SLEEP MONITORING IN THE ICU

Collaboration Application to Eastern AHSN

Case study 3: Near Infra-Red Spectroscopy

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23/03/2022

INTRODUCTION

Quality of sleep in the ICU has been long documented as very poor, leading to adverse patient outcomes and development of long-term sleep disorders. This is due to a variety of factors, such as care interruptions, noise, and medication. Despite a large research body, precise understanding of the causes and the effectiveness of possible solutions is still at square one.

A combination of electroencephalography (EEG) and near infra-red spectroscopy (NIRS) monitoring can be used to non-invasively and inexpensively examine ICU patient sleep state with unparalleled practicality, providing insight for real-time action and an evidence body for future solutions.

This document is a proposal for collaboration with the Eastern Academic Health Science Network for development, production and market delivery of a sleep-monitoring product, with the intent of leveraging the Network's expertise, advice and connections to assist the growth of this company in the UK healthcare sector.

The proposal is organised into three sections. Parts I and II will motivate the business case and value proposition, with Part I addressing the current system's issues and Part II detailing the innovations required to solve these problems. Part III will present an early-stage implementation plan for the resulting technology.

PART I – THE CURRENT SYSTEM

1. SLEEP IN THE ICU

1.1 IMPORTANCE OF SLEEP

Sleep is an indispensable part of regeneration and recovery for both the body and mind [1]. For patients with critical illness, this recovery process becomes even more important: there is a large body of research demonstrating its links to healing and survival in the ICU.

1.1.1 OVERVIEW OF SLEEP STAGES

During sleep, the human body transitions between four different sleep stages, characterised by brain electrical activity and various other physiological changes (Table 1). Frequency bands of brain activity (designated alpha to delta) and particular visible waveforms, measured with EEG, are key differentiators of sleep state.

Sleep stage	Other Names			Description of sleep stage
Awake				Predominantly alpha and beta, depending on whether eyes are open.
NREM (non-rapid eye movement)	N1	S1	1	Lightest sleep stage. >50% alpha activity replaced with lower-amplitude mixed-frequency (LAMF) activity, muscle tone in skeletal muscle, breathing at regular rate.
	N2	S2	2	Heart rate and body temperature drop. Specific waveforms are identifiable (sleep spindles, K-complexes). Long delta waves (>1s).
	N3 / SWS	S3	3	Deepest sleep stage. Significantly reduced frequency, high-amplitude delta waves. Difficult to awaken from. During this stage, the body repairs and grows tissues, bone and muscle, and strengthens the immune system. This stage is sometimes further separated into stages S3 and S4.
		S4		
REM (rapid eye movement)			4	Associated with dreaming, typically starting 90 mins after sleep start. EEG activity similar to awake individual, but no skeletal muscle activity. Breathing rate more erratic and irregular. Eye and diaphragmatic breathing muscles remain active.

Table 1. Stages of sleep and wakefulness [2]. SWS is an abbreviation for slow-wave sleep.

1.1.2 EFFECTS OF POOR SLEEP ENVIRONMENT IN THE ICU

Effect type	Effect description
Direct effects: Physiological	Weakening of immune system leading to increased infection risk. Reduced glucose tolerance. Increased protein catabolism. Adverse effect on hormone balance. Weakening of upper airway muscles, among other adverse effects on respiration.
Direct effects: Neurological	Psychotic states such as delirium. Increased perception of pain. Nightmares.
Highly correlated (to lack of sleep)	Morbidity. Post-traumatic stress disorder (PTSD). Long-term sleep disorders.

Table 2. Effects of lack of sleep in the ICU [3], [4].

Patients sleep lightly and intermittently in the ICU. The median sleep time found in one study was 5 minutes, with 1.7 care events per hour, and a median total of 5 hours per day (versus the generally accepted requirement for adults, 7-8 hours) [5]. This causes a host of problems that are detrimental to recovery and/or result in long-term illness that requires further healthcare expenditure later on.

1.1.3 PATIENT STORIES

Patients are a key stakeholder in the healthcare system, and patient experience is rightly considered a crucial part of value propositions for new companies [6]. Interviews with ICU survivors highlight a sense of "desperation for normal sleep," with sleep both during and after their intensive care experience being "tormented by nightmares," often returning the patient to the "dark and horrifying world" of the ICU [7]. This by itself motivates change.

1.2 CAUSES AND POSSIBLE INTERVENTIONS

A number of studies have looked into the factors that contribute to poor rest in the ICU. The key issues are shown in Table 3. It has been shown that some of these changes to care (such as the noise-related interventions) can reduce onset of sleep disorders. While some causes of sleep disruption cannot be easily alleviated, and many others have corresponding trade-offs, there is consensus that every effort must be made to promote SWS and REM sleep [8].

Sleep disorders in patients after discharge from the ICU are partly a consequence of the lack of sleep during their stay, but are more strongly linked to the trauma of their critical state and exposure to, for example, the death of other patients. Attempts have also been made to reduce this trauma via changes to care, though this is outside of the scope of the technological solutions considered in this report.

Sleep has been historically overlooked as a problem, but is gaining attention, with recent guidelines attempting to put some interventions into practice. However, there remains a large amount of uncertainty as to which effects are the most significant, and to what extent interventions can improve the situation. This, in turn, is largely due to a lack of viable *in-situ* data acquisition.

