiary. More information and further guidance on the direct costing for the large research infrastructure is available in the H2020 Online Manual on the Participant Portal. [↑](#footnote-ref-5)
5. Please refer to [General Annex H Evaluation Rules, Selection Rules, Operational Capacity](http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2018-2020/annexes/h2020-wp1820-annex-h-esacrit_en.pdf) [↑](#footnote-ref-6)
6. A third party that is an affiliated entity or has a legal link to a participant implying a collaboration not limited to the action. (Article 14 of the [Model Grant Agreement](http://ec.europa.eu/research/participants/data/ref/h2020/mga/gga/h2020-mga-gga-multi_en.pdf)). [↑](#footnote-ref-7)
7. ‘International Partner’ is any legal entity established in a non-associated third country which is not eligible for funding under Article 10 of the Rules for Participation Regulation No 1290/2013. [↑](#footnote-ref-8)
8. See article 37 of the [Model Grant Agreement](http://ec.europa.eu/research/participants/data/ref/h2020/mga/gga/h2020-mga-gga-multi_en.pdf). . For more information on the classification of Information, please refer to the Horizon 2020 guidance: <https://ec.europa.eu/research/participants/data/ref/h2020/other/hi/secur/h2020-hi-guide-classif_en.pdf>. [↑](#footnote-ref-9)