PROTOCOL

TES-HT 100 MEDICAL DEVICE CLINICAL INVESTIGATIONS

Title of the 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 code clinical investigation identifier:	**CLV-01-TES HT**
Protocol version number:	1.1
Date of issue:	02/07/2024
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
Investigators involved	Dr. Carmellino Salvatore, Dr. Perrone Anna Dr. Localzo Angelo, Dr. Russo Esau, Dr. Antonia Sorbo
Centers involved: HOSPITAL	EMERGENCY DEPARTMENT - PINETA GRANDE

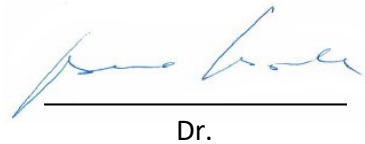
Contact Information

Promoter Contact Name.	Bruno Basile bruno.basile@temnografia.com
Name Contact for Vigilance Device	Daniele Giuseppe Gallo Daniele.gallo@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*, Standard UNI EN ISO 14155:2012 and as stated in this Protocol.



Dr. 02/07/2024 Date

Dr. Date

Dr. Date

Dr. Date

Index

Medical device information

Medical Device Identification.

TES HT model 100 devices are medical devices aimed at noninvasive detection of endocerebral lesions. It uses non-ionizing, ultra-low power electromagnetic waves in the frequency range 500- 6500 MHz.
TES HT devices are composed of the following parts:

- Graphic console for measurement and data processing;
- 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 of the '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.

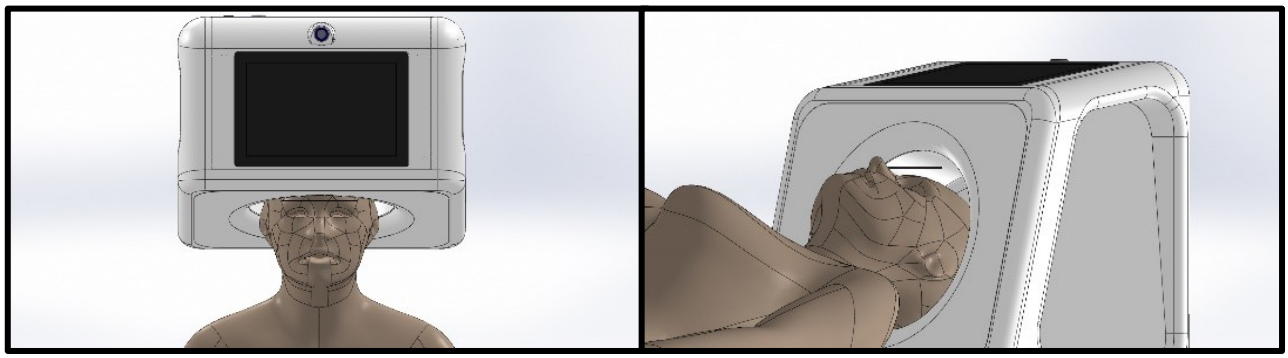


Figure 1-(a) Correct positioning TES HT100

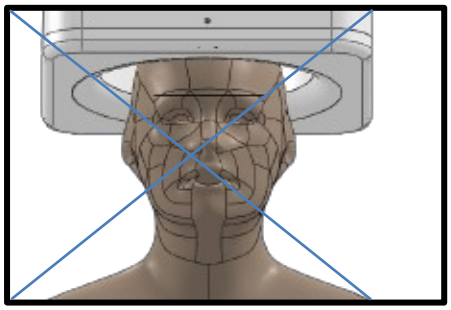


Figure 1-(b) Wrong positioning TES HT100

Manufacturer-related information

TES HT100 medical devices are mass produced *by B&B S.r.l. Table 1* shows the information related to the manufacturer.

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 injury 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.

The signaling of the presence of intra-cranial lesion or abnormality is of the '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 result, 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* - Materials of the device**

Materials Bulletin Device
● Mechanical structure
● 2 electromagnetic transducers
● Electronic control board
● Cables
● Button with integrated amber-colored LED
● Button with integrated blue color led
● Management electronic board
● Processing unit
● RF signal generation system

• Display module, *Human Interface Device* (HID)
• Mechanical structure for containing the console
• Lithium-ion battery 12V, 10 A/h

Mechanism of action

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 full 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

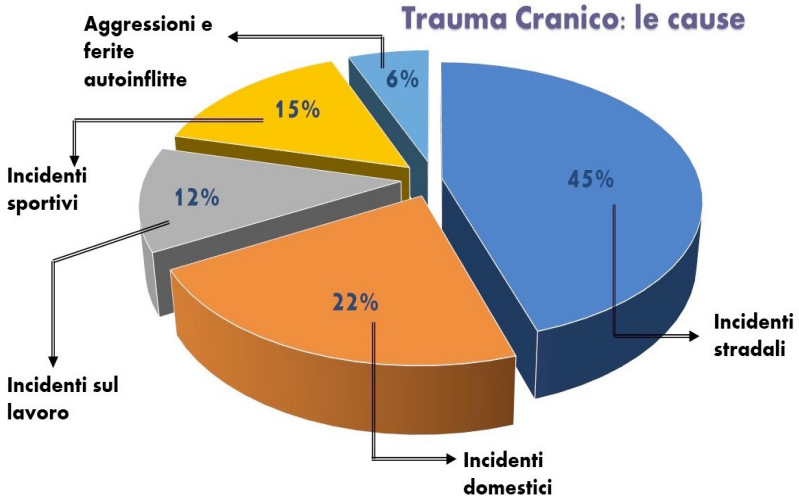
TES-HT 100 devices are designed and manufactured to be used by medical professionals without specific expertise. They allow the return of an automatic on/off type result regarding the presence of endocelebral lesions.
The steps for setting up and properly performing the examination will be explained 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.

