Evaluating novel near infrared spectroscopy devices for monitoring traumatic brain injury

Protocol version: 1.2

Jointly sponsored by the University of Cambridge and Cambridge University Hospitals NHS Foundation Trust

Contents

Summary

This project will utilise two non-invasive near-infrared spectroscopy (NIRS) devices for monitoring adults with severe forms of traumatic brain injury (TBI) within the neurocritical care unit (NCCU) at Addenbrooke's Hospital (Cambridge, UK).

This study is a pilot study for two novel NIRS devices. Both are non-invasive, non-ionising and are shown to be safe, having met all legal and regulatory requirements.

The first is a broadband NIRS (bNIRS) system commonly referred to as 'miniCYRIL'. It is an in-house device. It is based off similar devices that have previously been applied in monitoring brain-injured neonates at University College Hospital (UCH) (London, UK) but is an entirely separate device developed and maintained by ourselves.

The second is a high-density diffuse optical tomography (HD-DOT) device referred to as 'Lumo'. The hardware for which was provided by Gowerlabs Ltd (London, UK). The firmware underwent updating by their team before being provided to us. We have since applied modifications to prepare the device for a clinical environment and ensure safety with new firmware.

These devices are similar to NIRS devices currently applied within the NCCU but with additional modifications made by ourselves that we believe hold value in monitoring the pathology of brain-injured individuals.

To evaluate their effectiveness in monitoring TBI we will develop novel NIRS-based biomarkers and physiological metrics to monitor patient brain health. These will be compared against monitoring systems in the NCCU currently which are applied as standard treatment. Additionally, we will evaluate them against known occurrences of secondary insults (SIs) and patient outcomes. For this, we require patient physiological data and clinical notes. Furthermore we request the patient's ethnicity or skin tone information and approximate age, both of which are required for subject-specific modelling. A data protocol has been developed to ensure participant information is always stored securely and only deidentified data is used in the analysis and publication. Further information regarding the data protocol can be found in the dedicated chapter.

The study is designed to be as unobtrusive as possible and has been developed with input from several parties who have performed similar studies previously in clinical environments using NIRS devices. Additionally, we have hosted a public consultation, referred to as the patient and public involvement session (PPI), to allow those who have previously suffered from TBI to express any comments and concerns they have regarding the study before it starts.

Participants will be severe brain trauma patients admitted to the NCCU. They will undergo daily six hours of recording sessions, three hours per device. Upon discharge from the NCCU, device recordings will cease. An interim analysis will be performed after the initial 10 participants' data has been collected, which may adjust the recording length or data collected following approval from the ethics board. We then aim to recruit a further 40 participants. The study will not apply medical interventions and is not anticipated to affect the level of care a patient is receiving.

Total participant time in the study is expected to be six months, although recordings will only occur during admission to the NCCU which is typically a maximum of two weeks. The final contact with participants or their next-of-kin will be at the six-month outcome phone call. In the event the 6-month outcome is recorded in the participant's medical notes we will not conduct the phone call.

Due to their condition, participants will not be able to self-provide informed consent. Therefore, it will be collected from a personal consultee (their next of kin) if they are identified within 24 hours of the patient's admission to the NCCU, or from a professional consultee (the treating clinician) if not. We will aim to enrol patients within 24 hours of admission into the NCCU. Participants may withdraw themselves from the study if they regain capacity as assessed by the neurology department.

By completing this work, we hope to evaluate if bNIRS and HD-DOT hold the potential to monitor TBI pathology and improve treatment. This has the potential to further develop healthcare systems improving the standard of care.

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The data collection period of this study will take place within Addenbrooke's Hospital's (Cambridge, UK) NCCU. Equipment will be approved by their clinical innovation team and any other required groups before integration. The analysis will be completed at the University of Cambridge and conducted within two research groups. These are the Brain Physics Lab, located within the Division of Neurosurgery at Addenbrooke's Hospital and the Neuro Optics Lab, located within the Department of Electrical Engineering and Department of Physics.

Background

Below is a brief background on traumatic brain injury (TBI) and NIRS. The TBI section is limited to some key concepts that are referenced in this study.

Traumatic Brain Injury

TBI is a ubiquitous global occurrence. It continues to have a sizable impact on the population with an annual estimated 69 million cases worldwide (95% CI: 64–74 million) [1]. It is a complex injury with equally complicated pathologies, the consequences of which are extensive and potentially life-changing for those who suffer and their communities. It is estimated to cost 0.5% of global GDP [2].

TBI has a diverse pathology as there could be many potential causes, symptoms, consequences, and outcomes. The most cited causes of TBI are road traffic accidents (RTAs) and falls which are common in the elderly or intoxicated. Depending on a multitude of factors including age, location of impact, force of impact, type of incident, treatment available, and how rapidly treatment can be initiated, outcomes can vary. These factors will commonly see a patient who has recently suffered a sufficient impact to the head placed into one of three categories, mild, moderate, or severe TBI, each of which requires different levels of care.

Glasgow Coma Scale (GCS) and Glasgow Outcome Scale Extended (GOSE)

To classify brain-injured individuals GCS and GOSE are employed. GCS is the most widely used system to assess the level of consciousness a person is experiencing and does so by examining their speech, motor, and eye responses [3]. In GCS, scores of 13 to 15 are considered mild, 9 to 12 is moderate and 3 to 8 is severe.

GOSE is a common system for reporting a patient's functional outcome, usually 6- or 12-months post-injury by categorising the level of disability experienced. GOSE scores on a scale of 1 to 8, wherein 1 is death, 2 is a vegetive state, and 8 is an upper good recovery. 6 or 'upper moderate disability' and greater is often considered a good outcome for the patient and is the binary threshold for patient outcome in this document unless otherwise stated.

Mild TBI

As of 2023, mild TBI is the dominant of the three forms, accounting for around 75% to 90% of hospitalisations [4,5]. Worldwide it impacts approximately 42 million people each year, however, it is highlighted that not all seek or can access appropriate medical treatment due to cost and lack of understanding of the significance of the injury [6]. Thus, this figure could be higher due to unrecorded data. The outcomes for those who suffer are often better than those of moderate and severe forms, however, they can experience adverse effects in both the short and long term.

Mild TBI can be split categorically further into non-complicated and complicated mild TBI in which intracranial growths are expressed. They tend to experience poorer functional outcomes than non-complicated mild TBI victims at 3- and 6-month post-trauma intervals [7]. And report degraded quality of life scores at 3 months post-injury (quality of life after brain injury (QOLIBRI) 3-month, n=569, mild TBI (non-complicated): 19%, mild TBI (complicated): 26%, $p<0.05$), with the effect becoming insignificant at 6 months post-injury [7]. Some studies have demonstrated very little separating complicated mild TBI and moderate TBI regarding functional outcomes [8].

Moderate TBI

Moderate TBI lies between the mild and the severe forms. Because of this middle ground, it is often studied in combination with one of the other two, typically the latter, resulting in far fewer studies dedicated to it in isolation. This is despite mortality and morbidity rates being lower than that of

severe traumatic brain injury in 6-month outcomes (study completed in children and adolescents) [9]. This middle ground leaves moderate TBI with less guidance than severe TBI as is highlighted by Daniel Agustín Godoy et al. They state ICP is monitored in a minority of moderate TBI patients (8–20%) but clinically significant raised ICP (defined as >20mmHg and the level at which ICP management techniques are normally applied) is found in 50% of monitored cases [10].

