Technology for Health

Grant Competition
Application

Project Title:

Prevention of Delirium in the ICU using a smart lighting system: VitalSky

Topic Group:

Medical Device Design 1

1. Contact details

Main applicant

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Title

Prevention of Delirium in the ICU using a smart lighting system: VitalSky

1.1 Keywords

Delirium, ICU, Prevention ,Smart Lighting System, VitalSky

2. Summary

2.1 Research Summary

Delirium is a recurring problem for intensive care unit (ICU) patients. Of all patients in the ICU up to 80% suffer from delirium. Seven pathways have been identified to be able to positively influence delirium, these are: restoration of the circadian rhythm, activation of the body, induce relaxation, reorient to reality, provide a sense of security, provide a sense of control and provide a sense of connection. Several technologies have been developed to try and prevent delirium via one of these pathways. Examples are audio-related devices, light-related therapies and communication aids. However, each has their limitations, most commonly they do not use a multicomponent approach and therefore the results are still poor. Philips developed a system, called VitalSky, that may be more useful. This is a large lighting system attached to the ceiling of an ICU room that mainly targets the circadian rhythm and also induces a relaxing environment and helps reorient to reality. It has already been tested in combination with other environmental changes in a small clinical trial which showed promising results. However, the effect of VitalSky alone is yet unknown even though it already has a CE mark and officially in TRL 9. Therefore, our aim is to investigate the effectiveness of VitalSky when it uses the optimal parameters for the prevention of delirium in ICU patients. For this we set out a four year research plan divided into three work packages. In work package one the primary aim is to assemble all evidence currently available about the VitalSky and research what parameter settings would work best for delirium prevention. In work package two, the effectiveness of VitalSky on the circadian rhythm is investigated by exposing healthy subjects during a test of several days to VitalSky. Work package three tests the VitalSky on the ICU in an RCT where three groups are compared: a control group, VitalSky with parameter settings one, VitalSky with parameter settings two. If the study proves VitalSky to be effective, the optimised version of the product can be implemented in hospitals.

2.2 Utilisation Summary

Delirium is a condition of mental confusion and is characterized by symptoms like disorientation, confusion and cognitive impairment. Up to 80% of patients in the intensive care unit (ICU) experience delirium at some point during their stay. The development of delirium in the ICU can prolong an ICU stay for five to ten days. It doubles the mortality rate of patients in the ICU, triples the mortality rate of patients up to six months after hospital stay and the risk of cognitive impairment, like dementia, is nine times higher in patients with delirium in the ICU compared to those who do not develop ICU delirium. The overall recommendation and protocol for the treatment of delirium in the ICU is to limit pharmacological treatment due to its risk of side-effects and the focus should be on finding a non-pharmacological treatment. The VitalSky, a smart lighting system and non-pharmacological treatment, could possibly assist in the prevention of delirium. To ensure that the VitalSky is actually able to tackle the technological problem and solve the healthcare problem, prevention of delirium in the ICU, a four-year period of research will be conducted divided into three work packages. This research surrounds the technological problem: 'How can we optimise the VitalSky system to prevent delirium in ICU patients?'. The process of transferring the product to the market as a solution to the healthcare problem can be guided using a technology transfer (TT) model and an innovation strategy helps determine the success of the innovation. VitalSky primarily falls under the market pull strategy. The TT model

that might prove most applicable is the Gibson and Slimor's model. The expectation is that there will be a return on investment as the results will most likely outweigh the investment costs into the trials. Possible obstructions to utilization are: lack of clinical evidence, the results from work package one and the difference in measurement methods between work package two and three. These obstructions can be dealt with to mitigate the risks. The main market for VitalSky is composed of hospitals that have ICUs. Thus, the people in the ICU become the main end-users; those people are: the patients themselves and the doctors and nurses who work in the ICU. The User Committee is a vital and highly valued advisory body in the pursuit of its objectives, for this project it is composed from: Philips, Medisch Spectrum Twente and/or Hospital Charité Berlin, past ICU patients, NWO and Medical Device Directive representatives. The VitalSky has a Technology Readiness Level (TRL) of 9, since it has already been developed and is currently available in few European countries. An observational study has provided several grants.

3. Current composition of the research group

There are several parties (C. M. Kim, n.d.-a) involved in the development of VitalSky. The first is Royal Philips, who is the developer and proprietor of the technology. The research group also comprises a team of four research engineers from the University of Twente. Dr.ir.G.D.S. Ludden, ir.C.M. Kim and Dr.ir. G.J. Verkerke are research engineers from the Engineering Technology faculty. Dr.T.J.L. Van Rompay is from the faculty of Behavioural, Management and Social Sciences (BMS). The Department of Anaesthesiology and Operative Intensive Care Medicine (Luetz et al., n.d.) of Charité Hospital, Berlin were associated with the development of the first concept with the funds of two other companies, Art+Com and Graft. It is to be noted that The Royal Philips is one of the consultants of Art+Com and Graft.

4. Scientific description

Delirium is a recurring problem for intensive care unit (ICU) patients. Of all patients in the ICU up to 80% (C. M. Kim, n.d.-a)suffer from delirium. Delirium is characterized by a temporary mental state of confusion with a wide variety of symptoms. The patient has a disabled memory, can be confused, and can even have delusions. There are several causes and risk factors for delirium such as prior operation, increased age and a distressing environment as can be present in the ICU. Delirium has a negative impact on the prognosis of the patient. The patient can stay five to ten days longer in the ICU, has a two times increased risk of dying in the ICU, a three times higher risk to die in the six months after the ICU and can have a permanent cognitive impairment such as dementia. (C. Kim, 2020a)[bron, Kim,C. 2020, progress meeting] [bron: Philips, 2021. ("VitalSky: Effective, personalisierte lichttherapielosung"]

The current treatment of patients in the ICU consists of pharmacological therapy sometimes combined with non-pharmacological therapy. Pharmacological therapy can be used to decrease pain or treat the conditions of the patient. However, this involves sedation of the patient which can bring the patient in a certain 'state of mind' that might have a negative impact on the development of delirium. According to (das-taskforce, 2015…) and (C. M. Kim et al., 2021a)the use of pharmacological treatments is not favourable in treatment against delirium. Prevention of delirium is favoured, and non-pharmacological treatments are recommended for the prevention of delirium. Therefore, more research and development is conducted in non-pharmacological options such as technologies.

