PROTOCOL

TES-HT 100 MEDICAL DEVICE CLINICAL INVESTIGATIONS

Title of Study:	**"TES HT100 Clinical Outcomes - Clinical Validation of the TES HT100 Temnograph for Brain Injury Screening in Patients with Mild Head Trauma or Suspected Neurological Symptoms" (TESCO)**
Reference number or identification code of the clinical investigation:	**CLV-01-TES HT**
Protocol version number:	**1.2**
Date of issue:	27/01/2026
Promoter	Manufacturer and Sponsor: B&B S.r.l. Fienile road, 1 - 80013 - Casalnuovo (NA) +39 081-19189806
Scientific Responsible	DR.SSA CONTE MODESTINA ADRIANA

Centers involved and Principal Investigators

Center 1 - Emergency Room, Pineta Grande Hospital, Castel Volturno (Italy)
Principal Investigator: Dr. Conte Modestina Adriana
Investigators: Dr. Carmellino Salvatore, Dr. Perrone Anna, Localzo Angelo, Russo Esau, Dr. Antonia Sorbo

Center 2 - Emergency Department, Upper Silesian Medical Center, Ochojec (Poland)
Principal Investigator: dr n. med. Mateusz Majewski
Study Coordinator: Paweł Nowicki
Sub-investigators: Monika Nowicka, Anna Lis, Luiza Chmielewska, Bartek Blada, Tomasz Ilczak, Magdalena Augustyn, Amadeusz Żak, Urszula Uchwat, Małgorzata Cisowska, Katarzyna Maciejewska, Łukasz Basta, Norbert Ziółkowski, Tomasz Zawadzki, Jolanta Wołosianka, Jakub Gittner

Center 3 - Emergency Department, Medical University of Gdańsk (Poland)
Principal Investigator: prof. dr hab. n. med. Mariusz Siemiński
Study Coordinator: Paweł Nowicki
Sub-investigators: Jacek Szypenbejl, Piotr Woźniak

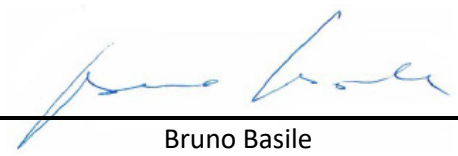
Contact Information

Name Contact Promoter	Bruno Basile bruno.basile@temnografia.com
Name Contact for Vigilance Device	Fabrizio Alfieri fabrizio.alfieri@temnography.com

PROTOCOL APPROVAL

The Investigators and the Promoter:

- Approve this Protocol;
- declare that the study will be conducted in accordance with *Good Clinical Practices*, the UNI EN ISO 14155:2012 standard, and as stated in this Protocol.



Bruno Basile	27/01/2026 Date
DR Modestina Adriana Conte	27/01/2026 Date
	Date

Index

Device information medical

The device under clinical investigation is the TES HT, model 100, equipped with software version 1.3 (or later) and firmware version 1.4 (or later). The hardware and software configuration used in the study coincides with that planned for commercialization.

TES HT model 100 devices are medical devices aimed at noninvasive detection of endocerebral lesions. It uses nonionizing, ultra-low-power electromagnetic waves in the frequency range of 5 0 0 - 6 5 0 0 MHz.

TES HT devices are composed of the following parts:

- Graphic measurement and data processing console;
- Battery charger/power supply.

The console inside includes the battery pack, radio frequency management and emission unit, processing unit, and a high-resolution display.

The indication of the presence of an intra-cranial lesion is 'on-off' type.

The positioning of the device is done manually by the operator (following the instructions in the Instruction Manual) as shown in Figure 1(a,b); the patient wears a disposable surgical-type headset while performing the examination, and the device never comes into direct contact with the patient's head. The complete examination has a duration of 5 minutes.

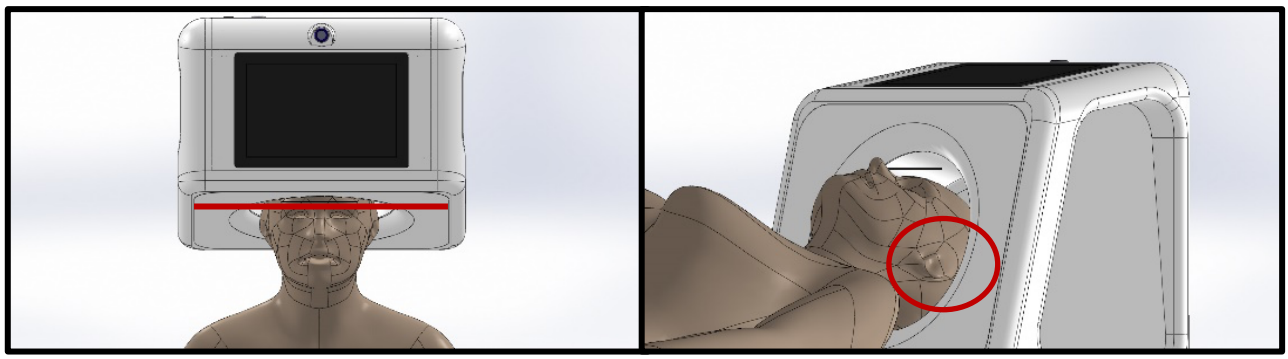


Figure 1-(a) Correct positioning TES HT100

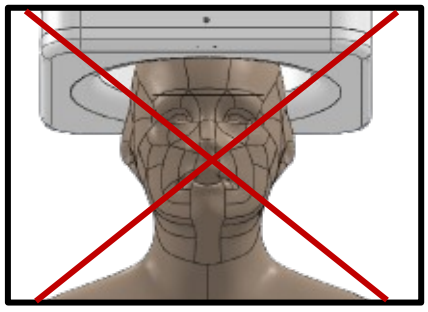


Figure 1-(b) Wrong positioning TES HT100

Information related to manufacturer

TES HT100 medical devices are mass produced by *B&B Ltd.* Information about the manufacturer is shown in *Table 1.*