Like mild, moderate TBI patients can be further divided into separate groups. One such is given the name 'talked and deteriorated'. This represents those who following a substantial impact to the head are assessed to have retain some verbal communication capability (talking either coherently or in a confused manner), however they go on to deteriorate into a worsened condition.

Mild and moderate TBI conclusion

While not the focus of this research mild and moderate TBI are important to consider when discussing the future of NIRS in TBI. Overall mortality of the forms is lower than severe however it is clear there are still substantial consequences for those who suffer TBI. Groups such as complicated mild TBI and 'talked and deteriorated' highlight the continuous nature of the injury and the importance of initiating clinically relevant and accurate monitoring with minimal delay. In the NIRS section examples are given of studies that provide some of the benefits of the larger devices while retaining the rapidly deployable and portable aspects of NIRS devices which may benefit these groups in which invasive monitoring is not warranted.

Severe TBI

Severe TBI has the highest morbidity and mortality rate. It requires intense therapeutic interventions over the acute phase of the injury with constant invasive and non-invasive neuro-monitoring required for increased chance of favourable outcomes in addition to substantial rehabilitation treatment. Patient monitoring will often include the use of invasive probes to allow for precise measuring of their condition. This includes managing physiological values such as intracranial pressure (ICP) which has been a focus of treatment for several decades now as recommended by the Brain Trauma Foundation (BTF) [22]. Recently treatment management based on multimodality monitoring, including brain oxygenation and cerebral autoregulation has shown some promise but is yet to be included as standard treatment [24,25].

Severe TBI treatment

Current treatment, particularly for those who are undergoing severe TBI, revolves around mitigating secondary insults. Secondary insults are injuries that occur after the primary impact and further sustain damage to the individual's health. Patient outcome is closely related to the healthcare team's ability to detect and mitigate these promptly with sustained secondary injuries correlating significantly with worsened outcomes [26].

In severe TBI due to the expansive monitoring warranted secondary injuries can be monitored and mitigated with invasive methods and treatment. However, this is only possible once the patient is in the neuro-care environment and often requires surgical installation of monitoring probes.

ICP and the gold standard

ICP monitoring and management is a standard method of treatment in the UK for those confronting severe traumatic brain injury (TBI) and follows the Brain Trauma Foundation's (BTF) 4th edition guidelines. Monitoring is achieved via the installation of an intracranial bolt in the patient's skull in which a pressure transducer is inserted. This provides a continuous measure of ICP in mmHg to healthcare professionals. This is considered the current gold standard of monitoring as the

transducer provides a direct measurement of pressure within the brain. However, due to the invasive nature of the procedure, it is only appropriate for those who are confronting severe TBI.

There are alternatives used for estimating ICP based on non-invasive methods. For example, Transcranial Doppler (TCD) which utilises ultrasound probes pressed against the patient's temples to monitor cerebral blood flow velocity with the main cerebral artery. This data can be applied to a model which estimates ICP based on this information. This method is not considered to be as accurate due to the secondary nature of the measurement and errors that may arise from the model. Additionally, TCD is not a perfect solution for several other reasons. For instance, it cannot be used on every patient as it requires a biological acoustic window which may not be present/sufficient in the patient, and it requires a high level of expertise to setup and continue monitoring (with probes requiring precise placement which can be disturbed by movement).

The study we are proposing here aims to compare our device with the invasive probe (the gold standard). This is the best way to evaluate its accuracy in humans as we can say with confidence if the changes in the ICP we are detecting are originating from changes of ICP in the participant. We will compare our device and model performance against the mmHg output of the intracranial probe. This will be achieved in a couple of ways. Firstly, reviewing relative changes in ICP from the probe and our estimation of ICP to calculate the error. And when a clinically significant change in ICP occurs (typically classed as >20mmHg), how accurately our machine learning models can detect and classify this event. The models' errors will use standard machine learning metrics such as calculating the mean square error (MSE) and area under curve (AUC) while the full results will be analysed with more advanced techniques such as Bland-Altman analysis.

Separate from this study, we are also comparing our device to the non-invasive methods (this is how we developed our current model of ICP estimation). But as this relies on measuring against devices that likely have their own inaccuracies which are of an unknown severity or rely on us assuming we have successfully increased or decreased ICP by an unknown amount (for instance if we ask a healthy participant to perform the Valsalva manoeuvre) it is not possible to say with certainty how inaccurate the device and model are.

The benefit of this research is it would develop a method of monitoring ICP non-invasively and in a cost-effective way while retaining a high degree of accuracy. Unlike other non-invasive methods such as TCD, this will use light which would make the device easier to set up and manage. This would therefore have benefits over current non-invasive methods.

Secondary insults

Another key aspect of TBI treatment is the management of secondary insults. These are injuries sustained after the initial trauma and are shown to be linked with worsened outcomes [26]. An example of a secondary insult we aim to monitor and evaluate the device performance of is intracranial hypertension (a clinically relevant raised ICP as discussed above). However, unlike the ICP monitoring where we know we will have the values of ICP to measure device and model performance against, we cannot know what other secondary insults will be present in the cohort. Additionally, we do not know how these injuries will present in our Near Infrared Spectroscopy (NIRS) devices due to the novelty of these systems.

Instead, we will record participants' treatment, outcomes (with the Therapeutic Intensity Level (TIL) and Glasgow Outcome Score (GOS) respectively), other monitoring devices and clinical notes to act as secondary measures of the participant's injuries. This will be used to inform models of secondary insults and intensity levels to evaluate if the device correlates with the outcome. This is similar to

other studies that have applied similar devices in other cohorts (typically neonatal [27]) and we will follow the statistical methods of those papers too. These are Pearson correlation coefficients, logistic regression and significance testing.

Where possible we may review in greater detail individual secondary insults with which we feel we have sufficient data collected with the device attached to the participant during the surrounding time of the insult. While this is a secondary measure of the injury, it will be used to inform future studies into areas that show promise of monitoring with the devices.

TBI conclusion

The purpose of the chapters above is not to provide a comprehensive view of TBI but to highlight some of the main challenges and considerations when developing medical systems for treatment. Within TBI there is a broad width of severity and a wide range of outcomes that can result in life-long disability or death in the most severe cases. Each of these demands different monitoring solutions that be applied in a niche scenario and as such it is imperative to critically assess new systems and techniques for treatment. By developing non-invasive and novel methods further we hope to gain new insights and techniques for managing the forms of TBI faced, further improving care.

NIRS

NIRS is a non-invasive, non-ionising, and portable neuroimaging technique. It quantifies changes in concentrations utilising near-infrared light (NIR) and is commonly applied to monitor oxygenated and deoxygenated haemoglobin in biological material.

First pioneered by Jobsis in the 1970s [11], subsequent research produced novel categories of devices. Some examples are, time-resolved NIRS, frequency-domain NIRS, bNIRS and HD-DOT. These devices and the fundamentals they are built on have been applied extensively in research and clinical settings providing insights into haemodynamic responses within the body. Studies have been completed with a variety of non-human primates, new-borns, healthy adult participants, unhealthy children and adult participants and more.

