

- 1. Title:** Assessment of Accuracy, Precision, and Feasibility of a Handheld Near-Infrared Light Device (InfraScanner 2000™) in Detecting Subdural and Epidural Hematomas in Patients Admitted to Duke University Hospital: A Pilot Study

Principal Investigator: Michael Haglund, MD/PhD

Co-Principal Investigator:

Investigator:

Investigator:

Investigator:

Investigator:

Study Coordinator: Robert Gramer, BS

Regulatory Coordinator:

Regulatory Specialist:

Statistician:

- 2. Purpose of the Study:** The goal of this study is to determine the sensitivity, specificity, and positive and negative predictive values of the portable near-infrared-based device (portable NIR-based device), the InfraScanner 2000™, to detect intracranial hematomas [epidural hematomas (EDH) and/or subdural hematomas (SDH)] in patients hospitalized at Duke University Hospital (DUH) who have sustained or who are suspected to have sustained head trauma and have consequently received a brain computed tomography (CT) scan(s).

Traumatic brain injury (TBI) is a global pandemic that affects over 10 million people annually, with the incidence expected to continue to mushroom in coming years (1). Severe TBI often results in intracranial hematoma formation that can rapidly increase intracranial pressure (ICP). If the bleeding does not tamponade, failure to alleviate the escalating pressure results in irreparable brain damage, and often death. In the case of an expanding intracranial bleed, a burr hole or decompressive craniotomy provide the only recourse to limit further brain injury and avert death. Typically, such a decision needs to be made in hours, if not minutes, following the insult. In order to pursue such intervention, however, the presence of a surgically intervenable bleed must be confirmed, and moreover, the location of the bleed must be established.

In industrialized nations, this is a trivial requirement, as CT scans are used ubiquitously to definitively diagnose EPH and SDH, readily and reliably triaging patients to surgical versus medical management. With 97% sensitivity, 98% specificity, 97% positive predictive value, 95% negative predictive value, and 96% accuracy in diagnosing Intracranial hematomas, CT scanning is exquisitely effective at identifying or ruling out acute extra-axial, intracranial bleeds in patients who sustain head trauma, making a gold standard in acutely assessing traumatic brain injury (TBI) (2). As a result, head CT has become commonplace, if not universal in assessing head trauma in industrialized countries, where virtually every hospital has one, if not a dozen scanners. In less than 10 minutes, a CT scan can noninvasively prove or reject acute intracranial bleeding. They

provide immediate insight into 1.) Whether there is in fact an intracranial bleed; 2.) In the case of a bleed, where below the cranium it has occurred and 3.) When done serially, gauge evolution, resolution, or stability of a bleed. This is invaluable information that directly impacts survival, as failure to perform a craniotomy in a patient with a rapidly expanding intracranial hematoma can swiftly lead to irreversible brain damage or even death. Moreover, performing such a surgery in the wrong location or in a patient who does not have a bleed amenable to surgical intervention can contribute extensive morbidity, exacerbating a patient's already tenuous mortality.

In less developed countries, CT scanners are often nonexistent. When they are present, they are extremely meager in number, peppered across treacherous geography, with scant transportation and emergency infrastructure. Even when accessible, they are commonly decommissioned due to a broken part, and are extremely cost prohibitive, with a single scan often costing the equivalent to multiple months' income for the populations who need them most. As a consequence, in the settings where TBI pervades and brain imaging is most critical to survival, obtainment of such imaging is often unachievable.

In resource-limited settings, techniques such as ultrasonic measurement of the optic nerve sheaths and latency of the pupillary reflex have been used to infer increased intracranial pressure. However, these techniques are notably crude. They provide no insight into the location or etiology of what is causing the presumed increase in pressure, typically indicate an ICP >30 but are poor at correlatively quantifying ICPs as they grow emergently high, and in the case of optic nerve sheath diameter specifically, take up to a day to manifest. Hence, while these modalities can corroborate that a particular patient has increased ICP, these techniques are inadequate in determining which patients stand to benefit from surgery, and for those who could, in informing the surgical approach that could save such patient's lives.

In 1997, the first ever handheld device that could definitively detect the presence and location of epidural and subdural hematomas was introduced (3). Initially named the Runman, the device was intended to detect intracranial hematomas in remote and military settings to triage which casualties should be airlifted to medical centers equipped to offer neurosurgery. After numerous iterations, the InfraScanner 1000™ was introduced in the mid 2000's. In 2010, the pivotal five-site double-blinded clinical trial was published, and ultimately led to FDA clearance of the InfraScanner 1000™. In the study, the Infrascanner 1000™ measurements were compared to CT scans of 365 patients, 96 of which were hematoma cases of various sizes, depths and locations. The study demonstrated high sensitivity (88%) in detecting hematomas > 3.5cc in volume and < 2.5 cm from the surface of the brain, and a specificity of 91%. Since then there have been numerous studies that have replicated these results and have substantiated that it is a capable tool for pre-hospital diagnosis of intracranial hematomas (3-13).

