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The Finnish study of intraoperative irrigation versus drain alone after evacuation of chronic subdural haematoma (FINISH): a study protocol for a multicentre randomized controlled trial

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Complete List of Authors:	Tommiska, Pihla; Helsinki University Central Hospital, Department of Neurosurgery; University of Helsinki Rahul, Raj; Helsinki University Central Hospital, Department of Neurosurgery; University of Helsinki Schwartz, Christoph; University Hospital Salzburg, Paracelsus Medical University, Department of Neurosurgery; Helsinki University Central Hospital, Neurosurgery Kivisaari, Riku; Helsinki University Central Hospital, Department of Neurosurgery; University of Helsinki Luostarinen, T; Helsinki University Central Hospital, Department of Anesthesiology and Intensive Care; University of Helsinki Satopää, Jarno; Helsinki University Central Hospital, Department of Neurosurgery; University of Helsinki Taimela, Simo; Helsinki University Central Hospital, Orthopedics and Traumatology; University of Helsinki, Finnish Centre for Evidence-Based Orthopedics (FICEBO) Jarvinen, Teppo; Helsinki University Central Hospital, Department of Orthopaedics and Traumatology; University of Helsinki, Finland and Finnish Centre for Evidence-Based Orthopedics (FICEBO) Ranstam, Jonas; Lunds Universitet, Clinical sciences Frantzen, Janek; Turun Yliopistollinen Keskussairaala, Department of Neurosurgery; Helsinki University Central Hospital Posti, Jussi; Turku University Hospital, Department of Neurosurgery and Brain Injury Centre Luoto, Teemu M.; Tampere University Hospital, Department of Neurosurgery; Tampere University Leinonen, Ville; Kuopio University Hospital, Department of Neurosurgery; University of Eastern Finland School of Medicine Tetri, Sami; Oulu University Hospital, Department of Neurosurgery; Oulu University Faculty of Medicine Koivisto, Timo ; Kuopio University Hospital, Department of Neurosurgery; University of Eastern Finland School of Medicine Lönnrot, Kimmo; Helsinki University Central Hospital, Department of Neurosurgery; University of Helsinki
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STUDY PROTOCOL

TITLE: The Finnish study of intraoperative irrigation versus drain alone after evacuation of chronic subdural haematoma (FINISH): a study protocol for a multicentre randomized controlled trial

AUTHORS: Pihla Tommiska*[1], Rahul Raj*[1], Christoph Schwartz[1,2], Riku Kivisaari[1], Teemu Luostarinen[3], Jarno Satopää[1], Simo Taimela[4,5], Teppo Järvinen[4,5], Jonas Ranstam[6], Janek Frantzén[1,7], Jussi Posti[7], Teemu Luoto[8], Ville Leinonen[9,10], Sami Tetri[10], Timo Koivisto[9], Kimmo Lönnrot[1,4]

1) Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
2) Department of Neurosurgery, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria
3) Division of Anaesthesiology, Department of Anaesthesiology, Intensive Care and Pain Medicine, Helsinki University Hospital, Helsinki, Finland
4) Finnish Centre for Evidence-Based Orthopedics (FICEBO), University of Helsinki and Helsinki University Hospital, Helsinki, Finland
5) Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
6) Department of Clinical Sciences, Lund University, Lund, Sweden
7) Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Centre, Turku University Hospital and University of Turku, Turku, Finland
8) Department of Neurosurgery, Tampere University Hospital and Tampere University, Tampere, Finland
9) Department of Neurosurgery, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland
10) Unit of Clinical Neuroscience, Neurosurgery, University of Oulu and Medical Research Center, Oulu, Finland

*equal contribution

Correspondence:
Rahul Raj, MD, PhD
Department of Neurosurgery
University of Helsinki and Helsinki University Hospital
Topeliuksenkatu 5, P.B. 266, 00029 HUS, Helsinki, Finland
Phone: +358504272516
Email: rahul.raj@hus.fi

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Full author list:

Pihla Tommiska, BM, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, pihla.tommiska@helsinki.fi

Rahul Raj, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, rahul.raj@hus.fi

Christoph Schwartz, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Department of Neurosurgery, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria, c.schwartz@salk.at

Riku Kivisaari, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, riku.kivisaari@hus.fi

Teemu Luostarinen, MD, PhD, Division of Anaesthesiology, Department of Anaesthesiology, Intensive Care and Pain Medicine, Helsinki University Hospital, Helsinki, Finland. teemu.luostarinen@hus.fi

Jarno Satopää, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, jarno.satopaa@hus.fi

Simo Taimela, MD, PhD, Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Finnish Centre for Evidence-Based Orthopedics (FICEBO), University of Helsinki and Helsinki University Hospital, Helsinki, Finland, simo.taimela@helsinki.fi

Teppo Järvinen, MD, PhD, Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Finnish Centre for Evidence-Based Orthopedics (FICEBO), University of Helsinki and Helsinki University Hospital, Helsinki, Finland, teppo.jarvinen@helsinki.fi

Jonas Ranstam, PhD, Department of Clinical Sciences, Lund University, Lund, Sweden, jonas.ranstam@mdas.se

Janek Frantzén, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Centre, Turku University Hospital and University of Turku, Turku, Finland, janek.frantzen@tyks.fi

Jussi Posti, MD, PhD, Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Centre, Turku University Hospital and University of Turku, Turku, Finland, jussi.posti@utu.fi

Teemu Luoto, MD, PhD, Department of Neurosurgery, Tampere University Hospital and Tampere University, Tampere, Finland, teemu.luoto@pshp.fi

Ville Leinonen, MD, PhD, Department of Neurosurgery, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland and Unit of Clinical Neuroscience, Neurosurgery, University of Oulu and Medical Research Center, Oulu, Finland, ville.leinonen@kuh.fi

Sami Tetri, MD, PhD, Unit of Clinical Neuroscience, Neurosurgery, University of Oulu and Medical Research Center, Oulu, Finland, sami.tetri@ppshp.fi

Timo Koivisto, MD, PhD, Department of Neurosurgery, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland, timo.koivisto@kuh.fi

Kimmo Lönnrot, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Finnish Centre for Evidence-Based Orthopedics (FICEBO), University of Helsinki and Helsinki University Hospital, Helsinki, Finland, kimmo.lonnrot@hus.fi

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04203550
Date of registration in primary registry	December 18, 2019
Secondary identifying numbers	N/A
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Contact for public queries	Kimmo Lönnrot, MD, PhD; email: kimmo.lonnrot@hus.fi; address: Töölö Hospital, Topeliuksenkatu 5, PB 266, 00029 HUS, Finland; phone: +358-50-427-0270
Contact for scientific queries	Kimmo Lönnrot, MD, PhD; email: kimmo.lonnrot@hus.fi; address: Töölö Hospital, Topeliuksenkatu 5, PB 266, 00029 HUS, Finland; phone: +358-50-427-0270
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Scientific title	The Finnish study of Intraoperative Irrigation versus drain alone after evacuation of chronic Subdural Haematoma (FINISH): A study protocol for a multicentre randomised controlled trial
Countries of recruitment	Finland
Health condition(s) or problem(s) studied	Chronic subdural haematoma (CSDH)
Intervention(s)	Active comparator: Irrigation (i.e. the subdural space is irrigated by repeated rinsing with body temperature saline solution with a syringe and blunt needle until surgeon considers exudate to be