4.1 Research contents / Introduction

As of late, research has identified seven pathways (C. M. Kim et al., 2021a) that help prevent delirium, visible in figure 1. These pathways each contribute in itself to the prevention and a combination of multiple will have a stronger impact than just one. These seven pathways are:

- Restoration of the Circadian Rhythm: regain and retain normal sleep-wake cycle
- Activation of the body: regain strength and endurance
- Induce Relaxation: prevent stress and stimulate a positive psychological state
- Reorient to reality: restore cognitive function and minimize confusion to reduce negative emotions
- Provide a sense of security: make the patient feel safe so stress is better coped with
- Provide a sense of control: control to prevent anxiety and stress
- Provide a sense of connection: prevent loneliness and anxiety

A method or technology designed to prevent delirium should act via one or preferably several of these pathways in order to achieve delirium prevention.

Figure 1: Pathways (C. M. Kim et al., 2021a) *to prevent Delirium*

Several attempts have already been made and studied to see their effect on the pathways and the subsequent prevention. One of which is the use of light therapy. The idea behind light therapy is that it should impact the circadian rhythm by suppression or stimulation of the melanin receptors(Luetz et al., n.d.) behind the eyelids. So far several studies (Pustjens et al., 2018; Simons et al., 2016; Smonig et al., 2019)been done with the use of light, either in the form of very bright light therapy, window light or the use of dynamic lighting throughout the day. However, the results have been quite inconclusive. Three studies (Estrup et al., 2018; Pustjens et al., 2018; Simons et al., 2016) using exclusively artificial dynamic light showed no difference in prevention whatsoever. One study (Patharajaroen S. et al 2018) using a very bright light therapy of more than 5000 lux did show a direct decrease in delirium incidence. The last study(Smonig et al., 2019) using window light did not showcase a decline in delirium incidence but did show a decrease in delirium symptoms.

Audio therapy is an umbrella term for multiple technologies using audio in some form to prevent delirium. One of which is the use of pre-recorded messages. A pre-recorded message (C. Kim, 2020b) could help the patient reorient to reality and provide a sense of security and connection. Two studies(Byun et al., 2018; Munro et al., 2017) were performed to assess the potential of this therapy and it was found that a text, especially from a familiar voice such as a mother, explaining the situation of the surgery and the post-operative environment caused a decline in incidence of delirium. Five studies (Cheong et al., 2016; Damshens et al., 2018; Johnson et al., 2018; C.-H. Lee et al., 2016; Sharda et al., 2019) were done to examine the effectiveness of music on delirium. These studies differed from each other in terms of personalization and the type of music. Still, even though none of the studies showed a direct effect on the incidence of delirium, almost all studies did show a positive effect on the symptoms related to delirium. Therefore, it might decrease the severity of delirium and subsequently the duration of delirium.

The third way is the video/videogame (C. Kim, 2020b). It is usually implemented as a videogame during the preoperative phase either displaying the steps of the procedures or something totally unrelated such as a film. Usage of one of these technologies is to provide a sense of security, relaxation and being connected. Virtually all studies found (Dwairej et al., 2020; H. Kim et al., 2015; J. Lee et al., 2016; Rodriguez et al., 2019; Waszynski et al., 2018) showed no significant effect on delirium incidence but did exhibit a decrease in anxiety levels which is correlated to delirium. However, most studies (Dwairej et al., 2020; H. Kim et al., 2015; Rodriguez et al., 2019) did include parental presence, so the effect of that on anxiety levels is hard to distinguish from the effect of the actual technology.

Fourth is Virtual Reality (C. Kim, 2020b) (VR). It is aimed at the pathways of relaxation, reorientation to reality and activation of the body. Three studies(Eijlers et al., 2019; Ryu et al., 2019; Suvajdzic et al., 2019) were conducted to assess the effectiveness of VR, but none of them displayed positive effects on direct delirium prevention and only one (Ryu et al., 2019) out of the three showed indirect impact in that it lowered preoperative anxiety.

Another approach is through the use of sleep aids (C. Kim, 2020b) either in the form of wearables or environmental changes. By blocking out all the environmental noise and/or the beeping of the machines in the ICU, you will enhance the sleep quality. Thus it acts upon the circadian rhythm pathway. Two studies are conducted around sleep aids. One (Demoule et al., 2017) showed an indirect effect on delirium prevention, since it increased the sleep quality and duration and decreased long awakenings by using wearable noise-blocking devices. Whether it directly prevented delirium was not measured. The other study (van de Pol et al., 2017) focused on environmental sound reduction using more strict protocols to prevent as much sound as possible and a significant decrease in incidence was measured combined with an increase in sleep quality.

The last approach is the use of communication support. Two technologies fall into this category. First, the use of an eye-tracking device (Garry et al., 2016; C. Kim, 2020b) which allowed the patient to communicate with the staff and practice simple memory games. Thereby it worked through the pathways of control and reorientation. Even though it proved to improve the patients happiness, the levels of frustration and confusion remained the same. A direct correlation to delirium incidence was not researched. The other study (bott)(C. Kim, 2020b; Nicholas et al., 2019) made use of a communication agent similar to Siri from Apple but in the form of an animated avatar. By serving as a communication tool a sense of control, connection and relaxation combined with a reorientation to reality was hoped to achieve. The results were very positive, showing both a direct and indirect link to a decrease in delirium cases on the ICU.

Even though a few of these technologies display promising results, there are still a lot of limitations (C. Kim, 2020b) regarding these technologies. For one, they usually focus primarily on only one specific pathway. Furthermore, there is little focus on improving a partients' distressing ICU environment. Next, the changing needs of the patient are not

accommodated in any of the studies. As a last point, there seems to be a limited understanding of the patient himself and his needs.

The pathways described above, are used in the development of a non-pharmacological solution by the company *Royal Philips*. This company is a technological firm that produces all kinds of products. Current development is an overarching project: the VitalMinds that contains three different components. These are:

1) Philips's ambience analysis, a measurement system of light and sound conditions.
2) The Philips VitalSky, a clinical light therapy.
3) Philips's delirium management maturity assessment. Assesses the impact of the current guidelines regarding delirium prevention and treatment to improve the patients care.

