Study Protocol

Title: Eye-Control Trial: Wearable Eye-Tracking Device as Means of Communication in the Critically Ill and Mechanically Ventilated Patient

NCT Number: NCT04582149

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Eye-Control Trial:

Wearable Eye-Tracking Device as Means of Communication in the Critically Ill and Mechanically Ventilated Patient

STUDY PROTOCOL

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Sponsor: EyeFree Assisting Communication Ltd., Tel Aviv, Israel

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SYNOPSIS

Title	Wearable eye-tracking device as means of communication in the critically ill, and mechanically ventilated patient
Short Title	Eye-Control Trial
Principal Investigator	Ofer Sadan, MD, PhD Assistant Professor, Department of Neurology and Neurosurgery, Division of Neurocritical Care Emory University School of Medicine
Study Description	The study will have two steps: (1) safety and efficacy phase, in which we will enroll up to 60 patients, with main goal to experience the use of the device in critical care settings, and better prepare for the second part (burn-in period); (2) a randomized controlled trial that will treat eligible and consented patients with either EyeControl or the current standard of care from a communication stand point. On a daily basis, all patients admitted will be screened according to the predefined inclusion/exclusion criteria. Eligible patients (or their LARs) will be approached by the study team to obtain consent. Once enrolled, and randomized to the intervention arm, the patients will be instructed how to use the EyeControl device and will keep the device on for as long as they would like. While on, the device will collect data as a potential monitor, such as time of wakefulness, and will screen for delirium by CAM-ICU questionnaire. At six months, we will contact the patient to assess his functional and cognitive performance using standardized questioners. Following this interview, the patient will end the participation in the trial.
Purpose	To determine the safety, tolerability, and ease of use of the EyeControl device and determine impact on communication and delirium in critically ill, ventilated patients in the intensive care unit.
Design	This is a single-center, Phase 1/2, two-step prospective, open-label, blinded-endpoint (PROBE) study evaluating the tolerability and efficacy of the EyeControl device.
Objectives	To evaluate the efficacy of a wearable communication device in preventing and treating ICU-delirium in critically ill patients who are admitted to the intensive care unit (ICU) and mechanically ventilated. The study will assess the safety, tolerability, and ease of use of the EyeControl device; examine its potential monitoring capabilities; determine the change in level of frustration and discomfort following use of the device; and measure long-term outcome of these critically ill patients.
Study Population	Critically ill patients who are admitted to the ICU at Emory University Hospital (EUH) who require mechanical ventilation for at least two days and are awake enough and cooperative to attempt working with the communication device (defined as Richmond Agitation Sedation Scale (RASS) score of -1 to 1).
Enrollment / Duration	Step 1: 60 Patients, approximately 8 months – No Long-Term Outcomes Step 2: 244 Patients, approximately 12 months – With LTO extending to 6 months
Subject Inclusion	• Intensive Care Unit (ICU) Admission • Mechanically ventilated for at least 24 hours • RASS between -1 to 1 at the time of screening (Note: minimal sedation is allowed including low-dose Fentanyl, Dexmedetomidine, Ketamine, Propofol, etc.)

Subject Exclusion	• < 18 years of age • Not admitted to the ICU • Inability to follow commands during screening • Known cerebral injury (acute or chronic) in the dominant hemisphere concerning for aphasia on clinical assessment • Significant pre-existing neurologic (i.e., dementia and/or cognitive deficiencies), psychologic, or baseline communication challenges that would confound outcomes assessments (including hearing loss) • Inability to blink or move eyes for any reason • Prisoner or incarceration • Inability or unwillingness to provide informed consent • Unwillingness to be contacted for follow-up
Outcome Measures	For the burn-in phase, the primary outcome will be time to successful operation of the device (see below for definition), and secondary outcomes include length, type and intensity of use (e.g. use for communication, entertainment, call for help etc), safety, and proof of concept of non-communication features of the device such as wakefulness time monitoring and CAM-ICU capturing. The primary end point of the second step will be number of alive and delirium days while in the ICU and on the ventilator up to 14 days from randomization, or to extubation or ICU discharge, the earliest. Secondary endpoints will include: proportion of patients who were able to operate and use EyeControl, the specific parameters of successful patients compared to those who were unable to operate it; the length and intensity of use; the correlation between the monitoring data and clinical data; and the cognitive and functional long term outcomes as assessed by telephone by the Critical care, Brain Dysfunction and Survivorship (CIBS Center from Vanderbilt University).

SCHEDULE OF EVENTS

SCHEDULE OF EVENTS	SCREEN ENROLL (DAY 0)	ICU admission	DAY 180
Procedure			
Eligibility Verification	X		
Informed Consent	X		
Lead diagnosis for ICU admission	X		
Physiologic Data (Vitals, GCS, etc)	X	X	
Neuroimaging (if available)	X	X	
Demographics	X		
Medical History	X		
Laboratory Results	X	X	
CAM-ICU q12h	X	X	
Discharge Data		X	
Clinical Endpoint Monitoring	X	X	X
General Questionnaire re: communication in ICU		X	X
Follow-up Assessments			
Neurocognitive Battery			X

TABLE OF CONTENTS

TABLE OF ABBREVATIONS

AE	Adverse Event
APP	Advanced Practice Provider
ARICU	Acute Respiratory Intensive Care Unit
CAM-ICU	Confusion Assessment Method in Intensive Care Unit
CCU	Cardiac Intensive Care Unit
CRF	Case Report Form
CTS-ICU	Cardiothoracic surgery Intensive Care Unit
EMR	Electronic medical record
ICU	Intensive Care Unit
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LOC	Level of Consciousness
LOS	Length of Stay
MD	Medical Doctor
MICU	Medical Intensive Care Unit
NeuroICU	Neuroscience Intensive Care Unit
RASS	Richmond Agitation Sedation Score
RN	Registered Nurse
SICU	Surgical Intensive Care Unit

BACKGROUND AND SIGNIFICANCE

Critically ill patients, who are mechanically ventilated, suffer not only from their acute, potentially devastating illness, but also from the lack of ability to communicate in an effective manner. On top of the mechanical change in air flow, communication challenges result from sedation, neurological injuries (primary brain injury or secondary encephalopathy), and delirium. Lack of communication can lead to increased frustration, anxiety, confusion and delirium and overall psychological stress, and could continue to the development of post- traumatic stress disorder (PTSD). On top of the subjective discomfort, the inability to communicate in an effective manner may impair medical care—for example, by failure to assess symptoms such as pain or breathing discomfort. In order to solve these difficulties, a new, wearable, eye-tracking communication device was developed (EyeContol).