While these results are extremely promising, the InfraScanner devices' utility has only been examined through the lens of pre-hospital decision-making. The sensitivity and specificity of the InfraScanner 2000™, introduced last year, has not been as exhaustively interrogated.

As the sensitivity and specificity in detecting intracranial hematomas approaches that of CT scanning, the prospect of using the InfraScanner 2000™ as a stand-alone diagnostic device for intracranial hematomas in low-resource settings that lack CT scans is highly intriguing. In geographical locations where TBI burden is highest and need for emergency craniotomies is most pressing, the inability to obtain CT scans precludes hundreds to thousands of life-saving surgeries everyday. The use of a handheld device that can be used repeatedly to reliably diagnose and track intracranial bleeding at no cost to a patient could revolutionize the prognosis of TBI for the majority of the 10 million people it affects annually.

This project intends to show that the InfraScanner 2000™ is capable of detecting and ruling out intracranial hematomas in TBI patients at DUH at rates similar to CT scan. This work will hopefully justify the use of the InfraScanner 2000™ as a definitive diagnostic tool in determining surgical versus medical management in CT-barren settings, such as Uganda where our group, Duke Global Neurosurgery and Neurology has been building neurosurgical and neurological care capacity over the past decade.

Aim 1: Determine whether the InfraScanner 2000™ detects epidural and/or subdural hematomas with adequate precision relative to CT scans to be used as a diagnostic tool for epidural and/or subdural hematomas.

Aim 2: Use these findings to inform the feasibility of conducting a future trial in which the InfraScanner 2000™ is used as a stand-alone diagnostic tool for intracranial hematomas, and therein, to determine candidacy for decompressive craniotomies in patients who suffer traumatic brain injuries in places where CT scans are not available.

- 3. Background and Significance:** Traumatic brain injury (TBI) is a steadily growing global pandemic responsible for immense mortality and morbidity, particularly in low- and middle-income countries (LMIC's). The World Health Organization (WHO) estimates that more than 10 million people sustain TBI resulting in death or significant irreversible deficits annually, the majority occurring in resource scarce settings. Most recent approximations suggest that Sub-Saharan Africa (SSA) bears the highest incidence of road traffic injury (RTI)-associated TBI in the world. At a frequency of 170 per 100,000 people, TBI in SSA occurs at a rate 1.5 times that of the global average(1). A great preponderance of these injuries is comprised by intracranial hematomas; injuries

that would often stand to benefit from surgical intervention. However, the virtual nonexistence of CT scanners in the majority of settings where these injuries occur, preclude countless patients from receiving life-saving surgery.

With approximately 90% of all injury-related deaths occurring in LMIC's, this already enormous chasm in mortality is expected to only grow wider as obtainability of personal motor vehicles burgeons at rates far exceeding these economically-stifled nations' faculties to build legislative, municipal, and medical infrastructure capable of equipoising the mushrooming incidence of TBI.

Sub-Saharan Africa's unprecedented paucity of medical resources is especially prominent in neurological care. At present there are 0.3 neurological beds, 0.03 neurologists, and 0.01 neurosurgeons per 100,000 Africans. This can be contrasted with Europe where, per 100,000 citizens, there exist 17.1 neurological beds, 4.84 neurologists, and 2.43 neurosurgeons – a respective 57, 161, and 243-fold resource disparity between these two continents. Even when compared to global averages, to which Africa's and myriad other LMICs contribute, per capita, the world's population benefits from greater than 12-times more neurological beds, 30-times more neurologists, and 56-times more neurosurgeons per capita than the average African (14).

Taking Uganda, where our group, Duke Global Neurosurgery and Neurology, has worked for over the past decade to bridge this gap, motorbikes pervade the landscape with motorbike accidents contributing the lion's share of the country's TBI. From a strictly commercial perspective, there are currently over 300,000 boda-bodas, or motorbike taxis, in Uganda's capital city of Kampala – a comparable number to the total motorcycle registration in New York State, which has an area 750-fold larger than Kampala. Despite the highly visible mortality and introduction of a nationwide helmet law, helmet usage remains 31% and 1% among drivers and passengers, respectively. In Uganda alone, this leads to tens of thousands of deaths due to head injuries every year.

