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 Mbarara Regional Referral Hospital

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Infrascanner Study
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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 Mbarara Regional Referral Hospital

2. **Study Team**

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3. **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 Mbarara Regional Referral Hospital (MRRH) who have sustained or who are suspected to have sustained head trauma.

   Traumatic brain injury (TBI) is a global pandemic that affects over 10 million people annually, with the incidence expected to continue to proliferate 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 decisions need to be made in hours, if not minutes, following the insult. In order to pursue such intervention, however, the presence of a surgically interveneable bleed must be confirmed, and moreover, the location of the bleed must be established.

   Typically, this is a trivial requirement, as CT scans are used ubiquitously to definitively diagnose EDH and SDH, readily and reliably triaging patients to surgical versus medical management. With 97% sensitivity, 98% specificity, 97% positive predicative 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 it a gold standard in acutely assessing 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 difficult to obtain in a timely manner. 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 frequently 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. Optic nerve ultrasound is typically positive only once ICP >30 mmHg (normal 7-15 mmHg), but is notably poor at correlatively quantifying ICPs as they grow emergently high. Optic nerve sheath diameter measurements take up to a day to manifest, long after irreparable brain damage has occurred. 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 within a reasonable timeframe, and for those who do, 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 trail 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.

A few years ago, the InfraScanner 2000™was introduced, prompting our group to validate it in a consecutive series of 500 head injury patients who obtained a head CT scan at Duke University Hospital (DUH). For all patients with CT-proven bleeds (n=104), irrespective of size, initial NIRD scans localized the bleed to the appropriate quadrant with a sensitivity of 86% and specificity of 96% compared to CT scan. For extra-axial bleeds >3.5ml, sensitivity and specificity were 94% and 96%, respectively. For longitudinal serial rescans with the NIRD, sensitivity was 89% (<4 days from injury: sensitivity=99%) and specificity was 96%. For all patients who required craniectomy or craniotomy, the device demonstrated 100% sensitivity.

With these results, the Duke Global Neurosurgery and Neurology (DGNN) proposes to initiate a trial to replicate our DUH findings at MRRH: using the Infrascanner 2000™ ***in the background of the current standard of care*** to quantify the accuracy of the device – the positive and negative predictive values – in diagnosing SDH/EDH relative to CT in the Ugandan setting.

We hope that, with positive results, this work can lay the foundation for a subsequent trial using the device to diagnose intracranial bleeds when CT scans cannot be accessed in a timely manner. Such a result could ostensibly improve neurocritical and neurosurgical care in Uganda when obtainment of a CT scan is not feasible in a rapidly deteriorating patient.

As the sensitivity and specificity in detecting traumatic 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 MRRH at rates similar to CT scan (i.e. replicate the results we have demonstrated at DUH in the Ugandan patient population). This work will hopefully justify initiation of a future trial using the InfraScanner 2000™ as a definitive diagnostic tool in determining surgical versus medical management in CT-barren settings, such as Uganda where our group, DGNN 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 TBIs in places where CT scans are not available.

4. **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 (LMICs). 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 LMICs, 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 legislatorial, 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 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 countrywide 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 LMICs, 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.

Despite the significant progress of the DGNN in helping to build neurosurgical capacity in Uganda, the diagnostic, non-operative, and critical care bandwidths for severely neurologically injured patients has remained lagged behind, with, as mentioned above, reported mortality outcomes at MRRH as high as anywhere in the world (15). While 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.

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 serve as the centerpiece of such a system providing near-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 to validate the high sensitivity, specificity, accuracy, and precision of the InfraScanner 2000™ in detecting traumatic intracranial bleeds we have previously demonstrated at DUH in patients presenting to MRRH. If able to detect intracranial hematomas with efficacy similar to CT in the Ugandan patient population, this data can be used to formulate a future trial using the device as a diagnostic tool to inform medicosurgical management for patients in which obtainment of CT scans is not feasible.

5. **Design, Procedures and methods:**
   A prospective cohort study to be conducted at MRRH Division of Neurosurgery. Has emergency ward, the neurosurgery team is led by a Neurosurgeon, Emergency Medicine program with consultants, radiology department. When applicable (conscious patient and/or family or patient surrogate/attendant 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 obtain one to numerous measurements from each patient during his or her hospital stay. When subjects are approached for subsequent study measurements, if the participant has regained the capacity to consent or has a patient surrogate/attendant present, the verbal script will be used to obtain consent. Participants will be asked at that time if prior measurements obtained may be used in the research.