Together the three components should help to gain insight into - and will help towards the prevention of delirium. VitalSky is, from the three components, the technological product developed for the prevention of delirium by patients in the ICU. It is a key component of the VitalMinds multi-component approach. The chosen pathway for the VitalSky is the restoration of the circadian rhythm. It is a product designed to obtain a better sleep-wake cycle that makes use of a smart light system, visible in figure 2. Next to enhancing and synchronizing the circadian rhythm, the VitalSky should support a pleasant and calming environment, encouraging reorientation, and supporting the cognitive stimulation of patients. The developed smart light system of Philips can operate using different kinds of parameters such as illuminance, luminance, light sources, colours, brightness, etc. The VitalSky has two designs, a basic design and an advanced design that differ in the length, size, and use of light. A current design exists of an artificial sky, placed above the bed, that is four meters in length and two meters in width and has 13.000 LEDs (different kinds) in the ceiling installation.

Figure 2: Philips VitalSky (Digital Nature, UT)

To test the VitalSky, a few trials and research have been performed. First, knowledge was gained in research towards the conditions and aspects to consider towards ICU patients. Effects of pain, sedation, and delirium were tested. Effects of these aspects could be an increase of anxiety or stress, reduced sleep, mental confusion which all can result in longer stays on the ICU's and reduce mortality. To prevent delirium a cause-effect connection needs to be found in order to develop a specific technology. From research (Deffland et al., 2020; Devlin et al., 2018), a certain connection in the decrease of delirium was found by obtaining a better sleep-wake cycle, also called the circadian rhythm.

Studies towards the various lights available and about the clinical use of the VitalSky were performed. One of these studies is the study performed by (Luetz et al., 2016). This study examined photometric parameters of different electric light sources in the ICU. The efficiency of the light is measured with respect to the gaze of the patient and the suppression of melatonin. The outcome of the study mentions the difference in the use of LED layers and RGB layers and the angle of placement above the bed of the patient. A LED light-ceiling revealed higher illuminance levels but also a higher circadian effective irradiance compared to the two different fluorescent lamps. Both outcomes are with respect to the thresholds of the suppression of melatonin (healthy young adults: 0,3 W/m^2 and healthy people > 60 years old: 0,6 W/m^2)(Brainard et al., 2001; Thapan et al., 2001). While this study shows some evidence of the working of the light towards melatonin and consequently the effect on sleep, it does not study the effect of preventing delirium. Therefore, this study is lacking evidence of the effective working of the VitalSky towards the prevention of delirium.

In the Charité University hospital in Berlin, a clinical trial of VitalSky has been performed. In 2013 two ICU rooms were furnished with a concept of the VitalSky. Evidence of reduction of delirium was found: 46% of the patients on the designed ICU compared to 76% in the standard rooms (Luetz et al., 2019). However, the design of the room did not only include the VitalSky but also other components. The area was changed into a better-looking environment,

noise reductions are applied, and more monitoring systems are in use. Hence, the effectiveness of the VitalSky itself towards prevention of delirium in the ICU has not been directly measured.

Looking at the VitalSky, the current development maturity or readiness level can be described as a nine, since the VitalSky is a fully developed product and has its CE mark. However, considering the limitations of the studies mentioned above, the maturity level should be a bit lower. A step back into the development process could be a good opportunity to find the real effectiveness of the VitalSky in the prevention of delirium and could increase its reliability.

The technological problem statement is a distillation of the limitations and opportunities of the VitalSky system in its current form. It is composed as follows: 'How can we optimise the VitalSky system to prevent delirium in ICU patients?'. The goal connected to this is to find an effective way to prevent delirium for ICU patients. For this, we want to research the best possible set-up of VitalSky to maximise the effectiveness of the current system in the prevention of delirium.

4.2 Time plan and division of tasks

The end product will be achieved over a four-year period of research divided into three work packages. Work package one will be about the experimental setup study . Work package two will focus on the amount of impact of light therapy on healthy subjects and work package three will focus on the optimization of VitalSky. A detailed description of each of the work packages can be found below.

Work package one:
Before doing a clinical study, certain research and evidence that will predict a positive outcome is necessary. Therefore, in this phase, the focus will be on the research towards an experimental setup study. Before entering an experimental set-up study, different parameters of the VitalSky need to be defined. The use of light involves different parameters of the technology such as the brightness, the use of dynamic lighting or static lighting, luminance, etc. Definition of the best options for the improvement of the circadian rhythm needs to be found.
For the next step research towards the clinical parameters must be defined. Different settings on the ICU, staff, patients, designs of the rooms play a role in the integration and testing of the VitalSky in the ICU. The duration of developing delirium, the usage of the VitalSky (how long, how often) are aspects to consider. Several studies can be carried out in order to identify all clinical aspects as well as possible.
In the end, the aim is to have the most complete document possible that will cover all aspects and provide evidence in the positive use of the VitalSky to prevent delirium by patients in the ICU. This can then be used to set up the most optimal methods in work package two and three. The estimation is that this would take about half a year up to a year to fully be completed, depending on the amount of researchers actively contributing to this.

Work package two:
Even though there already has been a small clinical trial involving a pre-concept of VitalSky in the prevention of delirium in ICU patients, the first step of the research will be focused on the impact of light therapy on the circadian rhythm. The research question that needs to be answered is if the VitalSky can influence the circadian rhythm on healthy patients. This will be tested by trying to disrupt the circadian rhythm using light therapy. If proven effective, this will serve as evidence that light therapy from VitalSky is able to influence the circadian rhythm and thus should be able to impact the prevention of delirium. This first phase can be performed on a relatively small scale with only a few test subjects and thus is not as risky financially compared to the second phase and especially the final phase. Even though prior research, albeit with its limitations as discussed before, already showed that VitalSky is able to impact the delirium incidence, this step is still mandatory. It proves that we are using the VitalSky system correctly and that it works via its intended pathway. This is vital before continuing to the next steps of actually using the system on ICU patients. Phase one is divided into several subdivisions:

1. Set-up test method in cooperation with Philips
2. Application of METC
3. Find 20 healthy test subjects
4. Perform light therapy and measure differences in circadian rhythm
5. Analyse results
6. Draw conclusions and publish paper

Task three requires a bit of elaboration. We want to use the VitalSky technology on a healthy subject and see if their circadian rhythm changes. In a prior study (Luetz et al., 2016), the potential of the VitalSky was measured by means of the circadian effective irradiance. If this value is beyond the threshold for maximum melatonin suppression (0,3 W/m^2 for young adults and 0,6 W/m^2 (Brainard et al., 2001; Thapan et al., 2001) it was assumed that the technology is able to impact the circadian rhythm. In this research we want to test whether this is valid in living patients instead of measuring a threshold value. Several measurement options for this can be used such as the

change in body temperature, melanin levels, a polysomnographic test, chronotype and cortisol levels. Especially a combination of multiple methods gives the most accurate indication of someone's circadian rhythm.

