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STUDY PROTOCOL

Open Access



Transcranial Doppler to guide early discharge after mild traumatic brain injury, the TRUST trial: study protocol for an open-label multisite noninferiority randomized controlled trial

Pierre Bouzat^{1*}, Tobias Gauss¹, Anais Adolle², Mathieu Roustit³, Jean-Luc Bosson⁴ and Karim Tazarourte⁵

Abstract

Background After mild traumatic brain injury (TBI), discharge from the emergency department (ED) relies on clinical examination and brain imaging, but triaging of these patients can be challenging in specific situations. Transcranial Doppler (TCD) after mild TBI may rule out early neurologic worsening. We hypothesize that patients with mild TBI and normal TCD can be safely discharged home immediately after the ED.

Methods This is a prospective, open-label, multisite, randomized controlled noninferiority trial. Eligible patients are mild TBI patients (Glasgow Coma Scale, GCS, 13–15 on admission) with minor lesions on brain CT scan or normal CT scan but one of the following risk factors: (1) GCS = 14 after CT scan; (2) alcoholic intoxication, (3) ongoing treatment with anticoagulants or anti-platelet therapy; (4) persisting nausea, vomiting, and/or headaches; or (5) early initial CT scan (< 4 h after TBI). Patients randomized in the intervention group have TCD within 12 h after TBI and can be immediately discharged from the ED if TCD is normal (diastolic flow velocity higher than 25 cm/s and pulsatility index lower than 1.25). Discharge of patients in the control group relies on clinical examination and brain imaging only. The primary outcome is the 3-month neurological outcome measured with the Extended Glasgow Outcome Scale (GOS-E). Secondary outcomes are the GOS-E at 1 month, the QOLIBRI (Quality of life after TBI) and EQ-5D-5L questionnaires at 1 month and 3 months after TBI, the Rivermead Post-Concussion Symptoms questionnaire at 1 month and 3 months after TBI, mortality within the first 3 months, the number of cerebral CT scans, length of stay in hospital, the number of thromboembolic events or diagnosed nosocomial infections, and the number of patients re-admitted to hospital in relation with the initial TBI. Inclusions have started in February 2020 and are expected to be complete by June 2025.

Discussion Transcranial Doppler in mild TBI patients may help immediate discharge from the ED after CT scanning.

Trial registration This study has been prospectively registered on clinical trial on June 14, 2019, NCT03989999.

Keywords Mild traumatic brain injury, Transcranial. Doppler, Neurologic outcome, Triage

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Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see <http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/>).

Title {1}	Transcranial Doppler to guide early discharge after mild traumatic brain injury, the TRUST trial: study protocol for an open-label multisite noninferiority randomized control trial.
Trial registration {2a and 2b}.	Clinical trial, NCT: NCT03989999
Protocol version {3}	Date: 10th of December 2024, Version 8.0
Funding {4}	TRUST is an investigator-initiated trial, supported by a non-profit grant from the French Ministry of Health (PHRCN-18-0217)
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Name and contact information for the trial sponsor {5b}	French Ministry of Health, Direction générale de l'offre de soins (DGOS), Sous-direction du pilotage de la performance des acteurs de l'offre de soins (PF), Bureau de l'innovation et de la recherche clinique (PF4), 14 avenue Duquesne—75350 Paris 07 SP
Role of sponsor {5c}	Funders have no role in trial design, conduction, data collection, nor analysis.

Introduction

Background and rationale {6a}

Traumatic brain injury (TBI) is a public health challenge of vast, but insufficiently recognized, proportions. Worldwide, more than 50 million people have a TBI each year, and it is estimated that about half the world's

population will have one or more TBIs over their lifetime [1]. Patients with mild TBI are the majority of patients admitted to the emergency department (ED) after head trauma [2]. Despite their reassuring presentation on admission, 5 to 20% of these patients will develop secondary neurologic deterioration in the first week after injury [3]. Neurological worsening adds to the burden of initial lesions and influences the post-traumatic neurologic outcome. It is estimated that up to 50% of mild TBI patients have an incomplete recovery defined as an Extended Glasgow Outcome Scale lower than 8 3 months after the insult [4, 5]. The triage of isolated mild TBI patients with no or minor lesions on initial CT scan remains poorly explored in the emergency department. Indeed, clinical examinations including the Glasgow coma score (GCS) and pupil size measurements are not accurate enough to detect patients at risk of neurologic worsening. While a cerebral CT scan has an excellent negative predictive value [6], the presence of minor brain lesions on CT correlates only weakly with subsequent neurologic evolution [7]. As a result, mild TBI patients with brain lesions on the initial CT scan are systematically directed to a standard ward, where neurologic monitoring consists of repeated CT scanning and/or clinical examinations [8]. Mild TBI patients with a normal CT scan on admission may be hospitalized as well (1) when their GCS after CT scan is lower than 15, (2) in cases of persisting nausea, vomiting or headache, (3) in cases of concomitant alcoholic intoxication, and (4) in cases of ongoing treatment with anti-platelet or anticoagulant [8]. This strategy leads to significant hospital stays with potential morbidity, whereas neurologic worsening rarely occurs. Therefore, in the emergency department (ED) the initial triage of patients with mild TBI is particularly challenging and additional tools are required to efficiently screen this population.