Literature review 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) 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 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 essential to determine the underlying cause and plan appropriate treatment in order to preserve visual function and prevent further neurological damage.
Head trauma can cause several 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 many 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 features, 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 in both mild head injury patients 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 injury 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 potentially related neurological disorders, 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, 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.

Study Objectives.

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

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

.

Ethical considerations

The TES-HT device clinical trial is performed in compliance with the Code 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 the Planning and Conduct of Clinical Investigations of Medical Devices (UNI EN ISO 14155:2012 STANDARD) and in compliance with EU Regulation 2017/745.

Arrangements 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 Template 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 prior 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, the following were adopted

the values found in the specialist literature [24]. As demonstrated in previously published studies, 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. Next The device was tested on a group of 98 volunteers at the Magnolia Clinic. in a real-world clinical setting. 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]

Information regarding clinical investigation

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.

Description of the study

The single-center, open-label study that aims to clinically validate the TES HT100 as a screening tool for noncritical care patients attending the emergency department either for mild head injury or with neurological symptoms. The study involves the enrollment of two separate cohorts of patients:

1) 425 Patients with mild head trauma
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

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 performing the temnographic examination with TES HT100, after signing the 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 possible transfer via 118 to the Stroke Unit U.O.S.D. | A.O.S.G. Moscati. 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.

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

Primary and secondary objectives

Primary objectives

- **Assess the diagnostic accuracy of the TES HT100**: 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 the 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 subgroups of patients**:
  - 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 end points

- *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 according to 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 result of the TES HT100 examination versus the CT scan report in subgroups of patients

Expected Results.

From a health care perspective of rationalizing resources, the TES HT 100 tool could be

useful to identify early on 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 further 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 evolution in the medical field reflects the need to enhance the diagnostic fieldwith 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
- 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 enroll

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.

Point of enrollment

Patients will be enrolled in the study within the emergency department of Pineta grande hospital. The patient is considered to be enrolled in the clinical trial from the moment he or she meets all the inclusion criteria of the study and after signing the *Informed Consent Form.*

Number of experimental medical devices expected to be employed

The number of TES HT100 devices that will be employed for this study is one.

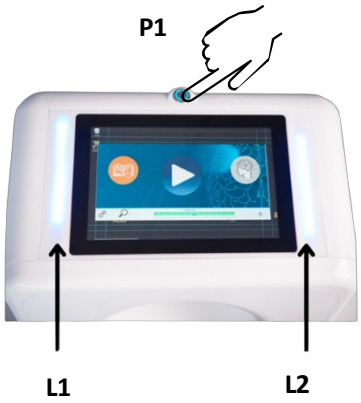
Duration of the study

The study is planned to last for 12 months.

Medical and surgical procedures and study follow-up

After positioning the device and the patient at the correct height, the authorized health care personnel, to start the measurements, presses the P1 button (Figure 3).
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, but simply follow the instructions in the Common Cleaning Manual;
- the patient can wear a disposable surgical cap.



Discontinuation and withdrawal of subjects from the clinical investigation

In case of premature discontinuation of studies, a Written Statement as to the reason for premature discontinuation 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.

Benefit-risk assessment.

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

professional electromedical devices.
The benefits that emerge from the use of 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 with 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.

Thus, the device demonstrates positive cost-benefit and timely and beneficial results.

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 with no brain injury (new or previous) and no 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. To this end, it is intended to demonstrate the primary hypothesis regarding a diagnostic performance of 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 posttrauma) and/or structural alteration of brain tissue identified

correctly by the 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 identified correctly 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)
- the negative predictive value: probability that the disease is not present when the test is negative as TN/(FN+TN)

Specificity and sensitivity 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.

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

Quality assurance, control procedures, data management and record keeping

Subject data will be recorded in a secure electronic data capture (EDC) with limited access. All changes made to 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 have been 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 the 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);
- Location where the examination takes place (emergency district or other), time, date and operator.
- Anonymous patient history

Deviations from the clinical evaluation plan

An investigator must not make changes 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 - Diversion to protect the life or physical well-being of a patient in an 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 noncompliance of the Protocol.

Adverse Events

The TES-HT device is a model of a temnographic device already in use in different settings for which no adverse events have been observed.
Any adverse events should be appropriately recorded and reported to the device production staff in the manner and timeframe stipulated in Article 90 of EU Regulation 201/745.

Data publication policy

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