Work package three:
In order to maximize the effect of VitalSky, it is important to know what parameter set-up of VitalSky works best to prevent delirium. To know this, the best possible way is to study VitalSky in a real, practical environment: the ICU. Here an RCT can be performed to obtain the highest level of evidence. This will act as a great enhancement of the existing proof of the small clinical trial performed earlier and thereby allow for an easy adoption by clinicians. The RCT will consist of three groups of ICU patients:

1. Control group (no intervention with VitalSky in any form)
2. VitalSky parameter settings one
3. VitalSky parameter settings two

The choice for the parameter settings in group one and two will be based on the outcomes of work package one. The number of parameter settings that can be clinically tested is linked with the financial and time possibility. Furthermore, each patient group should consist of an equal number of patients of course. Preferably, each group consists of at least 25 patients so it will have a 95% confidence interval. Depending on the financial possibility the number of patients in each group will grow accordingly. Our aim is to use the ICU environment of the Charité University Hospital located in Berlin or Marien Hospital in Wesel, since it already uses VitalSky. If our resources allow it, we could use a second hospital, preferably the Medisch Spectrum Twente (MST) in Enschede due to its close relationship with the University of Twente. We estimate that it will require about a year to include enough patients. After the trial, a statistical analysis regarding the incidence of delirium will be performed to see if there is any significant difference between the groups. In doing so, an estimate of the optimal parameters of VitalSky for delirium prevention and additional proof of the effectiveness of VitalSky in the prevention of delirium in general will be obtained.

The general subdivision of tasks for this work package is:

1. Set up experiment and consult Charité and MST
2. Apply for METC in both the Netherlands and Germany (depending on the hospitals included)
3. Perform experiment
4. Analyse results
5. Publish paper

As soon as the preliminary results of work package two are known and look favourable, the application for the METC can be applied. Since there is already a considerable amount of evidence backing the fact that it is possible to use light therapy to influence the circadian rhythm, the chance of work package three being performed is very high.

Planning
In order to finish the work packages in four years and to obtain results a planning can be made. The timeline can be described in four years. The first package and research goal is scientific research. This step is essential to continue to the other work packages. The dividing and specification of parameters is needed for package two. For package three, as mentioned above, packages one and two are necessary and need to be finished and have positive results to continue.

Year One: In this year the focus will be on scientific research. A full year will be reserved for this since this is the basic proof that is needed for work package two and three. If more valid research is available, work package one can earlier be finished, in perhaps a half year, and work package two can start. However if there is less valid research towards for example the use of the kind parameters, more research, trials and maybe even tests needs to be performed. Therefore extra time is planned. Might there be valid proof and research towards the choice of the parameters but other research is lacking a start on package two could be made.

Year Two: The second year is dedicated to work package two. In this stage the set-up for the experimental study will be determined with the help of the parameters concluded to be useful in year one. A year of defining the experiment, performing the experiment, evaluating and writing the end results is planned. For the experiment suggested, the aim is to acquire twenty test persons. Since developing delirium can occur in the first 24 h uptil 72 h (Choi et al., 2017), three days of isolation in a room with the VitalSky could be enough to determine the effects on a healthy patient. Development and purchase of VitalSky's is dependent on the cooperation with Hospitals (for work package three) and Philips. For this experiment a suggestion is to use four VitalSky's. The experiment should take about 15 days, but due to incidental actions or tasks it could take around twenty days. The experiment should be performed at a location where all other factors except the VitalSky will stay the same.

Year three and four: If the research question from work package two is positively answered and work package three conducts valid proof of research a clinical experiment can be performed. In this phase the effectiveness of the VitalSky towards prevention of delirium by patients in the ICU is studied. Therefore, a clinical experiment in an ICU setting needs to be set up. For the three groups of ICU patients consistency in the environment and hospital is critical. Only the VitalSky should be the variable. Depending on the hopital performing the experiment the amount of VitalSky's can be determined. In case a hospital such as the MST does not have any early trials, use of four new VitalSky's can be suggested. Two per parameter setting of the VitalSky where one patient will be in the ICU for an average of five up to ten days. In this way, by a minimum of 25 patients the clinical trial will last for four and a half months per group. This clinical experiment will have a maximum planning of two years.

At the end of the research in year four a closing questionnaire or research towards the wishes, experience and expectations of patients can be collected. This can be passed on towards Philips so that the most optimal design for both the prevention of delirium and patient can be developed.

Infrastructure
Work package one can be completely executed at the University of Twente by the involved researchers and in collaboration with the involved clinicians from the hospitals involved to get extra feedback. Work package two could be performed at the TechMed centre or maybe in a testing location of Philips. This all depends on what Philips has to offer. Work package three on the other hand has to be performed in a hospital. Preferably, this would be Charité in Berlin and if possible, MST in Enschede.

Phases of the planning
In figure 3, a schematic presentation of the four year plan can be found. The outlined boxes represent the time reserved for the work package. The light color filled rounds represent the most time line in case work package one is finished earlier.