Factor	**Elaboration**	**Changes/ Interventions**	**Plausi-bility**
Noise	A large number of alarms from devices such as heart monitors, ventilators, and intravenous pumps cause sleep disruption. The volume and number of alarms present in the ICU is a problem in itself, resulting in "alarm fatigue" and a volume arms-race to compete for attention. Other noise sources include talking, devices such as oxygen finger probes, doctor/nurse pagers, and televisions.	Adjusting alarms	Medium
		Minimising the volume/frequency of staff talking	High
		Keeping rooms' doors closed where possible	High
Light	Lights are often bright and active 24 hours a day. Since normal diurnal light intensity cycles help calibrate circadian rhythms, constant, bright illumination disrupts sleep.	Reducing light intensity	Medium
		Programming lights to diurnal cycles	Medium
		Providing blindfolds	High
Nursing interven-tions	Around 43 care visits happen per day per patient, for both event-driven and routine purposes. Some examples are: taking blood tests, changing treatment in line with results, administering drugs	Aggregating routine care interventions based on current sleep state	High*

	or eye drops, recording vital signs, changing sheets, and washing or turning patients in bed.		
Drugs	Pharmacological agents have been observed in a number of papers to have effects on particular sleep stages.	Limit, alter or discontinue therapy	Low
Pain/Stress	Critically ill adults experience moderate-to-severe rest pain and are under a large degree of mental stress, though both of these are subjective. This is caused by a combination of psychologic and physical factors.	Regular assessment of pain intensity & adjustment	Medium
Medical interven-tions	Mechanical ventilation, dialysis, postoperative period and intubation are the key interventions that affect sleep.	Changes to operating modes	Medium/ low
		Intervention timings	Medium*

Table 2. Effects of lack of sleep [3], [8], [9]. *These interventions are only possible with good knowledge of the patient's current sleep state.

2. CURRENT ASSESSMENT METHODS

A range of techniques are available to characterise sleep, however, each has drawbacks for *in-situ* application in the ICU. These are discussed in order of prevalence of use.

2.1 POLYSOMNOGRAPHY (PSG) [10]

PSG is the gold standard for sleep assessment. It comprehensively monitors the physiological parameters involved in Table 1, using a number of EEG channels, breath pressure and volumetric flow sensors, respiratory effort bands, pulse oximetry, visual cues such as body position and movement, and a microphone [11]. The signals can be manually annotated and classified by trained experts.

Advantages
Able to distinguish sleep stages reliably, providing quantity and quality of sleep.
Acts as the reference measure to which other techniques are compared.

Disadvantages
Each individual patient monitored must be continuously attended by a trained technician – completely infeasible for large-scale deployment.
Highly invasive, requiring a range of equipment to be wired and strapped to the patient. This is complicated further by competition for space with other required ICU equipment, and also hampers sleep.
PSG equipment is expensive to acquire.

2.2 ACTIGRAPHY [12]

This technique attempts to infer sleep/wake patterns based solely on movement data gathered using typically wrist-mounted accelerometers.

Advantages
Less invasive than PSG, allowing for continuous 24h monitoring.
Less expensive than PSG.
Does not require specialist technicians.

Disadvantages	Reporting of parameters has been inconsistent across studies – likely due to lack of consensus on certain definitions. Correlation to PSG is variable (dependent on the particular parameter), and detailed sleep staging is fundamentally unachievable when solely using movement data. In particular, REM sleep cannot be distinguished from NREM sleep. There is a lack of clinical trust due to proprietary algorithms and lack of validation vs. PSG in the ICU setting.

2.2.1 OTHER WEARABLE MONITORS [13]

There has been a significant rise in the "wellness device" market for sleep diagnostics in recent years, with projections of growth to $585bn by 2024 [14]. These tend to use a combination of actigraphy, manually entered data, microphones and pulse oximetry to estimate sleep parameters. The issues facing their use in the ICU are similar to those for actigraphy:

Advantages	Very inexpensive due to mass-market competition. Effective at detecting basic sleep parameters (time in bed).
Disadvantages	Many such devices have been found to be highly inconsistent with respect to each other, with poor agreement to PSG. Algorithms are almost invariably closed-source and proprietary, further eroding clinicians' trust.

2.3 PATIENT/NURSE ASSESSMENT [3]

Patient self-assessment and periodic (every 15 minutes) nurse assessment of sleep stage has been trialled. Self-assessment is only useful for patients with normal cognitive function, and even then, is an a fairly unreliable indicator (0.58 correlation coefficient to PSG data). As for nurse assessment:

Advantages	Non-invasive, easy to perform during routine nursing care.
Disadvantages	Typically overestimates time-to-sleep, and is highly inaccurate for other sleep quality indicators. Issues relating to data centralisation/loss due to human error. Place additional workload on nurses.

2.4 BISPECTRAL INDEX (BIS) [15], [16]

There has been very limited exploration of BIS as a sleep indicator in the late 1990s and early 2000s. BIS monitors are commercial devices licensed by Health Canada that present a numerical score from 0-100 derived from EEG data. It has seen its main application for monitoring the anaesthetisation status of patients during operative surgery, where patient awareness can lead to PTSD.

Advantages	Non-invasive. Technology is somewhat mature and trusted in operative surgery. Preliminary evidence of ability to differentiate between SWS and other sleep stages.
Disadvantages	SWS/N3 is the only sleep stage that can be distinguished with high sensitivity and precision (though some further predictive power is possible if an expert manually analyses the EEG signals) [17]

2.4.1 OTHER SINGLE-CHANNEL EEG-BASED METHODS [18], [19]

A variety of state-of-the-art machine learning algorithms have more recently been applied to classifying sleep based only on EEG readings. Some of these have obtained fairly high overall classification accuracies of 80-90%. The poorest performance tends to be on differentiating between waking and early sleep stages (typically below 50% precision & sensitivity). None have reached commercial maturity or have been applied to the ICU.