STUDY RATIONALE

COMMUNICATION IN THE CRITICALLY ILL

Critically ill patients, who are mechanically ventilated, suffer not only from their acute, potentially devastating illness, but also from the lack of ability to communicate in an effective manner. This is the direct result of the orotracheal tube or tracheostomy required for the mechanical ventilation, which does not allow speech to be produced. On top of the mechanical change in air flow, communication challenges result from sedation, neurological injuries (primary brain injury or secondary encephalopathy), and delirium.

Lack of communication can lead to increased frustration (Guttormson et al., 2014), anxiety, and overall psychological stress (Carruthers et al., 2017) and could continue to the development of post-traumatic stress disorder (PTSD) (Wade et al., 2012). On top of the subjective discomfort, the inability to communicate in an effective manner may impair medical care—for example, by failure to assess symptoms such as pain (Chanques et al., 2014) or breathing discomfort (Binks et al., 2017) by behavioral cues only.

DELIRIUM IN THE ICU

One of the dreaded complications in critically ill patients is delirium. Delirium is an acute form of encephalopathy, or brain dysfunction, that is manifested by waxing and waning changes in cognitive abilities during acute illness. Delirium is diagnosed in 48-83% of critically ill patients (Girard et al., 2018, Ely et al. 2001), and is linked to increased mortality (Ely et al., 2004). Several risk factors associated with delirium include older age, prior neurological injuries or neurodegenerative disorders, as well as the acuity of illness and admission in the ICU (Ely et al., 2001; Oldham et al., 2018). Disorganized sleep is also linked to higher risk of delirium (Dres et al., 2019; Marra et al., 2019a). Delirium is strongly correlated with worse outcomes, including longer length of stay in the ICU and the hospital, and increased mortality (Marra et al., 2019b). Treatment for delirium includes pharmacological (mostly anti-psychotic medications) and non-pharmacological interventions (Marra et al., 2019). Non-pharmacological interventions to prevent and treat delirium include early mobilization, frequent reorientation, etc. (Martínez et al., 2017). Recently, a large randomized controlled trial failed to show benefit for pharmacological interventions to treat and prevent delirium, leaving non-pharmacological interventions as the main treatment option for now (Girard et al., 2018). Lack of effective communication not only could impair such non-pharmacological interventions but limit the diagnosis of delirium in the first place (Rowley-Conwy, 2018). However, from a diagnostic stand point, others have shown a valid method to diagnose delirium even in mechanically ventilated patients (Ely et al., 2001).

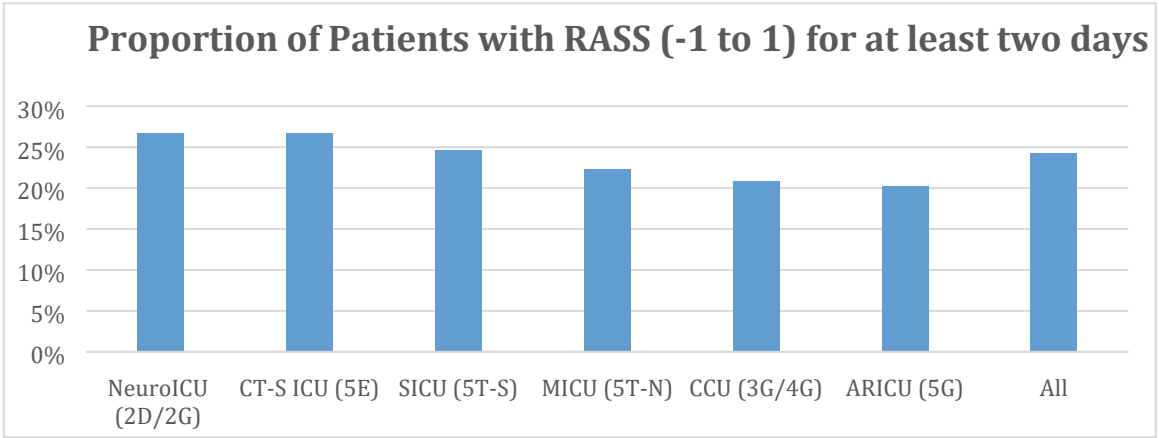
HOW MANY PATIENTS WOULD BENEFIT FROM A COMMUNICATION DEVICE?

On average, across the U.S., 39.5% of patients in the ICU at any given hour require mechanical ventilation (Wunsch et al., 2013). Estimating the number of patients who have an unmet communication need is difficult. Not all patients who are mechanically ventilated could communicate, even with assistance. For example, a patient who suffered a large stroke in the dominant hemisphere will suffer from aphasia and may not be able to communicate efficiently, with or without being ventilated. Similarly, in many critically ill patients, there is a need for continuous sedation, which limits the patient's ability to communicate.

Happ et al. (2015) estimated the number of patients who are mechanically ventilated and potentially could communicate. They found that 53.9% of patients who were mechanically ventilated for at least 48 hours were awake and following commands for at least 12 hours (one nursing shift).

Analyzing the data from the years 2016 to 2018 at EUH, there are, on average, 469±37 admissions to all ICUs per month. In order to identify the potential study population, we examined what proportion of patients were ventilated for at least two, three, or five days. We further calculated the duration of ventilator days for these patients, rate of tracheostomy, and the proportion of patients who had at least two days in which their RASS was documented as -1 to 1, suggesting that they were awake and cooperative enough to engage with a communication device.