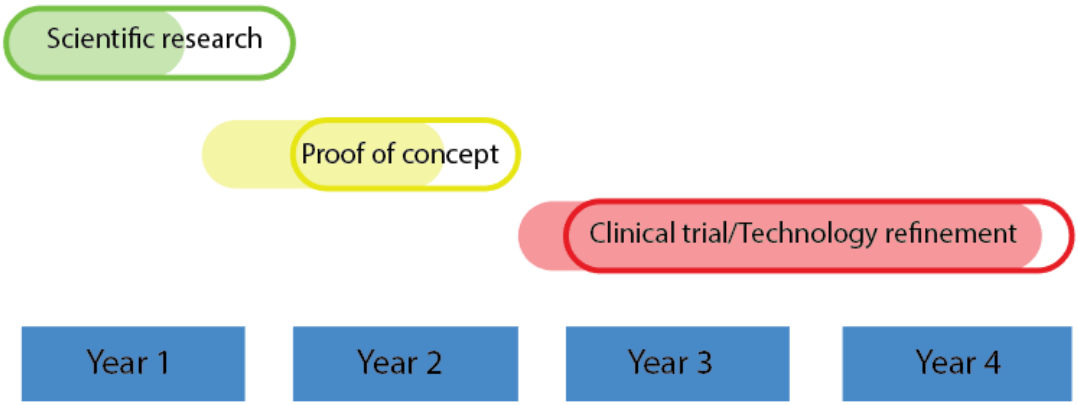

Figure 3 : Schematic presentation of the four years plan.

5. Utilisation plan

5.1The problem and the proposed solution

The first step in the improvement process of healthcare using technology, which will be addressed in the next paragraph, is to analyse the healthcare problem with the goal of reaching a technical problem statement. The usage of this cycle, visible in figure 4, will ensure in the end that the product is a solution to the healthcare problem.

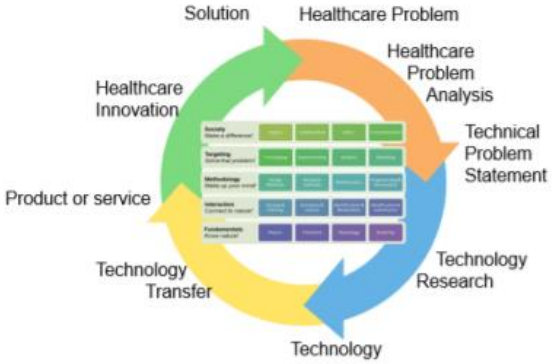

Figure 4: Cycle for improving healthcare using technology (ref)

Delirium (Cleveland Clinic, n.d.) is a condition of mental confusion and is characterized by symptoms such as disorientation, confusion and cognitive impairment. There are three types: hyperactive delirium where the patient becomes overactive, agitated or restless, hypoactive where the person is underactive, sleepy or slow to respond and a mixed version. Up to 80% of the patients in the intensive care unit (ICU) (C. M. Kim, n.d.-b) experience delirium at some point during their stay.
Consequences of delirium in the ICU (Kotfis et al., 2018) are an increased mortality, prolonged hospital stay and an increase in the mechanical ventilation, treatment costs and incidence of cognitive impairment during and after the ICU stay. Many factors increase the risk of delirium development, such as alcohol abuse, dementia, age and respiratory disease. Delirium is monitored and diagnosed inadequately and patients are treated often with sedatives and other calming medication to fight symptoms like agitation and the attempts of removing external devices. However, this medication, like benzodiazepines, actually is a risk factor for the development of delirium. Diagnosis of delirium in the ICU is done using questionnaires like the DSM-5, RASS, SAS, CAM-ICU and ICDSC. CAM-ICU is the test with very high specificity and sensitivity and is therefore highly recommended. As stated before, the healthcare problem is the prevention of delirium and at the moment there are no recommendations for any pharmacological solutions to prevent delirium. Many drugs have been tested and can affect the CNS pathways involving delirium development, but it is mainly stressed that pharmacological solutions can also increase the risk of developing delirium. The Society of Critical Care Medicine has proposed the ABCDEF bundle, which includes steps of intervention to prevent delirium and this technique has shown some promise in reducing the incidence of delirium in the ICU. This current prevention technique still has its limitations, for example the dependence on the medical staff.

Delirium has a negative impact on the prognosis and health of a patient and with that also a huge effect on the healthcare resources. The development of delirium in the ICU can prolong an ICU stay for five to ten days (Philips, n.d.) . It doubles the mortality rate of patients in the ICU, triples the mortality rate of patients up to six months after hospital stay and the risk of cognitive impairment, like dementia, is nine times higher in patients with delirium in the ICU compared to those who do not develop ICU delirium. In the USA, the yearly costs for the healthcare resources are 145 billion dollars and in the Netherlands the stay of a patient in the ICU for one day (Kuijper, n.d.) costs about €2500,-. A prolonged stay of five to ten days can therefore cost €12.500-25.000 per patient extra. The fact that there is no clear treatment of delirium causes the costs of the potential treatment ways to vary and there are also costs connected to the effects of delirium after ICU stay, like cognitive impairment.

There has been little research done about the effects of delirium treatment in the ICU. Pharmacological treatments (Kotfis et al., 2018) include the use of antipsychotic drugs, but limited proof has shown the efficacy of this approach. The Pain, Agitation, and Delirium (PAD) guidelines state no effective pharmacological approach in the treatment of delirium. The effect of treatment to cure delirium is proven by a negative CAM-ICU for 24 hours. Different non-pharmacological treatments have been tried in order to reduce the incidence of delirium, such as limitation of noise, adjusting lights to the circadian rhythm and adjustment of the room temperature. The confusion and anxiety caused by delirium require good communication between patient and staff to clarify to the patient their whereabouts and

condition. Limitation of sedation and early and daily rehabilitation have been seen to reduce the ICU delirium. The overall recommendation and protocol for the treatment of delirium in the ICU is to limit pharmacological treatment due to its risk of side-effects and the focus should be on finding a non-pharmacological treatment.

The previous paragraphs about the shortage of available prevention possibilities and treatment options emphasize on the necessity of a new health technology. As stated before, non-pharmacological prevention is preferred and an example of an idea is a modified ICU room that has a personalized light therapy system, noise reduction and a circadian rhythm. The aim of the noise reduction (C. M. Kim et al., 2021b) is to support cognitive stimulation and a better circadian rhythm reduces the level of confusion. To provide the patient with social interaction and medical advice, an app has been introduced as well. It relieves the burden on the nurses by giving personalized care to the patient. The technologies aim to reduce risk factors in order to prevent the development of delirium, such as reducing stress, anxiety and depression, supporting reorientation, improving the circadian rhythm and sleep quality, and increasing social interaction. There are eight different categories of technologies being used; audio, light, video/video game, virtual reality, sleep aids, communications support, other, and multicomponent approaches. At the moment these techniques are supposed to complement current treatment rather than replacing them. Several studies have been done validating or refuting the efficacy of these technologies. The categories all follow one or more of the seven pathways to delirium prevention mentioned in the systematic scoping review by Kim et al. The current ABCDEF bundle already targets the following pathways: restore the circadian rhythm, activate the body and activate the mind. However, there is still room for improvement. Limitations of the current technologies are that not all the pathways are yet being addressed, there are no real continuous solutions and the changing needs throughout the ICU are not properly regarded. The VitalSky, a smart lighting system, could possibly assist in the prevention of delirium. However, the optimal parameters of the VitalSky which result in the prevention are unknown and the technological problem statement therefore is: 'How can we optimise the VitalSky system to prevent delirium in ICU patients?'.