Many of these lives could be saved with prompt imaging and surgical intervention; however, CT scans are far too expensive (for both the government as well as patient) to introduce on a national scale throughout Uganda or similarly resource-scarce settings. With myriad lives lost due to lack of access to prompt brain imaging, an economically feasible alternative to CT scan must be validated to begin saving these tens to hundreds of thousands of otherwise savable lives lost annually in LMICs.

Based upon the scant literature regarding TBI within SSA, Uganda experiences among the highest rates of TBI and TBI-related mortality in the world. A recent study conducted in the intensive care unit (ICU) at Mbarara Regional Referral Hospital (MRRH), which serves the Western Region of Uganda, Rwanda, Eastern Democratic Republic of Congo, and northwestern Tanzania, revealed that head injury accounts for 74% of adult and 69% of pediatric trauma cases,

with an overall mortality of 60% for patients admitted to the ICU with head trauma(15). For comparison, a 2006 UK study showed that in head injury patients requiring intensive care, 77% survived to leave the ICU and a 67% survived to leave hospital, an ICU mortality rate nearly three-fold less than that seen in Mbarara (16). A 2014 Finish study with a similar ICU survivability of 79%, reported an additional 12% mortality in the same population at 6-months(17). While no long-term TBI survivability data exists for LMIC's, granted such significant post-discharge fatality in settings replete with vanguard healthcare resources and armed with robust long-term nursing and rehabilitative capacities, the ultimate survivability from severe TBI in SSA is presumably exceedingly rare. And at MRRH specifically, where in-patient mortality is unsurpassed and sub-acute convalescent services are nonexistent, this geographically vast TBI population assumes as bleak a fate as anywhere in the world.

Our group, Duke Neurosurgery and Neurology (DGNN), has been a unique presence in Uganda as well as SSA at large, traveling to Mulago National Referral Hospital (MNRH) in Kampala since 2007 to provide neurosurgical resources and training to local surgeons and trainees, expanding our outreach to Mbarara both of the past two years as well as Megno Hospital over the past year. To date, the DGNN has delivered 71 tons of medical equipment valued at \$9.5 million to MNRH and \$1 million to MRRH. Through the DGNN, the country's first neurosurgical residency program was established, which has since trained two neurosurgeons, increasing the country's total workforce by 50%, with six more currently being trained, with a goal by 2022 to have eight neurosurgical units with twenty neurosurgeons stationed within major district hospitals all across Uganda. This pursuit has afforded the group an exceptional relationship with the hospitals' administrators and personnel as well as the Ugandan Ministry of Health, while producing a gargantuan responsibility to build comprehensive neurological care for the population.

Despite the significant progress of the DGNN in helping to build neurosurgical capacity in Uganda, the non-operative and postoperative critical care for severely neurologically injured patients has remained largely unchanged, with, as mentioned above, reported mortality outcomes at MRRH as poor as anywhere in the world (15). While our work has improved neurosurgical care for any individual patient, and is steadily continuing to broaden access to neurosurgical care to the nation, the inability to readily diagnose intracranial bleeding in emergency situations has stifled the ability to furnish emergency neurosurgical care.

Over the past three years the DGNN has grown from a staff of 6 to a workforce of over 60, most notably adding three neurointensivists, two emergency medicine physicians, a neuropsychologist, an epidemiologist, as well as numerous anesthesiologists and nurses. Of particular note, the primary author reporting the dire outcomes at MRRH is Dr. Stephen Ttendo, the Chair of Anesthesiology at MRRH, the President of the Association of Anesthesiologists of Uganda, and the Chief of MRRH's ICU, and maintains unwavering dedication to improving

outcomes at MRRH. While he could be directing the department at an urban hospital where the resources are superior, the pay is greater, and the outcomes are better, he has chosen to dedicate his life's work to rural Uganda because that is where he sees the greatest healthcare need and capacity for improvement. In accord with this vision, the DGNN sees an undeniable niche at MRRH to establish a cost-effective, sustainable ICU that can dramatically reduce mortality. With readily available imaging as a cornerstone, this will hopefully lay the foundations for an international neurological referral hospital, while producing a highly practical critical care model that can be replicated in other LMIC's.

With a median age of 15.7 years, Uganda is second only to Niger in youth of its population. Currently, 69% of the Ugandan population is under the age of 25, and an estimated 80% of all Ugandans between 20 and 30 years earn a living by taxiing passengers. Granted the already globally unprecedented motorbike usage, the cultural ambivalence toward helmets, haphazard law enforcement, and still increasing motorbike density, the already appalling incidence of TBI is inevitably going to upsurge in coming years.