Data category	Information
	clear. The minimum volume of irrigation is 200 ml per operated side. A subdural drain is inserted 3–5 cm underneath the skull and parallel to it and kept as a passive drain for 48 hours) Experimental: No irrigation (i.e. after a small incision of the dura, a subdural drain is inserted 3–5 cm underneath the skull and parallel to it and kept as a passive drain for 48 hours)
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: All Accepts healthy volunteers: No Inclusion criteria: - Patients with a symptomatic unilateral or bilateral CSDH requiring burr-hole evacuation - Predominantly hypodense or isodense on imaging (CT/MRI) - Clinical symptoms correlating with CSDH - Patients with bilaterally operated CSDHs will be treated with the same protocol on both sides and analysed as a single study participant Exclusion criteria: - CSDH requiring surgical treatment other than burr-hole evacuation (e.g. craniotomy) - CSDH in a patient who has a cerebrospinal fluid shunt - Patients who have previously undergone any intracranial surgery - Comatose patients (GCS 8 or lower) with absent motor responses to painful stimuli; decerebrate or decorticate posturing - Patient's postoperative cooperation is suspected to be insufficient for drain usage (i.e. disoriented or semiconscious patient) - Patient has a haematogenic malignancy that has been actively treated within the previous five years - Patient has a central nervous system tumour or malignancy - Patient has an acute infection requiring antibiotic treatment - Patient has a high risk of life-threatening thrombosis (e.g. recent coronary stent, intracranial stent, recent pulmonary embolism, low pressure cardiac valve replacement [mitral- or tricuspid valve replacement]) and discontinuation of antithrombotic medication is not recommended
Study type	Prospective, randomised, controlled, parallel group, non-inferiority trial Allocation: Randomised Intervention model: Parallel assignment

Data category	Information
	Intervention model description: Prospective, randomised, controlled, parallel group, non-inferiority trial Masking: Quadruple (participant, care provider, investigator, outcomes assessor) Primary purpose: Treatment
Date of first enrolment	January 2020
Target sample size	540 participants
Recruitment status	Recruiting
Primary outcome(s)	Rate of reoperations of ipsilateral chronic subdural hematoma (time frame: 6 months from randomization)
Key secondary outcomes	Change of Modified Rankin Scale (time frame: 6 months), rate of mortality (time frame: 6 months), duration of operation, hospital length of stay, rate of adverse events (time frame: 6 months), change in volume of CSDH between baseline and 2 months

ABSTRACT

Introduction: Chronic subdural haematomas (CSDHs) are one of the most common neurosurgical conditions. The goal of surgery is to alleviate symptoms and minimize the risk of symptomatic recurrences. In the past, re-operation rates as high as 20–30% were described for CSDH recurrences. However, following the introduction of subdural drainage, re-operation rates dropped to approximately 10%. The standard surgical technique includes burr-hole craniostomy, followed by intraoperative irrigation and placement of subdural drainage. Yet, the role of intraoperative irrigation has not been established. If there is no difference in recurrence rates between intraoperative irrigation and no irrigation, CSDH surgery could be carried out faster and more safely by omitting the step of irrigation. The aim of this multicentre randomised controlled trial is to study whether no intraoperative irrigation and subdural drainage results in non-inferior outcome compared to intraoperative irrigation and subdural drainage following burr-hole craniostomy of CSDH.

Methods and Analysis: This is a prospective, randomised, controlled, parallel group, non-inferiority multicentre trial comparing single burr-hole evacuation of CSDH with intraoperative irrigation and evacuation of CSDH without irrigation. In both groups, a passive subdural drain is used for 48 hours as a standard of treatment. The primary outcome is symptomatic CSDH recurrence requiring re-operation within six months. The predefined non-inferiority margin for the primary outcome is 7.5%. To achieve a 2.5% level of significance and 80% power we will randomise 270 patients per group. Secondary outcomes include modified Rankin Scale, rate of mortality, duration of operation, length of hospital stay, adverse events, and change in volume of CSDH.

Ethics and Dissemination: The study was approved by the institutional review board of the Helsinki and Uusimaa Hospital District (HUS/3035/2019 §238) and duly registered at ClinicalTrials.gov. We will disseminate the findings of this study through peer-reviewed publications and conference presentations.

Trial Registration Number: NCT04203550

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a multicentre nationwide prospective randomised controlled trial, with a pragmatic trial design to increase generalizability.
- The study was designed in collaboration with patient organisation experts.
- The health care system in Finland facilitates the follow-up of patients (particularly with respect to our primary outcome, symptomatic CSDH requiring reoperation) as CSDH surgery is centralized to the five neurosurgical departments participating in the trial.
- Although the surgeon performing the surgery obviously cannot be blinded to the group assignment, we have tried to maintain the masking of the treatment allocation by not disclosing it in the health care records.

INTRODUCTION

Chronic subdural haematoma (CSDH) is the most common type of intracranial haemorrhage and one of the most common clinical diagnoses necessitating neurosurgical treatment. CSDHs are typically caused by minor head trauma and consecutive tearing of bridging veins, leading to a haemorrhage in between the dura mater and the arachnoid membrane. The delay in the actual diagnosis of CSDH can be quite substantial due to the difficulty of the diagnosis in the early phase when neurological symptoms – such as progressive headache, mental deterioration or confusion, or deterioration of the patient's overall health – are quite unspecific. However, when the disease progresses and causes more direct compression to the underlying brain tissue, more specific progressive neurological signs ensue, including motor and sensory deficits, dysphasia and epileptic seizures, and the diagnosis becomes more evident. If left untreated, CSDH may also lead to loss of consciousness or even death. The definite diagnosis of CSDH is most commonly based on computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. On a CT scan, CSDH is usually of hypo- or isodense character and will feature a concavo-convex shape between the skull and the cortex.

For symptomatic CSDHs, the treatment is operative. The mainstay of treatment includes burr-hole craniostomy and intraoperative intracranial irrigation followed by subdural drainage [1]. With current treatment strategies, the recurrence rate after CSDH treatment is approximately 10% [2]. Low risk of bias evidence exists on the role of subdural drain in recurrence rate reduction but the role of intraoperative irrigation is more controversial. Our literature review revealed a total of ten studies assessing the effect of intraoperative irrigation: only one study employed a randomised study protocol [3] while the others were retrospective analyses. Sample sizes ranged from 56 to 186 patients, and the most commonly used outcome was the rate of haematoma recurrence. Of these ten studies, two studies found that intraoperative irrigation was associated with a significantly lower recurrence rate in comparison to no intraoperative irrigation [4,5], six studies found no difference in recurrence rates between intraoperative and no intraoperative irrigation [3,6–10], and two studies found that no intraoperative irrigation was associated with a significantly lower recurrence rate compared to irrigation [11,12].

It is possible that intraoperative irrigation is an unnecessary prolongation of the surgical procedure, thereby increasing the risk for infections, rebleeding and the stress levels of patients undergoing the procedure under local anaesthesia. There is also evidence to suggests that irrigation *per se* may be harmful: There are reports of increased risk of treatment-associated morbidity and complications such as postoperative pneumocephalus [9,11,13] and also of direct irrigation-induced intracerebral and subarachnoid haemorrhage [14].

We designed a pragmatic, parallel group, randomised, controlled multicentre non-inferiority trial to compare the use of intraoperative irrigation with no intraoperative irrigation for the operation of symptomatic CSDH (by burr-hole craniostomy and subdural drainage for 48 hours). We hypothesise that a treatment that involves no intraoperative irrigation results in non-inferior outcome compared to a treatment that involves intraoperative irrigation. Non-inferiority of the new treatment (no irrigation) with respect to the gold standard treatment (irrigation) is of interest on the premise that the new treatment has some other advantages, such as shorter operative time and therefore reduced stress to patient, reduced cost, fewer adverse events (harm) and technically more simple [15]. We consider non-inferiority proven if the rate of recurrence in the no-irrigation group is within the pre-defined non-inferiority margin of the rate observed in the irrigation group together with no significantly increased risk of harm.

