SC1-PHE-CORONAVIRUS-2B

ENVISION

Intelligent plug-and-play digital tool for real-time surveillance of COVID-19 patients and smart decision-making in Intensive Care Units

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Project Abstract

Within only six months, over 7.4 million people have been diagnosed with SARS-CoV-2. In the most severely hit countries, more than 10% of infected patients have received treatment in Intensive Care Units (ICUs). Insufficient data and limited knowledge on the disease as well as the lack of tools to support the intensivist in making accurate, timely and informed decisions has led to high mortality rates.

Continuous surveillance, the collection and intelligent analysis of data from many sources, including ventilators and electrical impedance tomography, would allow intensivists to decide on the best suitable treatment to accelerate the recovery of the often comorbid COVID-19 patients, while reducing the burden on clinical staff and healthcare costs. This information would also increase our understanding of the yet unknown course of disease, supporting other stakeholders in the quest for new therapies.

In ENVISION, our multidisciplinary public-private consortium will advance an innovative digital tool, Sandman.MD, a real-time and plug-and-play monitoring app, to an intelligent decision-support system for monitoring, prediction and treatment of COVID-19 patients in ICUs – the Sandman.ICU – reaching Technology Readiness Level 9 and ready for CE marking by the end of the project. The app has been developed by our SME partner app@work and successfully introduced by several hospitals in Germany for use during the perioperative period. Sandman.ICU will be integrated into an AI-driven data analytics suite with predictive modelling tools and enhanced with a smart alert functionality. The digital tool will be validated and demonstrated in 13 hospitals across Europe. Our Health Technology Assessment expert partner will demonstrate the economic and societal value of Sandman.ICU, while an experienced SME will manage the innovation process in view of an immediate market uptake. The rollout will be supported by the European Society of Anaesthesiology and Intensive Care (ESAIC).

Revision history

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Partner short names

AAW	app@work GmbH
accelCH	accelopment Schweiz AG
accelDE	accelopment Deutschland GmbH
CCHT	Spitalul Clinic Judetan De Urgenta Pius Brinzeu Timisoara
CHUC	Centro Hospitalar e Universitario de Coimbra E.P.E.
DPT	Central Hospital of Southern Pest National Institute of Hematology and Infectious Disease
ESAIC	European Society of Anaesthesiology and Intensive Care
GUF	Johann Wolfgang Goethe Universität Frankfurt am Main
ICS-HUB	Institut Catala de la Salut – Bellvitge University Hospital
iDA	Intelligent Data Analytics GmbH & Co. KG
KC	Lietuvos Sveikatos Mokslu Universiteto Ligonine Kauno Klinikos
LMI	Löwenstein Medical Innovation GmbH & Co. KG
SE	Semmelweis Egyetem
TAU	Tampereen Korkeakoulusaatio SR
UCL	University College London
UMCG	Universitair Medisch Centrum Groningen
UMCL	Univerzitetni Klinicni Center Ljubljana
UMCM	Univerzitetni Klinicni Center Maribor
UMFCD	Universitatea de Medicina si Farmacie Carol Davila din Bucuresti
UNIPG	Università degli Studi di Perugia
UNITO	Università degli Studi di Torino

Abbreviations

AI	artificial intelligence
AKI	acute kidney injury
ARDS	acute respiratory distress syndrome
AUC	area under the curve
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
DVT	deep vein thrombosis
HTA	health technology assessment
ICER	incremental cost effectiveness ratio
ICU	Intensive Care unit
IQR	inter quartile range
MERS	Middle Eastern Respiratory Syndrome
PE	pulmonary embolism
PICS	post intensive care syndrome
QALY	quality-adjusted life years
SARS	severe acute respiratory syndrome
VTE	venous thromboembolisms

Executive Summary

The ENVISION project aims to **improve the treatment** of COVID-19 patients in intensive care units (ICUs) by using an innovative digital tool, the Sandman ICU. The Sandman ICU is a real-time and plug-and-play monitoring app and will be advanced to an intelligent decision support system for the monitoring, prediction and treatment of COVID-19 patients in ICUs. During the ENVISION project, the Sandman ICU will collect data from several European countries. Basing on these data, a team of AI experts within the project consortium will develop several intelligent data analysis tools, which will be implemented in the Sandman ICU towards the end of the ENVISION project.

Various envisioned applications (i.e. use cases) demonstrating the different possibilities of integrating AI into healthcare settings have been defined/identified by AI experts at the beginning of the ENVISION project. The strategies in the Health Technology Assessment Plan are based on these use cases. **Three categories** of use cases were identified:

1. An AI-based system that provides recommendations on treatment based on earlier observations and/or current clinical guidelines
2. An AI-based system that predicts sepsis
    a. At the onset of sepsis
    b. Before the onset of sepsis
3. An AI-based system that recommends the inclusion of a patient in a specific clinical trial

The **goal of this Health Technology Assessment Plan** is to provide a strategy and define methods to estimate health gains and (saved) costs related to the implementation of the Sandman ICU. In this assessment plan, an elaborate overview of the current literature on COVID-19 and ICU patients is presented. The current literature on COVID-19 is essential for the health technology assessment (HTA), as it describes the population to whom the treatment is targeted and describes statistics on various COVID-19 clinical outcomes, such as complications, mortality and post-ICU quality of life. We argue that the ENVISION AI-based tools can significantly improve the clinical outcomes of COVID-19 patients in ICUs. In addition to this, ENVISION is expected to reduce the treatment costs of COVID-19 patients in ICUs.

Several approaches are proposed to estimate the **health gains and (saved) costs** related to the implementation of the Sandman ICU. To show the effectiveness of the different use cases, we will use various outcome variables, i.e. survival, life years gained, length of stay, duration of mechanical ventilation and quality-adjusted life years (QALYs). The approaches for estimating the health benefits in use cases category 1 and 2b are relatively similar. In the first step, we indicate whether a treatment was done according to the recommendations or if a patient developed sepsis. Then, two proposed methods are presented to simulate the effect of early adequate treatment. The first uses matching, whereas for the second method, we will train a predictive machine learning model to predict the possible health gains of early adequate treatment.

A different strategy is proposed for use cases category 2a and 3. To estimate the health gains of predicting sepsis at onset, we will compare the sensitivity of the Sandman ICU with that of risk stratification scores and/or triage systems that are currently used in ICUs throughout Europe, whilst keeping the specificity constant. Then, for the increase in true positives, the gains in terms of survival, life years gained and QALYs are estimated. The possible benefits of an AI system that recommends clinical trials will be time savings for staff, the value of information and the faster filling up of clinical trials.

With the above methods, **reductions in mortality rate, length of stay and duration of mechanical ventilation** can be inferred. The **number of life years gained** can be estimated using reductions in the mortality rate. Moreover, **QALYs** will be estimated using the reductions in mortality rate, length of stay and duration of mechanical ventilation, and utility values of patients post ICU. The reductions in length of stay can be translated into reductions in the costs of ICU treatment. The costs of implementing the AI system will be analysed. The **incremental cost-effectiveness ratio** (ICER) will be calculated to evaluate the cost effectiveness of the AI system.

Towards the end of the Health Technology Assessment Plan, a **timeline** is introduced. This timeline is provisional and subject to changes, as it is highly dependent on the data collection and the work of partners in the project. Moreover, the HTA is highly dependent on the use cases implemented by the AI experts. Depending on the form of the data, not all use cases may be implemented, use cases may be adjusted or new use cases may come about. Similarly, the (amount of) data may not be suitable for the proposed HTAs. In addition, new information about COVID-19 in the form of literature is published daily. This information may influence the logic or feasibility of the plans proposed here. Therefore, the final results may differ from the methods described in this assessment plan.