This study will focus on two types of NIRS devices, HD-DOT and bNIRS. Thus far they have been applied in a very limited context within TBI, although both have limited previous exposure in academic research within select cohorts.

Below we will give brief insights into the devices intended for use in this study and traditional NIRS devices, and they are suitable for implementation into a severe TBI cohort.

Continuous wave NIRS

Continuous wave NIRS (CW-NIRS) devices operate by emitting a continuous wave of NIR light (typically two wavelengths around 735 nm and 850 nm) and measuring the attenuation of the returning light. A modified version of the Beer-Lambert law (mBLL) can be applied under select assumptions (e.g., light scattering remains constant) to calculate the concentration of chromophores. CW-NIRS devices are commonly applied to biological tissue and allow for regional oxygen saturation levels to be monitored non-invasively. Both the HD-DOT and bNIRS device applied in this study are considered CW-NIRS devices.

Rapid-sampling NIRS

NIRS devices traditionally use a sampling frequency of ~10 Hz, an order of magnitude larger than fMRI (0.5 to 1 Hz) [13]. By increasing the temporal resolution there are additional benefits over fMRI. For instance, it may allow for the removal of motion artefacts. However, there are additionally

benefits, as it also allows for additional information capture. For example, around 5Hz we can start to see heart rate (HR) in a photoplethysmogram which uses similar principles to NIRS [14]. Further increasing the sampling frequency allows for the pulse waveform to be captured in finer detail. Pulse analysis techniques can then be performed, and additional key metrics can be calculated with higher degrees of accuracy. Of the devices we use, the HD-DOT has rapid-sampling capabilities.

Broadband NIRS

BNIRS is similar to the traditional CW-NIRS in many ways. By applying NIR light to tissue from a source to a detector, changes in intensity within the channel can be attributed to changes in concentration under the same assumptions as used in CW-NIRS and mBLL. However, bNIRS differs in wavelength selection. It employs a broadband light source and NIR filter which allows for hundreds of wavelengths to be utilised as opposed to the two in traditional CW-NIRS devices. This is done to monitor chromophores that are harder to detect due to them appearing in lower concentrations than haemoglobin or differences in absorption spectra.

High-Density Diffuse Optical Tomography

HD-DOT refers to a category of devices that utilise a dense source-detector array. They can provide blood oxygen level-dependent (BOLD) 3D image reconstructions on wide field-of-view regions of the brain. They have the benefits of optical monitoring techniques such as the non-invasive, non-ionising ability to capture cerebral information at a resolution close to what functional magnetic resonance imaging (fMRI) is capable of [12]. However, they avoid some of the fMRI drawbacks such as high cost, high maintenance, non-portability, and extra consideration requirements for patients under special circumstances such as those with metal implants or that cannot be moved due to their medical requirements.

NIRS in TBI

Some NIRS devices currently hold a limited role in TBI monitoring. Devices such as spatially resolved NIRS (SR-NIRS) systems use emitters and multiple detectors at varying differences to monitor regional oxygenation states. They are commonly applied to patient's frontal lobes in the NCCU, although are rarely employed in clinical decision making. Research studies have shown that some NIRS systems can be successfully employed for non-invasive monitoring of cerebral autoregulation, brain oxygenation and to some extent, haematoma detection [15]. Rapid-sampling NIRS coupled with other devices can be used for non-invasive ICP estimates within non-human primates [23].

The models of devices we aim to introduce are not currently reviewed in a TBI cohort or have only been done in a limited way.

Aims and hypothesis

This study is designed as a feasibility investigation to evaluate bNIRS and HD-DOT in monitoring TBI cohorts. We have isolated three areas of focus to maintain a clear scope, avoiding unnecessary data collection and disruption to the medical teams and patients while maximising research gain.

Primary aims

This project aims to develop NIRS-based biomarkers and physiological metrics that could be applied to aid the treatment of those suffering from severe TBI during the acute and subacute phase of injury. By applying two novel NIRS devices, we aim to evaluate their capabilities in monitoring TBI pathologies. Two key points of discussion will arise from this work.

1. Can bNIRS be used to monitor patient brain physiology during the acute and sub-acute phase of TBI?
2. Can HD-DOT be used to monitor patient brain physiology during the acute and sub-acute phase of TBI?

To assess their capabilities three aims have been developed and will be the focus point of this research. The areas selected are supported by existing literature utilising similar methods to those we will apply.

1. To evaluate the use of rapid-sampling HD-DOT for non-invasive intracranial pressure (nICP) estimation.

Managing ICP is a key strategy in aiding TBI patients. Currently, it is achieved via invasive probes, which is not always appropriate or possible. By utilising a rapid-sampling HD-DOT device we aim to evaluate its ability to estimate ICP non-invasively by applying machine learning techniques. It is expected to see some reduction in accuracy compared to the invasive techniques, but most errors are anticipated to originate from non-clinically significant changes.

2. To investigate the feasibility of using HD-DOT and bNIRS systems for detecting secondary insults (SIs).

SIs are highly time-critical events and are commonplace in TBI pathology. NIRS has shown some favourable results in detecting SIs such as hematomas and delayed cerebral ischemia, however, performance has often fallen short of other clinical techniques. By utilising bNIRS and HD-DOT systems, we gain the ability to monitor standard NIRS metrics with increased resolution and additional chromophores which may enable more accurate detection of SIs.

3. To investigate the development of NIRS-based biomarkers for use in conjunction with other medical systems utilising multi-modal analysis and machine learning techniques.

NIRS is capable of monitoring regional oxygenation states which may provide an insight into brain health. Using this information in conjunction with other medical systems may provide additional insight into how the body is self-regulating. We propose investigating multi-modal analysis for the development of continuous markers to indicate physiological trends, utilising signals from either the HD-DOT or bNIRS device. These signals will be integrated with metrics obtained from other medical systems connected to the participant as standard medical procedure.

End of study

The study will end either on the collection of 50 participants or by the end date (31st December 2025), whichever is sooner. We aim to collect a minimum of 10 participants during the study duration.

Importance of study

Below is the justification for the research. We begin by discussing a broad and brief view of TBI and NIRS as well as the benefits of introducing new systems to aid in the treatment of head injuries before narrowing the focus onto why the specific devices are chosen for this study.

TBI

As discussed in the background chapter, TBI is a health issue that impacts a substantial proportion of the global population in the form of physical primary and secondary effects on the individual and their communities as well as requiring costly treatment. By undertaking medical research, we strive to either lower the cost of treatment, expand our monitoring capabilities or improve our scientific understanding of the injury to improve the overall global quality of life.

NIRS

NIRS devices are by design, a safe, non-invasive, non-ionising neuro-imaging technique that can provide insights into regional oxygenation states within the brain. They can provide continuous monitoring capabilities that are rapidly deployable and create minimal obstruction to patient access. They can be applied universally enabling those who cannot be monitored by other means to receive healthcare. Additionally, several further benefits stem from applying it to a TBI cohort as many of the NIRS limitations are not realised within the population. For example, motion artefacts can lower the quality of NIRS data, however, rapid movements are not anticipated from those suffering from severe head trauma while under medical supervision. Monitoring location is also anatomically favourable due to the lack of hair coverage on the forehead- allowing for the pre-frontal area to be monitored relatively easily without requiring patient readjustment minimising interruption.