In Uganda, there are currently 33 ICU beds, 6 government neurosurgeons, and 1 formally trained neurologist to serve, not accounting for the significant international referrals received from neighboring countries, the entire population of 41 million people (18, 19). Despite the profound dearth of care and exceptionally high mortality, Africans pay significantly more out of pocket for medical care than the world (83% versus 26%), which in the case of current TBI care, often leads to incurrence of significant familial hardship for improbable survival (14). This constellation of unmatched mortality, resource famine, and debt incurrence fashion SSA, and MRRH in particular, the ideal setting to pilot a minimal-resource, guideline-driven ICU system. The InfraScanner 2000™ can potentially server as the centerpiece of such a system providing zero-cost, immediately-available, sequential intracranial imaging to help make urgent surgical and medical decisions that can save an untold number of lives that are currently being forfeited due to lack of imaging.

To work toward this, this study proposes compare the sensitivity, specificity, accuracy, and precision of the InfraScanner 2000™ against brain CT scans at DUH. If capable detecting Intracranial hematomas with efficacy similar to CT, expanding the use of the such a device as a CT-substitute to detect intracranial hematomas in places devoid of CT facilities could revolutionize TBI care in LMICs.

4. **Design and Procedures:** When applicable (conscious patient and/or family or legally authorized representative is present) the study will be introduced to the patient and relevant parties prior to the research team approaching the patient. While head trauma frequently results in impaired cognition and/or consciousness, and due to the urgency of these circumstances patients are often not accompanied by kin, whenever appropriate, the purpose of the research and the

procedure will be explained in detail, using an IRB-approved verbal consent “script”, with all questions answered to the patient’s and/or representative’s satisfaction. Because patients who sustain head trauma injuries typically remain within the hospital for multiple days for monitoring and care, each participant may undergo multiple CT scans over the course of his or her hospitalization, affording the opportunity to one to numerous measurements from each patient during his or her hospital stay. When subjects are approached for subsequent study measurements, if the subject has regained the capacity to consent or has an LAR present, the verbal script will be used to obtain consent. Subjects will be asked at that time if prior measurements obtained may be used in the research.

Within 30 minutes following each CT scan, the study team will approach the patient to scan the patient’s cranium with the InfraScanner 2000™ (Image A). The procedure will entail placing 8 plastic light guides upon the patient’s scalp. The study team member will use the device to sequentially emit light through each of the 8 light guides so that the light is incident upon scalp (Image B). The device is engineered such that the light emitter and receiver are spaced ~4cm apart, allowing the light’s intensity to be measured between adjacent light guides (Image C). This entire procedure, including greeting the patient, placing the light guides, gathering the data, and removing the light guides should take ~10 minutes each time. The number of CT scans the patient receives determines the number of potential data collections. The patient will be approached by the study team following each CT scan to be scanned with the InfraScanner 2000™ (20). The patient and/or representative may refuse a scan during any encounter, and as such, the scan will not be done. For each patient scanned with the InfraScanner 2000™ they will be de-identified with a subject number, with age, sex, gender, skin color, hair color, hair thickness, mechanism of injury, Glasgow Coma Scale score, and mean time elapsed between CT scan and near-infrared measurement. These data will be stored in de-identified form on Research Electronic Data Capture (REDCap), Duke Box, and/or Microsoft Excel 2016 on a secured DHTS server (S:\NSU_IRB\Pro00087011).

The collection period for each research subject concludes 30-days following his or her initial measurement with the InfraScanner 2000™, patient discharge, or patient death.

- 5. Selection of Subjects:** Any patient, who presents to DUH with suspected head trauma who receives a brain CT scan will be considered for this study. Patients who are candidates for emergent surgical treatment (i.e. measurements cannot be obtained in the time while awaiting the results of the CT scan) will not be approached.
- 6. Subject Recruitment and Compensation:** The research team will approach potential research participants only after gaining permission from the physician in charge of the patient’s care. No compensation will be provided for participation in this study. Whenever possible, the study will be explained to the patient and/or

associated parties, and someone from the study team will always be available to answer any questions regarding the study.

- 7. Consent Process:** We are requesting waiver for informed consent (when the patient is unable to consent and no LAR is available) for this pilot study as 1.) It poses no perceptible risk to the patient's health and does not influence his or her care in any appreciable way; 2.) The majority of the patients of interest will be unconscious or mentally altered due to their presenting injury or medical condition. This will often times occur in an emergent setting where legal representatives, family, guardians, or other stewards will not be present within the timeframe required to obtain usable data. A verbal consent process will be used whenever the patient is able to consent or a legally authorized representative is present. Consent, or the decision not to participate, will be documented in the patient's chart.