The Health Technology Assessment Plan

ENVISION is an Innovation Action funded by Horizon2020 with the aim of **improving the treatment** of Coronavirus Disease 2019 (COVID-19) patients in intensive care units (ICUs). In several European countries, COVID-19 patients hospitalised in ICUs will be monitored with the Sandman ICU. The Sandman ICU collects data in ICUs from a variety of sources, such as ventilators and electrical impedance tomography. These data will be processed in real time using artificial intelligence (AI) to aid the clinical decisions of intensivists and ICU clinical staff. For example, the Sandman ICU could **recommend the best suitable treatment** for a patient, thereby improving survival chances and later quality of life.

The Sandman ICU will be implemented in 13 hospitals across Europe. The hospitals participating in the data collection are located in Germany, Hungary, Italy, Lithuania, Portugal, Romania, Slovenia, Spain and the UK. Data are collected from patients with COVID-19 in ICUs. All patients must consent orally to sharing their data with the ENVSION project. Currently, the project is still in the start-up stage, and data have yet to be collected. Basing on these data, a team of AI experts will develop several intelligent data analysis tools, which will be implemented in the Sandman ICU towards the end of the ENVISION project. The **goal of this assessment plan** is to provide a strategy that will estimate the health gains and (saved) costs related to the implementation of the Sandman ICU.

1 Context

In December 2019, a cluster of novel coronavirus-infected pneumonia was reported in the city of Wuhan. The disease, later referred to as COVID-19, quickly spread over the rest of the world, causing a global pandemic. Currently, millions of people have been infected with COVID-19, and nearly three million people have died (1). Whilst most patients experience mild or moderate symptoms, around 14% of COVID-19 patients develop severe symptoms, and 5% end up having a critical disease with complications (2). Daily, thousands of COVID-19 patients are admitted to ICUs around the world, causing healthcare systems worldwide to be overflooded and resulting in major disruptions in healthcare delivery (3).

In the next sections, we present an elaborate overview of the current literature on COVID-19 and ICU patients. Nevertheless, this is not an exhaustive overview. The current literature on COVID-19 is essential for the health technology assessment (HTA), as it describes the population to whom the treatment is targeted and describes statistics on various COVID-19 clinical outcomes, such as complications, mortality and post-ICU quality of life. We argue that the ENVISION AI-based tools can **significantly improve the clinical outcomes** of COVID-19 patients in ICUs. In addition to helping improve the outcomes of COVID-19 patients, ENVISION is expected to **reduce the treatment costs** of COVID-19 patients in ICUs. This overview will be followed by our strategies to estimate the health gains and (saved) costs related to the implementation of the Sandman ICU. We also included a timeline for implementation. The Health Technology Assessment Plan will be concluded with some additional information regarding the HTA of the Sandman ICU.

1.1 Demographics and outcomes of COVID-19 patients in ICUs

1.1.1 Characteristics of critically ill patients

The median age of patients admitted to the ICU is approximately 60 years (4–8). Some studies report that the median age of the ICU population decreased slightly during the COVID-19 pandemic (6). Around 59%–80% of ICU patients are male (5,6,8–10), and almost half of all patients have hypertension (7,10). Other frequently reported comorbidities are cardiovascular disease (7,10), hypercholesterolemia (7,10), diabetes mellitus (7,10) and malignancy (7). These comorbidities have an increased risk of fatal outcomes.

The length of stay of COVID-19 patients in the ICU is heterogeneous amongst different studies (11). Several researchers have conducted a meta-analysis and reported the length of stay. Rees et al. (12) examined 52 studies in and outside China. They reported a median length of stay of 8 (interquartile range (IQR): 5–13) days for patients in China and 7 (IQR: 4–11) days for those outside China. Chang et al. (11) evaluated several studies in the US and Europe and found a pooled mean duration of 7.78 (7.05–8.51) days. Serafim et al. (13) examined the mean length of ICU stay for five studies around the world and found a mean length of stay of 9.0 (95% Confidence Interval (CI) 6.5–11.2) days. Patients with a fatal outcome generally had a shorter length of stay than patients who survived (12). There was no significant difference in the length of stay over time (12).

1.1.2 Complications of COVID-19 in ICUs

The responses of the immune system to COVID-19 differ quantitatively and qualitatively amongst patients (14). COVID-19 ICU patients often contract severe complications. The common ones include sepsis, acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), venous thromboembolisms (VTE) and cardiovascular complications.

Hyperinflammation and coagulopathy increase the severity in COVID-19 (15). Severe COVID-19 is closely related to sepsis, and most COVID-19 deaths in the ICU are caused by viral sepsis (15). Some researchers argue that sepsis caused by Severe Acute Respiratory Syndrome Coronavirus-2 explains the majority of severe COVID-19 cases (16). In a small Chinese study, Zhou et al. (17) found sepsis to be the most frequent complication in hospitalised COVID-19 patients. The median onset of sepsis in this study was 9 days, and none of the COVID-19 patients with sepsis survived. Sepsis is a severe complication with a high mortality rate; the mortality rates for sepsis have been estimated to be 30%–50 % (18). More than 50% of patients who experience septic shock have a fatal outcome (18). Despite the severity of this complication, sepsis is often an undetected complication (19).

More than 80% of COVID-19 patients develop ARDS (11). However, the prevalence of ARDS differs greatly between studies, and ARDS often remains undetected (20). Patients with a higher age are at an increased risk of developing ARDS (21). Moreover, ARDS is associated with an increased risk of a fatal outcome (11). Some researchers suggest that COVID-19-induced ARDS has worse outcomes than ARDS from other causes (22).

Problems with the kidney ranging from the presence of proteinuria and haematuria to AKI are fairly common amongst COVID-19 patients in ICUs (23). Almost 90% of mechanically ventilated COVID-19 patients developed AKI (24). Moreover, almost a quarter of mechanically ventilated COVID-19 patients require renal replacement therapy (24). The risk factors for AKI include increased age, diabetes mellitus, cardiovascular diseases and hypertension (24). These factors are exactly the risk factors for COVID-19 ICU mortality (see Section 1.1.3). Researchers are not sure how similar COVID-19-induced AKI is to sepsis-induced AKI, and there is still much uncertainty regarding how COVID-19-induced AKI can be managed (25).

The prevalence of VTE differs greatly amongst different studies (26). VTE consists of pulmonary embolism (PE) and deep vein thrombosis (DVT) (26). In a systematic review, Nopp et al. (26) found that both hospitalised and non-hospitalised COVID-19 patients are at risk of developing VTE. More specifically, they estimated a prevalence of 22.7% (95% CI, 18.1–27.6), 18.7% (95% CI, 12.6–25.6) and 13.7% (95% CI, 10.0–17.9) for VTE, DVT and PE in ICU patients, respectively.

Next to pulmonary problems, systematic inflammatory responses, kidney problems and thrombosis, cardiac complications may also occur (27). Myocardial injury, myocarditis, acute myocardial infarction, heart failure and arrhythmias are all likely to be present in COVID-19 patients (27,28). Little is known about the prevalence of myocarditis in COVID-19 patients (28). Cases of myocarditis are mentioned throughout the literature, but proven cases with autopsies and endomyocardial biopsy are rare (28). In a systematic review, Pellicori et al. (29) estimated the prevalence of cardiovascular events based on biomarkers and imaging to be 8.7%–72%. Hence, there is much variability between studies in the prevalence of cardiovascular events. All these complications together lead to high mortality rates in the ICU, thereby emphasising the need for the improved treatment of COVID-19.