However, despite the many benefits traditional NIRS presents for monitoring head trauma, the devices are not commonly applied in clinical decision-making. While strengths have been shown within research, they are often super-seeded by invasive or single-snapshot methods, disallowing them to be used in clinical decision-making. By introducing more sophisticated devices we can evaluate their use in monitoring TBI and develop new methods that can aid in patient monitoring and recovery while retaining the many benefits NIRS provides.

BNIRS and HD-DOT

Two types of NIRS devices have been selected for use in this study, HD-DOT and bNIRS. They expand beyond the traditional NIRS systems in several ways but are based upon the same safe-by-design fundamentals. They have had very little exposure to clinical neuro-care environments to date due to their young age and lack of commercial availability. We are in a unique position of having both devices available to us for dedicated use in this study.

BNIRS

Of the devices, the bNIRS device is the only one to have previously been integrated into an adult neurocritical care environment. This was done in one study there were six individuals with TBI monitored while suffering from a single secondary insult (hypercapnia) to study its effects on cerebral cellular metabolism [16]. The study did not monitor the device's capabilities to track

cerebral autoregulation which is one of the most consistently strong performing areas of NIRS [15] and a current focus of TBI-treatment.

BNIRS holds additional potential due to its ability to detect other chromophores within the brain. This includes the redox state of CCO and is the only known method of doing this non-invasively. As this plays a vital role in neurovascular coupling, we could see benefits from monitoring this metric in patients with TBI as they may be undergoing self-regulating disability which may affect brain metabolism.

HD-DOT

The HD-DOT device has never been integrated into this environment within an adult TBI-cohort to the best of our knowledge. It offers the abilities of traditional NIRS but over a much wider field of view. The high-density aspect allows us to re-create BOLD signals over time at a fidelity comparable to functional MRI (fMRI) machines. Unlike fMRI, this can be applied to the patient continuously without restricting clinical access and for much less cost. This study will monitor part of the patient's pre-frontal lobe along with other NIRS devices, placed there as standard NCCU care, to monitor NIRS's ability to track TBI-related markers.

By increasing the temporal resolution, we also gain the ability to monitor pulse waveforms within the brain which can yield further information such as non-invasively estimating ICP [17,23]. This is the current main method of TBI management but is performed with invasive probes which are considered the gold standard. However invasive measurements have several disadvantages such as requiring a surgical procedure, infection risk, and not being possible or warranted in all groups. By developing non-invasive solutions we aim to build systems that can be applied to TBI patients while minimising risk and time-to-initiate monitoring.

Future research

This work is intended to act as an initial pilot study to inform future work. We have selected areas in which NIRS or similar devices have performed well previously but are not clinically applied. We believe that these are areas that hold considerable potential and upon evaluating their performance can be used to inform future studies and device development.

It is important to highlight, that while this work requires reviewing device ability in declining moderate and severe TBI as this will allow us to compare devices to the gold standard, mild forms of TBI will be considered as well in future work.

Patient and public involvement session

A public consultation session was held to allow detailed feedback on the study from those who have suffered from TBI as well as their carers. It was held on the 17th January 2024 and lasted for approximately one hour.

During this time the research protocol and justification was explained to the audience as well as example devices shown. The consent and subject recording procedure were given in detail.

Feedback from the session was very positive with no complaints or concerns raised. Many felt the work held a lot of value, particularly if non-invasive systems can be shown to be usable over invasive ones.

Additionally, we have and will continue to further work with members of the session who have been provided with our participant facing information sheets to help ensure they are understandable and comprehensible to those who have suffered from TBI injuries.

General research methods

Subjects

The subjects in this study will be those admitted to the NCCU in Addenbrooke's Hospital (Cambridge, UK). They will be individuals suffering from severe TBI (defined as GCS score ≤8) or moderate (defined as GCS score ≥ 9 and ≤ 12) TBI. Subjects must be undergoing invasive ICP monitoring.

This cohort has been selected for this study as they are confronting the most severe forms of TBI. This will allow us to capture data not possible in any other human group. Gathering and analysing these metrics will be crucial in evaluating the performance of the systems when considering their future use in TBI monitoring.

Mild TBI patients (defined as GCS score ≥13) are not included in this study as they do not undergo the same amount of monitoring and thus validation comparisons would be limited.

Eligibility criteria

Not all patients within the NCCU will be suitable for this study. The basis for this is due to unacceptable levels of risk to the patient, for example placing the devices may sustain further damage (on those with open head injuries). Or for study design purposes (for example not having ICP monitored via intracranial probe would make evaluating our devices ICP estimation impossible).

Potential participants will be screened by two parties, the treating clinician and ourselves. Treating clinicians will be the first to screen the patient. They will be provided with the participant criteria and be asked to only propose suitable patients. If they believe the participant would be unsuitable for the study, either because they do not meet the criteria they will not facilitate a meeting between ourselves and the next of kin. If the treating clinician believes the patient is suitable and the next of kin expresses interest in entering the patient on their behalf, they will refer them to us. We will then screen the patient and if they meet our criteria, request a meeting with the next of kin.

A screening log will be stored on a Cambridge University Hospital server. This is to ensure we can identify gaps within the sample cohort in our analysis. The screening log will consist of an approximate date and reason for patient rejection. It will contain no further data.

Inclusion criteria

To be included in the study patients must meet all the following criteria:

- Patient must be over 18 years of age.
- Patient must have either moderate or severe TBI.
- Patient must be admitted to the NCCU in Addenbrooke's Hospital (Cambridge, UK).
- Patients must have an ICP monitored via an invasive probe.

Exclusion criteria

Patients who meet one or more of the following criteria will not be able to partake in the research study:

- Patient is under 18 years of age.
- Patient is suffering prefrontal penetrating head wounds that prevents device placement.
- Participants enrolled on three or more research studies as in accordance with local guidelines.
- Moribund at presentation.
- Patients with infectious diseases.

Study procedures

Upon receiving consent (process discussed later) we will, where possible, begin recording the participant within 24 hours. This will allow us to capture data in the acute stage of injury in which secondary insults are common.

Initially, we will record for three hours per device per day, resulting in daily six-hour recording sessions for the participant. Three hours per device was selected as it was suggested by collaborators with extensive experience in similar studies. This will be assessed after the interim analysis period and may increase or decrease the recording length depending on the collected data. In the event recording length must be altered, the ethics protocol and documentation will be amended as required.