MATERIALS AND ANALYSIS

Overview of study design

FINISH is a multicentre, prospective non-inferiority randomised controlled trial, with the primary objective to compare intraoperative irrigation to no irrigation in the treatment of CSDH by single burr-hole craniostomy and subdural drainage. Except for randomisation to irrigation versus no irrigation, the management of study participants will not differ. Eligible participants are block randomised in a 1:1 allocation rate to one of two arms: i) intraoperative irrigation, or ii) no intraoperative irrigation.

The study is registered at ClinicalTrials.gov (NCT04203550) and this protocol has been written according to the Standard Protocols Items: Recommendations for Interventional Trials (SPIRIT) guidelines for reporting a randomised controlled trial study protocol (the SPIRIT Figure and Checklist are available as Additional File 1) [16].

Study settings

Participating sites are the neurosurgical departments at Helsinki University Hospital (Helsinki, Finland), Kuopio University Hospital (Kuopio, Finland), Tampere University Hospital (Tampere, Finland), Turku University Hospital (Turku, Finland) and Oulu University Hospital (Oulu, Finland). All these five units are tertiary referral centres and the only units delivering neurosurgical care in Finland.

Participant selection and recruiting process

We will screen all patients who are referred for CSDH surgery to the aforementioned departments of neurosurgery for trial eligibility. A standard clinical examination and a brain CT or MRI examination will be performed. Patients with clinical and imaging findings consistent with a diagnosis of symptomatic CSDH and considered to benefit from operative treatment of CSDH by single burr-hole evacuation will be asked to participate in the trial.

Inclusion criteria

- Patients with a symptomatic unilateral or bilateral CSDH requiring burr-hole evacuation
    - Predominantly hypodense or isodense on imaging (CT/MRI)
    - Clinical symptoms correlating with the CSDH
    - Patients with bilaterally operated CSDHs will be treated with the same protocol on both sides and analysed as a single study participant
- Patients older than 18 years of age

Exclusion criteria

- CSDH requiring surgical treatment other than burr-hole evacuation (e.g. craniotomy)
- CSDH in a patient who has a cerebrospinal fluid shunt
- Patients who have undergone any prior intracranial surgery
- Comatose patients (GCS 8 or lower) with absent motor responses to painful stimuli; decerebrate or decorticate posturing
- Patient's postoperative cooperation is suspected to be insufficient for drain usage (i.e. disoriented or semiconscious patient)
- Patient who has received active treatment for a haematogenic malignancy within the previous five years
- Patient with a central nervous system malignancy or tumour that may cause the patient's current symptoms or may interfere with the operation. For example, a small incidental meningioma without associated brain oedema, not in the vicinity of the planned burr-hole, is not an exclusion criterion.
- Patient has an acute infection that requires antibiotic treatment
- Patient has a high risk of life-threatening thrombosis (e.g. recent coronary stent, intracranial stent, recent pulmonary embolism, low pressure cardiac valve replacement [mitral- or tricuspid valve replacement]) and discontinuation of antithrombotic medication is not recommended

Informed consent

At the first appointment in the emergency department or the neurosurgical ward, the attending neurosurgeon will provide the patients with detailed written and oral information on the trial and ask patients to sign an informed consent form. Withdrawal from the study is possible at any time, without affecting the course of conventional treatment, in accordance with the latest version of the declaration of Helsinki 2013 [17]. Due to the nature and emergency aspects of the disease (mass effect on the brain causing confusion and disorientation, lowered level of consciousness requiring urgent surgery), some patients will not be able to give written consent prior to randomisation. If the patient is unable to give written consent prior to the

randomisation, delayed consent will be sought. In these cases, oral consent will be obtained from a close relative after providing information regarding the trial and the patient is randomised. Following randomisation, written consent will primarily be obtained from the patient. In case of the patient being unable to give written consent due to neurological disability, written consent is obtained from a close relative. In these cases, the close relative has the right to withdraw the patient's consent at any time. Patients who are eligible for the trial but are not willing to undergo randomisation will be asked to be included in a simultaneous, pragmatic follow-up cohort.

Participants will be asked to sign the local Biobank agreements in order to collect and store subdural fluid samples (see below) and two venous blood samples (2 x 10 ml).

Collected data

We will document data in the electronic Case Report Form (eCRF) preoperatively, intraoperatively and within 48–72h postoperatively, as well as at 6 weeks (±2 weeks) and at 6 months (see Table 1 for table of events). All patients' preoperative and postoperative head CTs or MRs images will be sent to the Picture Archiving and Communication System (PACS) of the methods centre (Helsinki University Hospital) for analysis. Ten percent of all images will be double read by independent assessors blinded to other patient information. To preserve confidentiality, all participants are allocated a unique study identifier during the recruitment process, which is used on all data collection forms. All study documentation is held in secure offices, and the study researchers operate according to a signed code of confidentiality. All data are entered into a password-secured database by the data managers.

Surgical technique

Current management of CSDHs at all participating centres includes single burr-hole evacuation with intraoperative irrigation followed by passive subdural drainage. As a routine, all burr-hole craniostomies are performed under local anaesthesia, often combined with intravenous sedation with benzodiazepines and/or opioids during the operation. General anaesthesia is only used if the neurosurgeon or the anaesthesiologist considers it unsafe to perform the procedure under local anaesthesia. Routine preoperative antibiotic is given according to local protocols (normally a second-generation cephalosporin 30–60 min prior to incision). Typically, the surgeon drills one 14-mm burr hole over the maximum convexity of the CSDH. In case of bilateral CSDHs, the surgeon performs the same procedure on both sides. If irrigation is utilized, after opening the dura, the surgeon irrigates the subdural collection with warm (body temperature) Ringer's lactate saline until rinsing

appears clear or at least 200 ml (in case of bilateral CSHD, 200 ml per side, i.e. 400 ml total). After that, the surgeon will insert the subdural drain 3–5 cm deep and parallel to skull. The position of the drain (anterior, posterior) is left to the discretion of the physician. Burr hole covers or haemostatics are not routinely used (e.g. Spongostan®, Tachosil®). The type of subdural drain is not standardized, but all study centres use 10F drains. Following drain insertion, the distal end is tunnelled approximately 4–5 cm from the incision and connected to a passive ventricular drainage bag (through a non-return valve) and the skin incision is closed in two layers (normally is absorbable 3-0 suture for subcutis/galea and non-absorbable 4-0 suture for skin). The drain is fixed to the skin in a secure way. The drain-to-skin fixation technique is left to the discretion of the operating surgeon. The drainage bag is positioned at bed level. The duration of subdural drainage is 48 hours (±12 hours) [18,19]. Patient mobilization is allowed during drainage. Prophylactic antibiotics during drainage are not routinely used.

Randomisation

Patients will be randomised in a 1:1 allocation ratio stratified only by study centre. We will use a random block randomisation technique, with a random block size of 4, 6 or 8. A member of the FINISH study group will carry out randomisation when the patient is at the OR at the beginning of the operation. The randomisation will occur just prior to skin incision. The randomisation is a built-in property in the online eCRF form system used in the trial (provided by Granitics Inc., Espoo, Finland).

Intervention

Irrigation group (IR)

A burr-hole craniostomy is performed as described earlier. The dura is opened sharply and 10 ml of subdural exudate is aspired with blunt aspiration needle for a CSDH sample to be stored at -75°C to be used for later analysis. Subdural space is irrigated by repeated rinsing with body temperature saline solution with a syringe and blunt needle until surgeon considers exudate to be clear. Minimum volume of irrigation will be 200 ml per operated side. The subdural drain is inserted 3–5 cm underneath the skull and parallel to it. Thereafter, operation is completed as described earlier. The total volume of irrigation as well as the duration of operation is recorded.

No-irrigation group (N-IR)

A burr-hole craniostomy is performed as described earlier. A small incision in the dura is made and 10 ml of subdural exudate is aspired with a blunt aspiration needle for a CSDH sample to be stored at -75°C to be used for later analysis. The subdural drain is inserted approximately 3–5 cm underneath the skull and parallel to it. Thereafter, the operation is completed as described earlier. The duration of the operation is recorded.