1.1.3 Mortality and risk factors

The mortality rates of critically ill COVID-19 patients are heterogeneous between studies (30,31). Armstrong et al. (31) estimated the ICU mortality rates of COVID-19 patients using a systematic review. This review contained 24 international studies with a total of 10,150 patients. They estimated a worldwide ICU mortality rate of 41.64% and an ICU mortality rate of 48.44% for patients from Europe. Remarkedly, the ICU mortality rate did not differ significantly between continents. ICU mortality rates dropped to 20%–25% over time (32,33). This change in ICU mortality rates was still significant when correcting for patient demographics and comorbidities (33). Advances in treatment, such as applying dexamethasone, may explain the drop in ICU mortality rates (33,34). To date, new treatments, such as remdesivir (35) and tocilizumab (36), have been developed and tested in clinical trials to reduce the mortality rates of COVID-19 patients.

Mortality is higher amongst older patients (4,5,17,21,37–42). Males, in general, are at risk of severe COVID-19 outcomes (5,37,38,40–42). In a meta-analysis involving 44,672 COVID-19 patients, males had an almost 1.7 times higher risk of a fatal outcome from COVID-19 (37). Moreover, patients with comorbidities have a higher risk of a fatal outcome (37,38,42), with hypertension being the most frequently mentioned (5,37,39,43). According to one study, hypertension leads to a 1.8-fold higher risk of severe COVID-19 and a 2.2-fold higher risk for mortality (39). Other frequently mentioned comorbidities with a higher risk of fatal outcome were cardiovascular disease (4,37,42), respiratory disease (5,37,38,42), chronic kidney disease (4,42), diabetes (4,5,37), hypercholesterolemia (5), obesity (42), dementia (42) and cancer (37,42).

1.2 Post-ICU survival of COVID-19 patients

To date, little literature is available on the long-term effects of COVID-19 infections. One of the largest studies with the longest follow-up was conducted by Huang et al. (44), who evaluated the health of 1,733 COVID-19 survivors from a Chinese hospital 6 months after discharge. However, only 4% of these patients stayed in the ICU. They found that 76% of the survivors experienced at least one symptom. Fatigue or muscle weakness, sleep difficulties and anxiety or depression were the most common symptoms. The proportion of women having symptoms 6 months after onset was higher than that of men, as well as for patients who received high-flow nasal cannula, non-invasive mechanical ventilation and invasive mechanical ventilation. However, men were more often severely ill. Patients who received respiratory support and/or mechanical ventilation had an increased risk of pulmonary diffusion

abnormality, fatigue or muscle weakness, and anxiety or depression. From these patients, 81% had fatigue or muscle weakness 6 months after discharge, 56% had lung diffusion problems, 41% experienced pain or discomfort, 32% had anxiety or depression and 14% had mobility problems.

Other researchers examined the health-related quality of life after ICU admission with other corona viruses. In a cohort from 15 years, Zhang et al. (45) found that 15 years after a severe acute respiratory syndrome (SARS) infection, 38% still had reduced lung diffusion capacity. The lungs of SARS ICU survivors made a substantial recovery in the first year after the infection, but their recovery stagnated, and pulmonary function after 1 year was equal to that at 15 years. Ahmed et al. (46) explored the long-term effects of corona viruses, such as SARS and Middle Eastern Respiratory Syndrome (MERS), after hospitalisation or ICU admission. They found that SARS and MERS survivors often suffered from impaired lung function, psychological problems and reduced exercise capacity up to 6 months after discharge. More specifically, they found that 27% (95% CI: 15%–45%) of SARS and MERS survivors had impaired diffusing capacity for carbon monoxide up to 6 months after discharge. This percentage remained high at 24.35% (95% CI 11.05%–45.46%) 6 months after hospital discharge. Furthermore, they found a high prevalence of post-traumatic stress disorder (39%, 95% CI 31%–47%), (33%, 95% CI 20%–50%) and anxiety (30%, 95% CI 10–61%). SARS and MERS survivors had a low health-related quality of life on the SF-36 up to 6 months after discharge. Beyond 6 months, the health-related quality of life increased slightly but was still lower than that of people with a chronic illness.

Critically ill COVID-19 patients often require mechanical ventilation (7). The valid predictors for post-ICU impairment for these patients are the Functional Independence Measure at 7 days post ICU discharge (47), length of stay in the ICU (47), patient age (47), earlier anxiety and/or depression (48), being divorced or separated (48) and not being discharged directly to home from acute care (48). The risks for long-term cognitive, physical and emotional complications increase with length of stay (49). ICU patients who receive mechanical ventilation often experience a reduced quality of life post discharge (48). The duration of mechanical ventilation influences pulmonary dysfunction and anxiety levels after discharge (50). Each extra day of mechanical ventilation has a significant effect on post-ICU disability (odds ratio 1.04 (CI 1.01, 1.08)), which ultimately leads to a reduced health-related quality of life (i.e. a utility score of 0.5 ± 0.26) (48). In addition, ICU survivors have a lower survival rate for at least 15 years, and length of stay has a significant effect on this survival rate (51). Comparable results can be expected from COVID-19. Researchers expect COVID-19 ICU survivors to be susceptible to post-intensive care syndrome (PICS) (52). Comorbidities that are highly prevalent for COVID-19 patients in the ICU are the most common comorbidities for people developing PICS (52). Considering the severity of the outcomes of COVID-19 ICU patients, studying the effectiveness of treatments is of great importance.

1.3 Costs of ICU for COVID-19 patients

COVID-19 heavily disrupted hospital funding around Europe (53). To manage the higher number of COVID-19 patients in Europe in ICUs, hospitals had to invest in new hospital beds, new ventilators and protective personal equipment (53). Many European countries provided additional funding for hospitals to cope with COVID-19 patients. For example, in 2020, German hospitals received €50–100 per patient to spend on protective personal equipment, and they also received a higher nursing fee per day to increase the amount of nursing care (53). In the Czech Republic, hospital fees were adjusted to adequately cover the costs for COVID-19 care (53).

Length of stay has a significant effect on the medical costs of a patient (54). Reducing the length of stay would considerably reduce medical costs. More than 85% of the variance in total hospital costs can be explained by length of stay in the ICU and hospital stay (54). The first day in the ICU is the most expensive day and costs up to five times more than a post-ICU hospital day in a regular ward (54).

Subsequent days cost more than twice as much as a post-ICU hospital day (54). Each extra day a patient spends in the ICU leads to approximately 1.5 extra days in a non-ICU bed (55). A key factor contributing to the higher costs in the ICU is the presence of mechanical ventilation (53,56). This increase in costs attributed to mechanical ventilation is the highest for respiratory diseases (56).

Czernichow et al. (57) estimated the average hospital costs per day for COVID-19 patients in 32 European countries. Using the costs for four different European countries (Denmark, Spain, France and the UK) and a relative cost index from Eurostat, they estimated an average cost per day of €883 for a general hospital admission, €1.925 for an ICU admission and €3.183 for an ICU admission with mechanical ventilation (57). The estimated costs of a COVID-19 ICU stay per day vary greatly per country. For example, in Croatia, the estimated costs for an ICU stay were €397 and €657 for an ICU stay with mechanical ventilation, whereas in Lichtenstein, these were €5.389 and €8.911. There are not yet any numbers available on the costs of a COVID-19 patient post hospital discharge.

2 Methods

2.1 Digital tools to enhance the treatment of COVID-19

One of the biggest challenges that intensivists and ICU medical staff face is the amount of data an ICU patient generates and the decisions that come with it. The health of a COVID-19 patient in the ICU can deteriorate quickly, meaning that ICU medical staff should strive to anticipate changes in health states and act promptly. In addition, considering the novelty of COVID-19, a consensus on treatment regimens is lacking in some cases (58,59). Digital tools exploiting AI may aid ICU medical staff in making these decisions. AI tools can process and analyse enormous amounts of data in real time and provide ICU medical staff with predictions on health states or treatment recommendations.