Table 1

Company name	B&B S.r.l.
Company headquarters	Fienile road, 1 - 80013 - Casalnuovo (NA)
VAT number or tax code	06342121214
PEC	bandbroadcast@pec.it
Office Tel.	+39 081-19189806
E-mail	direzione@temnografia.com
Website	https://www.bandbsrl.com/

Intended use and population for which the device is intended

The TES HT100 medical device is designed to rapidly identify brain lesions and/or potentially pathological changes in brain structure. TES HT models are designed to measure the interaction of electromagnetic waves with a person's brain under static conditions. They are intended for emergency units, such as ambulances, first aid stations, neurology, trauma and emergency medicine departments - including mobile ones. The devices can be used several times on the same patient without time limitation.

Detailed description of the device

The TES HT 100 device consists of Console and Charger. Table 2 describes the technical specifications of the TES HT100 device.

Table 2

Technical Specifications TES HT100	Specifications
Dimensions (mm)	420L x 400H x 340P
Weight (kg)	8.0
Power supply (V)	12V DC
Battery (mAh)	10000 mAh
Power (W)	60

Technical Specifications TES HT100	Specifications
Radio Transmitter	Precision Analyzer
Radio wave frequency (MHz)	500 - 6500
Maximum power of radio waves (mW)	250
Screen	10.1"
Connection	Internal Modem - SIM
Maximum number of exams that can be stored	1000
Cable length (mm)	Battery charger -> console =905 power supply -> battery charger =1180
Power supply weight (kg)	0,35
Power supply (V)	220 A.C.-12 D.C.

Signaling of the presence of intra-cranial lesion or abnormality is 'on-off' type. In the case of positive detection, the LED light clusters will signal this event by emitting a flashing red light signal; on the other hand, in the case of no negative outcome, they will signal this event by emitting a flashing green light signal. The report produced in PDF format is stored in the instrument and can be sent via internet connection to the prepared center at the end of the examination.
In TES-HT 100 devices there are components such as electromagnetic transducers, the control module, the electronics for transducer management, the power button (amber in color), the examination start/stop button (blue in color), and two sets of optical indicators that signal the status of the system at each stage of operation.
In terms of user interaction, the TES-HT 100 offers full functionality through the integrated physical buttons and also features a graphical touchscreen display, which allows for a graphical visualization of all phases of device operation

Figure 2- TES-HT 100 device

Table 3 shows the materials used in the manufacture of the TES-HT 100 device

***Table* 3-Device materials**

Materials Bulletin Device
• Mechanical structure
• 2 electromagnetic transducers
• Electronic control board
• Cables
• Button with integrated amber-colored LED
• Button with integrated blue color led
• Electronic control board
• Processing Unit
• RF signal generation system
• Display module, *Human Interface Device* (HID)
• Mechanical containment structure of the console
• Lithium-ion battery 12V, 10 A/h

Action mechanism

The technology of TES-HT devices is based on electromagnetic scattering over different dielectric tissues. Radiofrequency waves can easily penetrate the bone material of the cranial theca to reach the underlying tissues. Moreover, the dielectric composition of the brain is almost uniform, whereas blood and serum (for parenchymal lesions) have completely different "εr and σ (S/m)" dielectrics. This makes it possible to detect them within the brain with high contrast. Signal scattering in different frequencies and RF wave propagation are used in the specified range as 'radar' to detect abnormalities in the brain. The full range of frequencies used consists of hundreds of different frequencies. Each signal has a maximum sent power of less than 250 milliwatts. The complete diagnostic examination takes four minutes, and in this short time the total energy applied is minimal and discontinuous.

Training required for the use of the medical device by users

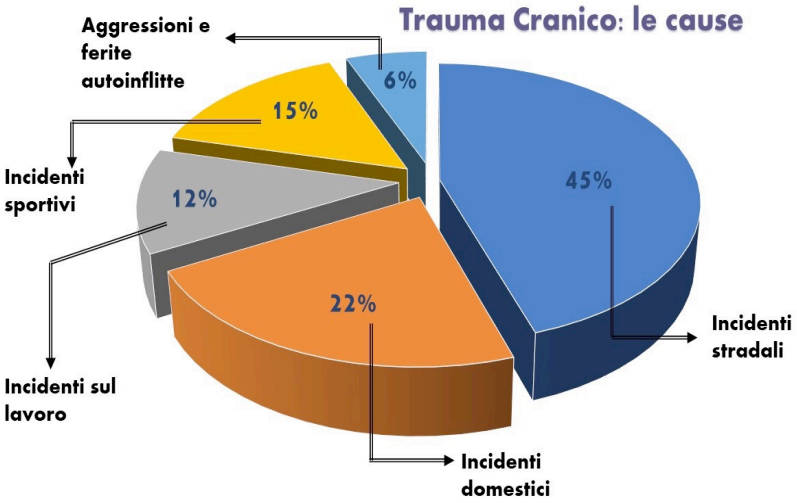
TES-HT 100 devices are designed and manufactured to be used by health care professionals without specific expertise. They allow the return of an automatic on/off type result regarding the presence of endocelebral lesions.
The steps for setting up and properly performing the examination will be explained to the personnel who will use the device at dedicated training event.
Copies of the user manual and a quick user guide will be provided with the device.