Transcranial Doppler (TCD) is a non-invasive technique that explores cerebral blood flow (CBF) velocities in the main basal cerebral arteries [9]. Blood flow in the basal cerebral arteries, as in the arteries of other vital organs (liver, kidney, and heart), has a prominent diastolic component. Diastolic flow velocity (FVd) reflects the degree of downstream vascular resistance, whereas systolic flow velocity (FVs) depends on upstream determinants, that is, cardiac output, ipsilateral carotid blood flow, and arterial blood pressure. Mean flow velocity (FVm) is the weighted flow velocity that takes into account the different velocities of the formed elements in the insonated blood vessel, and decreases with low CBF [10]. The flow velocity waveform is determined by the arterial blood pressure waveform, the visco-elastic properties of the cerebral vascular bed, and blood rheology. Therefore, in the absence of vessel stenosis or vasospasm,

shock, or profound anemia, the pulsatility index (PI) reflects the distal cerebrovascular resistance [11].

In patients with TBI, this technique can reveal a low diastolic flow velocity (FVd), a peaked waveform, and higher pulsatility index (PI) values during high vascular bed resistance induced by elevated intracranial pressure (ICP) or hypocapnia. TCD has been successfully used on admission to improve cerebral hemodynamics in patients with severe TBI [12]. In a previous single-center study including patients with normal (TCDB I) or mild brain lesions on an initial CT scan (TCDB II), we also found an association between TCD measurements on admission and neurological status a week following mild to moderate TBI. In this previous study, we found the thresholds of 1.25 and 25 cm/s respectively for the pulsatility index (PI) and diastolic blood flow velocity (FVd) to accurately predict early neurological worsening with 90% sensitivity and 91% specificity [13]. However, these cut-offs were proposed based on one single center study. External validation of TCD from multiple sites was performed in a multicenter observational study led by our group [14]. We further confirmed the additional value of TCD to predict neurologic worsening after mild-to-moderate TBI. More interestingly, TCD had excellent negative predictive value, suggesting that patients with normal TCD did not worsen within the first week after the trauma.

These encouraging results indicate that TCD, in combination with CT scan findings, could play a role in the management of patients with mild TBI. Whether a TCD-based strategy for the management of patients with mild TBI admitted in the ED is effective remains unknown. We hypothesize that patients with mild TBI and normal TCD can be safely discharged home immediately after the ED.

Objectives {7}

The main objective is to determine whether a TCD-based strategy is non-inferior to standard management in terms of the overall neurological outcome assessed with the Extended Glasgow Outcome Scale, GOS-E [15], at 3 months after mild TBI with no/minor lesions detected on a cerebral CT scan. A non-inferiority design was chosen because the tested intervention is expected to be no worse than usual care, while offering a faster and more cost-effective approach to discharge from the ED.

Secondary objectives are to assess the effects of a TCD-based strategy after a mild TBI on:

- 1- The overall neurological outcome at 1 month assessed with the GOS-E
- 2- The quality of life at 1 and 3 months after TBI assessed with QOLIBRI (Quality of life after TBI) [16] and EQ-5D-5L [17] questionnaires
- 3- Post-concussive syndrome at 1 and 3 months TBI assessed with the Rivermead Post-Concussion Symptoms questionnaire (“Rivermead positive” patients are patients with at least 3 symptoms rated ≥ 2 [18])
- 4- mortality at 3 months after TBI
- 5- Morbidity assessed by the number of cerebral CT scans (bounded at 1-month post-TBI), length of stay in hospital and the number of thromboembolic events or diagnosed nosocomial infections (bounded at 1-month post TBI).
- 6- Patient safety assessed with the number of patients readmitted to hospital in relation with the initial TBI (bounded at 1-month post-TBI).

Trial design {8}

TRUST is an open-label, multisite, noninferiority, randomized controlled trial, in which patients with mild TBI and no or minor brain lesions will benefit from usual care in the control group and from a TCD-based strategy with early discharge in the experimental group.

Methods: participants, interventions, and outcomes

Study setting {9}

Fourteen French academic hospitals and three non-academic French hospitals will participate in the study. All sites have ultrasound experience (at least 30% of the emergency physicians are certified in point-of-care ultrasonography). Half of the recruiting sites have already participated to our previous observational study on TCD in mild-to-moderate TBI [14]. Before the study starts, neurosurgeons of each participating center will be contacted and informed about the study design to obtain their agreement.

A list of all participating centers can be found on <https://clinicaltrials.gov>.