Several researchers have presented AI tools for ICUs. Ryan et al. (60) used machine learning to successfully predict ICU mortality in COVID-19 patients. They showed that mortality can be predicted 72 hours in advance using vital signs and laboratory data. Rehm et al. (20) developed an AI system that was able to detect the presence of ARDS and the occurrence of patient ventilator asynchrony. Other researchers have studied the prediction of sepsis for ICU patients. For example, Ibrahim et al. (61) compared various machine learning algorithms to predict sepsis. They used several subpopulations of septic patients with distinct organ dysfunction patterns. Using these distinctions, they were able to predict sepsis with an area under the curve (AUC) of 0.96. Several other researchers have used machine learning algorithms to detect sepsis 12–24 hours before onset (62,63). The detection of sepsis using AI seems to be more effective than other existing sepsis screening tools, such as Sequential Organ Failure Assessment score and systemic inflammatory response syndrome score (19). To date, little research is done on treatment recommendation using AI for COVID-19 patients in ICUs.

2.2 The AI-based systems of ENVISION

The **goal of ENVISION** is to develop and implement a digital tool called the Sandman ICU, which uses AI to improve the treatment options for COVID-19 patients in ICUs. The Sandman ICU will use real-time monitoring of various vital parameters and will support the decision making of medical staff. Each hospital bed in the ICU will have an iPad which will be connected to devices, such as a respiratory unit or a monitor. The Sandman ICU app will automatically process the data from the connected devices. Medical staff can also input additional information, such as medical history, laboratory values and applied medication. The data will be automatically processed with AI in a server. Medical staff can request that the Sandman ICU provide recommendations on medications, such as anticoagulants, or on treatment regimens, such as positioning.

The AI experts involved in the ENVISION project developed 10 different use cases demonstrating the different possibilities of integrating AI into healthcare settings. These use cases can be found in Deliverable D.3.2. The Health Technology Assessment Plan will be based on these use cases. We divided the use cases into three distinct categories:

1. An AI-based system that provides recommendations on treatment based on earlier observations and/or the current clinical guidelines
2. An AI-based system that predicts sepsis
3. An AI-based system that recommends the inclusion of a specific patient in a clinical trial

A general overview of all the use cases and the proposed categories can be found in Figure 1. In Section 2.2.1–2.2.3, we will elaborate on the three different categories of use cases. For each of these categories of use cases, an HTA strategy was developed (see Sections 2.4–2.6).

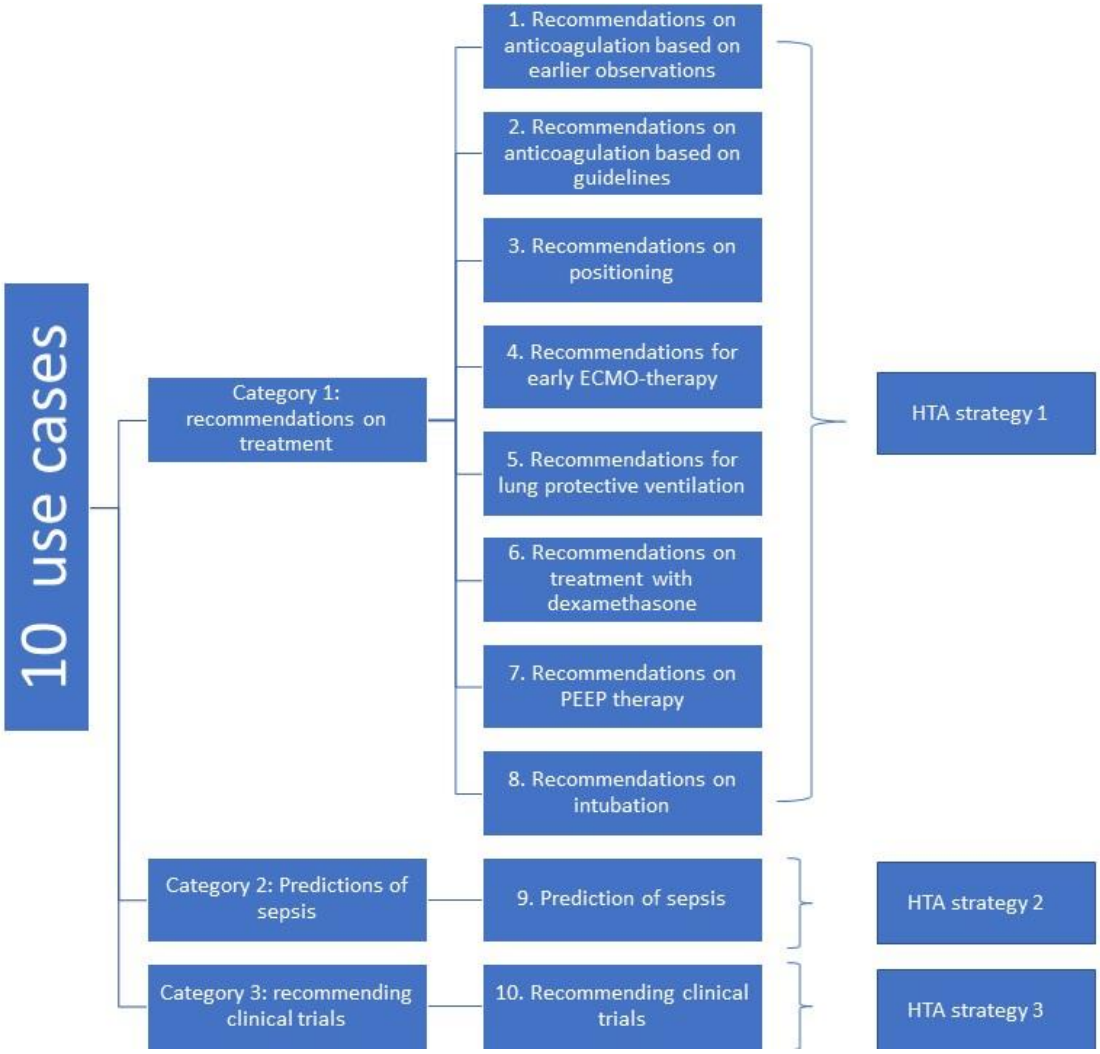

Figure 1. Overview of the use cases and the categories. For more info on each use case, refer to: Deliverable D.3.2 COVID-19 use cases and ICU scenarios.

2.2.1 Category 1: An AI-based system that provides treatment recommendations

The first category of use cases for the Sandman ICU consists of AI-based systems that provide **treatment recommendations** based on earlier observations and/or the current clinical guidelines. As an example, we will show how the Sandman ICU can provide recommendations on the use of dexamethasone. The Sandman ICU can inform the medical staff that a patient can benefit from dexamethasone treatment. This recommendation will be based on clinical guidelines available online, similar cases in Europe and the patient's record for certain pre-existing conditions. In addition, the Sandman ICU can calculate the best dose for the patient and the optimal treatment duration. Figure 2 shows how the Sandman ICU decides on the best treatment regime for dexamethasone. Note that for illustration purposes, we chose dexamethasone to represent this category of use cases, but a similar system can provide recommendations on anticoagulant treatment, positioning, timing of intubation and more. For an overview of all the use cases included in this category, please refer to Figure 1.