Analysis of the literature and rationale for clinical investigation

Mild head trauma

Mild traumatic brain injury (mTBI) is a significant medical condition that requires detailed analysis to fully understand its clinical, epidemiological, and management implications. This type of trauma represents a major cause of disability and mortality worldwide, with an incidence that varies significantly, reaching up to 694 cases per 100,000 population per year (1). Despite the term "mild," head trauma of this type can lead to serious short- and long-term consequences, underscoring the importance of accurate diagnosis and appropriate treatment (2)

The assessment of head injury severity is commonly based on the Glasgow Coma Scale (GCS), which classifies injuries into mild (GCS 13-15), moderate (GCS 9-12) and severe (GCS <8) (3). In Italy, each year, approximately 250 patients per 100,000 inhabitants require hospitalization due to head trauma, with a bimodal distribution by age, peaking between 16-35 years of age and over 70 years of age (4). The diagnosis of mild head trauma is mainly based on clinical manifestations such as loss of consciousness, amnesia, confusion, and altered mental status. The most common symptoms include confusion, amnesia, headache, dizziness, nausea and vomiting (5,6,7). Computed tomography (CT) scan is considered the gold standard for the diagnosis of head trauma (8). To improve diagnostic accuracy and reduce unnecessary radiation exposure, clinical scores such as the Canadian CT Head Rule (CCHR), the New Orleans Criteria (NOC), and the National Emergency X-Radiography Utilization Study II (NEXUS II) criteria have been developed and validated to identify patients in need of CT (9,10). However, a systematic review of the literature estimated a prevalence of CT abnormalities of 5% among patients with GCS = 15 and 30% for those with GCS = 13 (11).



Importantly, despite the classification of mild head injury, this condition may hide important short- and long-term risks for the patient, underscoring the importance of more thorough evaluation and management of patients with this condition (12). Other neurological conditions that may manifest with symptoms similar to those of mild head injury are given by: Syncope, for example, represents a temporary loss of consciousness due to transient cerebral hypoperfusion, and its prevalence in the general population is estimated to be around 3 percent per year (13). Spatial disorientation and loss of balance can result from various neurological conditions, including stroke, vestibular diseases, and neurodegenerative disorders. It is estimated that about 30 percent of elderly patients aged 65-74 years and up to 50 percent of those over 75 years have balance disorders (14). These symptoms, if neglected, can lead to serious complications, underscoring the importance of timely and accurate evaluation.

Speech disturbances, such as aphasia, and facial hemi-paresis are characteristic symptoms of stroke. Early intervention within 3-4.5 hours after symptom onset can significantly improve functional outcomes and reduce the risk of permanent disability (15). Stroke is a major cause of disability and mortality, with a huge impact on both individual health and overall health care expenditures (16).
Approximately 30% of stroke patients have visual disturbances (17). Detailed assessment of these symptoms is critical to determine the underlying cause and plan appropriate treatment in order to preserve visual function and prevent further neurological damage.
Head trauma can cause various neurological disorders, including memory loss, particularly when associated with traumatic brain injury (TBI). It has been shown that even a single traumatic event can cause structural and functional damage to the brain, thereby impairing short- and long-term memory (18). Head trauma has been shown to increase the risk of developing neurodegenerative diseases, such as Alzheimer's disease, which is often associated with cognitive deficits, including memory loss.
In recent decades, several technological solutions have been explored for the development of portable, noninvasive devices aimed at detecting endocranial injury and/or stroke. [19,20] Among the multiple options, the technology that has demonstrated clinically relevant results is on the use of electromagnetic fields at microwave frequencies. Extensive studies have shown the ability of this approach in detecting lesions such as internal bleeding and edema by exploiting the dielectric contrast between different tissue types [21].
As highlighted in [22], the use of radar imaging technology allows the detection of hot spots where there is inhomogeneity of electromagnetic characteristics, such as the presence of blood in the brain parenchyma. Recording these variations, combined with the use of an appropriate imaging algorithm and a hybrid method for reducing reflections generated by surface structures (e.g., such as the skin) allows one to distinguish healthy tissue (dielectric values of various human tissues have been widely characterized in the literature) from diseased tissue [23].

Rationale for the investigation

The objective of this clinical investigation is to validate the effectiveness of the TES HT100 device as a screening tool for the presence of brain injury both in patients with mild head injury and on patients with neurological symptoms not related to head injury. Having at one's disposal a rapid diagnostic address tool, only 5 minutes per examination, portable, nonoperator dependent, and most importantly harmless because it uses very low energy nonionized radio frequencies, that would allow rapid objective screening for the presence of brain lesions would allow for improved management of such patients afferent to the emergency department. Such instrumentation would allow rapid identification of patients, who even if not in critical situations, need further diagnostic investigation.
The literature supports the need for advanced diagnostic tools that can assist clinicians in the rapid and accurate assessment of complex neurological conditions. The rationale for this investigation is based on the need to improve the quality of care provided to patients with mTBI and other neurological conditions. The TES HT100 device interposes itself as an initial screening tool for the detection of brain lesions and neurological disorders potentially related to them, potentially enabling targeted management of patients. In addition, the adoption of the TES HT100 could lead to greater efficiency in the area of healthcare resources by reducing waiting times for diagnosis and optimizing

the use of diagnostic equipment. This could result in better utilization of hospital resources and an overall improvement in the quality of care provided to patients.

Objectives of the study

Clinical validation of the ability of TES HT 100 to identify brain injury or alterations in brain structure in patients with:

- mild head trauma
- neurological symptoms not attributable to trauma but not in critical condition.