Eligibility criteria {10}

Inclusion criteria

1. Adult patients between 18 and 85 years
2. with mild TBI (Glasgow Coma Scale 13–15 on ED admission) with one of the following:
 - * Patient with minor cerebral lesion on initial CT scan (TCDBII, i.e., no midline shift, visible basal cisterns and hemorrhagic lesion < 25 cc) and GCS 15 after CT scan.
 - OR * Patient with normal initial CT scan (TCDB I) with at least one risk factor:

GCS=14 after CT scan, and/or alcoholic intoxication.

and/or ongoing treatment with anticoagulants or anti-platelet therapy.

and/or persisting Nausea, and/or vomiting and/or headaches.

Early initial CT scan (<4 h after TBI).

3. Possibility to perform a TCD within 12 h after the insult
4. Stable hemodynamic parameters with a blood pressure greater than 90 mmHg, an SpO₂ greater than 92% and a hemoglobin concentration greater than 8 g/dl, or, in the absence of measured hemodynamic parameters or the absence of biological sampling, mention in the patient's medical record of a stable clinical examination in terms of hemodynamics and respiratory function.
5. Possibility of home supervision by a third-party
6. Affiliation to social security system
7. Patient signed consent form

Non-inclusion criteria

1. CT scan classified as TCDB III–VI
2. Penetrating head-trauma
3. Patient under mechanical ventilation
4. Hospitalization required by post-traumatic extracranial lesion, intoxication (except alcoholic), pre-existing condition (including congenital hemostasis disorders) or social factors, at the discretion of the physician
5. Internal carotid dissection
6. Posttraumatic lesion in the posterior cerebral fossa
7. Subject in exclusion period of another study
8. Pregnant women, breastfeeding women
9. Subject under administrative or judicial control, under protection

Who will take informed consent? {26a}

After verification of eligibility criteria, the investigator will inform the subject about the research and answer all his/her questions about its objective, the nature of any constraints, the foreseeable risks, and the expected benefits. The investigator will also detail the rights of the subject in the context of biomedical research. Because all eligible patients can be discharged to home, written consent by the patient is mandatory in this study after information.

The appropriate copies of the information document and the consent form will then be distributed as follows:

- A copy of the information document and informed signed consent form will be given to the subject.
- The original copy will be kept by the investigator in a safe place, inaccessible to third parties.
- At the end of the inclusion period or at the latest at the end of the study, a copy of each consent form will be transferred by the clinical trial monitor to the Sponsor.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

This is not applicable since there is no biological collection. No ancillary study is planned.

Interventions

Explanation for the choice of comparators {6b}

The comparator will be standard of care after mild TBI according to French recommendations (updated in 2022 [8]). This is the more recent guideline for the management of mild TBI in the emergency department. Discharge is left at the discretion of the treating physician depending on the neurological status and CT scan findings.

Intervention description {11a}

After the initial cerebral CT scan, the patient will be included in the study if he/she satisfies inclusion criteria.

In the control group, patients will be managed according to the French recommendations for mild TBI management (guidelines published in 2012 updated in 2022) [8]. According to these recommendations, eligible patients may be hospitalized or discharged. Discharge is left at the discretion of the treating physician depending on the neurological status and CT scan findings.

Every therapeutic or diagnostic procedures recommended by the French guidelines for mild TBI are allowed in this group, except:

- Biomarkers including S-100 protein dosing is not recommended for the discharge decision and is therefore not allowed in this protocol.
- TCD before discharge is not permitted.

Patient management in the intervention group will follow our algorithm:

TCD will be performed within 12 h of the brain injury. Transcranial color-coded sonography is now the reference method to measure cerebral blood flow velocities in the two middle cerebral arteries (MCA) [10].

Any ultrasound device with a specific TCD mode can be used. First, the clinoid process of the sphenoid bone and the brain stem are identified. Color-coded sonography allows the identification of the circle of Willis. Then the M1 segment of the MCA is located and manual angle correction is applied to measure flow velocity (cm/s). According to previously published studies, bilateral tracings are recorded for at least 10 cardiac cycles after a 30-s stabilized recording period. Time averaged mean (FVm), systolic (FVs), and diastolic blood flow velocities (FVd) in cm/s and the pulsatility index [(FVs - FVd)/FVm] are calculated. The most pejorative value from both sides is taken into account, i.e., the lowest FVd and the highest PI.

All TCD recordings must be stored by the investigating center with the patient's medical records.

If TCD is normal (FVd > 25 cm/s and PI < 1.25), the patient will return home under third-party supervision. An advice sheet will be given to the patient according to the French guidelines, and another one will be sent to the general practitioner. If the initial cerebral CT scan is performed early (< 4 h after TBI), the CT scan should not be controlled before patient discharge.

If the TCD is abnormal (FVd ≤ 25 cm/s or PI ≥ 1.25) the patient will be considered at risk of neurologic worsening, but there is no recommendation regarding the type of ward, and the discharge from hospital is left at the discretion of the attending physician following French guidelines for mild TBI management.

No other diagnostic procedure is allowed in the ED (S-100 protein dosing is not allowed). All therapies recommended by the French guidelines for mild TBI are allowed in this group.