Validating that this device can reliably identify intracranial bleeds can 1.) Streamline the care of persons who sustain traumatic brain injuries in resource-replete settings, such as a Duke patient, through providing insight into the extent and location of intracranial trauma in a pre-hospital setting, facilitating expeditions care upon arriving to the hospital; 2.) Revolutionize traumatic brain injury care and prognosis in resource-poor settings where CT scanners are not readily available (i.e. Uganda) by providing prompt intracranial imaging that is otherwise impossible to obtain, thus affording life-saving surgical intervention when warranted.

- 8. Subject's Capacity to Give Legally Effective Consent:** We expect that most of the subjects will be neurologically and/or cognitively impaired due to extent of head injury, multisystem trauma, and/or medical treatments. The study will be offered to patients 0 years of age and older. Since this is a minimal risk study in which we are de-identifying all patient data, with no conceivable risks to the patients or deterrents to the patients' standard of care, we are not requiring written consent for this study, however verbal declination by the patient or a patient representative will preclude any data collection. Consent or declination will be documented in the patient's chart. For patients younger than 18 years, we will speak with the parents whenever possible, and obtain their verbal permission to obtain each scan.
- 9. Study Interventions:** As described above, within 30 minutes following each CT scan, the study subject's cranium will be scanned with the InfraScanner 2000™ (Image A). To do so, 8 plastic light guides will be placed upon the patient's scalp. The study team member will use the device to sequentially emit light through each of the 8 light guides so that the light is incident upon underlying scalp (Image B). The device is engineered such that the light emitter and receiver are spaced ~4cm apart, allowing the light's intensity to be measured between adjacent light guides (Image C). This entire procedure, including greeting the

patient, placing the light guides, gathering the data, and removing the light guides should take ~10 minutes each time. The number of CT scans the patient receives determines the number of potential data collections. The study team will approach the patient within a 30-minute window following each CT scan, and when feasible, a comparative measurement with the InfraScanner 2000™ will be obtained.

10. Device Description/Mechanism: The following description is adapted from the InfraScanner White Paper (20): All biological tissue is, to differing extent, permeable to electromagnetic radiation of different frequencies and intensities. This can also be considered permeability to photons of different energy levels. This permeability to electromagnetic energy is the basis of all imaging based on transmission/scattering characteristics such x-ray, Computed Tomography, and near-infrared, NIR, imaging. From the principles of spectroscopy, it is also known that different molecules absorb different wavelengths of electromagnetic radiation (which is synonymously referred to as light at shorter wavelengths). Similarly, tissue scatters radiation to different degrees. The Infrascanner is concerned with NIR imaging of the hemoglobin molecules. From any light source, photons follow a characteristic path through the target tissue back to a detector on the same approximate plane as the source. While the light is severely attenuated due to the scattering and absorption process, it is nonetheless encoded with the spectroscopic signatures of the molecules encountered en route to the detector (Image C).

The principle used in identifying intracranial hematomas with the Infrascanner is that extravascular blood absorbs NIR light more than intravascular blood. This is because there is a greater (usually 10-fold) concentration of hemoglobin in an acute hematoma than in normal brain tissue where blood is contained within vessels. The Infrascanner compares left and right side of the brain in four different areas. The absorbance of NIR light is greater (and therefore the reflected light less) on the side of the brain containing a hematoma, than on the uninjured side. With specified wavelength ranges, optical light source(s) or emitter(s) and a photodetector are placed at a distance, which allows proper NIRS absorption measurements in a desired volume of tissue. The wavelength of 805nm is sensitive only to blood volume, not to oxygen saturation in the blood (Image D).

The Infrascanner is placed successively in the left and right frontal (F), temporal (T), parietal (P), and occipital (O) areas of the head and the absorbance of light is recorded. Specifically the placement is as follows:

Frontal Left/Right forehead, above the frontal sinus; Temporal In the Left/Right temporal fossa; Parietal Above the Left/Right ear, midway between the ear and the midline of the skull; Occipital Behind the Left/Right ear, midway between the ear and the occipital protuberance (Image B).

The difference in optical density (ΔOD) in each of the four symmetrical areas is calculated on a pair-wise basis from the following formula:

$$\Delta OD = \log_{10} \left(\frac{I_N}{I_H} \right) = \log_{10}(I_N) - \log_{10}(I_H)$$

where I_N = the intensity of reflected light on the normal side, I_H = the intensity of reflected light on the hematoma side.