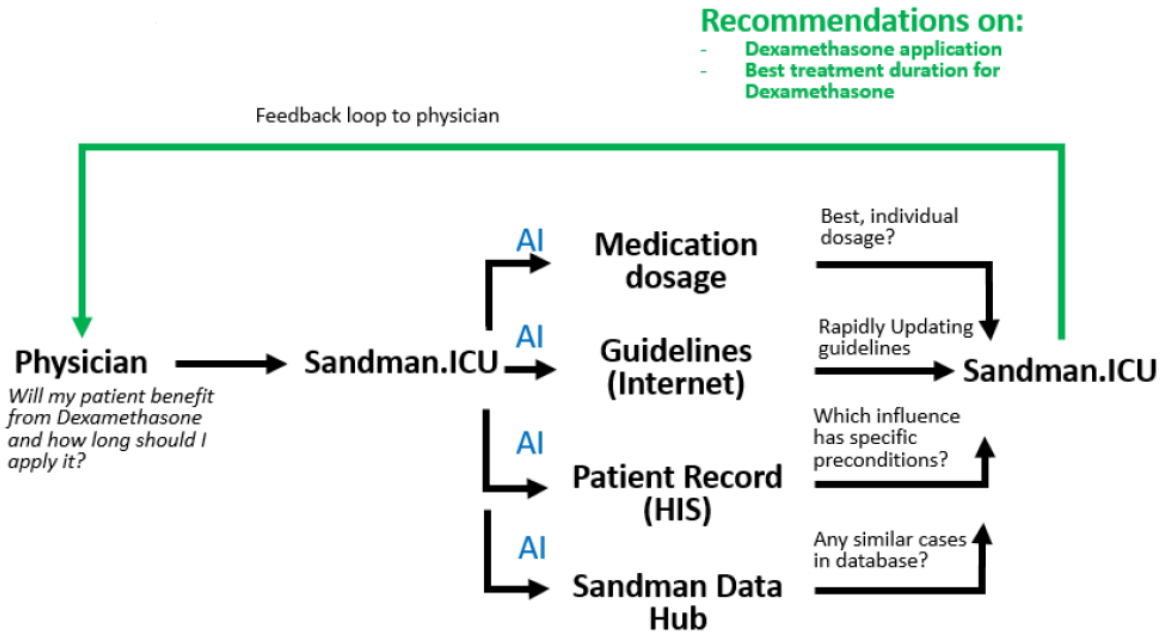

Figure 2. Flowchart of the recommendations of the Sandman ICU for dexamethasone. Other use cases in category 1 work according to a similar mechanism. Figure from Deliverable D.3.2 COVID-19 use cases and ICU scenarios.

2.2.2 Category 2: An AI-based system that predicts sepsis

The second category of use cases is the prediction of sepsis. Sepsis is a severe complication with a high mortality rate that often remains undetected. It is one of the most frequent complications in hospitalised COVID-19 patients. For a more extensive overview of sepsis in COVID-19 patients, please refer to Section 1.1.2. The Sandman ICU will be able to provide the doctor with a warning that a patient is possibly experiencing a sepsis infection.

Suppose the situation of a patient in the ICU is deteriorating. The patient's heart rate and breathing frequency have slowly increased over time, and they have a low blood pressure and a low body temperature. As these changes happened gradually over time, the ICU doctor did not suspect a superinfection on time. However, based on the respiratory status, vital status, laboratory parameters and medical history of the patient, the Sandman ICU provides the doctor with a warning that this patient possibly has a secondary infection. Basing on this, the doctor decides to order a microbiological test, and shortly after, the test comes back positive. Figure 3 illustrates the flowchart that the Sandman ICU uses to predict sepsis.

In the HTA, we will evaluate the effect of two types of predictions: **predictions of sepsis at onset** and **predictions of sepsis before onset**. The effect of predictions of sepsis at onset will be measured by comparing the predictions with the state of the art of sepsis detection, whereas the effect of predictions of sepsis before onset will be estimated using health economic modelling.

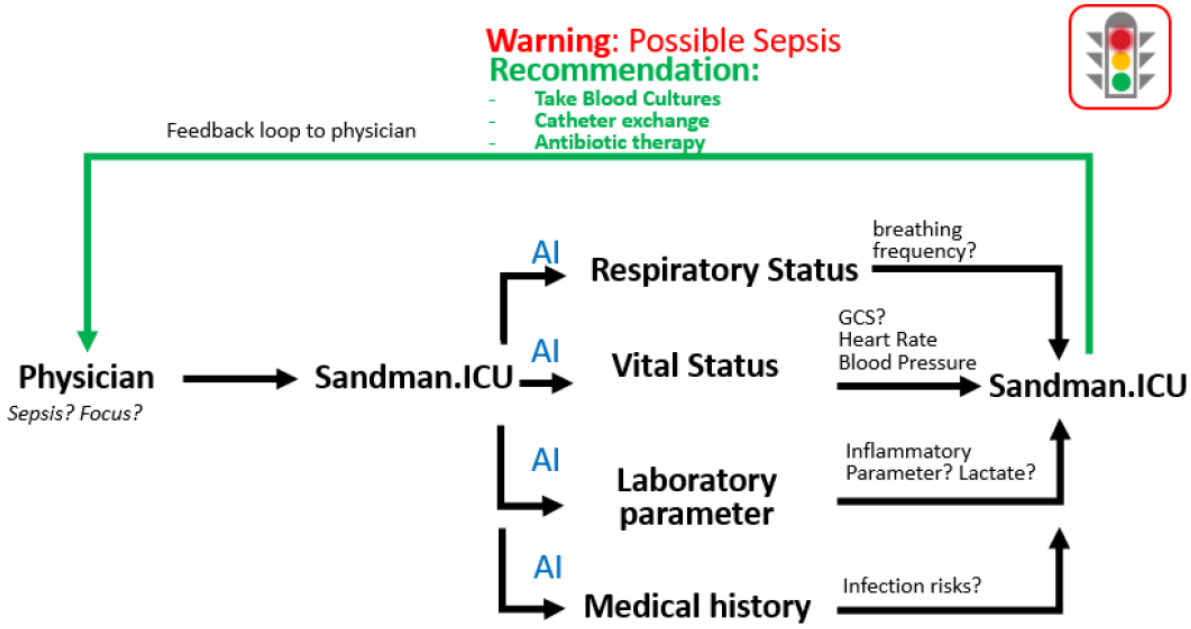

Figure 3. Flowchart of the predictions of the Sandman ICU for sepsis. Figure from Deliverable D.3.2 COVID-19 use cases and ICU scenarios.

2.2.3 Category 3: An AI-based system recommending clinical trials

The third category of use cases is an AI-based system that **recommends the inclusion of a specific patient in a clinical trial**. We will illustrate this with an example. Suppose a patient in the ICU had intensive medical treatment, but their situation is still deteriorating. The ICU doctor is considering including this patient in a clinical trial. However, there are multiple studies, and it will be time consuming for the ICU doctor to find a suitable study for this patient. The ICU doctor can consult the Sandman ICU, and basing on the respiratory status, vital status, laboratory parameters and medical history of this patient, the Sandman ICU will provide the ICU doctor with a suitable clinical trial for this specific patient. Figure 4 illustrates the flowchart for this use case.