Criteria for discontinuing or modifying allocated interventions {11b}

TCD should not be abandoned in the TCD group. In case of difficulties, investigators are asked to find an experienced member of staff to perform the examination. In case of doubts on the quality or interpretation, a dedicated email box will be created to help make decision making compliant with the protocol. Anechoic patient with no TCD acoustic window will be treated according to current French recommendations and followed at 1 and 3 months. They are not excluded from the study.

Strategies to improve adherence to interventions {11c}

All sites have ultrasound experience (at least 30% of the emergency physicians are certified in point-of-care ultrasonography). Centers will be visited by a qualified personnel from the coordinating center before their participation in the study to check their ultrasound device,

TCD experience, and to give a retraining session on the TCD technique if necessary.

Only physicians with an adequate background in transcranial ultrasonography will be allowed to perform TCD. A dedicated email contact will be available to verify TCD recordings if necessary.

Relevant concomitant care permitted or prohibited during the trial {11d}

Every therapeutic or diagnostic procedures recommended by the French guidelines for mild TBI are allowed except:

- S-100 protein dosing is not recommended for the discharge decision and is therefore not allowed in this protocol.
- TCD before discharge is not permitted in the control group

Provisions for post-trial care {30}

Post-trial care is not planned. Should prejudice linked to study participation occur, financial compensation will be provided by the insurance (Société Hospitalière d'Assurances Mutuelles—SHAM, 18 rue Edouard Rochet, 69,372 Lyon Cedex 08, France) contracted by the promotor.

Outcomes {12}

The primary outcome, following recommendations of the Common Data Elements on TBI (https://commondataelements.ninds.nih.gov/TBI.aspx#tab=Data_Standards), is the overall neurological outcome assessed by the extended Glasgow outcome scale (GOS-E) at 3 months after TBI. The GOS-E will be dichotomized as complete recovery (GOS-E 8) vs. incomplete recovery (GOS-E 1 to 7).

Secondary outcomes are (1) the GOS-E at 1 month, (2) the QOLIBRI (Quality of life after TBI) and EQ-5D-5L questionnaires at 1 month and 3 months after TBI, and (3) the Rivermead Post-Concussion Symptoms questionnaire at 1 month and 3 months after TBI ("Rivermead positive" patients are patients with at least 3 symptoms rated ≥ 2) (18). All these scales will be dichotomized and assessed at indicated time points. (4) mortality within the first 3 months, (5) the number of cerebral CT scans (bounded at 1-month post-TBI), (6) length of stay in hospital, (7) the number of thromboembolic events or diagnosed nosocomial infections (bounded at 1-month post TBI), and (8) the number of patients re-admitted to hospital in relation to the initial TBI (bounded at 1-month post-TBI).

Participant timeline {13}

The participant timeline is reported in Fig. 1 and in Spirit Figure.

Patients who arrive in the ED after a mild TBI (GCS 13 to 15 upon admission) and undergo a cerebral CT scan will be considered eligible for the study.

Brain CT scan interpretation and TCDB classification

According to standard practice, the attending senior radiologist will interpret the cerebral CT scan. Patients

will be eligible if their initial CT scan satisfied the Traumatic Coma Data Bank (TCDB) I or II classification, i.e., TCDB I: normal CT scan or TCDB II: diffuse injury with cisterns present, no midline shift, and/or no high- or mixed-density lesions of at least 25 ml. Any questions about the TCDB criteria should be directed to the radiologist. In case of serious doubts regarding lesion volume $\leq 25 \text{ cm}^3$, following a precautionary principle, the patient should not be included. When hemorrhagic lesions are diagnosed, a senior neurosurgeon should be contacted to rule out any pending neurosurgery.