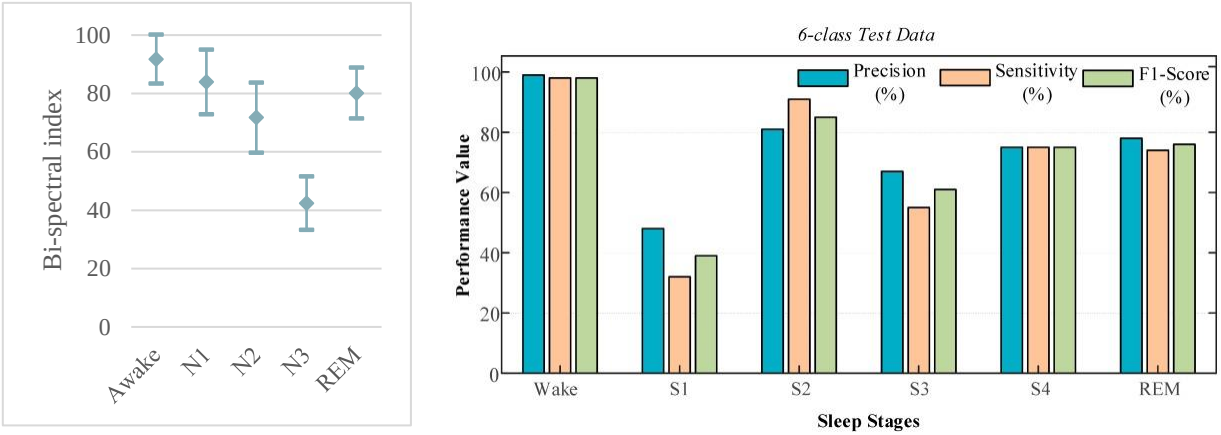

Figure 1. Left: Mean and standard deviations of BIS measurements for different sleep stages, constructed from results in [17]. Right: Classification accuracies for a machine-learning based sleep classification framework using single-channel EEG [18].

3. CONCLUSIONS

The overwhelming academic consensus is that more investigation is required into what factors in the ICU environment affect sleep most significantly, and to what extent interventions can improve the situation [4]. Additionally, real-time *in-situ* monitoring would allow scheduling of certain care interruptions so as to not interfere with sleep. However, existing data acquisition methods are either invasive and expensive or are unreliable and untrusted for all but the most basic sleep quality indicators. There is a strong need for a sleep measurement technique in the ICU that is proven, trusted, and non-invasive.

PART II – INNOVATION FOR SYSTEM IMPROVEMENT

1. ADDRESSING STAKEHOLDER NEEDS

1.1 STAKEHOLDER IDENTIFICATION

In order to create the optimal solution to this problem, satisfy as many stakeholders as possible, and fully assess business viability, the key stakeholders and their needs must be identified. It is also beneficial to identify mechanisms by which stakeholder satisfaction can be measured, or how their influence can be controlled.

Stakeholder	Interest/ Influence	Needs
ICU Patient	High/High **(Manage)**	The patient requires sufficient and restorative sleep to recover from their critical condition, and to not be left with debilitating sleep disorders after discharge. The former of these can be addressed with good knowledge of sleep patterns within the ICU. ***Measured by:*** *Patient outcomes (via clinical trials and continued study after approval), sleep diagnostic data.*
ICU Staff	High/High **(Manage)**	Intensivists and nurses must be able to do their jobs without excessive interference from any sleep monitoring device used. They must both have confidence that the device is safe. In order to organise disturbances, nurses need a clearly-displayed sleep status that is directly seen and proven to help patients. This must be seen as trusted and reliable. ***Measured by:*** *Proactive engagement and design feedback, patient outcomes. Accuracy/reliability via clinical trials.*
Researchers	High/High **(Manage)**	If device data is used to develop improvements to ICU care, it is essential that measurements are trusted by the scientific community, with a proven track record. One element of this is ensuring that any data processing algorithms are open-source. ***Measured by:*** *Clinical trials, further scientific literature body.*
Competitors	High/High **(Manage)**	Larger, established companies with a 'foot in the door' in the ICU or perioperative care may leverage their position to compete. ***Mitigated by:*** *Intellectual property protection.*
Investors/ Equity holders	Low/High **(Satisfy)**	These stakeholders require a profitable and economically robust business. ***Measured by:*** *Financial reports and performance.*
Involved trusts/ societies	Low/High **(Satisfy)** or High/High **(Manage)**	Trusts or societies related to sleep in the ICU, such as British Sleep Society (BSS), Intensive Care Society (ICU), and ICUSteps, should ideally be engaged in the success of the technology. This is especially the case if funding is provided by trusts. Other, general trusts (e.g., Wellcome) could become stakeholders via funding. These groups will require evidence of technology satisfaction and success. ***Measured by:*** *Patient outcomes/stories, clinical trials.*
Procurement leads in relevant hospitals/other	Low/High **(Satisfy)**	Since purchase of a sleep monitoring device is likely to be an up-front, relatively significant capital expenditure, budget will be sourced from public dividend capital (PDC) from the Department of Health and Social Care (DHSC). Since there is competition for the PDC available, a clear value

administrative staff		proposition must be demonstrated, to convince both the DHSC and hospital administration that the device is worth investment. The elements of strong value proposition are good care outcomes, patient experience and safety, given the revenue costs and capital costs required. ***Measured by:*** *Patient outcomes & demonstrated safety (clinical trials & continued study), financial estimates.*
Regulators (MHRA, HRA, CQC)	Low/High **(Satisfy)**	A high level of device safety must be demonstrated for use in the ICU. If medical device certification required, reliability and accuracy must also be demonstrated. If a class 3B laser is used, it may require approval from the Care Quality Commission. ***Measured by:*** *Clinical trials.*
Patient Families/ Dependants etc.	High/Low **(Inform)**	Those who care or depend on the welfare of the patient must be reassured and confident in the safety of any device used. Families may need to provide consent for use of the device. ***Measured by:*** *Proactive engagement, consent rates.*
Media	Low/Low **(Monitor)** or High/High **(Manage)**	Journalism and stories in the media about any new technologies used in the ICU should be carefully monitored, as there is a high incentive within this industry to generate attention. This could be positive or negative. ***Mitigated by:*** *Clear public information on benefits.*
Device Technicians	Low/ Low **(Monitor)**	The device should be easy to install, operate, and train technicians or hospital staff on. ***Measured by:*** *Design feedback, continuous improvement.*
Other interested parties	Low/ Low **(Monitor)**	Staff involved in patient care prior to ICU admission and after discharge will be affected by changes to the care pathway, as will health and life insurance companies. Contractors and manufacturers used will have effects on production and sales pipelines. Visiting ward staff (locums) are not internal to hospitals but must be considered for training purposes. ***Measured by:*** *Periodic review, consistent engagement.*

Table 3. Key identified stakeholders, their status, what their interests are and ways to track them.