Considerations ethics

The clinical trial of the TES-HT device is performed in compliance with the Standards of Good Clinical Practice (GCPs) and all other applicable regulations and administrative requirements.

The sponsor declares compliance with the Code of Good Clinical Practice for planning and conducting clinical investigations of medical devices in accordance with UNI EN ISO 14155:2020, Regulation (EU) 2017/745, and ICH-GCP guidelines, where applicable.

Modalities for obtaining informed consent.

Subject participation in this clinical study is voluntary.
Informed consent is obtained prior to the use of any experimental device, required by the study and/or test procedures or data collection.
Obtaining and documenting informed consent must be in accordance with the principles of ICH/GCP, the Declaration of Helsinki, and ISO 14155.
B&B S.r.l. will provide researchers with a specific Informed Consent Form for volunteers participating in this study. Any changes by the Sponsor require acceptance by *B&B S.r.l.* prior to use of the Template. The Template must be in a language understandable to the subject.
The process for obtaining informed consent includes:

- be conducted by personnel assigned or authorized to conduct the trial;
- include a description of all aspects of the clinical trial that are relevant to the subject's decision to participate in the entire clinical trial;
- avoiding any coercion or undue influence of subjects to participate;
- not waive or give the impression of waiving the subject's legal rights;
- use language that is simple and understandable to the subject or the subject's legal representative;
- provide time for the subject to consider participation and ask questions if necessary.

This Form must always be personally signed and dated by the subject or legal representative and the investigator and/or authorized designee. The original signed copy will be retained by the Sponsor. Failure to obtain subject consent will be reported by the Sponsor to the appropriate

regulatory body as required by them.

Preclinical evidence and previous clinical experience

The TES-HT100 device was initially subjected to a series of validation tests using phantoms designed to accurately replicate the properties of the human tissues of interest. For the generation of such phantoms, which replicate the dielectric characteristics of the head, values found in the specialist literature were adopted [24]. As previously published studies have shown, the use of such phantoms allow laboratory replication of close-to-reality clinical situations of injuries such as hematomas, contusions, and diffuse damage Laboratory experimental results validated the device's ability to successfully detect alterations in endocranial dielectric properties, with high specificity and sensitivity. These data are available as Internal data from B&B s.r.l.

For the fulfillment of essential safety requirements in accordance with European Regulation MDR 745/2017, a campaign was conducted to analyze, assess, and manage risks arising from the intended, reasonably foreseeable, and unforeseen use of the TES-HT100 device. Controls were defined and implemented to mitigate the identified risks. Residual risks are found to be acceptable in accordance with international standards and guidelines for risk management (ISO IEC 14971:2022). To ensure mechanical and electrical safety, the device was tested at laboratories for compliance with IEC 60601-1 standards, which cover general requirements for basic safety and essential performance of electromedical devices. These tests included checks for mechanical strength, electrical safety, protection against fire and electric shock hazards, and general robustness of the device. The device underwent electromagnetic compatibility testing according to IEC 60601-1-2 standards. These tests ensure that the TES-HT100 does not interfere with other medical devices and is resistant to electromagnetic interference. Validation fates of the software and the Usability of the graphical user interface were conducted. Then The device was tested on a group of 98 volunteers at the Magnolia Clinic. in a real clinical environment. The volunteers were monitored for the presence of neurological symptoms and brain lesions using TES-HT100. The data collected indicated high accuracy an excellent tolerability of the device, with no significant adverse effects. [25] Currently, TES-HT100 is the subject of a clinical investigation, conducted according to Good Clinical Practice ISO 14155, to EU Regulation 2017/745 following the clinical investigation guidelines MEDDEV 2.7/1 rev. 4. This study was approved by the Regional Ethics Committee for Clinical Trials of Tuscany-Italy Region on 17/04/2023. Preliminary data from that study, on 20 patients presented as an oral communication at the SIMEU congress (abstract ID 018) show that the device a near 100% congruity with CT outcome. [26]

Investigation information clinical

TES-HT devices are capable of detecting brain lesions. The answer is YES/NO.
Three different steps must be considered during the clinical investigation:

1) **Data collection** - In order to achieve the target number established with the Reference Sponsor.
2) **Data processing and comparison** - At this stage, data are processed for each patient using appropriate ID, and the result is linked to the respective diagnosis by the relevant personnel at the institution hosting the survey.

The purpose of the clinical investigation is to commercialize the device on a national/international scale.

Study Description.

The aim of the multicenter, open-label study is to clinically validate the TES HT100 as a screening tool for noncritical care patients attending the emergency department or for mild head injury or neurological symptoms.

The study involves the enrollment of two separate cohorts of patients in the following centers:

- **Center 1 - Emergency Department, Pineta Grande Hospital, Castel Volturno (Italy)**
- **Center 2 - Emergency Department, Upper Silesian Medical Center, Ochojec (Poland)**
- **Center 3 - Emergency Department, Medical University of Gdańsk (Poland)**

The study involves the enrollment of two separate cohorts of patients:

1) 425 Patients with mild head injury
2) 425 Patients with neurological symptoms not related to head trauma and not in a critical or life-threatening condition such as:
   - Syncope
   - Spatial disorientation and loss of balance
   - Speech disturbance and facial hemi-paresis
   - Visual impairment
   - Lack of memory and confusional state

As an indication, an enrollment of approx:
- [275] patients per cohort at Pineta Grande Hospital
- [75] patients per cohort at GCM Ochojec
- [75] patients per cohort at Medical University of Gdańsk.