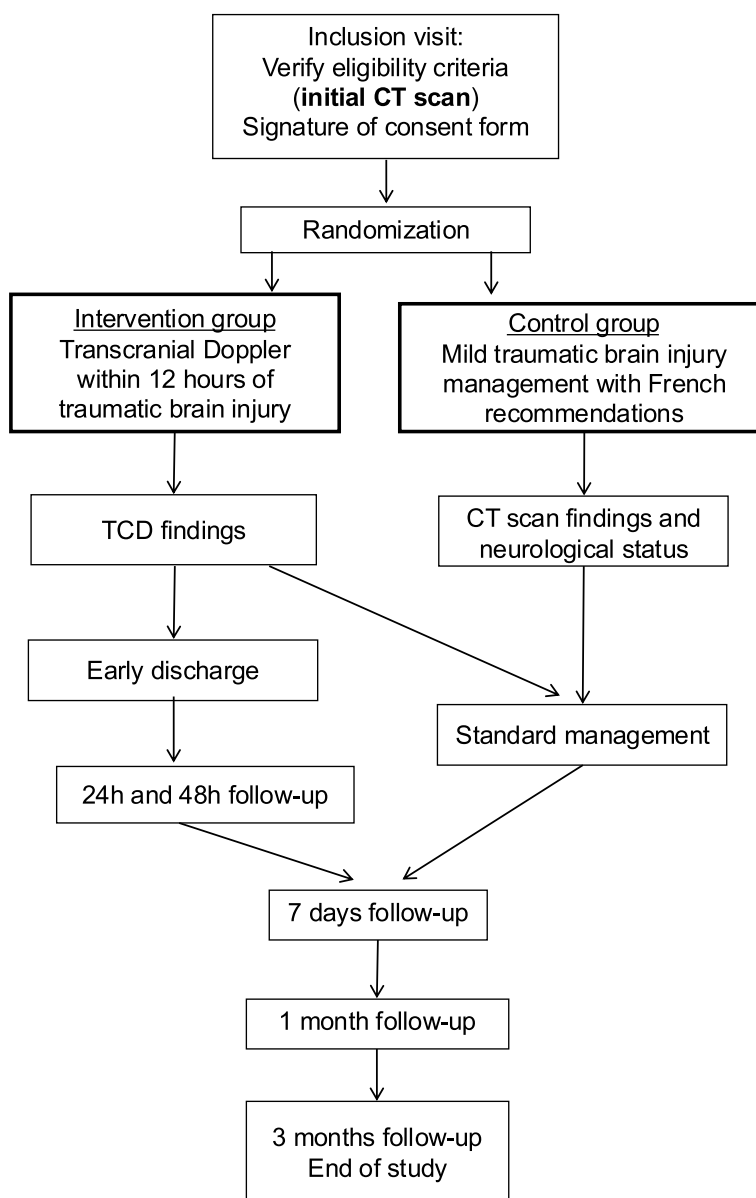


Fig. 1 Participant timeline

Control group

After inclusion, the patient will be managed according to the current French recommendations.

TCD group

TCD will be performed within 12 h after trauma.

If TCD is normal, the patient will be discharged at home with supervision by a third party. The investigator will have to pay special attention that the third party understands and agrees to the research terms. Surveillance procedures will be explained to the subject and their caregiver with the help of an information sheet. These procedures will be also sent to the patient’s general practitioner. Around 24 h and 48 h after discharge, the investigator or a designated person will carry out a medical follow-up by phone. The aim of this phone follow-up is to verify patient safety and propose appropriate care if necessary. Adverse events will be recorded.

If TCD is abnormal, the patient will be considered at risk of neurologic worsening. The type of ward and the discharge from the hospital are left to the physician’s discretion following French guidelines for mild TBI management, though TCD is a good indicator for relatively intensive neuro-monitoring.

In both groups, contact details of the patient and the treating physician will be sent to the coordinating center for blinded and centralized follow-up.

For the patients of both groups, around 7 days post TBI, the investigator or a designated person will carry out a medical follow-up by phone. The aim of this phone follow-up is to verify patient safety and propose appropriate care if necessary. Adverse events will be recorded.

At 1 month and 3 months, visits will be performed by the coordinating center. A designated person blinded to the randomization allocation of the including center will contact the patient by phone and carry out a phone interview, which will be recorded. He/she will ask the following sets of questions:

- The Extended Glasgow Outcome Scale (GOS-E) [19]
- The Rivermead Post-Concussion Symptoms questionnaire
- The QOLIBRI and EQ-5D-5L time-trade-off
- Questions about any Adverse Events (SAE)
- Questions about any hospital re-admission at 1 month only

For each re-admission, an anonymized medical record will be transferred to the coordinating center to assess, with a blinded review, whether re-admission is related to initial TBI, the occurrence of neurologic worsening, and the number of cerebral CT scans.

All questionnaires will be mailed to participants before the phone interview.

After the 3-month follow-up, patients will be able to participate in any other study.

Spirit Figure of the TRUST trial is shown below:

Timepoint	Study period						
	Enrolment	Allocation	Post-allocation			Close-out	
	-H12	0	H24*	H48*	D7	M1	M3
Enrolment:							
Eligibility screen	X						
Informed consent	X						
Pregnancy test ¹	X						
Allocation		X					
Intervention:							
Experimental group (TCD)		X					
Control group (standard)		X					
Assessments:							
Clinical parameters	X	X					
Paraclinical parameters	X						
Biological parameters	X						
Neurological assessments ²						X	X
Collection of AE/SAE			X	X	X	X	X

*Medical safety follow-up only in the TCD group

¹ Urinary pregnancy test can be performed

² Neurological assessments by phone interview and medical record analysis: GOS-E, EQ-5D-5L, RPQ, and QOLIBRI at 1 and 3 months

Sample size {14}

The sample size calculation is based upon the hypothesis that 20% of the population will have a GOS-E < 8 (i.e., incomplete recovery) at 3 months after TBI in the control group according to our two observational studies [13, 14]. The main objective is to show the non-inferiority of TCD-based strategy with early discharge, with a non-inferiority margin of 10% in the absolute between-group difference in the proportion of patients with a GOS-E < 8 at 3 months after TBI, i.e., a minimum of 70% of patients with complete recovery in the intervention group if our estimation of baseline risk in the control group is correct. The noninferiority margin was modified from 7.5% to 10% due to slow recruitment rate (modification approved in January 2025) and was set since incomplete recovery (Extended Glasgow Outcome Scale lower than 8 3 months after the insult) was reported in up to 30% of mild TBI patients in the recent literature [4, 5]. According to these hypotheses, a total

of 504 subjects would give the study 80% power to show the non-inferiority of the intervention, using a one-sided Z test with pooled variance and a one-sided alpha level of 2.5%. A total of 550 patients will be enrolled to account for 10% of protocol violations and losses to follow-up.