2. TECHNOLOGY OVERVIEW

A technology that has strong potential to solve the problems highlighted in this proposal is near infra-red spectroscopy. This technology and its applications to sleep are introduced here.

2.1 NEAR INFRA-RED SPECTROSCOPY (NIRS) [20], [21]

2.1.1 BASIC PRINCIPLES

NIRS is a non-invasive functional imaging technique that has existed in various forms for over 40 years. Visible light near the red end of the spectrum is able to penetrate somewhat through biological tissue (a familiar phenomenon to anyone who has shined a torch through their fingers). This penetration improves with increasing wavelength, owing to reduced scattering, until the absorption spectrum of water becomes significant at around 900 nm. The band of 700-850 nm, falling within the near infra-red part of the spectrum, turns out to be optimal.

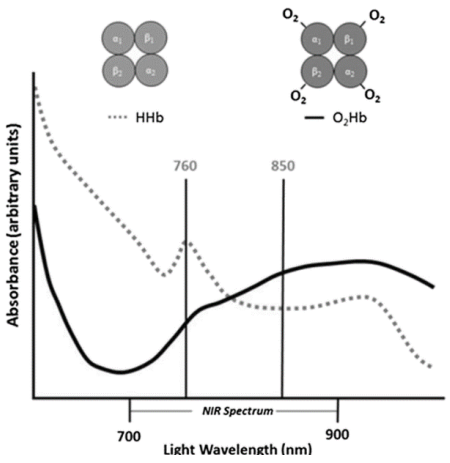

Figure 2. Absorption spectra of HHb and O_2Hb, with typical illumination wavelengths superposed [20].

If this region of wavelengths is shone into the brain, the main absorbing compounds are intravascular haemoglobin (Hb) in oxygenated and deoxygenated forms (O_2Hb and HHb), and to a lesser extent, mitochondrial cytochrome c-oxidase (cyt *c*.). The absorption coefficients of these molecules depend on wavelength in different ways. Therefore, probing the scattering at various wavelengths can reveal relative changes in their abundances.

2.1.2 CONTINUOUS-WAVE (CW) NIRS

Several types of NIRS devices exist to extract scattering information in different ways. The most mature and affordable technology, and the one relevant to this proposal, is CW NIRS. Its operating principle is to continuously illuminate regions of the brain with specific wavelengths of light. The amount of back-scattered light is measured at the same wavelengths. The modified Beer-Lambert law can be used to obtain optical density (OD) measurements, which are used to reconstruct relative concentrations of scattering species. Note that the total/absolute concentrations cannot be determined by this method: this is because the path length of NIR light in tissue is unknown without complex modelling techniques.

Illumination is commonly performed at either two or three discrete wavelengths (requiring laser diodes), or with a band of wavelengths. Using three wavelengths results in a higher signal-to-noise ratio (SNR) than using two, but is higher cost, due to the LED wavelengths required. Broadband systems give a lower SNR and are significantly bulkier, but can provide the additional information needed to extract cyt *c*. levels (rather than only HHb and O_2Hb). The number of channels is variable: many emitters and many detectors can be used simultaneously with appropriate signal coding, with the number of useful signals equal to some proportion of the product of emitter and detector counts.

2.1.3 CURRENT APPLICATIONS

Figure 3. Cerebral oximeters in action. Left: Medtronic device [22], Right: Masimo device [23].

The technology of NIRS is mature, established and trusted in relevant applications and areas of research, under various guises and configurations. The parameter typically extracted is the quantity of O_2Hb relative to the total Hb (i.e., HHb + O_2Hb), known as the relative oxygen saturation (SO_2) of the region imaged. These include:

- Pulse oximetry. This technology operates on the same principles as LED-based NIRS, and has become prevalent in the mass-market, for example in wrist-worn fitness devices [24].
- NIRS is frequently used in research, and is generally seen as a significantly cheaper, less invasive, but lower-resolution alternative to MRI for exterior regions of the brain. Complex NIRS configurations can analyse functional connectivity and brain activity via changes in oxygenation [25].
- Cerebral oximetry is a commercial alias of single-channel cerebral NIRS which has seen large-scale application in monitoring the perioperative period of cardiovascular operations. It has distinguished itself as being valuable for preoperative risk stratification, and for intraoperative alerts of adverse outcome due to cerebral desaturation. The literature supports its use and suggests that interventions based on its measurements are associated with improved outcomes. The market leaders are Medtronic and Masimo, and the modality used is single-channel, 2-LED illumination CW NIRS [26].

2.1.4 RECENT DEVELOPMENTS

There is a recent trend towards miniaturisation of LED-based NIRS technology, led by companies such as Artinis and Gowerlabs, as well an open-source initiative [27]–[29]. This is largely directed towards modularisation for functional imaging of large regions of the cerebellum. The cost of production has reduced drastically in modern systems. Commercial endeavours have also begun to move broadband NIRS technology into the neonatal ICU to monitor and combat brain hypoxia [30].

Figure 4. Modern commercial modular fNIRS systems. Left: Artinis [27]. Right: Gowerlabs [28].

2.2 ECG + NIRS FOR SLEEP [31]

Cerebral haemodynamics measured with NIRS have emerged as a useful source of information about sleep. Recent studies have moved from exploring functional connectivity of the brain during PSG-tagged sleep to investigating the predictive power of NIRS signals about the sleep stages themselves. This has shown that each sleep stage has characteristic changes in oxygenation, including a distinctive reduction in blood supply to the pre-frontal cortex (PFC) during REM sleep, and clear, asymmetric transitions between all sleep stages [32].

NIRS alone appears insufficient to obtain high classification accuracy (much like EEG) [33]– however, the two technologies provide orthogonal measures that, when combined, can reliably and accurately distinguish all stages of sleep. In addition, it is clear that the use of NIRS to reveal insights into sleep is still in its infancy, and there is significant opportunity for study into further potential benefits.