Blinding

Due to the nature of the treatment, it is not possible to blind the surgeon and OR staff from the treatment allocation. Measures to minimize bias include:

- The randomisation is timed as closely as possible to the time of surgery (just prior to skin incision)
- The patient will not be informed of treatment allocation
- Treatment allocation will not be documented in medical records (i.e. all personnel participating in patient care after the operation will be blinded to allocation)
- The study group members collecting postoperative data, outcome data, imaging data and performing the statistical analyses will be blinded to treatment arm over the entire course of the trial, until the data analyses are carried out.
- The primary and secondary outcome measures (see below) are all evaluated in blinded matter, i.e. the outcome assessor will be blinded with regard to treatment allocation

Emergency unblinding will occur only in exceptional circumstances when requested by the patient's clinical team (e.g. need to treat a serious adverse event [SAE]), when knowledge of the actual treatment is essential for further management of the patient.

Compliance to treatment allocation and possible crossover

- If the patient is randomised to the IR group and the intracranial irrigation volume is between 1 ml and 200 ml, the patient is not considered a crossover.
- If the patient is randomised to the IR group and the intracranial irrigation volume is 0 ml, the patient is considered a crossover (belongs to the N-IR group).
- If the patient is randomised to the N-IR group and 1 ml to 199 ml of intracranial irrigation is used, the patient is not considered a crossover.

- If the patient is randomised to the N-IR group and ≥200 ml of intracranial irrigation is used, the patient is considered a crossover (belongs to the IR group).
- In case of intervention failure (e.g. not being able to insert subdural drain, intended or unintended drain removal before 36h), the patient is not considered a crossover.

Primary outcome measure

Our primary outcome measure is the rate of reoperations of ipsilateral CSDHs within 6 months.

Indication for reoperation and reoperation technique

The decision to proceed to reoperation is made by the treating neurosurgeon and will be made by the same indications as the primary operation (i.e. symptom recurrence or insufficient resolution of clinical symptoms correlating to imaging findings [CT or MR imaging] of CSDH). All reoperations will be conducted according to the current standard (i.e. burr-hole with irrigation and subdural drain placement). In case of recurrence requiring reoperation, unblinding will not occur automatically, only in cases when the neurosurgery team treating the patient considers this information necessarily for optimal care of the patient.

Secondary outcome measures

The study is not powered for secondary outcome measure comparisons and these outcomes (analyses) will be considered exploratory. The secondary outcomes include:

1. Modified Rankin Scale at 6 months after operation
2. Mortality within 6 months of operation
3. Duration of the operation
4. Hospital length of stay (index hospital and need for further care)
5. CSDH volume reduction at 2 months after operation

Safety endpoints

Safety endpoints within 6-months of operation, including the number and severity of adverse events (AE) and procedure related adverse events (PRAE). Adverse events are categorized as serious adverse events

(SAE) and minor adverse events (MAE). Procedure related (severe and minor) adverse events will be reported separately.

SAE are defined as any inappropriate medical occurrence or effect that results in death, is life-threatening, requires hospitalization or prolongation of an existing inpatient hospitalization, results in persistent or significant disability or incapacity, or is another important medical event.

- Life-threatening in the definition of SAE refers to an event when the patient was at risk of death at the time of the event and does not refer to an event where the event might have hypothetically caused death. Prolonged hospitalization due to delayed transfer will not be considered an AE or SAE.

  Examples of SAEs are death, acute myocardial infarction, pulmonary embolism, systemic infection, acute cerebral infarction (PRAE), intracranial infection (PRAE), epileptic seizures (PRAE) and acute postoperative intracranial haematoma (PRAE).

MAE are defined as clinically mild manifestations, referent to that the patient might be aware of the event or symptom but the event or symptom is easily tolerated by the patient.

- Examples of MAEs are local wound infection manageable with oral antibiotics (PRAE), abnormal skin bleeding from the wound (PRAE), other local infection manageable with oral antibiotics and deep venous thrombosis not causing pulmonary embolism.

Follow-up

The follow-up period is 6 months. We will arrange a clinical outpatient follow-up visit for all patients at 4–8 weeks postoperatively (6 weeks ±2 weeks). Before that, a postoperative brain CT will be performed. If the patient was preoperatively using any form of antithrombotic medication, the medication is not routinely restarted without reasonable clinical indication before the control brain CT. All recurrences requiring surgery within 6 months and complications within 6 months will be recorded. At 6 months, functional outcome (mRS) will be assessed by a FINISH study group member by phone interview. Further, for each patient, mortality will be verified through the Finnish Official Cause-of-Death Statistics at 6 months. This statutory register is virtually 100% complete because each death, its associated official death-certificate, and the corresponding person information in the Finnish computerized population register are cross-checked.

Sample size

The trial is designed to ascertain whether drain without irrigation is non-inferior to drain with irrigation, with the rate of reoperations of ipsilateral CSDHs within 6 months as the primary outcome. We based the standard rate of reoperations (9.6%) on the results from a recent Cochrane review that reported the recurrence rates after CSDH evacuation followed by subdural drainage in six RCTs with more than 30 patients per treatment arm [2]. This yielded a maximum allowed margin of 9.0% to achieve non-inferiority. Following a consensus meeting with the trial investigators, the non-inferiority margin was lowered to 7.5%. Thus, with a non-inferiority margin of 7.5%, a 2.5% level of statistical significance (alpha = 0.025) and an 80% power (beta = 0.20), we will need 243 patients per study group [20]. Accounting for a drop-out rate of 10%, required group size increases to 270 per study group. Accordingly, we set the recruitment target at 540 patients.

Data management

All study data will be stored in an eCRF provided by Granitics Inc (Espoo, Finland). Data are entered locally by the local research team. Upon receipt of the data, the FINISH personnel, blinded to the group allocation, will make a visual check of the data and query all missing, implausible and inconsistent data. Hospital patient records will also be utilized to collect missing data and to interpret inconsistent or implausible data. Participant files will be maintained in storage (both in electronic and paper format) at the coordinating centre for a period of 15 years after completion of the study.

Data sharing

Data generated by our study will be made available as soon as possible and will be available upon reasonable request. Data access requests will be reviewed by the FINISH steering group. Requestors will be required to sign a Data Access Agreement. Only anonymized data will be shared.

Statistical analysis

The statistical analysis will be performed both according to intention-to-treat (ITT) and per protocol (PP) principles. We will claim non-inferiority of single burr-hole evacuation without irrigation and subdural drainage only if this outcome is supported both by the ITT and the PP analysis. The ITT analysis will be performed using the full analysis set (FAS), defined as all randomised patients in the groups allocated to by the randomisation. No exclusions other than caused by missing information will be made. No imputation will take place. The PP

analysis will be performed on the subset of FAS that is compliant with the protocol have a completed treatment, available measurements, and neither major protocol violations nor entry criteria violations.

Summary statistics will be presented for both groups. Continuous variables will be presented in terms of mean values or medians with standard deviations and interquartile ranges, respectively. Categorical variables will be presented with relative frequencies in percent.

The results from the statistical analysis will be considered to support a claim of non-inferiority if the upper limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) excludes a difference in the primary endpoint in favour of the irrigation group of more than 7.5%. The centre stratification of the randomisation will be accounted for in the calculation of the confidence interval.

Exploratory analyses of secondary and other binary endpoints will be performed using the Chi-squared test or logistic regression analysis. Continuous outcomes will be analysed using Student's t-test or ANCOVA. Potential effect modifiers (patient age, unilateral versus bilateral CSDH, use of antithrombotic medication, preoperative mRS and preoperative clinical status, haematoma density, haematoma size and presence of membranes on preoperative imaging) will be analysed by including interaction terms in statistical models.