All patients will follow the normal diagnostic-therapeutic procedure with priority access to CT examination according to severity and to which, as described below, only the examination with TES HT100 will be added, which has a maximum duration of 5 min (examination duration 4 min for acquisition and 1 min for data processing):

Patients with mild head trauma:
* the patient with mild head trauma following Acceptance Acceptance will be assisted and evaluated at Triage and will have a CT scan within 1 hr or more, followed by themnographic examination with

TES HT100, after signing informed consent for participation in the study;

Patients with neurological symptoms:
* the patient following Acceptance Acceptance will be assisted and evaluated at Triage and a CT scan will be performed in order to exclude the possible presence of stroke and, with reference to patients enrolled in the Pineta Grande Hospital emergency room, possible transfer via 118 to the Stroke Unit U.O.S.D. | A.O.S.G. Moscati. For the other 2 centers that have stroke units, patients will be transferred to the relevant departments. The temnographic examination with TES HT100 will be performed after the CT scan during the CT reporting phase, after signing the informed consent for participation in the study.

The TES HT100 examination will be performed by trained personnel, who will not have access to the CT report at the time of the examination with TES HT100.
The radiologist reporting the CT scan will be blinded to the TES HT100 result. TES results will be made available only after the CT report has been finalized and recorded.

Information on the data collection form (Appendix A) will be collected for each patient.

Primary and secondary objectives

Primary objectives.

- **To evaluate the diagnostic accuracy of the TES HT100**: To measure the sensitivity and specificity of the device in identifying brain lesions and structural brain changes in the cohorts of patients included in the study.
- **To establish the safety of TES HT100**: To monitor the incidence and type of possible adverse events associated with the use of the medical device during the study.

Secondary Objectives.

- **To evaluate the benefit of clinical use of the TES HT100**: To measure the efficiency of the device in improving the management of patients and hospital resources in the emergency department setting during patient screening.
- **To evaluate the diagnostic accuracy of the TES HT100 in various patient subgroups**:
    - Young patients (<65 years old)
    - Elderly patients (>65 years)
    - Patients with or without prior injury or undergoing brain surgery
    - Patients with or without neurodegenerative diseases

Primary endpoints

- *Receiver Operating Characteristic-Area under curve* (ROC-AUC) processing, depending on the sensitivity and specificity calculated by comparing the TES HT100 exam result versus the CT scan report.
- In order to establish the safety of the medical device, the rate of adverse events related to the use of TES HT100 will be calculated as provided in Regulation 2017/745 (MDR) (CNCCE Circular No. 4/2022)

Secondary endpoints:

- Descriptive evaluation of the potential benefits of using TES HT100 calculated as a function of the possible benefit applicable to each patient, in terms of operator time, procedures, and costs, that would be obtained by performing examination with TES HT 100 with the aim of directing the patient to the most appropriate diagnostic pathway.
- Analysis of the diagnostic performance of TES HT100 as a function of sensitivity and specificity calculated by comparing the TES HT100 exam result versus the CT scan report in subgroups of patients

Target Definition:

For the purpose of evaluating the diagnostic performance of TES HT100, the reference test (gold standard) is the encephalic computed tomography (CT) report.

All patients with at least one of the following acute or potentially clinically relevant intracranial lesions will be considered "CT-positive":
- intraparenchymal, subdural, and subarachnoid hemorrhage;
- cerebral contusion with edema;
- calcifications;
- presence of nodules of various nature (eg cysts);
- acute or subacute or previous cerebral ischemia;
- other acute or prior intracranial injuries,

Patients without such findings will be considered "CT-negative"

Expected Results.

In a health care perspective of rationalization of resources, the TES HT 100 tool could be useful to identify from the outset patients on whom to prioritize the diagnostic pathway, avoiding delays and at the same time avoiding dispersion of resources in terms of economics and staff time for the management of patients who do not need in-depth diagnostic investigation. We assume a diagnostic reliability of TES HT 100 greater than or equal to 90% and a sensitivity and specificity greater than 80%.
Technological developments in the medical field reflect the need to enhance the diagnostic field

with the introduction of diagnostic tools that are increasingly accessible, objective, fast and reliable, and above all harmless to the patient and health care providers.

Variables to be measured

TES HT examinations should be performed within 24 hours before or after the CT examination.

Systematic errors - bias

Systematic errors that may occur during the study are mainly related to the marked movement of the patient, who should avoid abrupt movements throughout the scan in order to reduce motion artifacts.

Patient selection

Patient inclusion criteria:

Group 1:
- age over 18 years
- acquisition of informed consent
- Patients referred to the emergency department for mild head injury

Group 2:
- age greater than 18 years
- acquisition of informed consent
- Patients afferent to the emergency department not for head trauma and not in a critical condition, with one of the following neurological symptoms:

  - Syncope
  - Spatial disorientation and/or loss of balance
  - Speech disturbance and/or facial hemi-paresis
  - Visual alterations
  - Lack of memory and/or confusional state

Exclusion criteria for both cohorts:

- age less than 18 years
- pregnant women
- metal plates or metal prostheses installed in the skull cap
- severe head trauma and/or with extensive lacerated contused areas
- patient in critical condition
- visible skull theca fracture

- failure to sign informed consent

The TES-HT device cannot be used in cases of metal plates or metal prostheses installed in the skullcap because their presence alters the outcome of the TES HT100 examination.

Number of patients expected to be enrolled

Considering that it is intended to prove the primary hypothesis that TES HT 100 succeeds in achieving a sensitivity and specificity of 90% when comparing to the outcome of the CT scan report, an AUC of 0.90 is obtained, a value indicative of its excellent reliability. Assuming that TES HT100 meets this performance, a sample size of about 384 subjects is needed to obtain a maximum error of 3% on the confidence interval in the 95% two-tailed test on AUC. In other words, the target AUC and sample size should allow 95% confidence that the AUC is within the range [0.87;0.93]. Given a 10% drop-out rate, a sample size of 425 subjects for each patient cohort is considered necessary. Although the sample size calculation was performed as was previously explained, we believe it is fair to consider, in the case where there is a large imbalance between positive and negative outcomes, a small adjustment on the precision of the AUC estimate. Specifically, we will consider a precision of 0.02 instead of 0.03.