We found that 27.8% of admissions to the ICU were intubated for at least 48 hours, while 18.9% were intubated for at least three days and 12.6% were intubated for at least five days. The mean number of ventilator days for patients ventilated for at least two days was 8.6, and 11.6 and 16.2 for patients ventilated for at least three and five days, respectively. Given the high mean number of ventilation days for the patients who are ventilated for at least two days, it seemed reasonable to further analyze this group as a the inclusion criterion. We further found that nearly 25% of the patients ventilated for at least two days had recorded RASS of -1 to 1 for at least two days, suggesting a window in which these patients could potentially communicate (see Figure 1A for breakdown by units). It was also found that 17.9% of patients ventilated for at least two days ended up being ventilated long- term, requiring a tracheostomy (see Figure 1B for breakdown by units). We hypothesize that this group, those who will need to be on the ventilator for a long period of time, will be the patient population that will mostly benefit from a wearable, eye-tracking-based communication device. At Emory, by this retrospective analysis of the past three years, we are estimated to screen about 130 patients per month who are ventilated for at least two days.



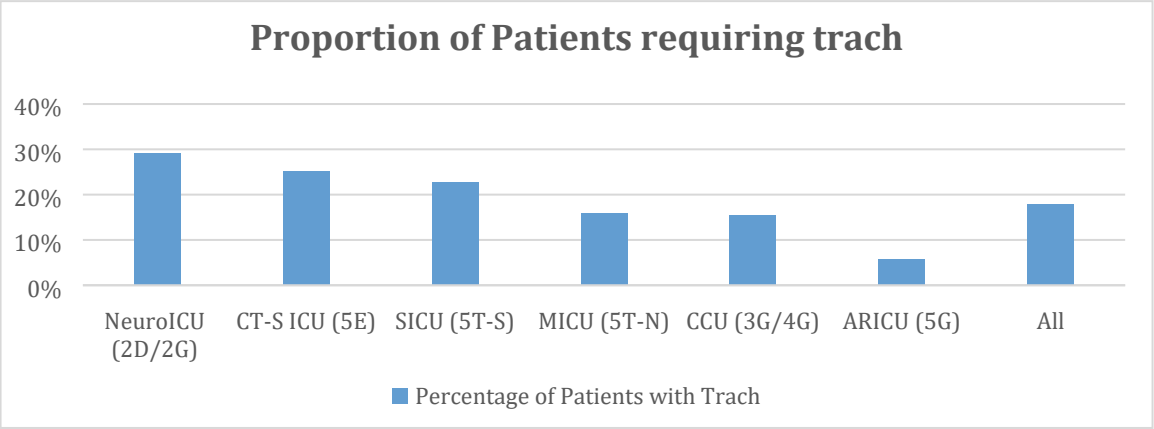


Figure 1: Breakdown of patients by units who are ventilated for at least two days and have RASS between -1 to 1 for at least two days (A) and patients who ended up requiring tracheostomy (B).

EYE-CONTROL DEVICE

Currently, the solutions for communication deficits in mechanically ventilated patients are mainly using yes/no communication, attempting to write, and communication boards that allow people to point at defined pictures or letters (Khalaila et al., 2011). Recently, technological advancements led to incorporation of more sophisticated communication devices, proving the feasibility of an eye-tracking approach, for example (Carruthers et al., 2017).

The EyeControl is a new, wearable, eye-tracking device (Figure 2) that facilitates communication by means of internal feedback to the patients with a bone-conducting speaker. In this way, the device can ask the patient what he or she wants to say, and the patient replies by eye gestures such as blinking or moving the eyes in a certain direction. This approach eliminates the need for calibration, as most eye-tracking devices that use a screen require, and is relatively easy to operate. It is currently being tested in general ICU-based settings in Tel Aviv, Israel, where the company reports nearly 100% success in teaching patients to use the device within minutes.

Figure 2: The EyeControl device.

This device has other potential advantages that could be utilized in the critical care settings. It could be used as a monitor; for example, it could record times that the patient has her or his eyes open as a marker for wakefulness (it could be an important indirect marker for quality and length of sleep); it could use its communication with the patient to assess for delirium (using known basic questionnaires such as the CAM-ICU); it could assess, to some extent, the ability to follow commands with blinking and eye movements. The device could be part of the non-pharmacological interventions to prevent and treat delirium. For example, it could state the day, time, and location to the patients every few hours.

The risk associated with the device seems very low. It is external, wearable, and could be easily removed with any signs of discomfort. No significant side effect was recorded from using this device according to the manufacturer.

STUDY PURPOSE

To determine the safety, tolerability, and ease of use of the EyeControl device and determine impact on communication and delirium in critically ill, ventilated patients in the intensive care unit.

STEP 1:

Primary Goal: Assess the safety, tolerability, and ease of use of the EyeControl device. The outcome measure for this goal will be the time of training required for a patients to successfully execute two tasks using the device: call for help and choose a predefined sentence for the device to say three times straight.

Secondary Goals:

1. Assess the proportion of mechanically ventilated, critically ill patients, with or without primary neurological injury, who could benefit and operate an eye-movement-tracking device as a means of communication.
2. Assess the type and length of the use done by the patient. For example, we will monitor how long a patient wears the device, uses it, and for what purpose (communication, call for help or entertainment).
3. Assess the EyeControl device as a diagnostic/monitoring tool for delirium in comparison to the bedside nurse assessment. Specifically, the device will record times of wakefulness for each 24h period of time, and will test for delirium using CAM-ICU. The later will be correlated with a live, verbal assessment done by a study team member.
4. Assess patient proficiency in device operation through daily orientation questionnaire.
5. Assess the change in level of frustration and discomfort patients and families feel in relation to communication with and without the device. These will be assessed by a questionnaire given to patients and families near their discharge.
6. Explore possible correlation between eye movements and clinical events by evaluating photographs of the eyes at the times of these events.

STEP 2:

Primary goal: Measure the time spent alive and non-delirious in the ICU up to 14 days from randomization with EyeControl-based communication compared with the standard of care, in a randomized-controlled fashion.