The primary endpoint will be investigated as described above using a confidence interval, which is equivalent to using a non-inferiority test with a one-sided p-value of 0.025 (or a two-sided of 0.05). The statistical testing of other endpoints will also be performed using a two-sided significance level of 0.05. The statistical analysis will be performed using appropriate statistical software packages.

Prior to the statistical analysis, a statistical analysis plan will be finalised and an independent statistician will approve a dataset with sufficient data quality for the statistical analysis. Another statistician blinded to treatment arm will perform the analyses.

Blinded data interpretation

As in previous studies [21,22], we will interpret the results of the trial according to a blinded data interpretation scheme [23]. In brief, an independent statistician will provide the Writing Committee of the FINISH trial with blinded results from the analyses with the groups labelled group A and group B. The Writing Committee will then contemplate the interpretation of the results until a consensus is reached and all alternative interpretations of the findings are agreed upon in writing. Once a consensus is reached, we will record the minutes of this meeting in a document coined “statement of interpretation”, which will be signed by all members of the Writing Committee. Only after reaching this common agreement will the data manager and independent statistician break the randomisation code and the correct interpretation chosen. A

manuscript will then be prepared and finalized for the publication of the results. Detailed minutes of blinded data interpretation meetings will be provided as a supplement to the trial manuscript.

Patient and public involvement

To achieve a more patient-friendly design for our trial, we recruited five patient experts from the European Patients' Academy on Therapeutic Innovation (EUPATI Finland, https://fi.eupati.eu/). They were asked to review the informed consent form and questionnaires of the study. These experts were asked to assess the burden of the intervention and time required to participate in the study, both of which they estimated to be reasonable. After the FINISH study is completed, we will deliberate together with EUPATI Finland on how to share the study results with the general public.

Data Safety and Monitoring Committee

Study monitoring is provided by the Clinical Research Institute of Helsinki University Hospital, who will ensure the quality of data collection and trial integrity. The monitoring is performed in accordance with currently valid rules and regulations, Good Clinical Practice (ICH-GCP) and the standardized instructions of the Clinical Research Institute Helsinki University Hospital.

The members of the Data Safety and Monitoring Committee (DSMC) are neurosurgeons independent of the trial and have neither financial nor scientific conflicts of interest with the trial. The DSMC will oversee the interim analyses. The purpose of the interim analysis is safety surveillance. The interim analyses are performed after 50, 100 and 200 patients. No efficacy-related early stopping is planned.

Ethics and dissemination

The study was approved by the institutional review board (IRB) of the Helsinki and Uusimaa Hospital District on November 13, 2019 (HUS/3035/2019 §238, updated 26.2.2020) and duly registered at ClinicalTrials.gov (NCT04203550).

All participating centres will obtain local institutional research approvals for the consent form template, the eCRF and any additional protocol amendments. Any protocol amendment will be communicated to the site investigators, the IRB, trial participants and trial registries as necessary.

Information about the study participants will be kept confidential and will be managed in accordance with the following rules: 1) all study-related information is stored securely at the clinical sites, 2) all possible study participant information in paper form is stored in locked file cabinets and is accessible only to study personnel, 3) all CRFs are identified only by a coded patient number, 4) all records that contain patient names or other identifying information are stored separately from the study records that are identified only by the coded patient number and 5) all local databases are password protected.

The results of the study will be published in an international journal and presented at (inter)national congresses. Trial results will be disseminated to the public in collaboration with EUPATI Finland.

DISCUSSION

To the best of our knowledge, this is the first large scale multicentre RCT comparing intraoperative irrigation with no intraoperative irrigation after burr-hole craniostomy and subdural drain placement for CSDH. The incidence of CSDH in Finland is approximately 18/100,000, reaching as high as 130/100,000 in persons over 80 years old [24]. As a consequence of the ageing population, more frequent use of antithrombotic medication and the improved access to diagnostics in most high-income countries, the incidence of CSDH is expected to increase in the future [25]. The risk of complications following CSDH is rather low, but reducing the risk of recurrence is essential to avoid over-hospitalization of otherwise fragile patients, which could be detrimental [26]. Current studies examining strategies to decrease risk of recurrence include the Swedish study of irrigation-fluid temperature in the evacuation of chronic subdural haematoma (SIC!) [27], the Dutch dexamethasone therapy versus surgery for chronic subdural haematoma (DECSA trial) [28], the British dexamethasone for adult patients with a symptomatic chronic subdural haematoma (Dex-CSDH) trial [29], and two Canadian studies looking at the role of tranexamic acid in the treatment of chronic subdural haematomas (TRACS trial, NCT02568124 [30] and TRACE trial, NCT03280212).

A multicentre RCT that could show a decrease in recurrence rates has the potential to set a new gold standard of therapy, which would influence the treatment of these patients all over the world. If subdural irrigation fails to show any benefit over no irrigation, it would translate to a reduction in the risk of iatrogenic surgical complications and shortened operation times. It may also enable opportunities to develop newer, minimally invasive surgical techniques, including only subdural drain placement. This would not only benefit the individual patient but also health care systems all over the world, considering the sharply increasing incidence of CSDH.

A major strength of the study is that the five participating centres cover 100% of the Finnish population in terms of provision of neurosurgical care. In Finland, the surgical treatment of CSDH is exclusively carried out in University Hospital clinics, meaning that the follow-up regarding the primary endpoint (recurrence) should be 100%. Also, in a highly digitalized healthcare system (local electronic healthcare databases since the early 2000s and nationwide electronic healthcare database since 2010) where every citizen has a unique personal identification number, the chances for successful follow-up regarding other endpoints is extremely high. A limitation is that it is impossible to blind the treating surgeon in relation to the treatment arm (irrigation or no irrigation). Furthermore, we cannot adjust for subtle differences in surgical technique between surgeons, although all participating centres as a whole perform the surgeries similarly. For example, the normal surgical

technique involves irrigation until the fluid is deemed to be clear. However, in order to ensure a sufficient amount irrigation, we set a minimum threshold of 200 ml (per side).

TRIAL STATUS

The trial started recruiting patients in January 2020 in Helsinki and the other centres will start recruiting during the spring of 2020.

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Footnotes

Trial sponsor: Helsinki University Hospital

Author statement: Kimmo Lönnrot, Rahul Raj, Christoph Schwartz, Riku Kivisaari, Jarno Satopää, Teemu Luostarinen, Teppo Järvinen and Simo Taimela designed the trial. Pihla Tommiska, Rahul Raj, Christoph Schwartz, Teemu Luostarinen, Jarno Satopää, Simo Taimela, Teppo Järvinen, Jussi Posti, Teemu Luoto, Ville Leinonen, Sami Tetri, Timo Koivisto and Kimmo Lönnrot have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

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Study administration structure

Writing Committee: Pihla Tommiska, Rahul Raj, Christoph Schwartz, Teemu Luostarinen, Jarno Satopää, Simo Taimela, Teppo Järvinen, Jussi Posti, Teemu Luoto, Ville Leinonen, Sami Tetri, Timo Koivisto and Kimmo Lönnrot

Steering Committee: Kimmo Lönnrot (chair), Riku Kivisaari (co-chair), Teemu Luostarinen (co-chair), Rahul Raj, Jussi Posti, Teemu Luoto, Ville Leinonen, Sami Tetri and Timo Koivisto

Methods Centre: Helsinki University Hospital: Rahul Raj (principal investigator), Jarno Satopää (co-principal investigator), Pihla Tommiska (co-principal investigator, data management), Maarit Tuomisto (research coordinator)

Central Adjudication Committee: Kimmo Lönnrot, Riku Kivisaari, Teemu Luostarinen, Rahul Raj, Jussi Posti, Teemu Luoto, Ville Leinonen, Sami Tetri and Timo Koivisto