To ensure that the product is actually able to tackle the technological problem and solve the healthcare problem, prevention of delirium in the ICU, a four-year period of research will be conducted divided into three work packages. Work package one entails the set-up of the trials conducted in package two and three and the scientific research to support the steps taken in order to mitigate the risks. The parameters being optimized to ensure the prevention of delirium will be determined during this phase as well as the setting of the parameters. It has already been concluded that improving the circadian rhythm is beneficial for the prevention of delirium in the ICU. Possible options for measuring the efficacy of influencing the circadian rhythm with the use of the product are the level of sleep quality and melatonin levels. After this establishment, the trial can be set up in such a way that the risks are mitigated.
Work package two will focus on the impact of the product on healthy subjects. The clinical trial on healthy subjects will be performed by trying to affect their circadian rhythm using the VitalSky. If the product is able to influence the circadian rhythm and therefore potentially the development of delirium, the testing of the VitalSky would evolve to work package three.
Work package three will focus on the optimization of VitalSky. This is done by testing the VitalSky in the operational environment, namely patients in the ICU. The trial will consist of a control group in the normal ICU environment and two groups with a modified ICU environment. In this modified ICU environment, the VitalSky is installed in addition to the normal ICU environment. One of these two groups with the modified ICU will have a certain setting to two parameters and the second group will have a different setting to the two parameters. As said before, these parameters and settings will be determined in work package one. The efficacy of the VitalSky in work package three will most likely be tested with the CAM-ICU, the most common way to diagnose delirium in the ICU. This last package will confirm whether the VitalSky is able to assist in preventing delirium in the ICU. It is important however that all the packages are worked out elaborately to ensure success. If all work packages are completed and the efficacy is proven, the product with the adjusted optimal parameters can be brought onto the market. The VitalSky has already received a CE-marking and the adjustments in parameters remain in its scope. Therefore, after these four years of research the product can be applied outside of science.

To successfully transfer this product to the market and therefore make sure that the product does indeed form a solution to the healthcare problem, multiple steps need to be taken. This process can be guided using a technology transfer (TT) model (Abdul Wahab, 2009) and an innovation strategy helps determine the success of the innovation. The two possible innovation strategies (Master of Professional Studies in Technology Entrepreneurship, 2016) are market-pull and technology-push pathway. From a developers perspective, the ideal approach is a combination of both pathways. This ensures that the market will have a demand for your product while also gaining the benefit of high financial return and technologic innovation. VitalSky primarily falls under the market pull strategy. The demand for a technology innovation capable of preventing delirium in the ICU is high, since there are currently no other solutions. That indicates a market-pull strategy. The innovative side of this technology is quite limited, because it is a combination of existing technologies. Therefore, the technology push strategy is less appealing.

The TT model (Abdul Wahab, 2009)that might prove most applicable is the Gibson and Slimor's model. It consists of three levels: technology development, technology acceptance and technology application. It includes aspects from all the models that were used before the 1990s and is not subject to inherent linear bias. Most importantly for this product, its main focus lies on the last level, technology application. The technology application level includes commercialization and emphasises the interpersonal communication between technology developers and users. This will mean for VitalSky that the feedback that was not gathered before, will be gathered with this model. So, even though the technology is at TRL nine, for the proper maturation of this technological development it is important to include the stakeholders more, especially the patient and medical personnel.
So, it is important that the development team interacts with the stakeholders, since this potentially increases the societal and economical value of the product. Knowledge utilization to accomplish this goal is an iterative process starting with the output, followed by the outcome and ending with the impact. The output are direct and immediate insights obtained by a research project. The outcomes are the changes that can be seen in the stakeholders behaviour, relationships, actions and activities. The impact looks at the social, ecological, cultural, industrial and economic changes. The interest lies mainly at the impact, which has three different approaches: outlook, plan and focus. This approach can help narrow the spectrum which is focused on and makes sure the right strategy is applied to transfer the appropriate technology onto the market. The application of the knowledge utilization technique (NWO, 2019) to the product is visible in the pathway in figure 5.

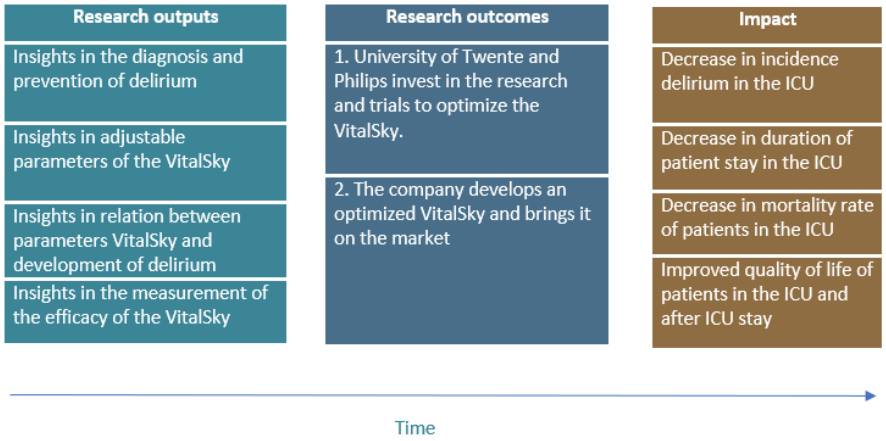

Figure 5: Impact pathway of the VitalSky

Since this is a non-invasive medical device, the product is relatively safe and does not need very expensive big RCTs to be qualified to use in a hospital. However, only one small clinical trial has been performed so far thus the evidence supporting the system is quite weak. This obstruction is accounted for by making sure that the trial group is large enough, at least 75 patients. The sample size (University of California San Francisco The Clinical & Translational Science Institute, n.d.) has been calculated to have 95% confidence interval using the "Sample Size Calculators for designing clinical research", after choosing the appropriate test: the comparison of proportions with a dichotomous outcome between two samples, using the Chi-squared statistic (or z test).