Secondary goals:

1. Assess the safety, tolerability, and ease of use of the EyeControl device; Specifically, we will assess on a daily basis for any adverse events related to the device. We will also document need for re-training on the device as a marker for ease of use.
2. Measure the length and intensity of use for communication and call for help; Intensity will be measured by the number of times the device is used and for which purpose as a categorical measure (eg, call for help, talk using predefined sentences, communicate using letter by letter dictation etc).
3. Correlate between the monitoring data and clinical data: the device will assess CAM-ICU independently, and a study team member will repeat this analysis and the documented results will be documented. We will also track any clinical decision making based on wakefulness time information (for example a decision to add melatonin agonist to promote sleep) ;
4. Measure the cognitive and functional long-term outcomes, by phone questioners, to be done in a blinded fashion at 6 months from ICU discharge.

STUDY DESIGN OVERVIEW

STUDY HYPOTHESIS AND RATIONALE

The study hypothesizes that effective communication could be part of prevention and treatment for ICU-delirium in critically ill, mechanically ventilated patients.

Lack of communication is a common, unmet need for these patients. It is believed that effective communication deprivation could be a contributing factor to the development of ICU delirium. It is further hypothesized that this communication gap could be matched by a wearable, eye-tracking-based communication device.

EyeControl is a wearable, easy-to-use device that could supplement current communication methods between the patient and the treating team (and family). Current standard of communication for the critically ill mechanically ventilated patients is limited to nodding, writing, and pointing at communication boards. The wearable device could potentially allow broader and more effective communication. It may have secondary benefits as well, as a monitoring device, an emergency-call device, and to improve patients' orientation.

STUDY DESIGN AND METHODS

This is a two-step trial, that will first have a "burn-in" phase to gain real-life experience with the device in critical care settings, and later in the second step transition into a randomized controlled study that measure the efficacy of the communication intervention on prevention and treatment of ICU-delirium. The study will be run across all ICUs at Emory University Hospital, a large, tertiary referral center. The different ICUs are detailed in Table 1.

STEP 1: ASSESS THE SAFETY, TOLERABILITY, AND EASE OF USE OF THE EYECONTROL DEVICE

On a daily basis all patients admitted to any of the ICUs at EUH will be screened for participating in the trial. Since during admission the patient could be first excluded and later meet inclusion criteria, the screening will continue for all patients on a daily basis (for inclusion/exclusion criteria, see below).

During screening, the patients' EMR will be accessed and/or their clinical status will be discussed with the treating team (RN, APP, MD) by a member of the study team in order to identify whether they meet inclusion/exclusion criteria. For example, the study-team personnel will identify if the patient is ventilated, for how long, and what is the patient's wakefulness and cooperation by nursing charting (e.g., RASS scale, nursing neurological and clinical assessment).

Of note, due to the different nature of neurologically injured patients in these settings (primary organ effected is the brain), we will enroll about 33-50% of the patients in this step from the neuroscience ICU. This approach will allow us to consider re-defining our parameters in the second step of the trial and design a pre-defied subgroup analysis.

Upon meeting inclusion criteria, patients and/or their LARs will be approached for consent (see below for consent process details). Consented patients will be instructed how to use and operate the EyeControl device. The primary outcome of this part of the study will be time to operate the device. Successful operation will be defined as the ability to use the device to call for help, and produce one predefined sentence out of several options, three different times.

Once the patient is able to operate the device, it will stay on the patient for as long as she or he would like it on, or until the patient is successfully extubated or discharged from the ICU, whichever is earliest. During the time the patient is wearing the device, apart from its original intention to serve as a communication device, the following features will be activated and tested:

a. Emergency call—if the patient is in distress, she or he could call for help by simply blinking three times. This will initiate a call for help from the device. We will monitor the use of this emergency call, its frequency, and causes for calling.
b. Wakefulness monitoring—the device will record the times in which the patient is awake by monitoring when the patient's eyes are open. This data will later be correlated with outcome measures such as delirium, LOS, and functional outcome. Changes in wakefulness time will also be correlated with ICU interventions such as adding a melatonin-agonist to promote sleep.
c. CAM-ICU validation—every shift, after the nurse and/or study team member assesses CAM-ICU, the device will repeat the test by using multiple-choice questions and ask the patient to choose the correct answers by blinking. We will later correlate the device's results with the nursing/study team ones.
d. Reorientation – at a defined time interval, if the patient's eyes will be open, the device will read the patient the current date/time/location.
e. Entertainment – patients will have the option to listen to music.
f. Family communication – Families will be supplied with a patient-unique link to record audio messages which the patient will be able to listen to through the device.

To address the secondary goal of proficiency with device operation, we will administer a daily orientation questionnaire via the device. If a patient fails this proficiency check, study staff will perform a device re-training module. The frequency and amount of necessary re-training will be captured as another data parameter.

During the study, we will collect clinical information from the patient's chart including: demographics, diagnoses, use of sedatives or medications that could change cognitive function, nursing charting (including neurological assessment), laboratory results, days on the ventilator, procedures, discharge destination, mortality, and functional outcome. All of these will be taken into account for the final analysis of the study. For example, this data could help us better identify which patients used the device more than others and which could benefit from its monitoring properties apart from its communication function.

As part of its operation, the device captures photographs and video of the patient's eyes (figure 3). In addressing the secondary goal of potential correlation between eye behavior and clinical events, we will explore this possibility by evaluating photographs of the eyes at the times of clinical events (i.e. hypoxia, new onset shock, or new onset sepsis). The device will activate the image data collection only after 50 consecutive frames of eye-in-the-image. This should be a safety index to verify that the device is only recording the eye. It will stop recording immediately when non-eye-in-the-image occurs. Data processing to decide if an eye is in the image is done locally on the device, so eventually only images of eyes should be collected. All external image data processing will be done following deidentification of the data, using the patient code only as an identifier.

Figure 3. Example photographs captured by the EyeControl device.

No randomization or blinding is planned for this step of the study, and no samples are planned to be collected.

STEP 2: MEASURE REDUCTION IN DELIRIUM-FREE AND ALIVE DAYS IN THE ICU WITH EYECONTROL-BASED COMMUNICATION COMPARED WITH THE STANDARD OF CARE.