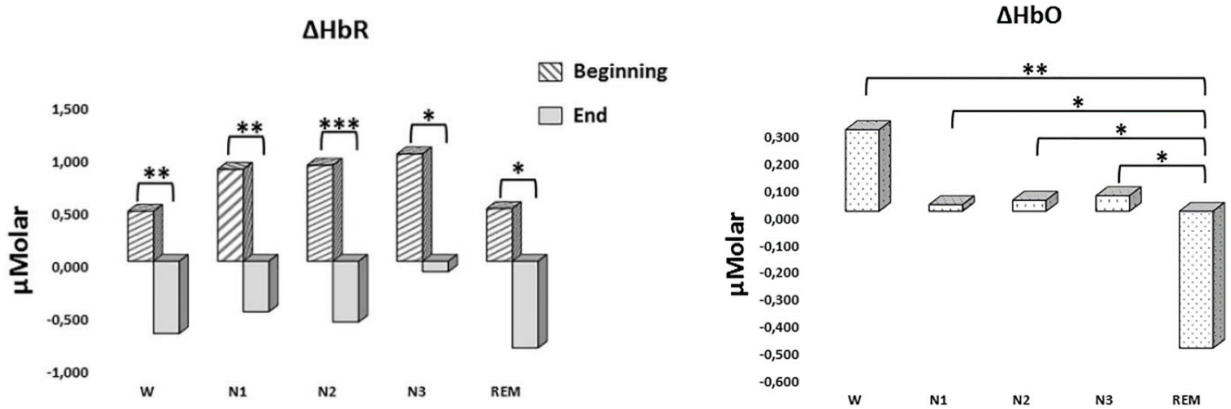

Figure 5. Selected figures from [32]. Asterisks: *p<0.05, **p<0.01, ***p<0.001

2.2.1 ADDITIONAL SENSORS

Certain additional monitors would be trivial and inexpensive to add to such a device and could increase its utility or predictive power. These include temperature sensors, optical sensors for the environment, a microphone, or an accelerometer.

2.2.2 INTELLECTUAL PROPERTY

Research was conducted into existing patents that might overlap with the intended functions of an ECG + NIRS sleep tracking device. Unfortunately, one related US patent has been filed by North Carolina State University and approved, detailing "Systems and methods for determining sleep patterns and circadian rhythms" [34]. Its intended use is for the wellness market, but it covers "determining a sleep pattern based on backscattered light… [and] conducting brain electrical activity monitoring and actigraphy to be correlated," which is likely sufficient for any technology considered here to be patent-infringing (although guidance in this regard from Eastern AHSN would be valuable). Promisingly, however, no relevant patents currently appear to exist in the UK or Europe.

2.3 CONCLUSIONS

The combination of ECG and NIRS is an ideal candidate for commercially and practically viable sleep tracking in the ICU, due to the non-invasiveness of both technologies, their clinical trust and maturity, their low cost, and the ability to protect intellectual property relating to this unexplored application in the UK and Europe.

3. DESIGN CONSIDERATIONS

3.1 DESIGN REQUIREMENTS

An analysis of the most critical design factors is useful for developing a product.

Keyword	Requirement	Importance
Unintrusive	System must not interfere with patient recover, patient care activities or ICU equipment. ***Consequences:*** *A minimal form factor device such as a* ***skin-mounted pad*** *is preferred to a cap or headband. The system should be* ***co-designed with ICU staff****. An* ***LED-based*** *system should be used, as a broadband system is infeasible in the technology's current state. If possible, the system should be* ***wireless****.*	**Demand**
Accurate	System must give clinically-trusted sleep staging outputs. ***Consequences:*** ***Clinical trials*** *and an academic* ***literature body*** *are required. Ideally, the system should be registered as a* ***Class 1m*** *(measuring) medical device.*	**Demand**
Approved, Safe	System must be approved by regulators and safe to use. ***Consequences:*** ***Clinical trials*** *are required if Class 1m certification opted for.* ***Laser safety*** *may need demonstration.*	**Demand**
Better	Device can deliver insights and improvements to patients' sleep that could not be achieved by alternative means. (This is crucial to the product's value proposition [6].) ***Consequences:*** ***Clinical trials*** *must demonstrate utility, and research use of the device should be highly encouraged to build up a* ***literature body****.*	**Demand**
Fit	System should comfortably fit all head shapes/sizes, hair types, etc. – it should certainly not *worsen* sleep. ***Consequences:*** ***Co-design with test users*** *is essential. Ideally, the device should not cover the hair, so a* ***skin-mounted pad or headband*** *should be preferred to a cap.*	**Demand**
Private	System should respect patient privacy and protect sensitive information. ***Consequences:*** *Data storage should be* ***on-site*** *and carefully managed.*	**Demand**
Open	Algorithms should be open source to satisfy clinicians. ***Consequences:*** *A* ***patent*** *will be required, or there will be few barriers to competitors seizing the market.*	**High**
Outputs	Readings should be presented in a quickly-decipherable way if they are to be used in real-time on the ICU ward. Readings should also be easily accessible for research purposes, ideally combined with other ICU data channels. ***Consequences:*** *A simple but visible* ***display*** *should be included in the product. A good option that presents itself is simply a coloured readout of the current sleep stage, along with a confidence score. Current ICU systems and* ***integration*** *options should be carefully considered.*	**High**
Welcomed	Patients and care-givers should be happy that the patient will receive monitoring via the device. ***Consequences:*** ***Engagement*** *with both groups should be aimed for. A* ***clinical champion*** *should be sought.*	**High**
Affordable	Device should come at a competitive cost. ***Consequences:*** ***Realistic markups*** *for the sector should be explored and compared to development costs. Cheaper* ***LED-based*** *technology should be used if possible.*	**Medium**
Easy	Ward staff and technicians should be able to easily operate/apply the system. ***Consequences:*** ***Co-design*** *with these stakeholders.*	**Medium**

Table 4. Key design requirements, their importance, and consequences.

3.1.1 MORPHOLOGICAL CHART

Given the design requirements in Table 4, a morphological chart noting possible manifestations of the product is shown in Appendix A1.