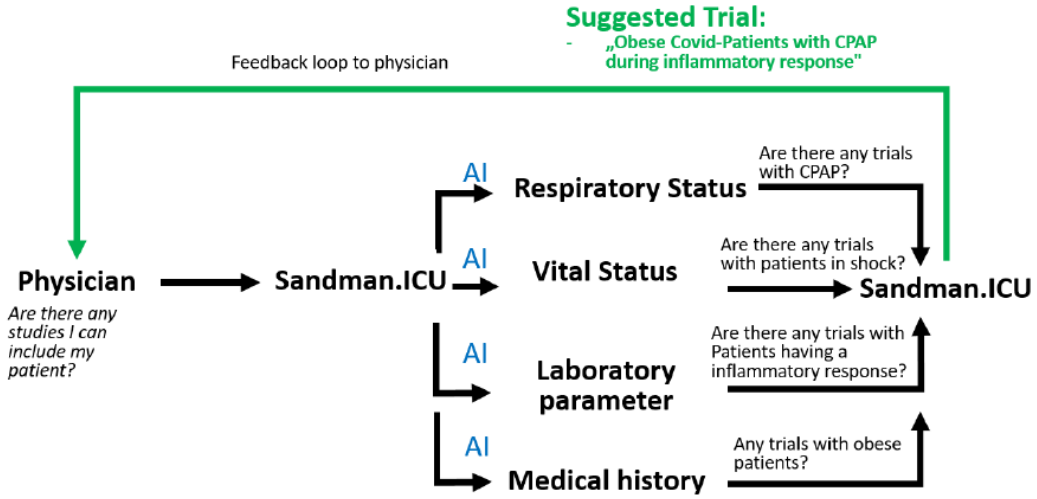

Figure 4. Flowchart of the recommendations for a specific patient to be included in a clinical trial. Figure from Deliverable D.3.2 COVID-19 use cases and ICU scenarios.

2.3 Defining the outcome variables

To express the effectiveness of the different use cases, we will use various outcome variables. One is **survival**. Considering the substantial number of patients with COVID-19 in ICUs worldwide, many lives can be saved by increasing the survival rate in ICUs. Related to this is the **number of life years saved**, which can be derived from a patient's life expectancy. Another outcome is the decrease in **the length of stay** or **duration of mechanical ventilation** of COVID-19 patients in ICUs. This would be beneficial for the current pressure on healthcare systems globally. Additionally, decreasing the length of stay has a direct impact on the patient's **quality of life post discharge**, which is the fourth outcome variable that we will consider. The first three outcome variables can be directly derived from the data for the no-treatment group. The treatment effect needs to be estimated using the economic models defined in the following sections. To estimate the **quality-adjusted life years (QALYs)** gained by the effects of the AI system, we aim to utilise the effect of reductions in the length of mechanical ventilation mentioned earlier (48).

The fifth outcome variable that will be considered is the **costs** of the ICU stay. To ensure exact information on these costs, we will ask all clinical partners to answer a few questions about the costs of treating a COVID-19 patient in the ICU per day. We will also use the costs of the development and implementation of the Sandman ICU.

In the next sections, we will introduce strategies on estimating these outcome variables for each category of use case. Furthermore, we will demonstrate how these outcome variables are used to perform the HTA.

2.4 Category 1: HTA for an AI-based system that provides treatment recommendations

Below, we illustrate two different methods on how we could assess the effectiveness of the first category of use cases. As an example, we will illustrate this with recommendations on anticoagulants. However, a similar approach can be taken for the other use cases that recommend a treatment based on the guidelines and/or data (category 1). Both methods start with creating a dummy variable that indicates if a patient was treated according to the recommendations of the AI system.

Suppose a patient with COVID-19 stays in the ICU for three days and starts to show signs of thrombosis. Further research reveals acute limb ischemia. The next step would be to administer a type of anticoagulant. Based on the patient's records, as well as the data of the Sandman data hub, a type of anticoagulant and a dose will be recommended by the AI system.

The goal of the HTA is to investigate the effectiveness of these recommendations. To do this, we will use the collected data, for which no recommendations were made by the AI system. To investigate the possible effectiveness of the AI system, we apply the system to the collected data and classify for each patient whether the recommended anticoagulant was given, as well as the recommended dose. The dose can be epsilon apart from the recommended dose, i.e.

$$\left|Dose_{given} - Dose_{recommended}\right| < \epsilon,$$

where $Dose_{given}$ is the actual applied dose of the anticoagulant, $Dose_{recommended}$ is the recommended dose by the AI system and ϵ is the threshold of the deviation between the recommended dose and the actual dose. The epsilon values will be obtained using expert elicitation. Expert elicitation is an established technique in HTA, particularly in situations where empirical evidence is limited (64). A dummy variable will show if the applied anticoagulant and the dose were consistent with the recommendations (group 1) or not (group 0). Patients receiving an anticoagulant that differed from the recommended anticoagulant and/or received another dose would probably have a different outcome when the AI system provides recommendations.

To investigate the effectiveness of the AI system, we assume that whenever the system provides the doctor with recommendations, the outcomes of patients in group 0 are equivalent to those of the patients in group 1 with similar demographical characteristics and comorbidities. We **match** the patients in group 0 with several patients from group 1 with similar demographical characteristics and comorbidities using a combination of exact matching and propensity scores. Then, we calculate the mean length of stay and the proportion of deaths of the matched patients. We will assume that this will be the length of stay and the proportion of deaths for the patients in group 0 in the case that the AI system would have been available.

The health gains and cost savings of using the AI system can then be estimated by subtracting the original length of stay from the new length of stay using the AI system. The same can be done for ICU survival.

Another possibility is to simulate the effect of the AI model using a **predictive machine learning model**. Two different assumptions should hold for this to be a feasible approach. First, the amount of data in the treatment group (1) should be sufficient. Second, the multidimensional distribution in the no-treatment group (0) and in the treatment group (1) needs to be similar. In case the multidimensional distributions are similar, we will filter for all the patients in group 1 and split this dataset into a training set and a test set. Then, using cross validation, we will train several machine learning models, i.e. (logistic) regression, support vector machine, random forest and XGBoost, on the training set to predict either survival or length of stay. The model with the best average performance on the validation set will be selected. This model will be tested on the test set, and the performance of the model will be measured using either AUC or mean squared error depending on the outcome variable. In case the model performs well, it discovers the (nonlinear) relationships between the outcome variables and several patient characteristics when following the recommendations of the AI system. Then, to simulate what would have happened if the ICU doctors of the patients in group 0 had followed the recommendations of the AI system, we will allow the model to predict the outcomes of the patients in group 0. The model will provide predictions for each patient, and these will be based on the underlying mechanisms of the (nonlinear) relationships between the outcome variables and several patient characteristics when following the recommendations. Then, to estimate the effect of the AI system, we can look at the differences between the predictions of the model and the real outcomes in terms of survival, ICU stay and costs.

2.4.1 Estimating health gains post ICU

Based on the estimated increased survival, the **number of life years gained** can be estimated using life expectancy tables. The reductions in the length of stay or duration of mechanical ventilation can be used to estimate the health-related quality of life post ICU. Both length of stay and length of mechanical ventilation have a significant effect on this (47,48). Currently, there is no research relating length of stay or length of mechanical ventilation with COVID-19 patients' health-related quality of life post ICU. Therefore, to estimate the long-term health gains, we assume for now that the effect is similar amongst all ICU patients. Earlier research has shown that each extra day of mechanical ventilation increases the risk of being moderately to severely disabled post discharge by 1.04 (48). Multiplying the reduction in the length of mechanical ventilation with 1.04 results in a decrease in the odds of being moderately to severely disabled post discharge. Hence, fewer patients will be moderately to severely disabled after ICU discharge. Research has shown that 6 months after discharge, patients with no to mild disability have a utility score of 0.77, whereas moderately to severely disabled patients have a utility score of 0.5 (48). To obtain the **QALYs gained** with the recommendations of the Sandman ICU, we can multiply the

differences between these utility scores (0.77–0.50 = 0.27) with the number of life years gained and the reduced proportion of moderately to severely disabled patients discharged from the ICU, i.e.

$$QALYs\ gained = 0.27 * n * p_{disabled,}$$

where *n* is the number of life years gained, and $p_{disabled}$ is the reduction in the proportion of moderately to severely disabled patients discharged from the ICU.