The second step will be similar to the operation of the first one, in terms of patient screening and enrolling. The main difference will be the randomization process. Patients will be randomized to use EyeControl for as much as they wish, versus the standard of care. Randomization will be done centrally, and will be stratified to the specific unit, gender and age, race and ethnicity.

The primary goal of the second step will be to measure the time spent alive and non-delirious in the ICU with EyeControl-based communication compared with the standard of care. Delirium will be defined as CAM-ICU positive, starting at day 1 of use (following the day of training), up to 14 days from randomization or ICU discharge, the earliest. However, patients could require moderate to deep sedation following randomization, for example due to new or evolving medical complication. Whenever the RASS is below (-1), CAM-ICU will not be measured, and will be charted as undetermined. Therefore, only days in which the patient will be CAM-ICU positive, will be counted towards the primary outcome. CAM-ICU positive days prior to randomization will not be counted towards the primary outcome.

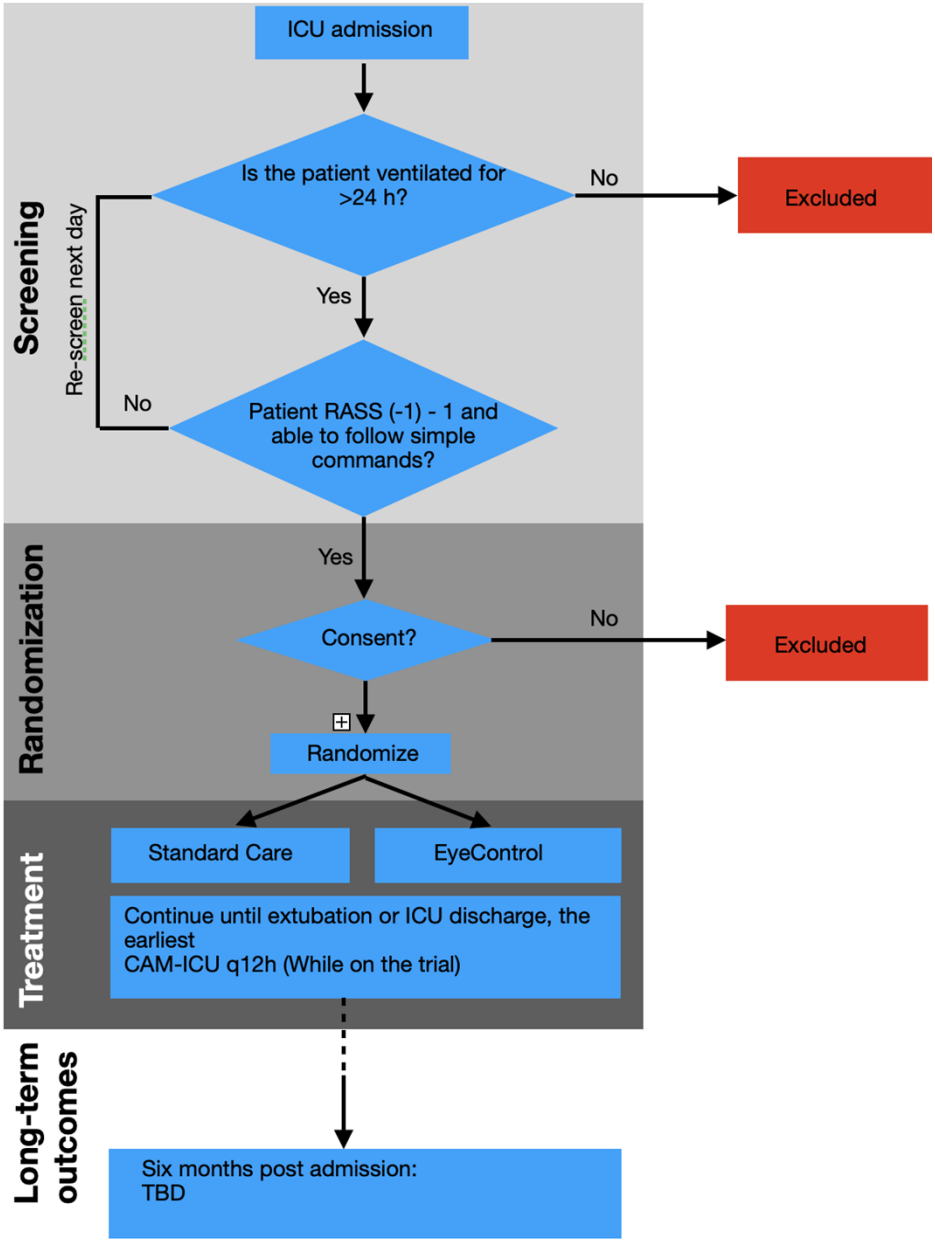
The secondary outcomes will include the following:

1. Assess the safety, tolerability, and ease of use of the EyeControl device. This will be achieved by daily review of advance events, and ask patients, families and clinical team regarding challenges of use.
2. Measure the length and intensity of use; We will measure time to first activation, as detailed under the primary goal of the first step, and on a daily basis we will collect data from the device including the number of hours a day the device was worn, how many times it was used for communication, and the type of communication (eg use of predefined sentences, call for help, using new sentences by dictation, entertainment listening etc).
3. Correlate between the monitoring data and clinical data, specifically validate CAM-ICU with nursing and/or study team independent assessment; and correlating wakefulness time with ICU interventions; We will collect from the device on a daily basis the times when the patient has his or hers eyes open, as a marker of wakefulness. We will also record interventions related to sleep and wake cycles, such as administration of

Melatonin or Melatonin agonists, night time antipsychotics, benzodiazepines etc. We will also perform a correlation between the device independent assessment of CAM-ICU, and the clinical team assessment.

4. Measure the cognitive and functional long-term outcomes, by phone questioners, to be done in a blinded fashion at 6 months from ICU discharge. This will include a pre-defined battery of tests, as detailed under the Long-Term Outcomes (LTO) Battery section below.

SUBJECT FLOW SCHEMA (STEP 2)



STUDY POPULATION AND SUBJECT SELECTION

Potential study population includes any patients admitted to the ICU. At Emory University Hospital, there are 121 active ICU beds as described in table 1.