Enrollment point

Patients will be enrolled in the following emergency departments:

- Pineta Grande Hospital, Castel Volturno (Italy)
- Emergency Department, Upper Silesian Medical Center, Ochojec (Poland)
- Emergency Department, Medical University of Gdańsk (Poland).

The patient is understood to be enrolled in the clinical trial from the moment he or she meets all inclusion and exclusion criteria and after signing the Informed Consent Form at the relevant center.

Number of experimental medical devices expected to be used.

Three TES HT100 devices are planned for the study, one for each participating center. All devices will be of the same hardware and software version and will undergo the same qualification and maintenance procedures.

Duration of the study

The study is planned to last 30 months.

Medical and surgical procedures and follow-up of study

After positioning the device and the patient at the correct height, the authorized healthcare personnel press the P1 button (Figure 3) to start the measurements.
The device signals the measurement status through the L1 and L2 indicator, which emits a flashing blue light optical signal.

After the first measurement, the device gives the result of injury detection. After the end of the measurement operation, the user can remove the device and the examination is finished. To turn off the device, the user presses the appropriate button. After using the device, the user stores the device in a safe environment with the following requirements:

- temperature 0°-+50° and humidity max 90%;
- the device does not require cleaning agents; just follow the instructions in the Manual for common cleaning;
- the patient can wear a disposable surgical cap.

The TES HT100 examination will be performed by trained personnel, who will not have access to the CT report at the time of the TES HT100 examination.
The radiologist reporting the CT scan will be blinded to the TES HT100 result. TES results will be made available only after the CT report has been finalized and recorded.

Discontinuation and withdrawal of subjects from clinical investigation

In case of premature termination of studies, a Written Statement as to the reason for the premature termination of the trial must be produced. Community and regulatory authorities, as appropriate, will be informed. Detailed information on how enrolled subjects will be handled will be provided later. In the event that the Sponsor discontinues participation in the study, TES-HT staff and regulatory authorities, as appropriate, will be informed in writing.

Evaluation benefit-risk

In consideration of risk/benefit, the TES-HT device appears to be absolutely harmless to both patient and operator. In fact, throughout its operation, the electromagnetic emission values are well below the electromagnetic emission values for professional electromedical devices.
The benefits that emerge from using the device can be divided into:

1) **Ease of use** - The device is easy to set up and its use does not require specialized personnel.
2) **Low risk to the patient** - The device does not emit ionizing radiation (as in the case of CT scanning) and emission levels are well below reference limits.
3) **Short scan** duration - The duration of one measurement is 4 minutes.
4) **Small size and easily transportable** - The small size makes TES HT a device that can be used in all emergency situations and in places where rapid transport to a First Aid Center is difficult.

The device shows, therefore, that the cost-benefit is positive and the results timely and beneficial.

Statistics

To evaluate the performance of the device, statistical sensitivity and statistical specificity will be calculated. Statistical sensitivity indicates the device's ability to correctly identify positive cases, i.e., patients with brain injury (prior or post injury) and/or structural alteration of brain tissue. Statistical specificity indicates the ability of the
device to correctly identify negative cases, i.e., patients without brain injury (new or prior) and without structural alteration of brain tissue. All TES HT examinations will be compared with the CT scan report, which will sanction the actual presence or absence of structural alterations of brain tissue. Comparison criteria such as Receiver Operating Characteristic-Area under curve (ROC-AUC), sensitivity and specificity will be used as statistical validation tools, all reported with 95% confidence interval for the entire enrolled population ("pooled" multi-center analysis). The ROC-AUC will be calculated using, as a continuous score, the percentage of cranial bone estimate (Q) generated by the TES HT software (as a surrogate for measurement quality) for each examination; in supportive analysis, the probability of CT-positive outcome can be modeled by logistic regression including the TES outcome (positive/negative) and Q as a continuous covariate. For this purpose, we want to demonstrate the primary hypothesis regarding a diagnostic performance of the TES HT 100 not less than 90% ROC-AUC compared to the outcome of the CT report, while maintaining sensitivity and

specificity of at least 80%. The minimum threshold of 90% is indicative of excellent instrument reliability.

To calculate the statistical sensitivity and specificity, the following data will be used:

	Brain injury present	**Brain injury absent**
Positive test	TP (True Positive)	FP (False Positive)
Negative Test	FN (False Negative)	TN (True Negative)
Total	TP+FN	FP+TN

- Number of true positive cases (TP): number of patients with brain injury (prior or post injury) and/or structural alteration of brain tissue correctly identified by device and confirmed by CT scan
- Number of false-negative (FN) cases: number of patients with brain injury (prior or posttrauma) and/or structural alteration of brain tissue not identified by the device but confirmed by CT scan
- Number of false-positive (FP) cases: number of patients without brain injury (prior or posttrauma) and/or structural alteration of brain tissue identified as positive by the device but confirmed as negative by CT scan
- Number of true negative cases (TN): number of patients without brain injury (prior or posttrauma) and/or structural alteration of brain tissue correctly identified by the device and confirmed by CT scan

Statistical sensitivity is calculated as TP/(TP+FN), while statistical specificity is calculated as TN/(TN+FP).
It will also be calculated:

- the positive predictive value: probability that the disease is present when the test is positive calculated as TP/(TP+FP) with 95% confidence interval.
- the negative predictive value: probability that the disease is not present when the test is negative as TN/(FN+TN) with 95% confidence interval.