A related obstruction could be that the results from work package one show that only one relevant parameter setting is worth investigating. To mitigate this, the initially planned two settings groups can be combined in one bigger group resulting in a study with a 2:1 ratio, like this: 25 patients in the control group and 50 in the VitalSky therapy group.
If after work package one there are more than two relevant parameter settings, a decisional matrix that will assess their probable impact power will be made. The resulting ranking will be used to choose what parameters will be investigated.
Another obstruction to the utilization is the assessment method of the efficacy of technological development. Since the product is to be used in the ICU and the first trial is to be performed with healthy subjects, the normal CAM-ICU, a checklist on delirium determination, is not applicable. Healthy subjects will almost certainly not develop delirium, so another assessment method should be found. This can be solved by looking at the fundamental principles that connect the problem, delirium, to the solution, the lighting system. The lighting system is supposed to work on the circadian rhythm (C. M. Kim et al., 2021b) and sleep quality, of which the effect could potentially be tested. This phase is therefore still prone to insecurities whether the improvement of the circadian rhythm (C. Kim, 2020b) will indeed have an influence on the development of delirium, but the scientific research supporting this statement mitigates the risk .
Lastly, a big potential obstruction of determining the efficacy in the final phase, the trial in the operational environment, is the abundance of different diagnoses of patients in the ICU which could influence the efficacy of the

product. This can also be potentially dealt with by making sure that the trial group is very large to minimize this influence.

Of course, it is also important for the investors to know the costs of this extensive research and future implementation and what the potential return on investment will be. The VitalSky system (C.M. Kim MSC, 2021) costs around €200.000. For the trials in work package two and three, about four systems will be necessary. The systems used in work package two can also be used in package three, thus no new systems have to be bought for that phase Therefore, the total cost for the systems during the trials in package two and three is €800.000. The VitalSky system is, as stated before, already being used in the Marien Hospital (Blume, 2020) in Wesel with no other changes to the ICU environment. If this is going to be the operational environment in which the trial in work package three is conducted, it can easily result in an upscale of the participants or a shortening of the overall trial period.
Up to 80% of the patients in the ICU experience delirium at some point during their stay, which results in a prevalence of 35.233 per year (Haas et al., 2015). In the Netherlands the stay of a patient in the ICU for one day costs about €2500. A prolonged stay of five to ten days due to delirium can therefore cost €12.500-25.000 per patient extra. For 35.233 patients this would result in an amount of €440.412.500 in extra costs due to delirium.
Therapeutic costs, conceivably within the form of extra sedation, which can lead to more disillusionment, more medications, and higher costs. Antipsychotics have expanded in delirium treatment calculations in spite of the fact that supporting information is restricted and may have extra costs in pharmacies. In addition, delirium is related with a number of complications that can increase the cost of treatment, including aspiration, nosocomial contamination, and immobilization, which can be reflected within the extra costs of ventilation, diagnostic radiology, and costs of diagnosis laboratory (Vasilevskis et al., 2018). Cognitive impairment (Kotfis et al., 2018) is a common consequence of delirium in the ICU and the influence of this impairment on daily life will be costly as well, for example the costs of caregivers.
An example of a possible pitfall that needs to be considered about these calculations is the purchase of the VitalSky is an investment and that it will probably take a few years before there is a return on investment.

5.2 Potential users

The main market for VitalSky is composed of hospitals that have ICU. Thus, the people in the ICU become the main end-users; those people are: the patients themselves and the doctors and nurses who work in the ICU. The key players when developing such a product are the hospital developers (the people who make the decisions of what products to use when building or renovating a hospital), the owners and managers (the people that approve and provide the budget), the people that interact everyday with the product while working in the ICU (doctors and nurses from the ICU) and the company who develops the product (Philips).

To transfer a potential working technological development onto the market, the VitalSky with the correct settings in terms of dynamic light and brightness to prevent delirium, the strategy must be established first. In the case of VitalSky, most likely a market pull strategy should be applied. As there is no non-pharmacological way to solve delirium in the ICU yet, it triggers the potential of the VitalSky with different settings to start filling the gap. Testing the VitalSky with different settings in the operational environment will show whether the VitalSky can meet the market demand.

The approach for the market pull strategy shows that the market response to the technology should be tested. First however, research must be done to find which settings show the greatest potential and the technology should be developed/adjusted accordingly.

Next, the product can be tested. In the first stage the product will be tested on healthy patients, so it can be determined how efficient it is to influence the circadian rhythm. After this is established, the last step is to test it in an operational environment on patients in the ICU. In this RCT there will be three groups: a control group that receives normal ICU treatment, one group that will receive parameter settings one from the VitalSky therapy and the other group will receive parameter settings two of the same therapy.

To develop the right strategy that will ensure the most efficient technology transfer, we have done a theory of change diagram, see figure 6. The diagram facilitates a better understanding of the problem at hand and the probable solution for maximizing the project's impact. The problem analysis revolves around delirium. The underlying knowledge-related causes of the problem is the lack of knowledge about delirium, how to prevent it and how to diagnose delirium. It mainly affects consciousness, hence the lack of knowledge. But in the modern era, more and more attention is given to stress and how it affects our life, thus the idea of stress affecting our mind is also looked into. The loss of homeostasis can definitely lead to stress that can build up. Thinking in this way, the problem of change in the environment from the comfort of one's home to the highly unnatural clinic-centered ICU room

becomes clear. The impact pathway is centered around preventing delirium. As a main idea, delirium can lead to a longer stay in the ICU and some patients develop long term cognitive impairment. When there will be more insight in delirium and its prevention, the impact will be seen in the patient's quality of life and in the financial resources spent in his/her treatment. The intermediate outcome can be found at the hospital, where better patient outcome is expected and at the device manufacturer's level as the production of goods creates value and revenue.