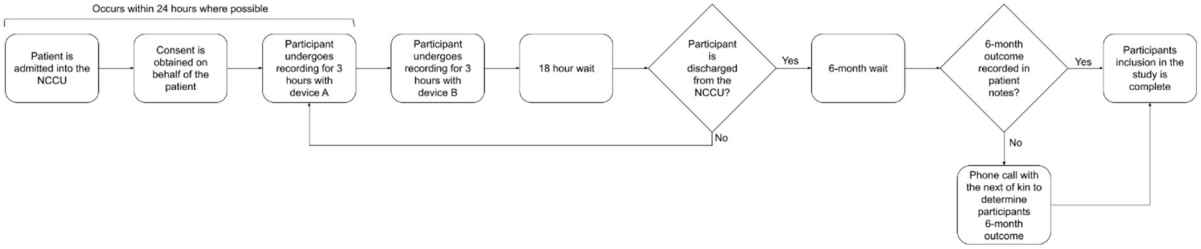

Figure 1

Study procedure for participants. Note: this assumes continued consent. In the case of revoked consent, we would withdraw the patient immediately and remove all their data.

A recording session will consist of two separate recordings: the first with the rapid sampling HD DOT system (device A) and the second with the bNIRS system (device B). We will begin recording with one device, recording for three hours, remove the first device, place the second device, record for three further hours, and remove the second device (the order of the devices may vary). For data recording and storage, we will use the in-place research storage system. Data acquired via the NIRS devices will be transferred via encrypted memory stick to the brain physics database servers.

Team members will remain within the building when devices are recording in case they are needed. Additionally, team members may take notes regarding participant movement, for example, patient restlessness. Note-taking will pertain to the patient being moved and device placement. It will not include any personal data.

Devices will be placed on the participants' foreheads. Placement will be off-centre, approximately 2 cm above the brow on the participant's left side unless obstructed by injury, in which case we will use the contralateral side. The devices attach via double-sided adhesive body tape. Training for device removal will be provided to the staff before the introduction of the devices into the NCCU. Devices are not expected to interfere with other medical systems monitoring the participant. A single probe from the currently used NIRS system may have to be removed, although this should not affect patient care. They will be removed only if necessary and when permission is granted by the treating clinician.

Devices are not expected to cause participant discomfort as the adhesive tape is designed for human skin contact. The devices are not particularly heavy (they have been used on brain-injured babies without issue [18,19]) and do not heat up beyond 45°c to prevent heating of the skin.

Participant comfort is a major consideration in this study. Where able we will adjust the study recording time to suit participants, their visitors, and the medical staff.

If a participant's family visits during a recording session, we will respectfully step aside from the participant's bedside to prioritise the visitor's privacy. However, we will remain close to the participant and the device, and request that the device remains on during this time to maintain data continuity and ensure accurate recordings. By implementing these practices, we aim to minimise the study's impact for our participants and their visitors throughout the study.

Recruitment and sample size

The total number of participants will not exceed 50.

Recruitment will take place through the NCCU. As a patient is admitted, their next of kin will meet with the treating clinician who will discuss the opportunity to enter the study if the patient is suitable for such. We will not recruit via other methods.

Sample size calculations

It is not possible to derive a minimum number of participants as to the best of our knowledge there are currently no other studies that utilise a HD DOT device within a TBI cohort. Therefore, a power analysis cannot be completed for this study. BNIRS studies have demonstrated some success in monitoring TBI participants (n=6) [16], however, they focus on a single secondary insult and therefore cannot be used in a power analysis for this study.

As this is a pilot/feasibility study we will use the information gained in this study to inform other potential future studies. Additionally, a power analysis will be complete after the interim results to ensure significant results are attainable under the current study implementation.

Consent

Within the NCCU the patient cohort comprises individuals confronting severe TBI. A significant proportion of these patients are anticipated to be under heavy sedation, in states of coma, or rendered unconscious to varying extents. Additionally, several of them may necessitate intubation or have restricted limb movement due to their injuries, leading to constricted verbal and motor abilities. Therefore, their cognitive functions, encompassing decision-making, memory recall, and critical thinking, will be adversely affected, in addition to other limitations placed on them due to their condition. Consequently, adhering to the traditional protocol of informed consent collected directly from study participants from this cohort would be either not possible or unsuitable and unethical.

Consent procedure

If the next of kin can do so (as judged by the clinician and themselves), they will be asked to act as a personal consultee to represent the patient's best interests. If they are unwilling to represent the patient or the clinician feels they cannot be asked to do so for any reason the patient will not be included in the study.

The next of kin will be identified by the dedicated team in Addenbrooke's Hospital as is standard practice. They will be met by the clinician who will explain that they have the potential to include the patient in a study including a brief description of the study procedures. During this initial meeting the treating clinician will enquire if they believe entering the patient into the study represents their best wishes and if the next of kin expresses interest, the treating clinician will in turn inform us so that we can facilitate a meeting if the patient meets our criteria. This provides the next of kin with the option of refusing to speak with us should they not want to.

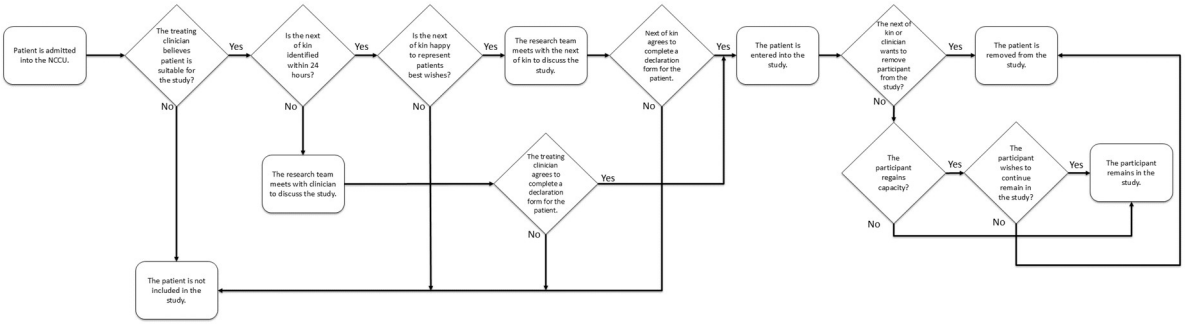

Figure 2

Consent procedure

Cultural mediators will be provided if next of kin is not able to sufficiently communicate in English. In the event we are unable to open a clear communication channel between the next of kin and ourselves after they have been identified, the patient will not be included in the study.

In the event the patient has no next of kin available, or they are not identifiable we will request the treating clinician to act as a professional consultee on the patient's behalf until the next of kin is identified.

The next of kin or professional consultee will receive an information sheet explaining the study and they will have the opportunity to ask questions before entering the patient into the study. We will provide two hours after meeting them to decide if they believe entering the study would best represent the patient's wishes. This is to ensure we still have time to record patients while in the acute stages of injury. Upon receiving consent, we will aim to start recording within 24 hours. Additionally, the patient's GP will be duly informed of their inclusion in the study. The consent forms will be securely stored under lock and key. The consultee will be provided with a copy.

Remote consent procedure

Addenbrooke's NCCU extends its services to the broader East Anglia region. Consequently, it is possible that patients may be transferred from locations beyond the immediate local area, and therefore the next of kin may not be present with the patient at the time of admission. Alternatively, logistical constraints may prevent the next of kin from being able to travel. Therefore, we seek to establish the option for remote consent in this study. This will enable the personal consultee to still represent the patient's best interests while not being able to be physically present. When obtaining consent remotely, we will provide identical information to the in-person consent procedure and facilitate the opportunity for inquiries through video conferencing software, phone calls and emails. Consent forms will be transmitted via email.