Recruitment {15}

All sites have ultrasound experience (at least 30% of the emergency physicians are certified in point-of-care ultrasonography). Before the start of the study, a feasibility questionnaire has circulated between all centers, and they were asked for potential inclusions in the study. They all agreed to include between one and two patients each month. Regular newsletters will be sent, and all participating centers are part of a national network for trauma care (GITE group).

Assignment of interventions: allocation

Sequence generation {16a}

Allocation will be predefined by the Department of Data Management and Biostatistical Analysis of the Grenoble Alps University Hospital according to one list per participating center, obtained with a random number generator. The randomization will be performed with blocks of random size.

Concealment mechanism {16b}

Allocation sequence is implemented through the eCRF by the computer after checking all inclusion and non-inclusion criteria in each participating center. Therefore, the investigating team cannot modify inclusion decision after allocation.

Implementation {16c}

One independent statistician generates the allocation sequence. Unblinded investigator (trained medical doctor in the emergency room) enrolls participants and assigns participants to interventions.

Assignment of interventions: blinding

Who will be blinded {17a}

The investigating team, trial participants, and care providers are unblinded during all the study. To overcome evaluation bias, the primary outcome and secondary outcomes at 1 and 3 months are centralized with blinded evaluation by outcome assessors in the coordinating center. Statisticians will also be blinded.

Procedure for unblinding if needed {17b}

Not applicable since the study is open-label.

Data collection and management

Plans for assessment and collection of outcomes {18a}

An electronic case report form (eCRF, CSONline by cleansight) will be created for the study. The persons

responsible for completing the eCRF will be clearly identified in the task delegation document.

Grenoble University Hospital is the sponsor of the study and is responsible for study oversight and quality controls. Data are collected by the investigating centers staff on the electronic case report form. Pseudo-anonymized data are stored by and belong to the sponsor. Investigating sites are monitored by a dedicated department, independent of the scientific team and investigators who designed the project. Centers are visited regularly to control patient data, ethics, patient safety, respect of masking protocol, and investigational products handling and storage. The primary endpoint is monitored in all patients.

All visits will be the subject of a monitoring report in writing. A copy will be sent to the Principal Investigator.

Plans to promote participant retention and complete follow-up {18b}

The primary outcome is collected at 3 months (GOSE). This endpoint is obtained through a dedicated questionnaire by the coordinating site. To limit loss to follow-up, several contacts are collected: general practitioner, patient's relatives with phone numbers and emails. Patient follow-up will be performed until 3 months.

Data management {19}

Data management will follow Grenoble-Alpes University Hospital procedures (data validation, blind review before database freezing, back up). A data entry dictionary will be made available to investigators and their teams, and traceability of requests for corrections and corrections made on the eCRF.

Confidentiality {27}

In accordance with the law (Articles L.1121-3 and R.5121-13 of the Public Health Code), persons with direct access to data will take all necessary precautions to ensure the confidentiality of information relating to experimental drugs, research, and the persons involved, particularly with regard to their identity and the results obtained. These persons, in the same way as the investigators themselves, are subject to professional confidentiality.

During or at the end of the interventional research, all patient data collected and transmitted to the sponsor by the investigators will be pseudo-anonymized. Under no circumstances should the names or addresses of the patients be exposed. Only the first letter of the subject's surname and first name will be recorded, accompanied by a coded number specific to the research, indicating the order of inclusion of the subjects.

The promoter will ensure each participant's approval through written informed consent and assure access

to their individual data and that no personal data are retained except for the bare minimum required for quality control.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

This is not applicable.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The statistical analysis plan will be written in accordance with the CONSORT statement for noninferiority trial analysis [20].

Primary outcome

Following international guidelines for interpretation of noninferiority trials [21, 22], the primary outcome analysis will be performed in the as randomized population, and the data set for the per-protocol analysis will be considered of equal importance to reach robust interpretation. The primary outcome analysis will be thus undertaken in the as randomized population including all randomly assigned patients except patients with consent withdrawn, and under the “per-protocol” principle, including all randomly assigned patients except patients with consent withdrawn, those who would not have been eligible for randomization according to the inclusion/non-inclusion criteria, those who were not managed according to the allocated strategy and those without data for the primary outcome.

The percentage of GOS-E < 8 3 months after the traumatic brain injury will be estimated in each group and tested using a one-sided test on the absolute proportion difference between groups with a limit delta of non-inferiority of 10% (comparison of the 97.5% one-sided confidence interval of the difference between the two proportions with the noninferiority cut-off).

Secondary outcomes

The GOS-E at 1 month will be compared between the two groups using an ordinal logistic regression (Fisher’s exact test will be first used to assess statistical significance).