Table 1: Intensive care units (ICUs) at Emory University Hospital

ICU	No. of Beds
Medical ICU (MICU, 5T-N)	17
Surgical ICU (SICU, 5T-S)	23
Neuroscience ICU (2D/2G)	40
Cardiothoracic surgery ICU (5E)	20
Cardiac ICU (CCU, 3G/4G)	14
Respiratory ICU (4A, 6A, 5G, 6G)	28
Total	142

PARTICIPANT SELECTION AND SAMPLE SIZE

According to our retrospective analysis, we intend to screen all admissions to all the ICUs at EUH on a daily basis and identify patients who were ventilated for at least two days as the initial screening. For those who meet these criteria, a further investigation into the patients' chart will occur by the study team to identify the inclusion/exclusion criteria. We will obtain a de-identified list of screen failures and the reason for the failure.

INCLUSION CRITERIA

- Intensive Care Unit (ICU) Admission
- Mechanically ventilated for at least 24 hours
- RASS between -1 to 1 at the time of screening (Note: minimal sedation is allowed including low-dose Fentanyl, Dexmedetomidine, Ketamine, Propofol, etc., as long as the RASS is in the predefined range).

EXCLUSION CRITERIA

- < 18 years of age
- Not admitted to the ICU
- Inability to follow commands during screening (at a minimum: open and close eyes, move eyes to one side or the other).
- Known cerebral injury (acute or chronic) in the dominant hemisphere concerning for aphasia on clinical assessment
- Significant pre-existing neurologic (i.e., dementia and/or cognitive deficiencies), hearing loss (with inability to hear through a bone-conduction speaker), psychiatric, or baseline communication challenges that would confound outcomes assessments
- Inability to blink or move eyes for any reason
- Prisoner or incarceration
- Inability or unwillingness to provide informed consent
- Unwillingness to be contacted for follow-up

Patients who meet the inclusion and do not meet any exclusion criteria will be approached for consent, as will be described below.

SAMPLE SIZE

From our retrospective analysis (described in the introduction), we expect about 130 patients per month for the initial screening (ventilated for at least two days). The same patient could be ineligible on a certain day, but become eligible later in the admission (e.g., due to the severity of the illness, the patient is deeply sedated for the first few days, and later sedation is weaned). This will allow us to recruit more patients, at different time points of their admission. Even with this in mind, it would be reasonable to assume that about half of these initially screened patients will not be eligible at any point of their admission due to any one of the exclusion criteria. Of those who will be eligible, we expect a high rate of consent, due to the low risk and the potential benefit of using the device while in the ICU. We therefore expect a rate of about 30 patients a month to be enrolled.

For the first step, we will plan to enroll up to 60 patients, and at least a third of the sample will be from the neuroscience ICU, and specifically patients with an acute brain injury

Given that there are no prior data, there is no clear criteria that would justify a specific number. We believe that having 40 to 60 patients work with this new device would be sufficient to draw initial conclusions about its use and specific indications according to the study aims as stated above.

For the second part of the trial, power calculations are based on previously published BRAIN-ICU trial. In that observational trial patients had 6.8±5.2 delirium/coma-free days within the first 14 days of admission, with an overall rate of about 50% rate of delirium. For the present trial, we considered a 2 day reduction in the time spect delirious as clinically significant. Given these parameters, the present trial will require 248 patients (N = 124 per arm) to achieve sufficient power (80%, $\alpha = .05$) to detect a 2 day difference. In general, a sample size of 248 will provide sufficient power to detect a standardized mean difference of 0.38 (assuming minimal asymptotic relative efficiency of Mann-Whitney U test), an odds ratio of 2.14 for binary variables (assuming maximal variance for a binomial distribution), and a Cohen's *ƒ* of 0.18.

SUBJECT PROCEDURES AND GUIDELINES

Please See Schedule of Events on Page 4 of this protocol.

DATA COLLECTION

As mentioned above, we will collect clinical data from the chart, as well as data from the device per patients. Data could be, for example, what type of use did the patient practice with the device (call for help? communicate? listen to music or e-books?), for how long was the device worn, wakefulness timing and CAM-ICU results.

We will also collect the long-term results from the phone-based questioners.

Clinical data, as well as device-originating data, will be coded to allow de-identification during analysis, and stored in a HIPPA-compliant database (e.g., RedCAP).

SUBJECT HOSPITAL DATA

a) Consent material (study files)
b) EyeControl measurement session data
c) Demographic information: age, weight, height, gender, ethnicity
d) Clinical status on admission (main diagnosis, procedures, or operations done)
e) CAM-ICU
f) Lab results, imaging, vitals, and charting during the ICU stay
g) List of current medications, dose, and route of administration
h) Medical history
i) Previous and current head and brain imaging
j) Previous and current EEG, if available
k) Outcome measures: modified Rankin scale on discharge, discharge disposition, modified Rankin scale on follow-up clinic visits
l) Responses of the patient and family members to a structured questionnaire regarding communication and use of the device
m) Device training success and frequency for proficient utilization
n) Eye photographs/video to explore possible relation to clinical events

Every study file will contain a fully signed consent form. The study files will be stored in a locked cabinet in a locked office.

LONG-TERM OUTCOMES (LTO) BATTERY

Evaluations will be done using a specially-designed battery of tests that evaluates key aspects of functioning and behavior. This battery, which takes ~40 minutes to complete, will assess cognition, mental health (depression and PTSD), quality of life, and employment - all of which have been shown to be adversely affected in between 1/3 and 2/3rds of survivors of sepsis. The questioners will be executed by the Critical care, Brain Dysfunction and Survivorship (CIBS Center from Vanderbilt University). This battery has been successfully used by researchers in multiple studies at Vanderbilt Medical Center and elsewhere - it is well tolerated by patients, easy to administer and

to understand, and is very sensitive to the detection of even minor difficulties. Tests comprising the battery (by domain and name) are as follows: Cognition -Attention (Digit Span), Delirium (Telephone Confusion Assessment Method), Executive Functioning (Hayling Test), Language (Controlled Oral Word Association Test or COWA), Memory (Paragraph Recall from the Wechsler Memory Scale IV), Orientation (Telephone Interview for Cognitive Status), Reasoning (WAIS-IV Similarities); Functioning – Activities of Daily Living (Katz ADL), Employment (Employment Questionnaire), Instrumental Activities of Daily Living (Functional Activities Questionnaire); Mental Health - Depression (Beck Depression Inventory-II), PTSD (Post Traumatic Stress Disorder Checklist for the DSM V); Quality of Life – EQ5D.