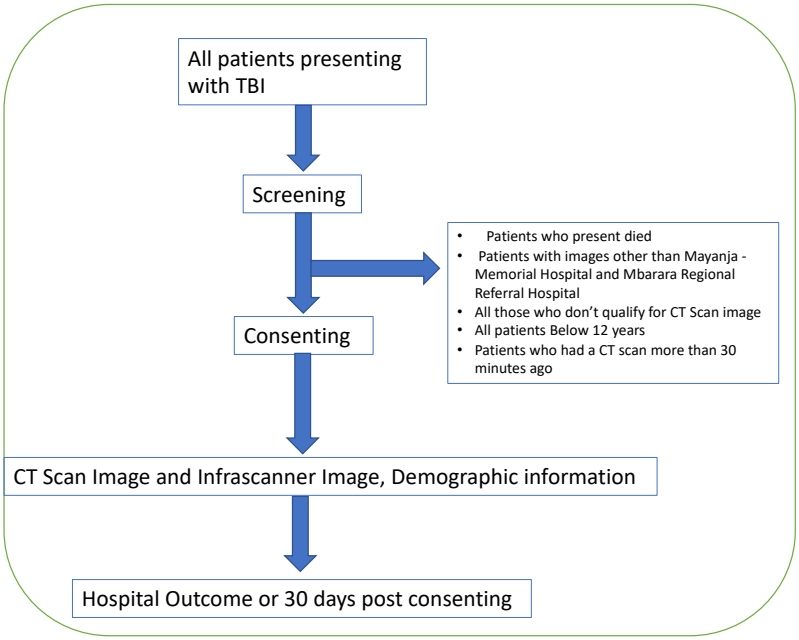
   Upon presentation to the casualty unit at MRRH and/or within 30 minutes prior to each CT scan, the study team will approach the patient or the patient's surrogate/attendant **for permission to scan the patient's cranium with the InfraScanner 2000™ (Image A) and following the CT scan with the second Infrascanner (Image B).** If permission is granted, the study team member will sequentially measure the optical absorption for each of the 8 quadrants of the scalp (frontal, temporal, parietal, and occipital bilaterally) . The device is engineered such that the light emitter and receiver are spaced 4 cm apart, allowing the light's intensity to be measured between adjacent light guides. This entire procedure, including greeting and scanning the patient twice should take <15 minutes. Should the patient obtain a subsequent CT scan(s) the number of scans the patient receives determines the number of potential data collections. The patient will be approached by the study team at the time of each CT scan and can decline participation during any individual encounter without withdrawing from the study.

   The collection period for each research participant concludes within 30-days following his or her initial consent, patient or patient surrogate/attendant decision to withdraw from further participation, hospital discharge, or patient death; whichever occurs first.

6. **Participant Recruitment and Compensation:** Potential research participants will be approached by the research assistants. To avoid bias and potential coercion, the clinical team will not be involved in the participant recruitment. The research assistant will be graduate nurse. They will be trained in the consent process, and will make it abundantly clear that agreement or refusal to participate in the study will not influence the patient's care in any way.

7. **Consent Process:** After being made aware of the study by the research assistant and agreeing to hear more about the study, the prospective participant and/or the patient surrogate/attendant will be given more information about the study. Upon admission to MRRH for suspected head trauma, the research assistant will introduce the patient or the patient's patient surrogate/attendant to the presence of the study. If the consenting party agrees to hear about the study, The research assistant will greet the patient and will speak with patient and/or patient surrogate/attendant, thoroughly describing the protocol and reason for the study. All consenting study personnel will be trained in the consent process, and will provide ample reassurance to the patient or consenting party that the decision to participate will not, in any way, affect his/her medical care. Care will be taken to thoroughly answer all questions prior to obtaining final consent. The patient and/or patient surrogate/attendant will be clearly informed that the research protocol is completely optional, that participation will not affect the treatment they receive, and that, should they give consent, they are free to withdraw from the study at any time. They will be afforded indefinite time to make their decision to participate or withdraw from the study up unto: 1. 30 days following initial consent or 2. When they definitively will no longer receive brain CT scans / are discharged from medical care. The consent process will occur in the casualty unit at MRRH or at the CT scan of Mayanja Memorial hospital. The study team will be readily available to the patient, patient surrogate/attendant, and/or patient's relatives throughout the study for any questions or concerns they may have.

8. Data collection
   Once the participant is identified he will be assessed whether they met the inclusion criteria of the study. In they do, they will then be consented and and enrolled in the study. Data Collection will follow the follow chat below.



9. **Participant's Capacity to Give Legally Effective Consent:** We expect that most of the Participants will be neurologically and/or cognitively impaired due to extent of head injury, multisystem trauma, and/or medical treatments. Since this is a minimal risk study, we will offer study participation to subjects with diminished abilities if they have a patient surrogate/attendant. For patients with less severe injuries as well as those who are later into their hospitalization with resolving injuries, we expect a minority of subjects to be cognitively intact and capable of autonomously making decisions about their routine medical care. For such patients, they can consent without need for patient surrogate/attendant. The study will also be offered to patients 0 years of age and older. For patients younger than 18 years, we will obtain assent from the participants, when he or she is cognitively able, and consent from their patient surrogate/attendantor parents.