Data Safety Monitoring Board: Martin Lehecka (MD, PhD, A. Prof, Helsinki University Hospital, Finland), Frederick A. Zeiler (MD, PhD, A. Prof, Rady Faculty of Health Sciences, University of Manitoba, Canada), Jiri Bartek Jr. (MD, Karolinska University Hospital, Stockholm, Sweden)

Table 1: Table of events

Assessment	Baseline	Surgery	48–72h	6 weeks	6 months
Informed consent	X				
Randomisation		X			
Demographics	X				
Antithrombotic medication	X		X	X	X
Neurological symptoms	X		X	X	X
Residence and mobility	X			X	X
Imaging	X			X	
Surgical details		X			
Modified Rankin Scale	X		X	X	X
Survival status					X
Need for ipsilateral CSDH reoperation					X
Adverse events			X	X	X

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	4-6
Protocol version	3	Date and version identifier	footnote
Funding	4	Sources and types of financial, material, and other support	27
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 27
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	27
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	28

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	9
	6b	Explanation for choice of comparators	9
Objectives	7	Specific objectives or hypotheses	10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11, 12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13, 14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13, 14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15, 16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	17
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17, 18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17, 18

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	20
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16, 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13, 18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	27
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	27
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

The Finnish study of intraoperative irrigation versus drain alone after evacuation of chronic subdural haematoma (FINISH): a study protocol for a multicentre randomized controlled trial

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Complete List of Authors:	Tommiska, Pihla; Helsinki University Central Hospital, Department of Neurosurgery; University of Helsinki Rahul, Raj; Helsinki University Central Hospital, Department of Neurosurgery; University of Helsinki Schwartz, Christoph; University Hospital Salzburg, Paracelsus Medical University, Department of Neurosurgery; Helsinki University Central Hospital, Neurosurgery Kivisaari, Riku; Helsinki University Central Hospital, Department of Neurosurgery; University of Helsinki Luostarinen, T; Helsinki University Central Hospital, Department of Anesthesiology and Intensive Care; University of Helsinki Satopää, Jarno; Helsinki University Central Hospital, Department of Neurosurgery; University of Helsinki Taimela, Simo; Helsinki University Central Hospital, Orthopedics and Traumatology; University of Helsinki, Finnish Centre for Evidence-Based Orthopedics (FICEBO) Jarvinen, Teppo; Helsinki University Central Hospital, Department of Orthopaedics and Traumatology; University of Helsinki, Finland and Finnish Centre for Evidence-Based Orthopedics (FICEBO) Ranstam, Jonas; Lunds Universitet, Clinical sciences Frantzen, Janek; Turun Yliopistollinen Keskussairaala, Department of Neurosurgery; Helsinki University Central Hospital Posti, Jussi; Turku University Hospital, Department of Neurosurgery and Brain Injury Centre Luoto, Teemu M.; Tampere University Hospital, Department of Neurosurgery; Tampere University Leinonen, Ville; Kuopio University Hospital, Department of Neurosurgery; University of Eastern Finland School of Medicine Tetri, Sami; Oulu University Hospital, Department of Neurosurgery; Oulu University Faculty of Medicine Koivisto, Timo ; Kuopio University Hospital, Department of Neurosurgery; University of Eastern Finland School of Medicine Lönnrot, Kimmo; Helsinki University Central Hospital, Department of Neurosurgery; University of Helsinki
Primary Subject Heading:	Surgery

Secondary Subject Heading:	Neurology
Keywords:	NEUROSURGERY, Neurological injury < NEUROLOGY, SURGERY

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STUDY PROTOCOL

TITLE: The Finnish study of intraoperative irrigation versus drain alone after evacuation of chronic subdural haematoma (FINISH): a study protocol for a multicentre randomized controlled trial

AUTHORS: Pihla Tommiska*[1], Rahul Raj*[1], Christoph Schwartz[1,2], Riku Kivisaari[1], Teemu Luostarinen[3], Jarno Satopää[1], Simo Taimela[4,5], Teppo Järvinen[4,5], Jonas Ranstam[6], Janek Frantzén[1,7], Jussi Posti[7], Teemu Luoto[8], Ville Leinonen[9,10], Sami Tetri[10], Timo Koivisto[9], Kimmo Lönnrot[1,4]

1) Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
2) Department of Neurosurgery, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria
3) Division of Anaesthesiology, Department of Anaesthesiology, Intensive Care and Pain Medicine, Helsinki University Hospital, Helsinki, Finland
4) Finnish Centre for Evidence-Based Orthopedics (FICEBO), University of Helsinki and Helsinki University Hospital, Helsinki, Finland
5) Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
6) Department of Clinical Sciences, Lund University, Lund, Sweden
7) Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Centre, Turku University Hospital and University of Turku, Turku, Finland
8) Department of Neurosurgery, Tampere University Hospital and Tampere University, Tampere, Finland
9) Department of Neurosurgery, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland
10) Unit of Clinical Neuroscience, Neurosurgery, University of Oulu and Medical Research Center, Oulu, Finland

*equal contribution

Correspondence:
Rahul Raj, MD, PhD
Department of Neurosurgery
University of Helsinki and Helsinki University Hospital
Topeliuksenkatu 5, P.B. 266, 00029 HUS, Helsinki, Finland
Phone: +358504272516
Email: rahul.raj@helsinki.fi

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Full author list:

Pihla Tommiska, BM, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, pihla.tommiska@helsinki.fi

Rahul Raj, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, rahul.raj@helsinki.fi

Christoph Schwartz, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Department of Neurosurgery, University Hospital Salzburg, Paracelsus Medical University, Salzburg, Austria, c.schwartz@salk.at

Riku Kivisaari, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, riku.kivisaari@hus.fi

Teemu Luostarinen, MD, PhD, Division of Anaesthesiology, Department of Anaesthesiology, Intensive Care and Pain Medicine, Helsinki University Hospital, Helsinki, Finland. teemu.luostarinen@hus.fi

Jarno Satopää, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, jarno.satopaa@hus.fi

Simo Taimela, MD, PhD, Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Finnish Centre for Evidence-Based Orthopedics (FICEBO), University of Helsinki and Helsinki University Hospital, Helsinki, Finland, simo.taimela@helsinki.fi

Teppo Järvinen, MD, PhD, Department of Orthopaedics and Traumatology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Finnish Centre for Evidence-Based Orthopedics (FICEBO), University of Helsinki and Helsinki University Hospital, Helsinki, Finland, teppo.jarvinen@helsinki.fi

Jonas Ranstam, PhD, Department of Clinical Sciences, Lund University, Lund, Sweden, jonas.ranstam@mdas.se

Janek Frantzén, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Centre, Turku University Hospital and University of Turku, Turku, Finland, janek.frantzen@tyks.fi

Jussi Posti, MD, PhD, Division of Clinical Neurosciences, Department of Neurosurgery and Turku Brain Centre, Turku University Hospital and University of Turku, Turku, Finland, jussi.posti@utu.fi

Teemu Luoto, MD, PhD, Department of Neurosurgery, Tampere University Hospital and Tampere University, Tampere, Finland, teemu.luoto@pshp.fi

Ville Leinonen, MD, PhD, Department of Neurosurgery, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland and Unit of Clinical Neuroscience, Neurosurgery, University of Oulu and Medical Research Center, Oulu, Finland, ville.leinonen@kuh.fi

Sami Tetri, MD, PhD, Unit of Clinical Neuroscience, Neurosurgery, University of Oulu and Medical Research Center, Oulu, Finland, sami.tetri@ppshp.fi

Timo Koivisto, MD, PhD, Department of Neurosurgery, Kuopio University Hospital and University of Eastern Finland, Kuopio, Finland, timo.koivisto@kuh.fi

Kimmo Lönnrot, MD, PhD, Department of Neurosurgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland and Finnish Centre for Evidence-Based Orthopedics (FICEBO), University of Helsinki and Helsinki University Hospital, Helsinki, Finland, kimmo.lonnrot@hus.fi

ABSTRACT

Introduction: Chronic subdural haematomas (CSDHs) are one of the most common neurosurgical conditions. The goal of surgery is to alleviate symptoms and minimize the risk of symptomatic recurrences. In the past, re-operation rates as high as 20–30% were described for CSDH recurrences. However, following the introduction of subdural drainage, re-operation rates dropped to approximately 10%. The standard surgical technique includes burr-hole craniostomy, followed by intraoperative irrigation and placement of subdural drainage. Yet, the role of intraoperative irrigation has not been established. If there is no difference in recurrence rates between intraoperative irrigation and no irrigation, CSDH surgery could be carried out faster and more safely by omitting the step of irrigation. The aim of this multicentre randomised controlled trial is to study whether no intraoperative irrigation and subdural drainage results in non-inferior outcome compared to intraoperative irrigation and subdural drainage following burr-hole craniostomy of CSDH.