ELECTRONIC AND PAPER DATA COLLECTION SYSTEMS

REDCap is a secure online database for building and managing research data supported by Emory. All data collection will be input into the electronic data capture system. When subjects are enrolled, they will be sequentially assigned a unique subject code. This unique code will be used in the REDCap database. A centralized subject key that links subject identification with the unique subject code will be maintained in a secured and password protected electronic format.

Data Handling – For the duration of the study, the Investigator will maintain complete and accurate documentation including but not limited to medical records, study progress records, laboratory reports, case report forms, signed informed consent forms, correspondence with the IRB and adverse event reports, and information regarding subject discontinuation or completion of the study.

Source Documentation – Source documents are defined as original documents, data and records. Investigator will maintain source documents in the subject's medical records and/or subject binders, which confirm the data entered on the electronic case report forms.

CRF Completion – Data collection based on source-documented hospital and/or chart reviews will be performed accurately on the eCRFs by research personnel.

Retention of Study Records – Study records will be retained at all sites for a minimum of 3 years following the end of subject recruitment and follow-up activities.

Data Quality – Routine regulatory monitoring of regulatory compliance will be conducted by the Departmental Clinical Trials Regulatory Specialist.

STATISTICAL ANALYSIS PLAN

Step 1: Step 1 of the present trial focuses on describing device usage and acceptability. Continuous data will be described using medians and interquartile ranges. Categorical variables will be described using frequencies, percentages, and 95% confidence intervals. No statistical hypothesis testing will be conducted.

Step 2:

Primary Outcome: The time spent alive and non-delirious in the ICU

Covariates/Confounders: age, gender, race, baseline education level, unit to which the patient was admitted to, need for tracheostomy, severity of illness by SOFA or APACHI score on admission and randomization day, categorical reason for admission (e.g. sepsis, ARDS, elective surgery, stroke etc), diagnosis of delirium prior to randomization and the presence of an acute central neurological injury.

Unadjusted Analyses: The time spent alive and non-delirious in the ICU will be evaluated using the stratified variant of the Mann-Whitney U test. In this analysis, patients will be stratified by ICU setting. For other variables, the unadjusted comparison will depend on the type of variable. In general, continuous variables will be compared using a Mann-Whitney U test and categorical variables will be compared using the χ^2 test.

Adjusted Analyses: The time spent alive and non-delirious in the ICU will be evaluated using a multi-level/mixed-effects quantile regression (median/50^{th} percentile) while controlling for the previously listed covariates. The multi-level/mixed-effects model will be used to account for clustering within ICU setting. In the event that the regression fails to estimate properly, the covariates will be used to generate propensity scores and patients will be stratified into ≥5 propensity score strata. The time spent alive and non-delirious in the ICU will then be analyzed using the stratified variant of the Mann-Whitney U test. Analyses of the secondary outcomes will depend on the type of variable. Continuous variables will be analyzed using multi-level/mixed-effects quantile regressions (median/50^{th} percentile), binary variable will be analyzed using multi-level/mixed-effects binary logistic regressions, ordinal scales will be analyzed using multi-level/mixed-effects ordinal (cumulative logit) logistic regressions.

Missing Data: In the event of substantial missing data, data will be imputed using a multiple imputation procedure. The type of procedure (e.g. fully conditional specification, hot decks etc.) and the number of imputed data sets will be determined by the amount of missing data and the pattern of missingness.

HUMAN SUBJECTS

ETHICAL CONDUCT OF STUDY

The study will be conducted in accordance with the current guidelines and in accordance with local applicable laws and regulations. All investigators and research personnel will have appropriate human subjects training (i.e., CITI).

INSTITUTIONAL REVIEW BOARD (IRB)

The IRB will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted after IRB approval has been obtained. The protocol, sample ICF, advertisements (if applicable), written information given to the subjects, safety reports, progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

INFORMED CONSENT

A written or electronic consent form that complies with the policies of local IRB will be utilized. The informed consent form should include the following elements and be in compliance with 21CFR Part 50:

- Title of the protocol
- Name of the investigator
- Study objectives and purpose
- Detailed description of the procedures
- Explanation of the responsibilities of the subject during follow-up interviews
- Any foreseeable risks, anticipated benefits, available alternatives
- An explicit statement of confidentiality
- Non-compensation for participation
- Right to withdraw at any time
- Signature section
- Number to contact the site investigator or a member of the study team with any questions.

Informed Consent will be obtained by the site investigator or designee prior to any research activities. The informed consent form should be the IRB approved version corresponding to the version of the IRB approved protocol, and may occur through and electronic informed consent form approved by Emory IRB. There is no activity required in the screening process that is not typically considered standard of care evaluation for mild traumatic brain injury. A partial-HIPAA wavier will be sought for screening purposes to ensure eligibility prior to being approached for informed consent.

As part of the informed consent process, the patient will be informed of the ability to withdraw participation from the study at any time, without penalty or change in their ongoing healthcare. The study team should discuss any concerns about the study with the patient.

In case of an eConsent process, the patient and/or LAR will be supplied with a link to a HIPPA-approved cloud-based service (RedCAP), in which there will be a copy of the latest version of the IRB-approved consent. The patient and/or LAR will have the ability to sign the consent electronically as an alternative to the written (paper) one.

SUBJECT CONFIDENTIALITY

All data (case report forms, laboratory specimens, imaging, and other records) kept at the site will be physically and electronically secured to maintain subject confidentiality. Paper records and computers with subject data will be stored in locked office or cabinet. Computer records will always be password protected, and encrypted when possible. The study database is maintained behind a secure firewall, access is password protected for all data entry and access. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB or other regulatory agencies.