In the case of digital signatures, the forms will be printed and digital copies, along with emails, will be deleted to maintain confidentiality. Participants using digital signatures will be advised to keep a copy for their records.

Regained capacity

Participants will not have decision-making capacity while admitted to the NCCU, however, they may regain capacity after being discharged. This is typically assessed by the neurology department in the hospital as standard care. We will monitor this in the patient clinical course up to 6-months coinciding with the time we complete the 6-month outcome phone call.

In the event the participant's recovery state is recorded, and they are deemed to have regained capacity we will contact them to ask if they would like to remain in the study, providing them with study details. In the event the outcome is known but the participant is not deemed to have recovered we will not be able to ask if they would like to continue in the study and will continue to use the personal consultee (unless there was no next of kin, in which case we will use the professional consultee). In the event the outcome is not known we will conduct a 6-month outcome phone call to gain this information for our study (procedure discussed later), but we **will not** assess if the participant has regained capacity. After this we will inform the next of kin if the participant is to regain capacity, they are free to withdraw themselves at any time by contacting the details on the information sheet. We will then stop monitoring the participant's clinical course.

Participant demise

In the event of the participant's demise, study data will be kept unless the next of kin requests the participant is withdrawn from the study. In this case, all data recorded from the participant will be removed from the study and any analysis. If we have already published results from the study, we will not be able to remove data. This will be made clear in the information sheet and consent form.

Consent withdrawal

Consent can be withdrawn at any time of the study. To do so the next of kin or professional consultee must inform one of the research team members with contact details provided on the information sheet. The withdrawal process is explained on the information sheet.

If a participant regains capacity as assessed by a neurology specialist, their right to withdraw is given to them. Their withdrawal after regaining capacity can happen at any time and is explained in the information sheet.

Safety

This study will be carried out in a complex environment, involving interactions with severely injured and vulnerable participants. It will be crucial to integrate effectively with the medical team, minimising distractions and being resource-conscious to avoid burdening their duties. Safety considerations are of utmost importance for this study. In the following paragraphs several safety aspects are discussed. Detailed electrical documentation for the devices will be provided to the clinical innovation team at Addenbrooke's Hospital to demonstrate device safety.

NIRS devices present a safe and non-invasive approach to brain monitoring. They utilise light in the near-infrared range which is non-harming and safe for humans under all conditions. The devices selected for this study have met all relevant legal and regulatory requirements. Their safety is further demonstrated by previously completed studies which involved other brain-injured cohorts.

For example, a similar bNIRS device (using similar components but a separate device) has been applied in prior investigations completed at University College Hospital (London, UK) involving newborns with brain injuries with no safety issues were reported [18]. The HD-DOT device has also been applied in the monitoring of newborns [19] although the system applied in this study has been updated by Gowerlabs Ltd and modified by ourselves for this project. Modifications were made to alter the cap design to minimise participant discomfort and disruption to medical care during the study as well as ensuring the device could be disinfected. We also added additional safety monitoring measures.

Both devices will undergo evaluation by the clinical innovation team at Addenbrooke's Hospital before being introduced into the NCCU. In addition, we will provide a training and familiarisation session with the devices and study procedures for the medical staff within the NCCU before commencement. This approach is to allow the staff to feel confident in handling the devices, including how to remove them in the unlikely event a team member is unable to. It also provides them the opportunity to voice any concerns or queries they might have regarding the devices or the study.

Additionally, all standard safety measures for the environment will be applied for this study, this includes the following.

Hospital guidelines on safeguarding, and study protocols to ensure the safety of study participants, other patients and the medical care team within the NCCU.

No-fault insurance for the study design, management and conduct will be arranged through the University of Cambridge's insurance office, in addition to the clinician's insurance for claims and the patient's NHS indemnity rights.

Contact details will be provided to all team members to allow for queries and concerns to be communicated from the clinical team or participants' next of kins.

All team members directly involved in recording participants will have obtained a research passport before the study starts. Research passports require an advanced DBS background check and an occupation health assessment including blood screening to be completed.

Data protocol

This study requires collecting data from several sources and compiling them into a single location for analysis. This will include non-identifiable data such as physiological recordings (e.g., heart rate) and clinical notes (e.g. injuries suffered) as well as limited identifiable data from participants (e.g., age and skin tone). This data is required for a comprehensive analysis to be performed and information that will not benefit the final analysis is not recorded. All data will be treated as confidential and not shared outside of the research team without de-identification steps. The analysis will be performed on deidentified data.

Information collected for this can be split into three categories. Injury-specific data, non-injury-specific data and recording notes.

Non-injury specific data

The non-injury-specific data contains two key bits of participant information: participant's age and skin tone or ethnicity. These will be stored on the NHS electronic health record (EHR) and retrieved from there upon the participant's entrance into the study. This is personal data and will follow a de-identification procedure before being transferred to a separate server (the Brain Physics Database) for processing.

Justification of personal data collection

Age is a powerful predictor of outcome in TBI [20], as such it will be used in models to improve their accuracy. There is also research suggesting that NIRS can benefit from using the age of a participant as an input to create a more accurate model for predicting patient outcome [21].

We will not store the date of birth of the participant and instead use a binned age category (e.g., 25-30 years old). This is in accordance with the protocol set up for data de-identification within the Brain Physics Database.

Ethnicity or skin tone. As NIRS is a light-based device, factors that influence light-coupling, such as skin pigmentation are required for the analytical purposes. This will be used in models to achieve improved results (for example, increasing the integration time to improve signal quality). By recording the participant's ethnicity or skin tone, we can measure device performance across groups and ensure that we are developing methods that can work for everyone.

Injury specific data

The injury-specific data will include data from both the NIRS devices we are using, and other medical systems monitoring the participant as part of standard care upon admission to the NCCU. This will include non-identifiable information such as heart rate, blood pressure, ICP, rsO2, PbtO2, temperature and more. These are required for analysis (for instance, heart rate and blood pressure are used to filter data and build metrics, ICP and PbtO2 will allow us to compare our device accuracy). Further information requested includes the participant's clinical notes containing information regarding the secondary insults suffered and medical interventions applied. Participant six-month outcome is also requested to evaluate device performance. CT or MRI scans are requested for subject-specific modelling.

Recording notes

When recording with NIRS data it is common practice to make notes of events which may impact the recording quality. This includes noting motion artefacts and adjustments made during the recording and the time of the event. This will not include any identifying information and the data will be stored on a password-protected Cambridge University Hospital laptop.

Transferring data to the brain physics database

The Brain Physics Database operates under separate ethical approval (REC 23/YH/0085) which we will adhere to. Data is de-identified by clinical staff within the NCCU as part of their job. The de-identification process follows a k-anonymity protocol that ensures individual participants are unlikely to be identified from the data following completion of the process.

To ensure we can trace data back to the participant (as required for checking 6-month outcome) a participant ID is provided to each participant in the study and will be stored on the NHS servers alongside their data. This participant ID will be a 'P' followed by a 2-digit random number to ensure it does not contain chronological ordering information of the participant. Deidentified data will be stored under this participant ID on the Brain Physics Database.