10. **Study Interventions:** As described above, upon arrival to the casualty unit and/or within 30 minutes of each CT scan, the study team will scan the study participant's cranium with the InfraScanner 2000™ (Image A). The study team member will use the device to sequentially emit light through fiberoptic light guides rested upon the patients scalp so that near-infrared light can be emitted in each of the quadrants (Image B). The device is engineered such that the light emitter and receiver are spaced 4 cm apart, allowing the light's intensity to be measured between adjacent light guides (Image C). This entire procedure should take <10 minutes. The number of CT scans the patient receives determines the number of potential data collections. The patient will be approached by the study team at the time of each CT scan and can decline participation during any individual encounter without withdrawing from the study.

11. **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 (CT), 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 IN = the intensity of reflected light on the normal side, IH = 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 is 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).

12. **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. All data obtained with the Infrascanner 2000™ will be blinded from physicians participating in the care of study patients to avoid any deviation from standard of care.

13. **Costs to the Subject:** No additional costs to the patient will be incurred as a result of this add-on research protocol. The participant will receive UGX 15000 as stipend for participating in the study.

14. **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 MRRH who have sustained or who are suspected to have sustained head trauma. For those who go on to obtain CT scans, 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 10% of patients are anticipated 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. Analyzing the effects of extracranial hematomas, lacerations, and swelling on the performance characteristics of the device
    4. Estimating Receiver Operating Characteristic (ROC) curves with patient and scan as the units of analysis (20).

    Study Design:
    a) Eligibility: All patiets with suspected TBI and meet the WHO and Brain Injury (BI) trust criteria for CT scaning
       Inclusion criteria
       Patients with suspected TBI above 12 years with suspected TBI and meet the BI criteria for CT scan
       Patients that present with CT that was taken within 30 minutes
       Patients with TBI that occurred more than 48 hours
       Patietns with suspected TBI who present to Mayanja Memorial Hospital for CT scan but managed at Mbarara Regional Referral Hospital
       Patients who do not present with CT scan images and cannot afford to pay for a CT Scan, will be included in the study and the study team will pay for their scans.

       Exclusion Criteria

Patients who present died
Patients with images other than Mayanja Memorial Hospital and Mbarara Regional Referral Hospital

b) Standard of comparison:
All patients entered into the trial will undergo at least one cranial scanning using the InfraScanner 2000™ at the time of presentation. For patients who go on to get a CT scan, they will be scanned using the InfraScanner 2000™ within 30 minutes of each subsequent CT. Patients and care providers will be blinded to the results of 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. For patients who never go on to obtain a CT scan, their InfraScanner 2000™ results will be analyzed in the context of clinical data.

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 (21). 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} +/- 1.645*$SE(P_{Sens})$ where $SE(P_{Sens})= [(P_{Sens})(1- P_{Sens})/N$; N denotes the number of true positives.

With 68 patients with positive findings of hematoma (i.e. CT-proven SDH/EDH) sensitivity can be estimated to within at most +/- 0.099 with 90% confidence. Assuming 20% of patients have true hematomas detected, 340 patients who obtain CT scans must be accrued (10). We estimate that 50% of patients will obtain CT scans. Accounting for this, and allowing for a 5% dropout rate the required sample size for this trial is 720 total participants. With 272 patients having negative findings for hematoma via CT, specificity can be estimated to within at most +/- 0.05 with 90% confidence.

d) Interim Analysis

An interim analysis will be conducted once 150 patients with accompanying CT scans have been enrolled in the study to estimate the prevalence of hematomas at MRRH. 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 120 patients per month will be accrued and studied at MRRH. Study enrollment should thus be completed within approximately 6 months. The collection period for each research participants concludes within 30-days while in hospital following his or her initial consent, patient or surrogate/ patient attendant decision to withdraw from further participation, or hospital discharge, or patient death; whichever occurs first.

15. 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.

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

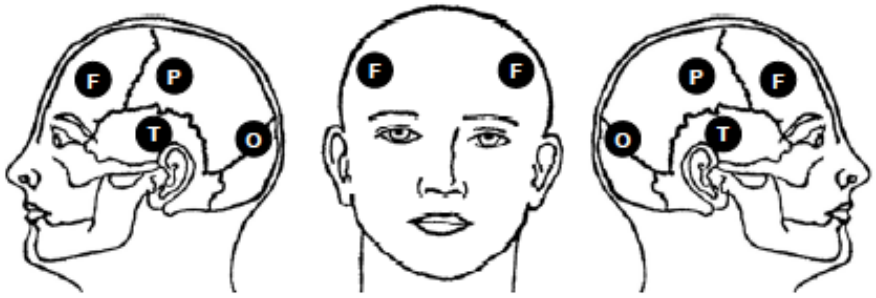
16. Privacy, Data Storage, and Confidentiality: Participants will be given as research numbers. Data will be stored on secured Qualtrics database and de-identified CT scans stored in a secure box folder. For analysis, data will be fully de-identified. Research materials will be stored in a locked cabinet in the Neurosurgery office in the Department of Neurosurgery and in digital form on the DHTS-maintained server.