3.2 REGULATORY NOTES

3.2.1 MEDICAL DEVICE CERTIFICATION [35]

A Class 1m medical device quantitatively measures a physiological parameter and displays it in legal units, or is intended to be used in such a way that inaccuracies could cause significant harm to users. Clinical trials can include verifying the accuracy of such a device, as well as proving safety – both in terms of direct harm and harm due to taking incorrect decisions based on measurements.

Both EEG and NIRS signals, if directly available, would qualify the device as Class 1m as they measure physiological parameters with units. Displaying a sleep stage alone would not, unless changes to care result from measurements (which is the entire purpose of the product) – this would fall under Class 1 regulation due to skin contact, which only requires notification of authorities.

However, it is clear from the design requirements that the device must be clinically trusted if it is to be used in the ICU for patient safety reasons and because of the general scepticism to current non-PSG sleep characterisation tools. Additionally, the objective of applying this technology is to enable changes to ICU care: in order to inform interruption timings or provide evidence for future care strategies, a high degree of trust in readings is essential. This, in turn, makes extensive validation essential for the product's value proposition to the NHS.

As a result, the device should be certified under the umbrella of a Class 1 measuring medical device (Class 1m). This will require clinical trials.

3.2.2 LASER SAFETY

Related cerebral oximetry devices have achieved Class I laser classification (the safest) [36], [37]. There is no reason to believe that laser power requirements will be substantially different in this case, or that risks of device slip and laser illumination of the retina will be changed, so laser safety certification/precautions are unlikely to be required.

3.3 ARE SIMPLER SOLUTIONS ENOUGH?

It is clear that there are two levels of application of sleep monitoring data in the ICU: direct, real-time monitoring to adjust care interruptions, and research-oriented analysis in order to adjust care strategies. For the latter, detailed sleep staging is necessary. However, for the former, it may be sufficient to have an approximate indicator of sleep by simpler technology: only sleep/wake classification is required, and if parameters are tuned to minimise false negatives of the "sleep" state, false positives may not be an issue. Of the techniques analysed in Section 2.2 of Part I, actigraphy alone or EEG alone (i.e., BIS) seem the most promising. There are still problems, however:

- BIS is poor at distinguishing N1 and REM sleep from wakefulness, which together consist of 25-30% of total sleep time in normal adults [38] (and N1 is responsible for a greater proportion

when sleep is frequently interrupted). It may therefore not improve interruption rates significantly.

- Actigraphy performance is unreliable and depends on the particular device used, and devices have not been clinically validated and trusted.
- More importantly, if a simpler solution is put in place, there will be a reduced case for procurement of more accurate equipment in the NHS. This would make research into care strategies less feasible, as better data is required. This data will likely never be available unless NIRS technology is packaged in the initial product, ultimately preventing improvement to the system.

Note that there is a possibility of NIRS alone being enough to classify sleep. However, EEG is an easy addition that would be required in initial trials anyway to ascertain this, at which point removing it would not make sense due to the increased confidence it would provide in results.

3.4 SYSTEM INTEGRATION

A variety of medical devices performing measurement functions are present in the ICU. A bedside monitor displays summary physiological information such as heart rate, blood oxygen, and body temperature, while numerous other parameters are monitored at both very high sample rates (e.g., ECG) and very low sample rates (e.g., measurements of particular molecules from blood samples).

Handling the data from all these sources in a centralised way is a difficult task which has received much recent attention. Existing clinical information systems (CISs) tend to only incorporate data at a maximum sample frequency of ~1 Hz. For in-depth research analysis into the effects of high-bandwidth ECG/NIRS data on patient outcomes, and integration/correlation with other types of measurement, this presents logistical problems.

This shows a need for co-production with ICU staff, and careful consideration of how data flows should be handled and integrated as the environment changes and evolves under its current attention (this is something that Eastern AHSN could assist with).

4. CASE FOR ADOPTION

4.1 VALUE PROPOSITION

As highlighted in Section 1.1, a strong value proposition demonstrates significant improvements to care (better patient outcomes, better patient experience and high safety), given the ongoing and capital costs required.

4.1.1 IMPROVEMENTS TO CARE

Monitoring sleep state has the potential to affect care outcomes both directly (adjustment of care interruptions) and indirectly (improvements to care strategy based on analysed sleep data). As noted in Part I, Section 1.1.3, poor sleep has a marked negative effect on patient experience, which will be targeted in the same way. Clinical trials will demonstrate safety, but by comparison to existing cerebral oximetry and EEG methods, complications are highly unlikely.

4.1.2 FINANCIAL ESTIMATES

Costs are difficult to estimate at this early stage, but it clear that construction cost of the technology will be relatively low. The market value of a BIS system provides an approximate grounding for system up-front costs at $13,500 (≈£10,000) [17]. Disposable probes will be likely required to ensure sterility and maintain strength of any adhesives used, and some maintenance will be required, resulting in ongoing costs – suppose these contribute 10% of the system price in costs annually. The UK has approximately 4,100 critical care beds nationally (Europe has ≈70,000 total), organised into up to 20 operational delivery networks [39]–[41]. This results in capital cost of around £2.7m per network, and a total of £55m and £5.5m respectively in capital and ongoing costs if all UK networks adopted the device. These numbers could be greatly increased if devices are also sold to the general research market, separate to the ICU. This will be discussed further in Part III.