Data is transferred via encrypted drive by one of a limited number of members of the Brain Physics Laboratory, according to the operating procedure approved for the Brain Physics Database. Access to the database is automatically revoked upon study completion.

While data will be transferred to the brain physics lab database, it will not be stored with the standard of care (SOC) devices data. It will remain segregated on the database. This is required as it allows us to analyse the data using our standard tools and techniques that work with the Brain Physics database.

Analysis of data

We will use the University of Cambridge computers and laptops to analyse the de-identified data. This may include the university's performance computer. Data will not be transferred out of the country.

Raw data will not be shared outside of team members. Data may be shared outside of the team if it has been averaged with other participants to ensure that it does not represent an individual. This is required for presenting study results.

Data will be deleted from the high-performance computer and any University laptops immediately after use.

Analysis

Technical implementation

The data collected from the study is high frequency as is required for estimating ICP with a non-invasive device. As an example, a three-hour recording with the HD-DOT device results in ~1GB of data equating to around 500 million data points (~300MB/recording hour). Additionally, there will be other high-frequency data streams from other medical systems. In total, we anticipate each participant to have approximately 25GB of data associated with them. If we were to assume the maximum number of participants recorded this would equate to around 1.25TB of data in total. This will be stored on servers dedicated to high-frequency patient data.

Analysing this on a local PC will not be possible. We will instead use systems such as the University of Cambridge's high-performance server (https://www.hpc.cam.ac.uk/high-performance-computing) to compute models. This will only be provided with the de-identified data and will follow the Brain Physics Database and University of Cambridge high-performance computer security protocols.

Interim analysis

To minimise unwarranted monitoring and disruption to the NCCU, an interim analysis will be conducted after the initial ten participants. The decision to select ten participants is recommended by study collaborators with NCCU study experience and based on previous studies conducted with the bNIRS and HD-DOT devices.

The interim analysis will assess both the bNIRS and HD DOT devices. The insights gathered from this analysis will serve as a guide for the future direction of the study. We may adjust study protocol such as recording time and will amend ethics as required. This will allow us to either reduce monitoring time/total number of participants if possible or pause the study and reassess if it will not be able to achieve its aims.

During the interim analysis, the following aspects of the study will be reviewed:

Participant comfort - The comfort of the participants is a major consideration for this study. The majority of patients in the NCCU are sedated or unconscious and unlikely to notice devices being placed and removed. However, incapacity, along with other factors such as intubation may prevent participants from expressing their discomfort. We will note down any attempts to remove the monitoring devices along with other observations that may indicate discomfort such as restlessness while the device is placed. We do not anticipate this being an issue as the devices have been used in many previous studies, including on newborn babies [18,19] and adult participants [16]. Neither group expressed signs of discomfort. In the case of clear major discomfort to the participant, we will immediately remove the device and stop recording.

Bland Altman analysis and correlation techniques - these will be used in the identification agreement and correlation of our NIRS device and the devices used within the NCCU currently. While we may expect some value changes due to the separation between areas monitored, a Bland-Altman analysis will be performed to ensure they are in line. This will be done on the quantification of HbO and HbR over separate epochs of time and estimated intracranial pressure.

Preliminary power analysis - we will perform a power analysis on any of the tests that showed promising results but remained statistically insignificant. This will allow us to consider if it is possible to achieve a significant result with the remaining number of potential participants.

Machine learning models

There will be several potential machine learning models built and tested on the data.

Non-invasive intracranial pressure (nICP) estimation - using the rapid-sampling HD DOT device we will capture the pulse waveform of the participant [17,23]. We will use this data to test our current nICP estimation model (currently trained without ground truth data) to evaluate its accuracy and improve model performance.

Secondary insults classification – Convolutional neural networks and recurrent neural networks will be used to classify secondary insults. This will involve using data reduction techniques, pulse rejection methods and signal filters to eliminate and classify predictions.

Machine learning for predicting outcomes - It has been shown that sustained secondary insults lead to worsened patient outcome [26]. Thus, if we can accurately classify secondary insults or poor autoregulation performance, we may be able to use this to predict patient outcomes. This can then be used to validate the device's performance.

Assessing accuracy of models - For assessing accuracy on machine learning models, we will use metrics such as accuracy, precision, f1-score and recall.

Final analysis

The final analysis will include the models used in the interim analysis as discussed above but on increased datasets to further improve model accuracy and robustness. Additionally, due to continued data collection, participant 6-month outcomes will be available and used in the patient outcome model. Participant's outcome prediction will be based on multiple criteria. This includes non-injury-related metrics such as age and injury-related values such as TIL, GCS score on admission, autoregulation capacity, and SIs. Participants' de-identified data and NIRS recordings will be used in a model to predict participant outcomes. For this, we will likely use a binary classification model such as logistic regression or random forest based on the GOSE score criteria used in other studies, where GOSE > 6 is considered a favourable outcome. This will not be possible to do during the interim analysis as we will not have participant 6-month outcomes available. Metrics used to assess accuracy will be ROC and AUC scores primarily.

A screening log analysis will also be performed as this study aims to discuss the capabilities of HD-DOT and bNIRS in TBI, it is critical to assess where the devices were not applied in the study. This will be a histogram of the reason for rejection and a discussion of the most common reasons. In the event the screening log is larger than anticipated, more advanced techniques may be applied.

Outcome phone call

To assess device accuracy, we will measure the devices against patient outcomes. Patient outcome correlates with other measures we are attempting to monitor such as autoregulation and secondary insults and by evaluating our device against outcome we can review with greater accuracy if NIRS can be applied in TBI.

Therefore, we will request that the next of kin provide us with the 6-month outcome of the patient where the outcome is not recorded in the clinical notes of the participant. Outcomes will be classed by us using the GOSE scale and the questionnaire will be as follows:

1. Is the patient deceased?

   Yes = 1 (Dead)

   No = Proceed to the next question

2. Is the patient in a vegetative state or comatose?

   Yes = 2 (Vegetative State)

   No = Proceed to the next question

3. Does the patient require assistance for most daily activities due to severe disability?

   Yes = 3 (Lower Severe Disability)

   No = Proceed to the next question

4. Does the patient have some independence in daily activities but still require some assistance or supervision?

   Yes = 4 (Upper Severe Disability)

   No = Proceed to the next question

5. Is the patient living independently but with significant disability, albeit with assistance?

   Yes = 5 (Lower Moderate Disability)

   No = Proceed to the next question

6. Is the patient capable of living independently but with some issues in social or occupational functioning?

   Yes = 6 (Upper Moderate Disability)

   No = Proceed to the next question

7. Does the patient have almost normal functioning but with minor deficits or limitations?

   Yes = 7 (Lower Good Recovery)

   No = Proceed to the next question

8. Does the patient exhibit complete or near-complete recovery, resuming almost normal activities and lifestyle?

   Yes = 8 (Upper Good Recovery)

   No = The questionnaire concludes here

Dissemination of results

To minimise intrusion, we will not inform participants or their families of publications arising from this study. All publications resulting from this study will be published in open-access journals, ensuring they are publicly available. We will regularly update our social media channels and website with the latest publication details and results. Links to these channels will be provided in the information sheet, enabling participants to access and stay informed about the study's findings, should they wish to do so. In the event they want an update but cannot access the journals or find the terminology inaccessible, they may contact us with the contact details provided on the information sheet. In this event, we will endeavour to communicate the outcome of the study in a way accessible to them. We also aim to contribute to open public science talks where we can further disseminate our results into the public domain.