2.4.2 Relating the costs to the treatment benefits

With the above methods, reductions in the length of stay using the AI system can be inferred. This can be translated into **reductions in the costs** of ICU treatment and possibly to reductions in the costs of post ICU care. To **evaluate the cost effectiveness** of the AI system, we calculate the incremental cost-effectiveness ratio (ICER). Using the ICER, we will compare the costs with the benefits of the AI system. Hence, we can look at the increased survival rate, number of saved life years and the QALYs gained compared to the costs.

2.5 Category 2: HTA for an AI-based system that predicts sepsis

2.5.1 Predictions of sepsis at onset

To estimate the benefits of Sandman ICU warnings for a possible superinfection, we need to estimate the increase in detected sepsis cases. For this, a similar approach will be taken as in the paper of Calvert et al. (19). To estimate the increase in true positives, we will **compare the sensitivity** of the Sandman ICU with that of the risk stratification scores and/or triage systems currently used in ICUs throughout Europe, whilst keeping the specificity constant. This will be done in several discrete time moments, i.e. at onset, one hour after onset, four hours after onset and eight hours after onset. At each of these moments, we will calculate the sensitivity for equal specificity of the Sandman ICU, as well as of the other frequently used risk stratification scores and/or triage systems. If the Sandman ICU detects sepsis at onset for a certain patient, whereas the risk stratification scores and/or triage systems detect this infection four hours later, this patient has the benefit of receiving the treatment 4 hours earlier. Ferrer et al. (65) estimated the effect of delayed adequate treatment in patients with sepsis in the ICU using generalised estimation equations. They found a linear increase of approximately 1.42% in the risk of mortality every hour the treatment was late. Using the data collected by the Sandman ICU, we can estimate the effect of delayed adequate treatment for COVID-19 patients in ICUs in a similar fashion. These effects on mortality can then be used to estimate the differences in mortality of using the Sandman ICU compared with the risk stratification scores and/or triage systems currently used in ICUs around Europe. Finally, to estimate the reductions in the length of stay with timely adequate treatment, we will use generalised estimation equations. The possible increase in true positives using the Sandman ICU can then be used to estimate the total decrease in length of stay.

2.5.2 Predictions before the onset of sepsis

The early identification and treatment of sepsis are important factors that increase the odds of survival (65). In an ideal scenario, an ICU doctor would detect that a patient is developing sepsis before the onset of the sepsis. AI may pick up on **nonlinear relationships** between variables that are predictive of sepsis but are impossible to observe for humans. This gives rise to the opportunity to detect sepsis hours before onset. The possible benefits of knowing that a patient will develop sepsis are difficult to estimate because in general, this knowledge is not present. Therefore, to estimate the effects of knowing that someone will develop sepsis within a certain time frame, we will use **expert elicitation** (64). Experts will

be asked to reply to a few questions about administering medication before the onset of sepsis. The following is an example: What are the adverse effects, in terms of length of stay and fatal outcomes, of sepsis treatments for false positives, that is, when the AI system predicts that a patient is going to develop sepsis, but they do not? Conversely, what are the beneficial effects for true positives?

Then, to estimate the effects of predictions of sepsis, we will take an approach similar to that taken in Section 2.4. To ensure that our estimations are not biased by overfit, we will use the test set used by the AI experts of ENVISION to evaluate the AI system. Then, we will label all patients who developed sepsis during their stay as 1 and all the other patients as 0. We will apply the AI system to the test set and identify the true positives, i.e. all patients who were predicted to develop sepsis and indeed developed it. These patients could have benefitted substantially from early adequate treatment. To estimate the health gains these patients could have received, we assume that adequate treatment before the onset of sepsis leads to the prevention of sepsis. Therefore, we can assume that the outcomes of these patients would have been similar to those of the patients who did not develop sepsis. We will **match** each true positive in group 1 using propensity scores with the patients in group 0 with similar demographic characteristics and comorbidities. Then, we can assume that the outcome of these patients in group 1 would have been similar to the mean outcome of the matched patients in group 0.

In the case that there are sufficient data and the multidimensional distributions between the patients who developed sepsis and those who did not are relatively similar, we could train **a machine learning model** on the test data of the patients who did not develop sepsis. This model will then predict survival and length of stay and will be based on the dynamics of patients who did not develop sepsis. Then, to simulate the effect of early adequate treatment, we will use this model to predict the outcomes of the true positives. This will simulate the effect of the prevention of sepsis. The differences between the predicted outcomes and the true outcomes are the possible health gains of the model.

However, treatment for sepsis might also have some **adverse effects** in cases in which it is unnecessary. To estimate these effects, we need to identify the false positives, that is, those patients who were predicted to develop sepsis but did not actually do so within a certain time frame. Combining the number of false positives with the adverse effects of receiving an unnecessary treatment for sepsis (obtained from expert elicitation) derives the adverse effects of the AI system. Then, to estimate the health gains of the AI system, we will combine the health gains of early adequate treatment for the true positives with the possible adverse effects of receiving unnecessary treatment for sepsis.

2.5.3 Estimating health gains post ICU

To estimate the health gains post ICU of an AI-based system that predicts sepsis, we will use a similar approach as that taken in Section 2.4.1.

2.5.4 Relating the costs to the treatment benefits

Treatment benefits will be related to the cost using the ICER. The ICER for the prediction of sepsis for COVID-19 patients in ICUs can be calculated in a similar fashion as in Section 2.4.2.

2.6 Category 3: HTA for an AI-based system recommending clinical trials

Hospitals spend much time selecting the right patients for trials. A possible use case of the Sandman ICU would be to automatically assign patients to trials. The use of this application can help **save much time**—time which can be spent more efficiently. The time saved using this system can be estimated and translated into **saved costs**. Trials are important for the development of new treatments. Filling trials with more patients reduces the uncertainty in the estimation of treatment effects, which can be

translated into the value of information (66). Moreover, when trials are filled up earlier, the analysis of effectiveness can be done in an earlier stage, meaning that successful treatments can be applied earlier in practice. As an example, we can take the trial for dexamethasone (34). In this trial, researchers found that the proportion of patients with a fatal outcome was significantly reduced in the treatment group (i.e. 29.3% vs. 41.4%) (34). This means that starting this treatment earlier may have saved many patients. However, the effects of different treatments vary between trials. Estimating the benefits of filling up trials earlier is therefore very challenging, and the cost-effectiveness of this use case may be difficult to demonstrate, although saving time is something that will always be worthwhile in usually understaffed ICU departments.

3 Overview of the proposed strategies

Figure 5 shows an overview of the proposed strategies to estimate the health gains and saved costs per category of use case. The effectiveness of the first two categories of use cases will be expressed using the estimate of increased survival, reductions in the length of stay and mechanical ventilation, life years gained and QALYs. For both use cases, the costs will be analysed, and the cost effectiveness will be evaluated with an ICER. A use case will be considered cost-effective in a specific country whenever the cost per QALY is lower than the cost effectiveness threshold. For the third category of use cases, we will consider the time savings for staff, the value of information and the benefits of filling samples of trials faster.