Methods and Analysis: This is a prospective, randomised, controlled, parallel group, non-inferiority multicentre trial comparing single burr-hole evacuation of CSDH with intraoperative irrigation and evacuation of CSDH without irrigation. In both groups, a passive subdural drain is used for 48 hours as a standard of treatment. The primary outcome is symptomatic CSDH recurrence requiring re-operation within six months. The predefined non-inferiority margin for the primary outcome is 7.5%. To achieve a 2.5% level of significance and 80% power we will randomise 270 patients per group. Secondary outcomes include modified Rankin Scale, rate of mortality, duration of operation, length of hospital stay, adverse events, and change in volume of CSDH.

Ethics and Dissemination: The study was approved by the institutional review board of the Helsinki and Uusimaa Hospital District (HUS/3035/2019 §238) and duly registered at ClinicalTrials.gov. We will disseminate the findings of this study through peer-reviewed publications and conference presentations.

Trial Registration Number: NCT04203550

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a multicentre nationwide prospective randomised controlled trial, with a pragmatic trial design to increase generalizability.
- The study was designed in collaboration with patient organisation experts.
- The health care system in Finland facilitates the follow-up of patients (particularly with respect to our primary outcome, symptomatic CSDH requiring reoperation) as CSDH surgery is centralized to the five neurosurgical departments participating in the trial.
- Although the surgeon performing the surgery obviously cannot be blinded to the group assignment, we have tried to maintain the masking of the treatment allocation by not disclosing it in the health care records.

INTRODUCTION

Chronic subdural haematoma (CSDH) is the most common type of intracranial haemorrhage and one of the most common clinical diagnoses necessitating neurosurgical treatment. CSDHs are typically caused by minor head trauma and consecutive tearing of bridging veins, leading to a haemorrhage in between the dura mater and the arachnoid membrane. The delay in the actual diagnosis of CSDH can be quite substantial due to the difficulty of the diagnosis in the early phase when neurological symptoms – such as progressive headache, mental deterioration or confusion, or deterioration of the patient's overall health – are quite unspecific. However, when the disease progresses and causes more direct compression to the underlying brain tissue, more specific progressive neurological signs ensue, including motor and sensory deficits, dysphasia and epileptic seizures, and the diagnosis becomes more evident. If left untreated, CSDH may also lead to loss of consciousness or even death. The definite diagnosis of CSDH is most commonly based on computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. On a CT scan, CSDH is usually of hypo- or isodense character and will feature a concavo-convex shape between the skull and the cortex.

For symptomatic CSDHs, the treatment is operative. The mainstay of treatment includes burr-hole craniostomy and intraoperative intracranial irrigation followed by subdural drainage [1]. With current treatment strategies, the recurrence rate after CSDH treatment is approximately 10% [2]. Low risk of bias evidence exists on the role of subdural drain in recurrence rate reduction but the role of intraoperative irrigation is more controversial. Our literature review revealed a total of ten studies assessing the effect of intraoperative irrigation: only one study employed a randomised study protocol [3] while the others were retrospective analyses. Sample sizes ranged from 56 to 186 patients, and the most commonly used outcome was the rate of haematoma recurrence. Of these ten studies, two studies found that intraoperative irrigation was associated with a significantly lower recurrence rate in comparison to no intraoperative irrigation [4,5], six studies found no difference in recurrence rates between intraoperative and no intraoperative irrigation [3,6–10], and two studies found that no intraoperative irrigation was associated with a significantly lower recurrence rate compared to irrigation [11,12].

It is possible that intraoperative irrigation is an unnecessary prolongation of the surgical procedure, thereby increasing the risk for infections, rebleeding and the stress levels of patients undergoing the procedure under local anaesthesia. There is also evidence to suggests that irrigation *per se* may be harmful: There are reports of increased risk of treatment-associated morbidity and complications such as postoperative pneumocephalus [9,11,13] and also of direct irrigation-induced intracerebral and subarachnoid haemorrhage [14].

We designed a pragmatic, parallel group, randomised, controlled multicentre non-inferiority trial to compare the use of intraoperative irrigation with no intraoperative irrigation for the operation of symptomatic CSDH (by burr-hole craniostomy and subdural drainage for 48 hours). We hypothesise that a treatment that involves no intraoperative irrigation results in non-inferior outcome compared to a treatment that involves intraoperative irrigation. Non-inferiority of the new treatment (no irrigation) with respect to the gold standard treatment (irrigation) is of interest on the premise that the new treatment has some other advantages, such as shorter operative time and therefore reduced stress to patient, reduced cost, fewer adverse events (harm) and technically more simple [15]. We consider non-inferiority proven if the rate of recurrence in the no-irrigation group is within the pre-defined non-inferiority margin of the rate observed in the irrigation group together with no significantly increased risk of harm.

MATERIALS AND ANALYSIS

Overview of study design

FINISH is a multicentre, prospective non-inferiority randomised controlled trial, with the primary objective to compare intraoperative irrigation to no irrigation in the treatment of CSDH by single burr-hole craniostomy and subdural drainage. Except for randomisation to irrigation versus no irrigation, the management of study participants will not differ. Eligible participants are block randomised in a 1:1 allocation rate to one of two arms: i) intraoperative irrigation, or ii) no intraoperative irrigation.

The study is registered at ClinicalTrials.gov (NCT04203550) and this protocol has been written according to the Standard Protocols Items: Recommendations for Interventional Trials (SPIRIT) guidelines for reporting a randomised controlled trial study protocol (the SPIRIT Figure and Checklist are available as Additional File 1) [16]. A summary of the trial is shown in Additional File 2.

Study settings

Participating sites are the neurosurgical departments at Helsinki University Hospital (Helsinki, Finland), Kuopio University Hospital (Kuopio, Finland), Tampere University Hospital (Tampere, Finland), Turku University Hospital (Turku, Finland) and Oulu University Hospital (Oulu, Finland). All these five units are tertiary referral centres and the only units delivering neurosurgical care in Finland.

Participant selection and recruiting process

We will screen all patients who are referred for CSDH surgery to the aforementioned departments of neurosurgery for trial eligibility. A standard clinical examination and a brain CT or MRI examination will be performed. Patients with clinical and imaging findings consistent with a diagnosis of symptomatic CSDH and considered to benefit from operative treatment of CSDH by single burr-hole evacuation will be asked to participate in the trial.