Specificity and sensitivity, with 95% confidence interval, will also be evaluated for different subgroups of patients enrolled such as:

- Young patients <65 years old
- Elderly patients >65 years old
- Patients with or without prior injuries or who have undergone brain surgery
- Patients with or without neurodegenerative diseases
- Patients enrolled by center

In exploratory secondary analysis, the variable "center" may be used:
- as a stratification factor for describing device performance at individual sites;
- as a covariate in statistical models to assess the presence of any systematic differences between centers.

An interim analysis is planned for the respective cohorts of patients under study when the thresholds of 150 and 300 patients enrolled in each cohort are reached.

Quality assurance, control procedures, data management and retention of documentation

Subjects' data will be collected through a centralized Electronic Data Capture (EDC) system, which allows the enrollment center to be identified through a site code.

The coordinating center, in collaboration with the Sponsor, will ensure harmonization of procedures among centers by:

- initial and periodic training of investigators;

- in-person and/or remote monitoring;

- centralized review of data quality.

Each center will maintain its own Investigator Site File (ISF), while the Sponsor will maintain the overall Trial Master File (TMF).

All changes made to the clinical data will be captured in an electronic *audit trail* and available for review by the Sponsor or its representative. The software and database associated with data acquisition and storage are designed to meet compliance with applicable laws and regulations, regarding data processing. Data collected on study subjects are in accordance with the ICH/GCP Guidelines valid in the European Union. Records must be kept for ten years after completion of the device trial.

Each data collected should contain:

- ID of the examination performed on TES-HT (ID generated by TES-HT for each examination);
- Examination location (emergency district or other), time, date and operator.
- Anonymous patient history
- Enrollment center identification code ("center variable")

Deviations from the assessment plan clinical

An investigator must not make changes to or deviate from this Protocol except to protect the life and physical well-being of an emergency subject. An investigator must notify both the Sponsor and the manufacturer of any major deviation from the investigative plan designed to protect the life or physical well-being of a subject in an emergency.
Such notice will be given as soon as possible, but no later than 5 working days after the emergency

occurs.

All deviations from the investigation plan, with the reason for the deviation must be collected in the appropriate document, which must contain:

- patient data;
- place, date and time;
- signature of the investigator.

Deviations will be reviewed and evaluated on an ongoing basis, and corrective and preventive procedures will be applied if necessary.

Deviations will be classified according to the following definitions:

- Type A - Deviation to protect the life or physical well-being of a patient in unforeseen emergency.
- Type B - Deviation based on medical judgment.
- Type C - Deviation due to misunderstanding of Protocol requirements.
- Type D - Deviation due to an out-of-control situation.
- Type E - Deviation due to oversight, error or non-compliance of the Protocol.

Patient flow and enrollment diagrams.

In order to transparently describe the path of patients within the study, a flow chart will be prepared in accordance with international recommendations for diagnostic accuracy studies. The chart will report, for each of the two cohorts (mild head injury and nontraumatic neurological symptoms) and for the entire population:

- the number of patients evaluated for eligibility;

- the number of patients excluded, with the main reasons (e.g., exclusion criteria, lack of consent, inability to perform TES or CT scan);

- the number of patients enrolled who performed both HT100 TES and CT;

- the number of patients with incomplete or non-assessable data for the primary analysis;

- the number of patients included in the final statistical analysis.

Where appropriate, the flow chart may be further detailed by enrollment center to highlight any differences in the inclusion and follow-up process among participating sites. The flow chart will be included in the final report and may be used in any scientific publications resulting from the study.

Adverse Events

The TES-HT device is a model of a temnographic device already in use in different settings for which no adverse events were observed.

Adverse events (AEs), serious adverse events (SAEs), device-related serious adverse events (SADEs), and device deficiencies will be collected and classified according to the definitions in Regulation (EU) 2017/745 and UNI EN ISO 14155:2020.

The principal investigator of each center is responsible for timely notification to the Sponsor of each SAE and SADE, within 24 hours of knowledge. The Sponsor, when required, will notify the

relevant authorities and ethics committees according to applicable national regulations.

Publication policy of data

B&B S.r.l. will submit a study of results for publication (regardless of the outcome of the investigation) after its conclusion or termination. *B&B S.r.l.* adheres to the established collaboration criteria *of the International Committee of Medical Journal Editors* (ICMJE; http://www.icmje.org).

Bibliography

1. Brazinova A, Rehorcikova V, Taylor MS, Buckova V, Majdan M, Psota M, et al. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. J Neurotrauma. 2021 May;38(10):1411-40.

2. Judith E. Tintinalli, Steve Stapczynski, John Ma, Donald M. Yealy, Garth Meckler, David Cline, Emergency Emergency Medicine, 8th edition, Padua, Piccin Nuova Libraria, 2018

3. Mckee AC, Daneshvar DH. The neuropathology of traumatic brain injury. Handb Clin Neurol. 2015;127:45-66. doi: 10.1016/B978-0-444-52892-6.00004-0. PMID: 25702209; PMCID: PMC4694720

4. Treatment of minor and severe head trauma. National reference guidelines. SINCH (Italian Society of Neurosurgery). Rusticali B. et al. 2006

5. Kay T, Harrington DE, Adams R, Anderson T, Berrol S, Cicero K, Dahlberg C, Gerber D, Goka R, Harley P, Hilt J, Horn L, Lehmkuhl D, Malec J. Definition of mild traumatic brain injury. Journal of Head Trauma Rehabilitation. 1993;8(3):86-87

6. Practice parameter: the management of concussion in sports (summary statement). Report of the Quality Standards Subcommittee. Neurology 1997;48:581.