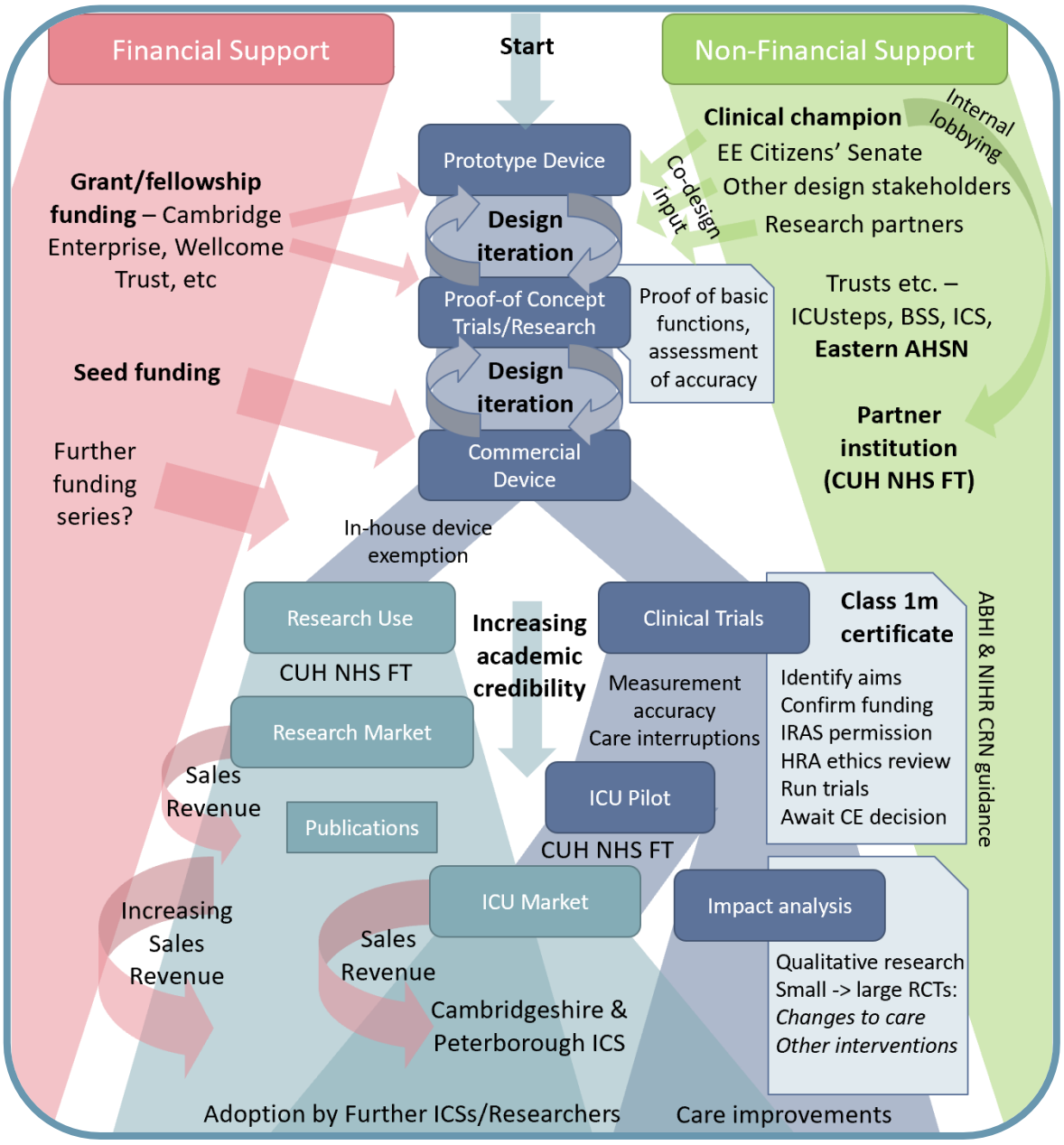

Figure 6. Schematic roadmap of action plan for improvement.

PART III – ACTION PLAN FOR IMPROVEMENT

See Figure 6 for a pictorial roadmap of the steps that this company should take.

1. INITIAL PARTNERS & FUNDING

The first step that must be taken before bringing a device to market is to demonstrate that an EEG+NIRS system functions as required via proof-of-concept research and trials. This will also give insights into further capabilities and allow assessment of how accurate the readings are likely to be. As part of the design process, as well as during design of a commercial product based on results of these initial trials, iteration will be required based on the inputs of key stakeholders. Building a strong initial team is therefore very important.

2.1 CLINICAL CHAMPION

One of the most important and knowledgeable stakeholders to get involved is an ICU clinician. This will provide invaluable design feedback and insight, and will allow for internal lobbying to bring their NHS institution on board as the product matures. This will be a mutually beneficial partnership, as involvement in academic research is an important requirement for clinicians to advance within the NHS. A local clinician from a hospital within the Cambridge University Hospitals NHS Foundation Trust, or a partner from elsewhere in Cambridgeshire & Peterborough integrated care system (ICS), would be the most convenient.

2.2 FUNDING

Initial funding could be provided by a range of grants or fellowship funds from sources like Cambridge Enterprise or the Wellcome Trust, more niche but relevant trusts and societies (eg. ICUsteps, BSS, ICS), angel investors, or many other alternatives.

2.3 STRATEGIC CO-PRODUCTION

Product stakeholders or other team members who should be brought on board and involved in co-production include at least one of each of:

- Patients, via organisations such as the East of England Citizens' Senate;
- ICU Nurse, to improve understanding of ward activities & practical interaction with the device;
- EEG physicist, to aid with analysis and integration into existing systems;
- NIRS specialist as a research partner, to aid with understanding of the technology;
- Engineers, to develop the device and understand technical constraints;
- Business-savvy partners, to help with creation of a business case, ideally with experience in dealing with the NHS - ideally, Eastern AHSN could aid here;
- Research partners, to help understand research market (see Section 3.6).

3. CLINICAL TRIALS

3.1 TRIALS REQUIRED

As discussed in Part II, Section 3.2.1, the device should be registered as a Class 1m medical device unless sleep stage alone is reported. Broadly, trials will have to be set up to assess:

Accuracy	Individual NIRS/EEG measurement accuracy (Comparison to existing devices, high-quality phantom-based evaluation). Sleep measurement/classification accuracy (comparison to PSG) – this is not essential for certification as it is not a value with legal units, but evidence is useful. Initial classification accuracy results will be obtained in proof-of-concept trials.
Safety	Small-scale randomised controlled trials (RCTs) to assess device safety (e.g., misuse, unintended damage or consequences) and whether care changes are beneficial and substantial. Large-scale RCTs over multiple sites and populations to increase statistical power and show reproducibility.