In summary: The Infrascanner includes three components: (1) the Scanner, (2) the Disposable Shield and (3) a Cradle. The Scanner includes a safe NIR diode laser and a silicon detector. The light to and from the laser and detector are optically coupled to the patient's head through the disposable shield optical fibers. The optical fibers are long enough to reach through hair and contact the scalp. The optical fibers are placed 4 cm apart allowing optimal detection of hematomas. The extended fiber optics eliminates the need to shave off any hair. And because the fiber optic piece is disposable it prevents cross contamination. The detected light passes through an optical NIR band-pass filter in order to minimize background light interference. Electronic circuitry is included to control laser power and the detector signal amplifier gain. The detector signal is digitized and analyzed by a single board computer, SBC, in the Scanner. The SBC receives the data from the detector and automatically adjusts the settings of the Scanner to ensure good data quality. The data is further processed by the SBC and the results are displayed on the screen. Readout of the scan provides information on the severity of a hematoma and identifies the region of the brain bleeding. A higher optical density in the scanned region indicates a larger hematoma (20).

- 11. Risk/Benefit Assessment:** There are neither any specific clinical benefits to the research participant, nor are there any direct incentives, financial or otherwise, provided to the research participant. There is no known health risk of interval, short-term use of the device.
- 12. Costs to the Subject:** No additional costs to the patient will be incurred as a result of this add-on, intraoperative research protocol.
- 13. Statistical Considerations:** Objectives: The primary objective of this study is to estimate the test characteristics (sensitivity, specificity, and the false positive and false negative rates) of the portable NIR-based device (InfraScanner 2000™) in the identification of any size hematoma among patients hospitalized at DUH who have sustained or who are suspected to have sustained head trauma and have consequently received a brain CT scan(s). The results of the CT scan(s) will serve as the gold standard. The sensitivity, specificity, and the false positive and

false negative rates will be estimated at the patient level and at the scan level. Approximately 90% of patients are expected to have more than one CT scan.

A secondary objective is to estimate the test characteristics of the InfraScanner 2000™ in identification of hematomas within its detection limits (volume >3.5 mL and depth <2.5 cm) compared to CT scan results as the gold standard.

Exploratory objectives include:

1. Examining the impact of factors such as hematoma type, location, and patient age on test characteristics of the InfraScanner 2000™
2. Determining the minimum resolution detectable by the InfraScanner 2000™
3. Estimating Receiver Operating Characteristic (ROC) curves with patient and scan as the units of analysis (21).

Study Design:

a) Eligibility:

Any patient who presents to DUH with suspected head trauma and receives a brain CT scan will be considered for this study. Based on previously reported data, we expect that SDH or EDH will be present in approximately 20% of patients overall.

b) Standard of comparison:

All patients entered onto the trial will undergo at least one cranial scanning using the InfraScanner 2000™ within 30 minutes of CT. Patients will be scanned using the InfraScanner 2000™ within 30 minutes of each subsequent CT. Patients will know the results of the CT but not the InfraScanner 2000™. The standard for comparison will be determined as follows. A CT result that is positive for hematoma will be considered a true positive and a CT result that is negative for hematoma will be considered a true negative. In cases where the results of the CT are negative for hematoma and the results of the InfraScanner 2000™ are positive consideration of further follow-up will be given on a case-by-case basis.

Definitions of Sensitivity, Specificity, False Positive, False Negative

Let A^+ denote the event that the test is positive for hematoma and B^+ denote the event that a hematoma is present. Sensitivity, $P(A^+/B^+)$, will be defined for each patient (scan) as the probability that a true hematoma as determined by CT scan will be detected (22). Similarly, let A^- denote the event that the test is negative for hematoma and B^- denote the event that a hematoma is not present. Specificity, $P(A^-/B^-)$, will be defined as the probability of being negative for hematoma on the InfraScanner 2000™ scan within 30 minutes of CT given the patient has no hematoma present.

The false positive rate will be defined as $P_{F+} = P(B^-/A^+) = P(A^+/B^-)[1 - P(B^+)]/P(A^+)$. Similarly, the false negative rate will be defined as $P_{F-} = P(B^+/A^-) = [1 - P(A^+/B^+)]P(B^+)/[1 - P(A^+)]$. Estimates for the false positive and false negative rates will be provided for a range of values for the prevalence of hematomas.

c) Sample Size

Computation of the required number of patients is based on estimating the sensitivity of each method to within at most ± 0.10 with 90% confidence. The 90% confidence interval for the sensitivity is given by $P_{Sens} \pm 1.645 * SE(P_{Sens})$ where $SE(P_{Sens}) = \sqrt{P_{Sens}(1 - P_{Sens})/N}$; N denotes the number of true positives.