The quality of life will be estimated using QOLIBRI and EQ-5D-5L scales at 1 month and 3 months. The Student *t*-test (or non-parametric Mann–Whitney test if normality conditions are not met) will compare the outcomes between the two groups.

For qualitative secondary outcomes: mortality, Rivermead Post-Concussion syndrome (“Rivermead positive”

patients are patients with at least 3 symptoms rated ≥ 2), thromboembolic events or diagnosed nosocomial infectious events, re-admission to hospital in relation to the initial TBI, we will use the Chi2 test (or Fisher’s exact test if the Cochran criterion is not met) to compare outcomes between the two groups.

Quantitative secondary outcomes: number of cerebral CT scans within hospital stay and length of stay in hospital will be compared between the two groups using a regression model fitted to the nature of the data (for example a Poisson regression or negative binomial regression).

The threshold for statistical significance will be 5% for all secondary objectives.

Interim analyses {21b}

No interim analysis is planned.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Planned subgroup analyses include analyses of the primary and secondary outcomes in the population with abnormal CT scan on admission.

In the intervention group, the relationship between TCD pattern and outcomes will also be tested.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

For the primary outcome in the as randomized population, missing data will be replaced considering a plausible missing at random assumption. The missing GOS-E at 3 months will be first replaced by its value at 1 month after traumatic injury, when available. If GOS-E is also missing at 1 month, multiple imputation by chained equations using a logistic regression model considering the main factors related to the outcome will be applied to replace missing values at 3 months.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

Information from the full protocol will be published in a peer-reviewed journal and the study is registered in <https://clinicaltrials.gov>. The relevant data analyzed during the development of this study protocol are available upon request from the corresponding author.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

Coordinating center: Grenoble University Hospital is the sponsor of the study and is responsible for study oversight and quality controls.

Steering committee: Pierre Bouzat, Tobias Gauss, Mathieu Roustit, Anais Adolle, Jean-Luc Bosson, Karim Tazarourte.

Data management team: Jean-Luc Bosson, MD, PhD, and Mathieu Roustit, MD, PhD, CHU Grenoble Alpes, Grenoble, France.

Composition of the data monitoring committee, its role and reporting structure {21a}

The sponsor appointed a data safety monitoring board (DSMB) that meets every year to analyze safety data (expected and unexpected adverse events). The DSMB is composed of members independent of the research and makes recommendations about protocol termination, modifications, or continuation without modifications.

Adverse event reporting and harms {22}

Adverse events are reported to the sponsor by investigating sites and are analyzed by the sponsor safety departments following European regulation on clinical trials on medicinal products.

Reporting of serious adverse events (SAEs)

To comply with regulatory requirements regarding the reporting of serious adverse reactions to health authorities, the investigator agrees to investigate each event, meet the required notification deadlines, and provide all necessary information for its analysis.

All serious adverse events (SAEs) must be reported by the investigator to the sponsor, regardless of their suspected causal relationship with the investigational strategy.

The investigator must complete and sign the SAE reporting form and attach copies of relevant laboratory test results, clinical examination reports, or hospitalization records related to the SAE. Pertinent negative results must also be included. All documents should be anonymized and must include the patient's code and study number. The initial report must be supplemented with any additional relevant information within 8 days.

All SAEs occurring in a participant enrolled in the study must be reported:

- From the date of signing the informed consent form,
- Throughout the entire follow-up period of the participant in the trial,
- After the end of the scheduled follow-up, if the event is considered possibly related to the research.

Expected serious adverse events (SAEs)

The following serious events are considered expected in this study: neurological deterioration, seizures, severe

nosocomial infections, thromboembolic events, and hospital readmissions related to traumatic brain injury (TBI).

Expected non-serious adverse events

All post-concussive symptoms are expected in this study. The most common include the following: headaches, dizziness, fatigue, irritability, anxiety, insomnia, attention deficits, memory impairment, psychomotor slowing, tinnitus, blurred vision, sensitivity to noise and light, reduced taste and smell, nausea, vomiting, and depression.

All SAEs will be reported in the trial publication.

Frequency and plans for auditing trial conduct {23}

An audit initiated at the request of the sponsor or health authorities may be conducted at any time by trained, independent inspectors. The purpose is to ensure the quality of the research, the validity of its results, and compliance with the law and regulations. The auditors/inspectors must have direct access to the source and medical data and to any useful document related to the conduct of the clinical study. The confidentiality of the data and the anonymity of the subjects will be respected.

The investigators agree to comply with the sponsor's and the competent authority's requirements for an audit or inspection of the research.

The audit may apply to all stages of the research, from the development of the protocol to the publication of results and the classification of data used or generated in the research.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Any substantial modification, i.e., any modification likely to have a significant impact on the protection of participants, validity and on the results of the research, on the quality and safety of the products tested, on the interpretation of the scientific documents that support the conduct of the research or on the methods of conducting the research, is subject to written amendment submitted to the sponsor; the latter must obtain, prior to its implementation, a favorable opinion from the ethics committee and an authorization from the national agency for drug safety. All amendments are validated by the sponsor and by all the research stakeholders concerned by the amendment before submission to the ethics committee and the national agency for drug safety. All amendments to the protocol must be made known to all investigators participating in the research. The investigators declare compliance with the protocol. Any amendment that modifies the management of the subjects or the benefits, risks and constraints of the research is the subject

of a new participant information note and a new consent form. The obtainment of informed consent follows the identical procedure as described above.