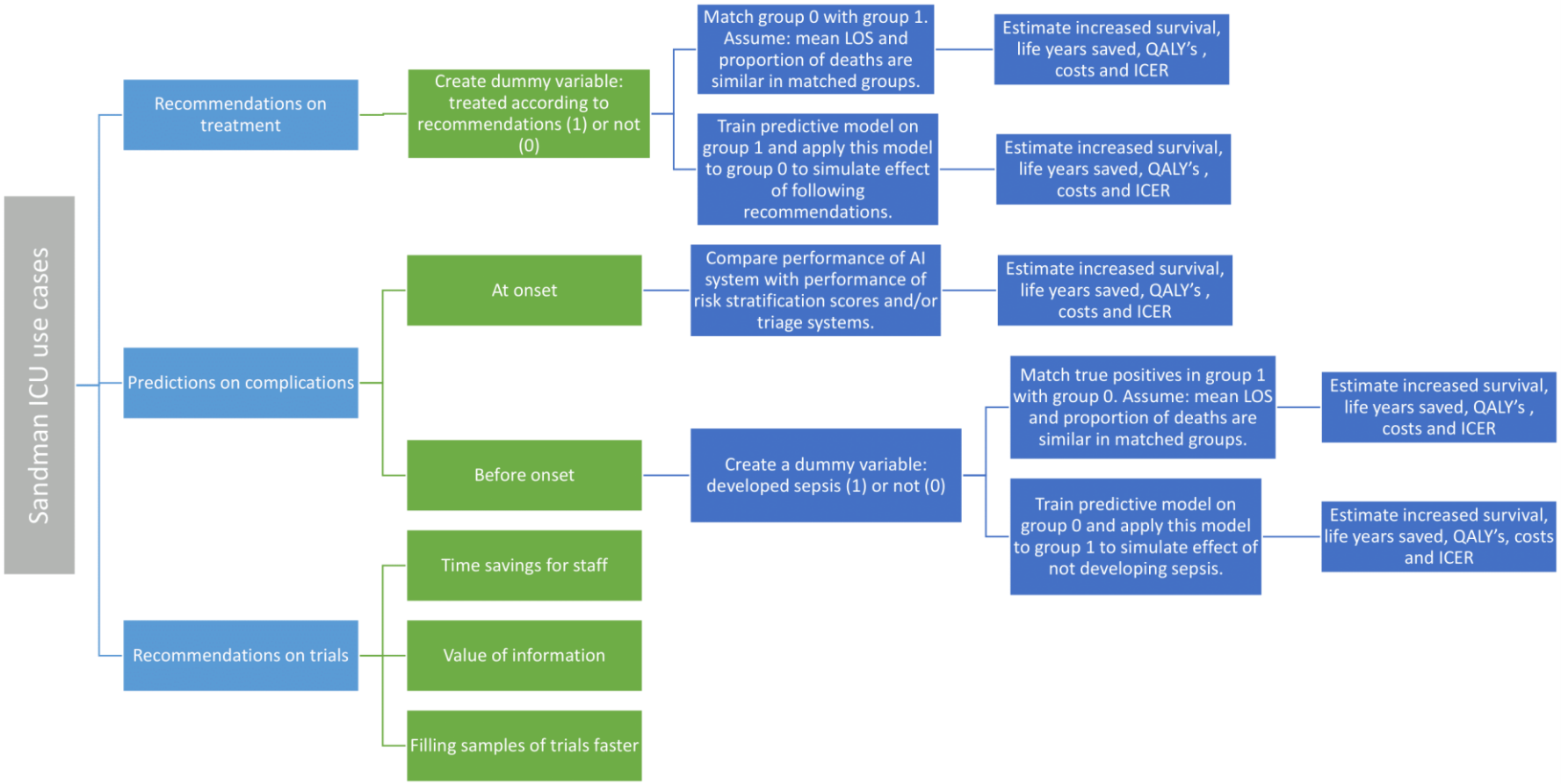

Figure 5. Overview of the proposed strategies to estimate health gains and (saved) costs per type of use case.

4 Implementation

A **timeline** for the implementation of the HTA is represented in Figure 6 below. Note that this plan is highly dependent on the data collection, as well as on the implementation of the AI done by the AI experts. This timeline is therefore subject to changes.

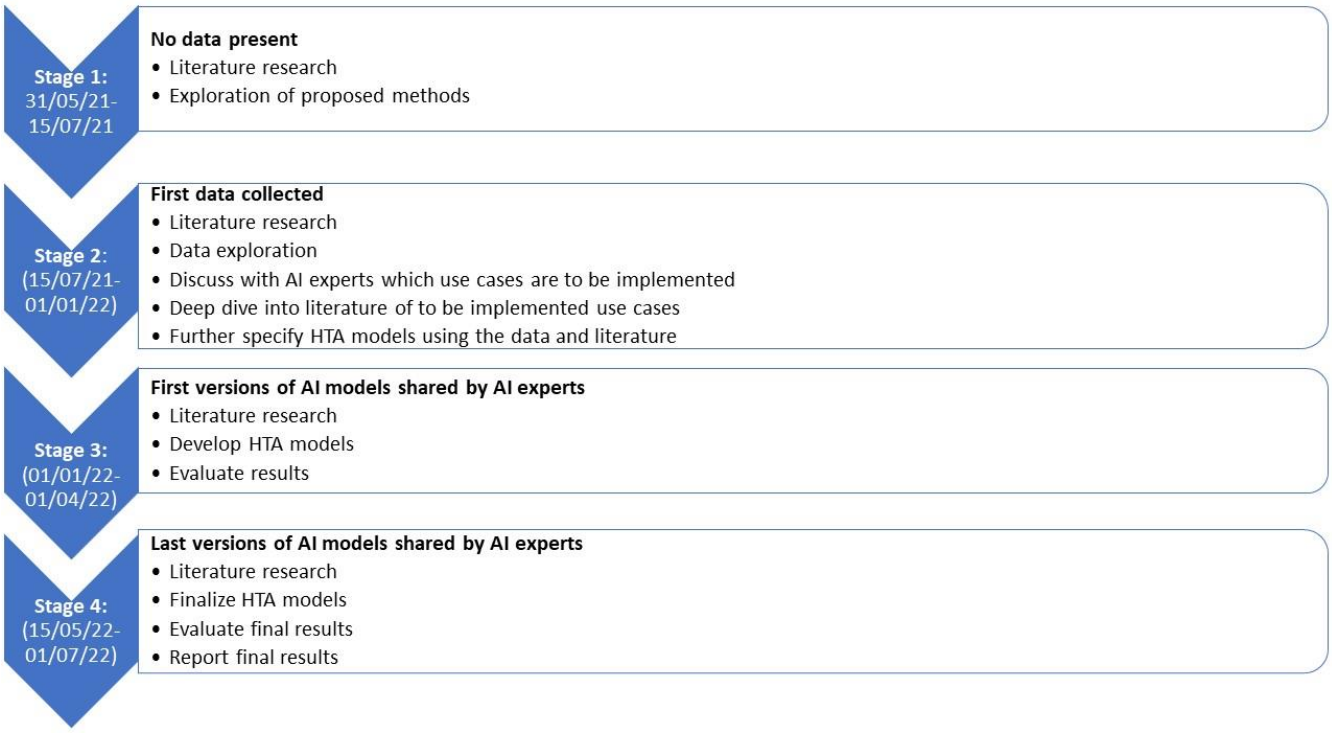

Figure 6. Timeline for the implementation of the HTA.

5 Additional information

The methods presented in this assessment plan are based on the use cases developed by the AI experts and clinicians in ENVISION. These use cases were developed before the data collection of the Sandman ICU started. Depending on the form of the data, not all use cases may be developed, use cases may be adjusted or new use cases may come about. These factors have an impact on the HTA. Similarly, the (amount of) data may not be suitable for the proposed HTAs. New information about COVID-19 in the form of literature is also published daily. This information may influence the logic or feasibility of the plans proposed here. Therefore, the final HTA may differ from the methods described in this assessment plan.

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