Administrative Summary: Based on an interim analysis conducted after 200 patients were studied, the proportion of patients with hematomas is 0.13. This is lower than the 20% originally expected. The sample size computation was thus revised as follows.

Original sample size computation

With 68 patients with positive findings of hematoma, sensitivity can be estimated to within at most ± 0.099 with 90% confidence. Assuming 20% of patients have true hematomas detected, 340 patients must be accrued (10). Allowing for a 5% dropout rate the required sample size for this trial is 360 subjects. With 272 patients having negative findings for hematoma, specificity can be estimated to within at most ± 0.05 with 90% confidence.

Revised sample size computation

With 68 patients with positive findings of hematoma, sensitivity can be estimated to within at most ± 0.099 with 90% confidence. Assuming 13% of patients have true hematomas detected, 523 patients must be enrolled to observe positive findings in 68 patients. With 455 patients having negative findings for hematoma, specificity can be estimated to within at most ± 0.038 with 90% confidence.

d) Interim Analysis

An interim analysis will be conducted once 150 patients have been enrolled on study to estimate the prevalence of hematomas at DUH. The adjusted 90% confidence interval estimate for sensitivity will also be constructed. Based on these results the trial may be amended to enroll fewer or more patients.

e) Accrual

It is anticipated that at least 60 patients per month will be accrued and studied at DUH. Study enrollment should thus be completed within approximately 6 months. Patients will be followed for up to 30 days

following the initial measurement with the InfraScanner 2000™, discharge, or death whichever occurs first. We do believe this figure is feasible, as 60 head CT scans at DUH is less than the quoted number of 80 by the manager of head CT at Duke.

This target monthly number for enrollment, though ambitious, is feasibly obtainable. This number is less than the estimated number of head CT scans obtained at DUMC per month (~80), as quoted by the manager of CT services at Duke. Furthermore, this is the number of all head CT scans, not just those that have evidence of EDH/SDH, at Duke as we intend to show positive and negative predictive value of the InfraScanner 2000™, to rule in and rule out EDH/SDH. Thus with the buy in from the team, we believe that 60 scans per month is a robust but realistic target.

Data and Safety Monitoring: Patients will be under continuous supervision during the entirety of each data collection period. Outside the ~10 minute window of each collection period, the patient is not subjected to any research intervention or influenced by the research in any way. As part of their treatment, patients will be under hospital care for their diagnoses for which they were admitted, and the research team will be in continual contact with the team regarding their clinical status and enrollment in the study. These data will be stored in de-identified form on REDCap, Duke Box, and/or Microsoft Excel 2016 on a secured DHTS server (S:\NSU_IRB\Pro00087011). Temporary documentation of MRNs and CT scan dates/times will be stored on an excel spreadsheet saved on the secure network drive as described in the RDSP. Once the MRNs and CT scan dates/times from Maestro Care are assigned a unique protocol ID, only de-identified data will be documented and the temporary excel spreadsheet destroyed upon statistical analysis (to ensure data is complete).

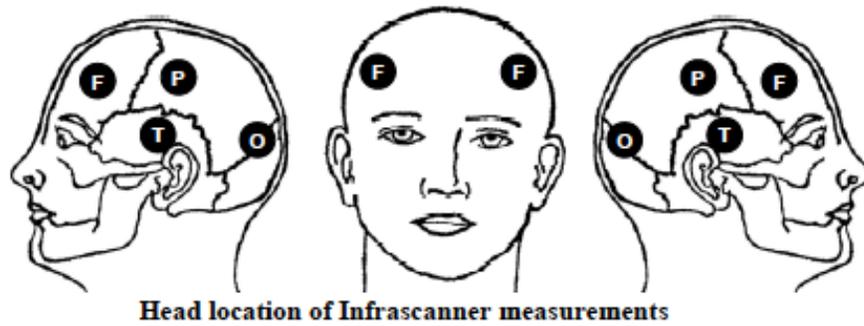
The PI will be responsible for securing and monitoring the data, including a quarterly review of data storage procedures. The data will be stored

14. Privacy, Data Storage, and Confidentiality: Patients will be numbered as experimental subjects. Data will be stored on a HIPAA-compliant DHTS-maintained server (S:\NSU_IRB\Pro00087011) within a REDCap repository, Duke Box, and/or Microsoft Excel 2016 database. Data used for analysis on local machines within the Department of Neurosurgery will be fully de-identified. Experimenters' notes will be stored in a locked cabinet in the PI's office in the Department of Neurosurgery and in digital form on the DHTS-maintained server. Patient's protected health information or any information that can be used to uniquely identify an individual patient will be temporarily stored in the protected network drive until a unique study code is assigned and then destroyed. The key to the unique code will be stored in the locked cabinet in the PI's office. Regulatory binders are stored with the CRC in Dr. Michael Haglund's office.