7. Duhaime AC, Beckwith JG, Maerlender AC, et al. Spectrum of acute clinical characteristics of diagnosed concussions in college athletes wearing instrumented helmets: clinical article. J Neurosurg 2012;117:1092

8. Lefevre-Dognin C, Cogné M, Perdrieau V, Granger A, Heslot C, Azouvi P. Definition and epidemiology of mild traumatic brain injury. Neurosurgery. 2021 May;67(3):218-221. doi: 10.1016/j.neuchi.2020.02.002. Epub 2020 May 6. PMID: 32387427.

9. Mower, William R. MD, PhD; Hoffman, Jerome R. MA, MD; Herbert, Mel MBBS; Wolfson, Allan B. MD; Pollack, Charles V. Jr. MA, MD; Zucker, Michael I. MD for the NEXUS II Investigators. Developing a Decision Instrument to Guide Computed Tomographic Imaging of Blunt Head Injury Patients. The Journal of Trauma: Injury, Infection, and Critical Care 59(4):p 954-959, October 2005. | DOI: 10.1097/01.ta.0000187813.79047.42

10. Haydel, Micelle J., et al. "Indications for computed tomography in patients with minor head injury." *New England Journal of Medicine* 343.2 (2000): 100-105.

11. Borg J, Holm L, Cassidy JD, et al. Diagnostic procedures in mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med 2004; :61.

12. Kelly JP, Rosenberg JH. Diagnosis and management of concussion in sports. Neurology 1997; 48:575.

13. Kenny RA, Bhangu J, King-Kallimanis BL. Epidemiology of syncope/collapse in younger and older Western patient populations. Prog Cardiovasc Dis. 2013 Jan-Feb;55(4):357-63. doi: 10.1016/j.pcad.2012.11.006. PMID: 23472771.

14. Agrawal Y, Carey JP, Della Santina CC, Schubert MC, Minor LB. Disorders of balance and vestibular function in US adults: data from the National Health and Nutrition Examination Survey, 2001-2004. Arch Intern Med. 2009 May 25;169(10):938-44. doi: 10.1001/archinternmed.2009.66. Erratum in: Arch Intern Med. 2009 Aug 10;169(15):1419. PMID: 19468085.

15. Vitti E, Hillis AE. Treatment of poststroke aphasia: A narrative review for stroke neurologists. Int J Stroke. 2021 Dec;16(9):1002-1008. doi: 10.1177/17474930211017807. Epub 2021 Jun 6. PMID: 33949274; PMCID: PMC8645656.

16. Saini V, Guada L, Yavagal DR. Global Epidemiology of Stroke and Access to Acute Ischemic Stroke Interventions. Neurology. 2021 Nov 16;97(20 Suppl 2):S6-S16. doi: 10.1212/WNL.0000000000012781. PMID: 34785599.

17. Rowe F, Brand D, Jackson CA, Price A, Walker L, Harrison S, Eccleston C, Scott C, Akerman N, Dodridge C, Howard C, Shipman T, Sperring U, MacDiarmid S, Freeman C. Visual impairment following stroke: do stroke patients require vision assessment? Ageing. 2009 Mar;38(2):188-93. doi: 10.1093/ageing/afn230. Epub 2008 Nov 21. PMID: 19029069.

18. McHugh T, Laforce R Jr, Gallagher P, Quinn S, Diggle P, Buchanan L. Natural history of the long-term cognitive, affective, and physical sequelae of mild traumatic brain injury. Brain Cogn. 2006 Mar;60(2):209-11. PMID: 16646125.

19. R. Solimene, B. Basile, J. Browne, A. Cuccaro, A. Dell'Aversano and G. Ruvio, "An Incoherent Radar Imaging System for Medical Applications," 2021 IEEE Conference on Antenna Measurements & Applications (CAMA), Antibes Juan-les-Pins, France, 2021, pp. 493-498, doi: 10.1109/CAMA49227.2021.9703549

20. Cuccaro, A.; Dell'Aversano, A.; Basile, B.; Solimene, R. Microwave radar imaging as a tool for medical diagnostics. *Eng. Proc.* **2023** , *56* , 303. https://doi.org/10.3390/ASEC2023-16522

21. Gabriel S., Lau R and Gabriel C. (1996). The dielectric properties of biological tissues: II . *Measurements in the frequency range from 10 Hz to 20 GHz. Phys. Med. Biol.* 41 , 2251-2269

22. Rafique, Umair, et al. "Ultra-wideband antennas for biomedical imaging applications: a survey." *Sensors* 22.9 (2022): 3230.
23. Gabriel C., Gabriel S., Corthout E.: 'The dielectric properties of biological tissues: I. Literature survey', Phys. Med. Biol., 1996, 41, pp.2231-2249
24. Islam, M.S., Islam, M.T. & Almutairi, A.F. Experimental tissue mimicking human head phantom for estimation of stroke using IC-CF-DMAS algorithm in microwave based imaging system. *Sci Rep* **11**, 22015 (2021). https://doi.org/10.1038/s41598-021-01486-x

25. Vaia S, Iavarone A et al; HT temnography intheearly diagnosis of brain lesions due to ischemic or hemorrhagic sroke. Int. J. of Adv. Res. 11 (Oct). 2023 pp.191-195] (ISSN 2320-5407). www.journalijar.com

26. https://www.simeu.it/w/upload/uploadFile/file/comunicazioni-libere.pdf