This must be balanced with the interests of industry partners who have contributed to the study. Any publications will require unanimous consent from all internal parties prior to their release.

Bibliography

1. Dewan, Michael C et al. “Estimating the global incidence of traumatic brain injury.” *Journal of neurosurgery* vol. 130,4 1080-1097. 27 Apr. 2018, doi:10.3171/2017.10.JNS17352
2. Maas, Andrew I R et al. “Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research.” The Lancet. Neurology vol. 16,12 (2017): 987-1048. doi:10.1016/S1474-4422(17)30371-X
3. Teasdale, G, and B Jennett. “Assessment of coma and impaired consciousness. A practical scale.” Lancet (London, England) vol. 2,7872 (1974): 81-4. doi:10.1016/s0140-6736(74)91639-0
4. Brazinova, Alexandra et al. “Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review.” *Journal of neurotrauma* vol. 38,10 (2021): 1411-1440. doi:10.1089/neu.2015.4126
5. Cassidy, J David et al. “Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury.” Journal of rehabilitation medicine ,43 Suppl (2004): 28-60. doi:10.1080/16501960410023732
6. Gardner, Raquel C, and Kristine Yaffe. “Epidemiology of mild traumatic brain injury and neurodegenerative disease.” Molecular and cellular neurosciences vol. 66,Pt B (2015): 75-80. doi:10.1016/j.mcn.2015.03.001
7. Voormolen, Daphne C et al. “Outcomes after Complicated and Uncomplicated Mild Traumatic Brain Injury at Three-and Six-Months Post-Injury: Results from the CENTER-TBI Study.” Journal of clinical medicine vol. 9,5 1525. 18 May. 2020, doi:10.3390/jcm9051525
8. Kashluba, Shauna et al. “Neuropsychologic and functional outcome after complicated mild traumatic brain injury.” Archives of physical medicine and rehabilitation vol. 89,5 (2008): 904-11. doi:10.1016/j.apmr.2007.12.029
9. Kennedy, Lori et al. “Moderate and severe TBI in children and adolescents: The effects of age, sex, and injury severity on patient outcome 6 months after injury.” Frontiers in neurology vol. 13 741717. 3 Aug. 2022, doi:10.3389/fneur.2022.741717
10. Godoy, Daniel Agustín et al. “Moderate Traumatic Brain Injury: The Grey Zone of Neurotrauma.” Neurocritical care vol. 25,2 (2016): 306-19. doi:10.1007/s12028-016-0253-y
11. Jöbsis, F F. “Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters.” Science (New York, N.Y.) vol. 198,4323 (1977): 1264-7. doi:10.1126/science.929199
12. Eggebrecht, Adam T et al. “Mapping distributed brain function and networks with diffuse optical tomography.” Nature photonics vol. 8,6 (2014): 448-454. doi:10.1038/nphoton.2014.107
13. Cui, Xu et al. “Speeded near infrared spectroscopy (NIRS) response detection.” PloS one vol. 5,11 e15474. 11 Nov. 2010, doi:10.1371/journal.pone.0015474
14. Szabolcs B and László H. “The minimal sampling frequency of the photoplethysmogram for accurate pulse rate variability parameters in healthy volunteers.” Biomedical Signal Processing and Control, 68:102589, 2021
15. Roldán, María, and Panayiotis A Kyriacou. “Near-Infrared Spectroscopy (NIRS) in Traumatic Brain Injury (TBI).” Sensors (Basel, Switzerland) vol. 21,5 1586. 24 Feb. 2021, doi:10.3390/s21051586
16. Tachtsidis, Ilias et al. “Analysis of the changes in the oxidation of brain tissue cytochrome-c-oxidase in traumatic brain injury patients during hypercapnoea: a broadband NIRS study.” Advances in experimental medicine and biology vol. 701 (2011): 9-14. doi:10.1007/978-1-4419-7756-4_2

17. Fischer, Jonas B et al. “Non-Invasive Estimation of Intracranial Pressure by Diffuse Optics: A Proof-of-Concept Study.” Journal of neurotrauma vol. 37,23 (2020): 2569-2579. doi:10.1089/neu.2019.6965
18. Bale, Gemma et al. “Near-Infrared Spectroscopy Measured Cerebral Blood Flow from Spontaneous Oxygenation Changes in Neonatal Brain Injury.” Advances in experimental medicine and biology vol. 1232 (2020): 3-9. doi:10.1007/978-3-030-34461-0_1
19. Frijia, Elisabetta Maria et al. “Functional imaging of the developing brain with wearable high-density diffuse optical tomography: A new benchmark for infant neuroimaging outside the scanner environment.” NeuroImage vol. 225 (2021): 117490. doi:10.1016/j.neuroimage.2020.117490
20. Maas, Andrew I R et al. “Predicting outcome after traumatic brain injury.” Handbook of clinical neurology vol. 128 (2015): 455-74. doi:10.1016/B978-0-444-63521-1.00029-7
21. Duncan, A et al. “Measurement of cranial optical path length as a function of age using phase resolved near infrared spectroscopy.” Pediatric research vol. 39,5 (1996): 889-94. doi:10.1203/00006450-199605000-00025
22. Carney Net al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery. 2017 Jan 1;80(1):6-15. doi: 10.1227/NEU.0000000000001432. PMID: 27654000.
23. Relander FAJ et al. Using near-infrared spectroscopy and a random forest regressor to estimate intracranial pressure. Neurophotonics. 2022 Oct;9(4):045001. doi: 10.1117/1.NPh.9.4.045001. Epub 2022 Oct 11. PMID: 36247716; PMCID: PMC9552940.
24. Hawryluk GWJ et al. A management algorithm for patients with intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive Care Med. 2019 Dec;45(12):1783-1794. doi: 10.1007/s00134-019-05805-9. Epub 2019 Oct 28. PMID: 31659383; PMCID: PMC6863785.
25. Tas J et al. An Update on the COGiTATE Phase II Study: Feasibility and Safety of Targeting an Optimal Cerebral Perfusion Pressure as a Patient-Tailored Therapy in Severe Traumatic Brain Injury. Acta Neurochir Suppl. 2021;131:143-147. doi: 10.1007/978-3-030-59436-7_29. PMID: 33839835.
26. Volpi, P.C., Robba, C., Rota, M. et al. Trajectories of early secondary insults correlate to outcomes of traumatic brain injury: results from a large, single centre, observational study. BMC Emerg Med 18, 52 (2018). https://doi.org/10.1186/s12873-018-0197-y
27. Bale G, Mitra S, Meek J, Robertson N, Tachtsidis I. A new broadband near-infrared spectroscopy system for in-vivo measurements of cerebral cytochrome-c-oxidase changes in neonatal brain injury. Biomed Opt Express. 2014 Sep 5;5(10):3450-66. doi: 10.1364/BOE.5.003450. PMID: 25360364; PMCID: PMC4206316.