SUBJECT WITHDRAWAL

In those who wish to discontinue participation, no further data will be collected. Data collected prior to withdrawal will remain in the study database. Those wishing to discontinue participation will also have the informed consent document explained to them, will have any questions answered and will be asked to review and sign an informed withdrawal from the study, however, subjects are not required to complete this document to withdraw. Standard consent procedures will be used. If subjects withdrawal prior to reaching the 30 day outcome visit they will not be counted toward the subject totals in their respective cohort. These subjects will be considered 'incomplete' and coded separately in the electronic database.

SAFETY MONITORING PLAN

No Data and Safety Monitoring Board is necessary for this prospective trial. No untoward medical occurrence is expected due to subjects' participation in this research. Adverse events In the event subjects report medical illness during follow-up phone calls they will be advised to seek medical evaluation (i.e., emergency department, primary care, etc). During the course of this study, if the principal investigator and/or research personnel believe there are unseen clinically relevant adverse events [related to wearing Eye Control Device], all events will be reviewed by the PI with the clinical team and relevant information reported to the local IRB as unanticipated problems. If an immediate safety concern is discovered by the clinical team, this will be addressed immediately by the study PI and may require no further wearing of the headset.

COMPENSATION FOR TIME AND EFFORT

There will be no compensation for time or effort. The study will occur while the patient is in the ICU, and no travel will occur.

REFERENCES

Binks AP, Desjardin S, Riker R. ICU Clinicians Underestimate Breathing Discomfort in Ventilated Subjects. Respir Care. 2017 Feb;62(2):150-155. PMID: 27965421

Carruthers H, Astin F, Munro W. Which alternative communication methods are effective for voiceless patients in Intensive Care Units? A systematic review. Intensive Crit Care Nurs. 2017 Oct;42:88-96. PMID: 28365174

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Chanques G, Pohlman A, Kress JP, Molinari N, de Jong A, Jaber S, Hall JB. Psychometric comparison of three behavioural scales for the assessment of pain in critically ill patients unable to self-report. Crit Care. 2014 Jul 25;18(5):R160. PMID: 25063269

Dres M, Younes M, Rittayamai N, Kendzerska T, Telias I, Grieco DL, Pham T, Junhasavasdikul D, Chau E, Mehta S, Wilcox ME, Leung R, Drouot X, Brochard L. Sleep and Pathological Wakefulness at Time of Liberation from Mechanical Ventilation (SLEEWE): A Prospective Multicenter Physiological Study. Am J Respir Crit Care Med. 2019 [Epub ahead of print]. PMID: 30818966.

Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA. 2001 Dec 5;286(21):2703-10. PMID: 11730446

Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004 Apr 14;291(14):1753-62. PMID: 15082703

Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, Douglas IS, Malhotra A, Owens RL, Feinstein DJ, Khan B, Pisani MA, Hyzy RC, Schmidt GA, Schweickert WD, Hite RD, Bowton DL, Masica AL, Thompson JL, Chandrasekhar R, Pun BT, Strength C, Boehm LM, Jackson JC, Pandharipande PP, Brummel NE, Hughes CG, Patel MB, Stollings JL, Bernard GR, Dittus RS, Ely EW; MIND-USA Investigators. Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness. N Engl J Med. 2018 Dec 27;379(26):2506-2516. PMID: 30346242

Guttormson JL, Bremer KL, Jones RM. "Not being able to talk was horrid": A descriptive, correlational study of communication during mechanical ventilation. Intensive Crit Care Nurs. 2015 Jun;31(3):179-86. PMID: 25579081

Happ MB, Seaman JB, Nilsen ML, Sciulli A, Tate JA, Saul M, Barnato AE. The number of mechanically ventilated ICU patients meeting communication criteria. Heart Lung. 2015 Jan-Feb;44(1):45-9. PMID: 25261939

Khalaila R, Zbidat W, Anwar K, Bayya A, Linton DM, Sviri S. Communication difficulties and psychoemotional distress in patients receiving mechanical ventilation. Am J Crit Care. 2011 Nov;20(6):470-9. PMID: 22045144

Marra A, Kotfis K, Hosie A, MacLullich AMJ, Pandharipande PP, Ely EW, Pun BT. Delirium Monitoring: Yes or No? That Is The Question. Am J Crit Care. 2019 Mar;28(2):127-135. PMID: 30824517

Marra A, McGrane TJ, Henson CP, Pandharipande PP. Melatonin in Critical Care. Crit Care Clin. 2019 Apr;35(2):329-340. PMID: 30784613

Martínez F, Donoso AM, Marquez C, Labarca E. Implementing a Multicomponent Intervention to Prevent Delirium Among Critically Ill Patients. Crit Care Nurse. 2017 Dec;37(6):36-46. PMID: 29196586.

Oldham MA, Flanagan NM, Khan A, Boukrina O, Marcantonio ER. Responding to Ten Common Delirium Misconceptions With Best Evidence: An Educational Review for Clinicians. J Neuropsychiatry Clin Neurosci. 2018 Winter;30(1):51-57. PMID: 28876970.

Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, Moons KG, Geevarghese SK, Canonico A, Hopkins RO, Bernard GR, Dittus RS, Ely EW; BRAIN-ICU Study Investigators. Long-term cognitive impairment after critical illness. N Engl J Med. 2013 Oct 3;369(14):1306-16. PMID: 24088092

Rowley-Conwy G. Barriers to delirium assessment in the intensive care unit: A literature review. Intensive Crit Care Nurs. 2018 Feb;44:99-104. PMID: 29054400.

Wade DM, Howell DC, Weinman JA, Hardy RJ, Mythen MG, Brewin CR, Borja-Boluda S, Matejowsky CF, Raine RA. Investigating risk factors for psychological morbidity three months after intensive care: a prospective cohort study. Crit Care. 2012 Oct 15;16(5):R192. PMID: 23068129

Wunsch H, Wagner J, Herlim M, Chong DH, Kramer AA, Halpern SD. ICU occupancy and mechanical ventilator use in the United States. Critical Care Med. 2013 Dec;41(12):2712-2719. PMID: 23963122