Image A (20)

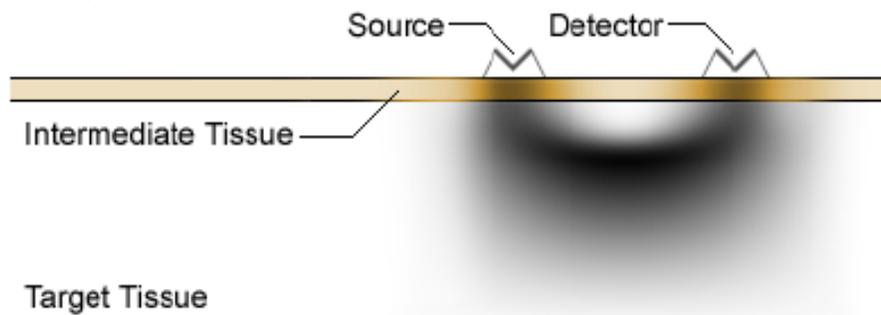


Image B (20)



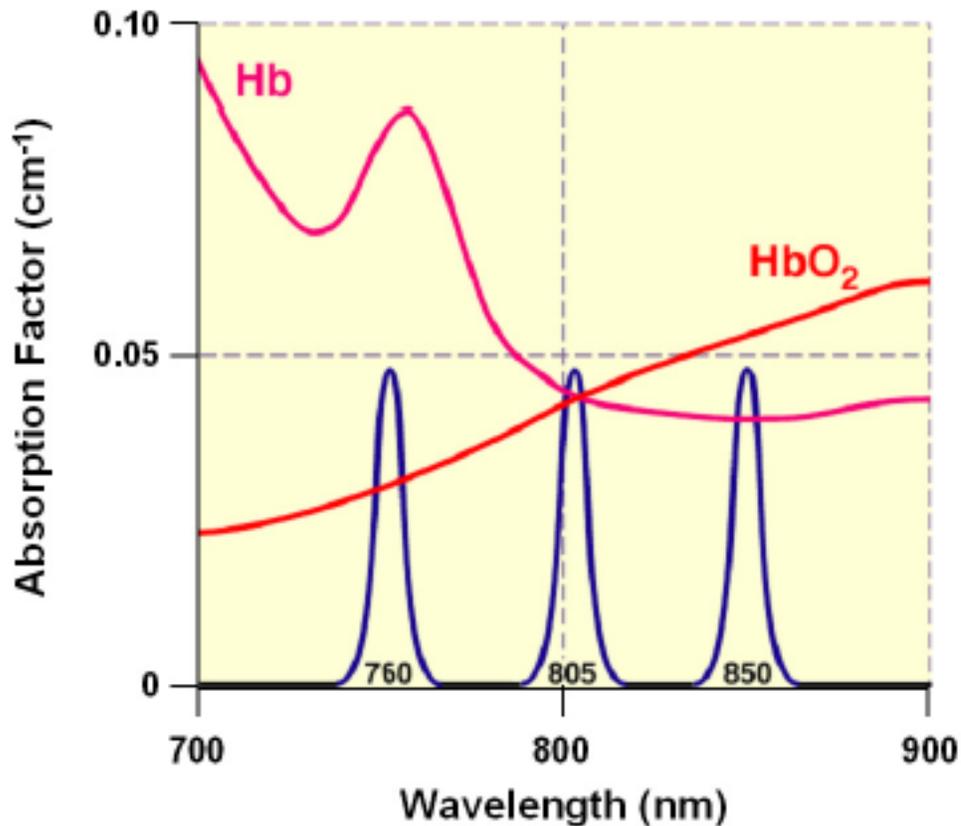
Frontal	Left/Right forehead, above the frontal sinus
Temporal	In the Left/Right temporal fossa
Parietal	Above the Left/Right ear, midway between the ear and the midline of the skull
Occipital	Behind the Left/Right ear, midway between the ear and the occipital protuberance

Image C (20)



Simulated photon diffusion path through target tissue from source to detector.

Image D (20)



Absorption of light by oxygenated and deoxygenated hemoglobin

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