Dissemination plans {31a}

Results will be reported through scientific conferences and peer-reviewed publications following CONSORT recommendations [23]. All participants can be informed of the study results at the end of the trial on request. Any written or oral communication of research results must receive prior approval of the coordinating investigator and of any committee established for the research.

The publication of the main results must indicate in the acknowledgements the name of the sponsor, and investigators, methodologists, biostatisticians, and data managers who substantially participated in the research, and possibly members of the committees formed for the research, and the name of the funding source. The name of any person contributing to writing or editing the manuscript, if not already in the author list, should also be given in the acknowledgements. Publication will follow international standards of writing and publishing (The Uniform Requirements for Manuscripts of the ICMJE) and respect the criteria for authorship.

Discussion

This trial will test the impact of a TCD-based strategy on early discharge after mild TBI. The result of this trial may accelerate discharge of mild TBI patients from the ED in situations where physicians may have risk factors for early neurologic worsening. We will also have specific information regarding patients with minor lesions on brain CT, and the relationship of TCD pattern and neurologic outcome will be also explored.

Transcranial Doppler is mainly used after severe TBI to monitor brain hemodynamics [10]. Several therapeutic actions may be guided in this context. The use of TCD to rule out neurologic worsening after mild TBI is novel and only observational studies explored the association of TCD pattern and early neurologic deterioration. Thresholds for pulsatility index and diastolic blood flow velocity to predict neurologic worsening were set and validated in previous observational studies led by our group [13, 14]. Since TCD had an excellent negative predictive value in these studies, our primary research question will focus on the noninferiority of a TCD-based strategy for immediate discharge from the ED compared to standard of care using an overall assessment of neurologic outcome, i.e., the Extended Glasgow Coma Scale. There is no other ongoing randomized clinical trial on this topic registered in the clinicaltrials.gov website. The study will include patients with at least one risk factor to delay discharge from the ED such as minor lesions on brain CT scan or

normal CT scan but persisting symptoms, early imaging, or ongoing antiplatelet/anticoagulant therapies [8]. These situations are often considered as problematic for early discharge and emergency physicians currently discharge these patients without any additional safety measurement on top of clinical exam and brain imaging.

The strengths of this study are the multisite design, the blinded primary outcome assessment, and the selection of centers with TCD education, which will improve protocol adherence. We also acknowledge some limitations. First, investigators are not blinded, but masking the TCD intervention is not feasible. Second, the 10% noninferiority margin may be seen as large since incomplete recovery is expected to happen in 20% of the patients included in the control group. However, incomplete recovery is reported with large variation in the recent literature, and recalculation of the sample size with modification of the noninferiority margin was necessary due to a slow recruitment rate. Third, despite the selection of centers with TCD experience, we cannot exclude that some emergency physicians are not confident with the technique.

Trial status

The trial has obtained all authorizations, and recruitment started in February 2020. Protocol version reported here is version 8, December 10th, 2024. To date, 520 participants have been recruited. During the COVID-19 pandemic, fewer participants than expected have been recruited, which has brought about a recalculation of the sample size. Enrollment is expected to be completed by June 2025.

Abbreviations

DSMB	Data safety monitoring board
eCRF	Electronic case report form
ED	Emergency department
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale Extended
TCD	Transcranial Doppler
TCDB	Traumatic Coma Data Bank

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Authors' contributions {31b}

PB and KT designed the trial. JLB and MR developed the methodology and the statistical plan. TG and AA extensively revised the protocol. All authors approved the final version.

Funding {4}

TRUST is an investigator-initiated trial, supported by a non-profit grant from the French Ministry of Health (PHRCN 2018, n°18-0217).

Data availability {29}

Only the principal investigators, the DSMB, and the statisticians will have access to the final data set. There is no plan to share data but they are made available for audits and inspections. Anonymized patient data or full set can be made available on reasonable request. Patients or their relatives are informed that anonymized data can be shared with other groups or used for further studies and have the opportunity to refuse personal data sharing.

Declarations

Ethics approval and consent to participate (24)

Protocol was approved by the Institutional Review Board Ile de France V, on July 2, 2017, and authorized by the French competent authority (Agence Nationale pour la Sécurité du Médicament, ANSM) on June 17, 2019 (documents provided as additional files). The study is carried out following Good Clinical Practices, the principles of the Declaration of Helsinki, and European legislation. Written, informed consent to participate will be obtained from all participants.

Consent for publication (32)

Although it is not anticipated, owing to the trial design, publication of any personal information about a patient will require her/his consent.

Competing interests (28)

PB, TG, KT, MR, JLB, and AA have no conflict of interest to declare.

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