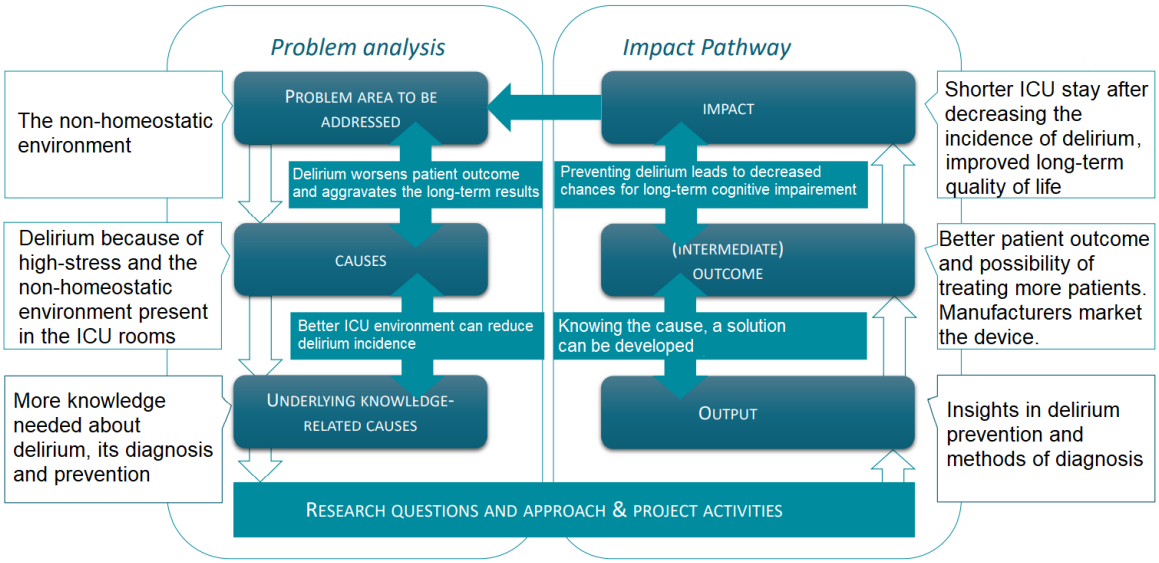

Figure 6 : Theory of change for delirium prevention

The User Committee is a vital and highly valued advisory body in the pursuit of its objectives. The first member of the user committee is the developer of the future product, Philips. It is crucial that they agree with what is needed from the product and that they will push in the same direction the pulling is done by the end-users. The University of Twente and Medisch Spectrum Twente (MST) and/or the Charité University Hospital provide the necessary combination, transfer, and conversion of knowledge. The research power is crucial when developing an adequate product in healthcare. The past ICU patients have a role of approval when participating in the user committee. Even if they might not have proper knowledge of the technicalities of delirium prevention, they have first hand experience of it. Besides, if Philips wants to build a patient-centered ICU room, it is impossible to do it without the patient's input and feedback. NWO chairs the meetings and ensures that valorisation opportunities are optimally utilised. For the need to conform with the European legislation, a representative of the Medical Device Directive MDD will provide expertise about the CE mark (Prof. Dr. Christian Johner, n.d.).

5.3 Past performance

There are clinical trials to prove that an improved ICU environment has an effect on delirium incidence. A trial was conducted by Charité University Hospital in Berlin on 74 mechanically ventilated patients with an expected ICU length of stay >48 hours were included in this prospective cohort study. The incidence of ICU delirium was significantly lower among patients treated in the modified rooms (46%) compared to patients treated in the standard rooms (76%, p = 0.017) (Luetz et al., 2019). The idea of VitalSky is based on this clinical trial.
VitalSky has a central control unit and luminous ceilings to enhance and synchronize circadian rhythm in critically ill patients, providing time orientation and a calm environment. The system's features consist of an additional option of playing calming nature scenes in full-color, soft-focus video and the future enablement of cognitive training. VitalSky also integrated three superior quality workplace lighting features, supporting efficient care delivery without disturbing the patients.
The artificial sky measures four meters in length and two meters in width. The ceiling installation has 13.000 LEDs. During the 24-hour cycle, the artificial light mimics the sunlight outside and replicates the rising sun in the morning. Circadian-effective light therapy and sound management are the two basic components of the VitalSky system. VitalSky is developed and currently available in Germany, Austria, Switzerland, Finland and Sweden. Because of this, we consider this technology to have a Technology Readiness Level (TRL) of 9. Dr. Marc Achilles from Marien Hospital (Blume, 2020) in Wesel, the first hospital in which VitalSky was installed states: "An observational study by the Charité Hospital in Berlin has shown that the 24-hour light therapy with VitalSky reduces delirium incidences by over 50 percent. We haven't had this much recovery success in any other area of intensive care medicine as with these simple atmospheric tools."

There were several grants provided for the observational study with 74 people on the modified (new lighting system) ICU rooms in Charité University Hospital, Berlin. This also emphasises the need for a solution for patients with delirium in ICU. The German Federation of Industrial Research Associations on behalf of the Federal Ministry of Economic Affairs and Energy financially supported the rebuilding of the ICU. They also have grants from Grünenthal, grants from Dr. F. Köhler Chemie, grants from Roche, grants from MSD, grants from Orion Pharma, grants from Outcome Europe Sàrl, grants from B. Braun Melsungen, grants from AiF, grants from BDA, grants from BMBF, grants from DKH, grants from DLR, grants from German Research Society, grants from GIZ, grants from inner university grants, grants from Stifterverband, grants from European Commission, personal fees from ConvaTec International Service GmbH, personal fees from Pfizer Pharma, personal fees from Vifor Pharma, personal fees from Fresenius Kabi, personal fees from Georg Thieme Verlag (Luetz et al., 2016).
As said before, the most important researchers of this research group are from the University of Twente. This research project, so called "Digital Nature" is being supported by the Top Technology Twente Connecting Industry program (TKI Topsector HTSM). Philips is the main developer of this technology and so it is also considered as one of the fund providers of this technology.

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Kim et al. Scoping review

USA US Patent PCT/EP 2015/067731: „System for influencing the sense of a person and room equipment having such a system"

European Patent 15 753 627.7: System zur Beeinflussung der Sinne einer Person und eine Raumausstattung mit einem solchen System

European Patent 3 174 588: Automatisches Erzeugen von visuellen Stimuli

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