3.2 ASSISTANCE

A large amount of aid is available in designing and carrying out these trials. Clinical research networks such as Eastern CRN as well as authorities such as larger associations such as the Association of British Healthcare Industries are examples of such assistance. Eastern AHSN would also be of great utility.

3.3 IN-HOUSE EXEMPTIONS

Assuming a partner NHS institution has been brought on board (such as one within Cambridge University Hospitals FT), exemptions would be available from clinical trial requirements (assuming no actions are taken based on results) under MHRA regulations. This would allow pilot research use of the device, kicking off its academic credibility.

3.4 PRE-CERTIFICATION SALES

Clinical trials relating to measurement accuracy are expected to take a significantly shorter time than assessment of safety and the effects of care interruptions. Once these initial trials are passed, and a Class 1m certificate for measurement purposes is obtained, the product could be sold to the research market (see next section). However, even before this stage, the product is valuable as a sleep stager and could be sold on the understanding that EEG and NIRS measurements would be activated in due course, generating initial revenue. During this period, the product could be marketed in relevant conferences and via research use/exposure.

3.5 THE RESEARCH MARKET

Carrying out clinical trials and gaining trust in the performance in the product will take a significant amount of time, potentially the better part of a decade. ICUs will not adopt the technology until both of these are addressed. This makes for a very long-term, high-risk business strategy with significant up-front investment. Luckily, a stepping-stone market exists with lower barrier to entry.

A monitoring technology such as the proposed device would also have significant value in the sleep research field. Within sleep science, there is a lack of validated, non-invasive, inexpensive and user-friendly measurement techniques: those available are mostly the same as the methods discussed in Part I, and have the same set of drawbacks. PSG once is again the only fully trusted technique, but its invasiveness prohibits many *in situ* and large-scale studies. Actigraphy is the next most used, but cannot fully stage sleep, and the flood of unreliable wellness devices has cultivated a scepticism within the academic community [13] – against which the maturity and acceptance of EEG and NIRS combined would provide a unique competitive edge.

The barrier to entry in the research market is significantly lower, due to the possibility of pre-certification sales and the fact that only measurement capability needs to be demonstrated. The market is also potentially larger and procurement processes are less competitive. Therefore, there is a strong case to initially target this market in parallel with carrying out the further clinical trials required for use in the ICU. Assuming this goes well, publications generated using the technology will also help demonstrate device reliability and increase clinical trust for ICU adoption.

3.6 POST-MARKET SURVEILLANCE, TRIALS, IMPACT ANALYSIS

Continued research and analysis into the safety of the device, the quality of the data, the effect and impact of interventions will continue to be analysed. Patient stories and measured positive impacts can aid with marketing of the product. Further research on gathered sleep data will inform future care strategies in the longer-term.

4. GENERAL STRATEGY

4.1 BROAD TIMELINE

Stage	Description	Optimistic timeline	Pessimistic timeline
Device prototyping	Initial iterative design process is complete, with a device ready for testing.	3 mo	1 y
Proof-of-concept	Proof-of-concept trials result in publication successfully demonstrating capabilities.	9 mo (1 y)	2 y (3 y)
Commercial device	Commercial device is ready (partially in parallel with proof-of-concept trials).	1 y (1.5 y)	2 y (5 y)
Research use	First research used within partner institution, leveraging exemptions, results in publication.	6 mo (2 y)	1.5 y (6.5 y)
Research sales	First sales to research groups. Initial sales likely to be pre-certification.	6 mo (2.5 y)	1.5 y (8 y)
Initial Certification	Certification for measuring function.	1.5 y (4 y)	2.5 y (9 y)
Full ICU certification, ICU pilot	All proposed clinical trials for use in ICU completed and approval gained.	3 y (4.5 y)	6 y (11 y)
ICU market sales	First sales into broader ICU market after pilot.	1 y (5.5 y)	2 y (13 y)
Research into care improvements	Data provided by the device provides insights into the care process, allowing for future improvements to ICU care.	3 y (8.5 y)	6 y (17 y)

Table 5. Broad timeline for milestones in company roadmap. Bracketed times in the right-hand columns indicate total time until completed, accounting for potential overlaps in different activities.

5. RISKS & MITIGATION

A number of risks are present in this proposal due to its speculative and long-term nature. Some of the most important risks to consider, their impacts, and mitigations are shown in Table X.

Risk	Effects	Mitigation	Severity	Likelihood
Rejection by the clinical community	Severely hindered NHS/market adoption	Clinical trials, open-source algorithm, strategic co-design	**Very High**	**Low**
Device does not accurately stage sleep	Business plan infeasible	Plan possibility of alternative cheap PSG for the ICU (eg. EEG & actigraphy-based)	**Very High**	**Low**
HRA approval fails unexpectedly	Delays, potentially existential threat	Careful design & clinical trials	**Very High/ High**	**Low**
Harm caused by device	Possibly no HRA approval, media backlash, delays	Careful design & risk analysis, thorough clinical trials	**High**	**Very low**
Rejection by research market	Reduced revenue during trials pre-ICU adoption	Good marketing, further market analysis, accurate measurements, Strategic co-design	**High**	**Medium/ Low**
Public/media backlash (due to failure case/ response to sleep monitoring)	Difficulty in ICU market adoption	Clear and positive communication & messaging, robust design, clinical trials	**High**	**Medium/ Low**
Design issues (e.g., ICU compatibility, fit not universal)	Delays and design re-iteration, extra costs	Strategic co-design	**Medium**	**Medium**
Cost too high to be competitive	Lower ICU adoption rates/research sales	Good design, focus on value proposition	**Medium**	**Medium**
Unable to gain in-house exception	Delays to development of research body	-	**Medium**	**Medium/ Low**

Table 6. Key risks to the company's strategy, with their impacts, potential mitigations, as well as their severity and likelihoods.

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APPENDIX A.1: MORPHOLOGICAL CHART

See right.

(Apologies for the terrible formatting here!)