17. Limitation of study
The study does not take into account those with brain swelling and contusions which may affect the outcome.

18. Data Sharing Plan
Data from this study will be shared equally by the principal investigators. We plan to publish to papers from this work. For the first paper first author will be a local investigator and will also be the corresponding author (Either Dr. Ttendo or Dr. Kitya). The author will be an international Investigator (Dr. Tony or Dr. Haglund), the same order will be followed for the last authors. The order will change for the second paper.

Image A (20)

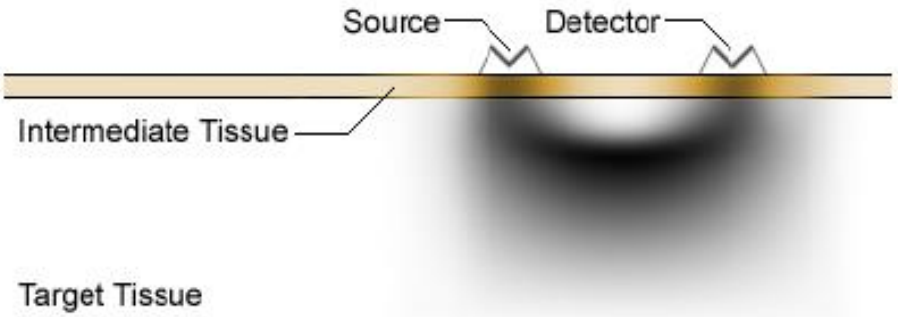
Image B (20)



Head location of Infrascanner measurements

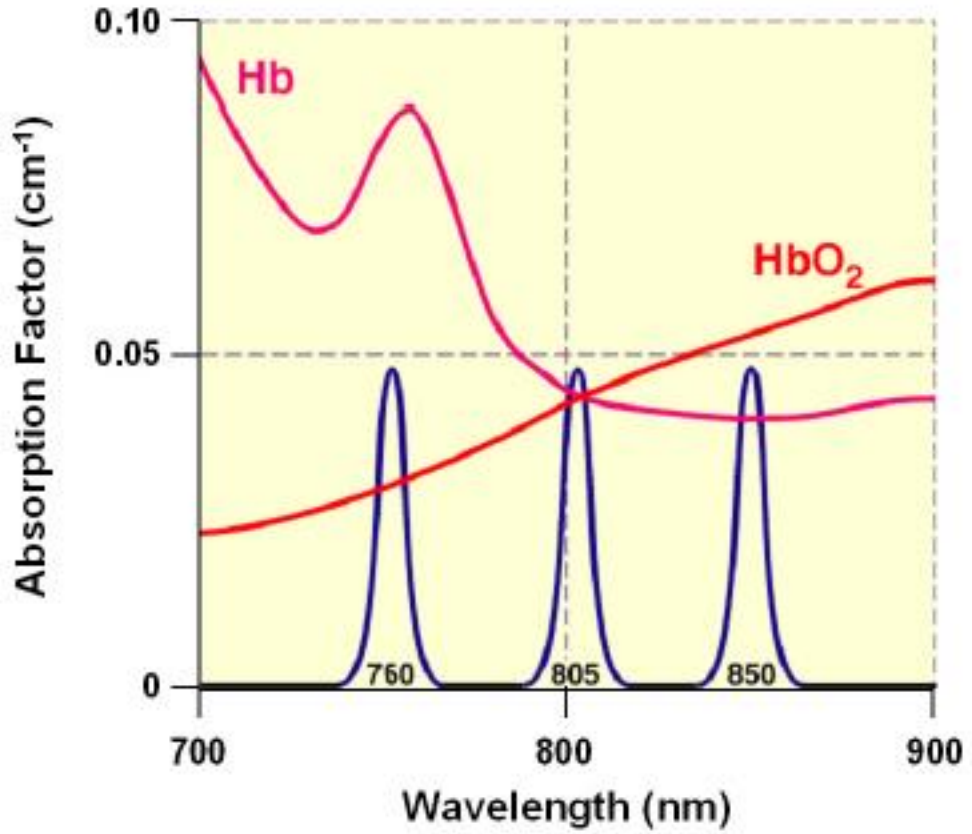
Frontal	Left/Right forehead, above the frontal sinus
Temporal	In the Left/Right temporal fossa
Parietal	Above the Left/Right ear, midway between the ear and the midline of the skull
Occipital	Behind the Left/Right ear, midway between the ear and the occipital protuberance

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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