Inclusion criteria

- Patients with a symptomatic unilateral or bilateral CSDH requiring burr-hole evacuation
    - Predominantly hypodense or isodense on imaging (CT/MRI)
    - Clinical symptoms correlating with the CSDH
    - Patients with bilaterally operated CSDHs will be treated with the same protocol on both sides and analysed as a single study participant
- Patients older than 18 years of age

Exclusion criteria

- CSDH requiring surgical treatment other than burr-hole evacuation (e.g. craniotomy)
- CSDH in a patient who has a cerebrospinal fluid shunt
- Patients who have undergone any prior intracranial surgery
- Comatose patients (GCS 8 or lower, absent motor responses to painful stimuli; decerebrate or decorticate posturing), where rapid hematoma evacuation is required
- Patient's postoperative cooperation is suspected to be insufficient for drain usage (i.e. disoriented or semiconscious patient)
- Patient who has received active treatment for a haematogenic malignancy within the previous five years
- Patient with a central nervous system malignancy or tumour that may cause the patient's current symptoms or may interfere with the operation. For example, a small incidental meningioma without associated brain oedema, not in the vicinity of the planned burr-hole, is not an exclusion criterion.
- Patient has an acute infection that requires antibiotic treatment
- Patient has a high risk of life-threatening thrombosis (e.g. recent coronary stent, intracranial stent, recent pulmonary embolism, low pressure cardiac valve replacement [mitral- or tricuspid valve replacement]) and discontinuation of antithrombotic medication is not recommended

Informed consent

At the first appointment in the emergency department or the neurosurgical ward, the attending neurosurgeon will provide the patients with detailed written and oral information on the trial and ask patients to sign an informed consent form. Withdrawal from the study is possible at any time, without affecting the course of conventional treatment, in accordance with the latest version of the declaration of Helsinki 2013 [17].

Due to the nature and emergency aspects of the disease (mass effect on the brain causing confusion and disorientation, lowered level of consciousness requiring urgent surgery), some patients will not be able to give

written consent prior to randomisation. If the patient is unable to give written consent prior to the randomisation, delayed consent will be sought. In these cases, oral consent will be obtained from the next of kin after providing information regarding the trial. Following oral consent from the next of kin, the patient can be randomised. Following randomisation and surgery, written consent will primarily be obtained from the patient. However, in case of the patient being unable to give written consent due to neurological disability, written consent is obtained from the next of kin. In these cases, the next of kin has the right to withdraw the patient's consent at any time. Patients who are eligible for the trial but are not willing to undergo randomisation will be asked to be included in a simultaneous, pragmatic follow-up cohort.

Participants will be asked to sign the local Biobank agreements in order to collect and store subdural fluid samples (see below) and two venous blood samples (2 x 10 ml).

Collected data

We will document data in the electronic Case Report Form (eCRF) preoperatively, intraoperatively and within 48–72h postoperatively, as well as at 6 weeks (±2 weeks) and at 6 months (see Table 1 for table of events). All patients' preoperative and postoperative head CTs or MRs images will be sent to the Picture Archiving and Communication System (PACS) of the methods centre (Helsinki University Hospital) for analysis. Ten percent of all images will be double read by independent assessors blinded to other patient information. To preserve confidentiality, all participants are allocated a unique study identifier during the recruitment process, which is used on all data collection forms. All study documentation is held in secure offices, and the study researchers operate according to a signed code of confidentiality. All data are entered into a password-secured database by the data managers.

Surgical technique

Current management of CSDHs at all participating centres includes single burr-hole evacuation with intraoperative irrigation followed by passive subdural drainage. As a routine, all burr-hole craniostomies are performed under local anaesthesia, often combined with intravenous sedation with benzodiazepines and/or opioids during the operation. General anaesthesia is only used if the neurosurgeon or the anaesthesiologist considers it unsafe to perform the procedure under local anaesthesia. Routine preoperative antibiotic is given according to local protocols (normally a second-generation cephalosporin 30–60 min prior to incision). Typically, the surgeon drills one 14-mm burr hole over the maximum convexity of the CSDH. In case of bilateral CSDHs, the surgeon performs the same procedure on both sides. If irrigation is utilized, after opening the dura,

the surgeon irrigates the subdural collection with warm (body temperature) Ringer's lactate saline until rinsing appears clear or at least 200 ml (in case of bilateral CSHD, 200 ml per side, i.e. 400 ml total). After that, the surgeon will insert the subdural drain 3–5 cm deep and parallel to skull. The position of the drain (anterior, posterior) is left to the discretion of the physician. Burr hole covers or haemostatics are not routinely used (e.g. Spongostan®, Tachosil®). The type of subdural drain is not standardized, but all study centres use 10F drains. Following drain insertion, the distal end is tunnelled approximately 4–5 cm from the incision and connected to a passive ventricular drainage bag (through a non-return valve) and the skin incision is closed in two layers (normally is absorbable 3-0 suture for subcutis/galea and non-absorbable 4-0 suture for skin). The drain is fixed to the skin in a secure way. The drain-to-skin fixation technique is left to the discretion of the operating surgeon. The drainage bag is positioned at bed level. The duration of subdural drainage is 48 hours (±12 hours) [18,19]. Patient mobilization is allowed during drainage (drain is kept open). Prophylactic antibiotics during drainage are not routinely used.

Randomisation

Patients will be randomised in a 1:1 allocation ratio stratified only by study centre. We will use a random block randomisation technique, with a random block size of 4, 6 or 8. A member of the FINISH study group will carry out randomisation when the patient is at the OR at the beginning of the operation. The randomisation will occur just prior to skin incision. The randomisation is a built-in property in the online eCRF form system used in the trial (provided by Granitics Inc., Espoo, Finland).

Intervention

Irrigation group (IR)

A burr-hole craniostomy is performed as described earlier. The dura is opened sharply and 10 ml of subdural exudate is aspired with blunt aspiration needle for a CSDH sample to be stored at -75°C to be used for later analysis. Subdural space is irrigated by repeated rinsing with body temperature saline solution with a syringe and blunt needle until surgeon considers exudate to be clear. Minimum volume of irrigation will be 200 ml per operated side. The subdural drain is inserted 3–5 cm underneath the skull and parallel to it. Thereafter, operation is completed as described earlier. The total volume of irrigation as well as the duration of operation is recorded.

No-irrigation group (N-IR)

A burr-hole craniostomy is performed as described earlier. A small incision in the dura is made and 10 ml of subdural exudate is aspired with a blunt aspiration needle for a CSDH sample to be stored at -75°C to be used for later analysis. The subdural drain is inserted approximately 3–5 cm underneath the skull and parallel to it. Thereafter, the operation is completed as described earlier. The duration of the operation is recorded.

Blinding

Due to the nature of the treatment, it is not possible to blind the surgeon and OR staff from the treatment allocation. Measures to minimize bias include:

- The randomisation is timed as closely as possible to the time of surgery (just prior to skin incision)
- The patient will not be informed of treatment allocation
- Treatment allocation will not be documented in medical records (i.e. all personnel participating in patient care after the operation will be blinded to allocation)
- The study group members collecting postoperative data, outcome data, imaging data and performing the statistical analyses will be blinded to treatment arm over the entire course of the trial, until the data analyses are carried out.
- The primary and secondary outcome measures (see below) are all evaluated in blinded matter, i.e. the outcome assessor will be blinded with regard to treatment allocation

Emergency unblinding will occur only in exceptional circumstances when requested by the patient's clinical team (e.g. need to treat a serious adverse event [SAE]), when knowledge of the actual treatment is essential for further management of the patient.

Compliance to treatment allocation and possible crossover

The per protocol treatment is 0 ml of intracranial irrigation in the N-IR group and ≥200 ml (per operated side) of intracranial irrigation in the IR group. In the event of protocol breach, crossovers will be handled as follows:

- If the patient is randomised to the IR group and the intracranial irrigation volume is between 1 ml and 200 ml, the patient is not considered a crossover.
- If the patient is randomised to the IR group and the intracranial irrigation volume is 0 ml, the patient is considered a crossover (belongs to the N-IR group).

- If the patient is randomised to the N-IR group and 1 ml to 199 ml of intracranial irrigation is used, the patient is not considered a crossover.
- If the patient is randomised to the N-IR group and ≥200 ml of intracranial irrigation is used, the patient is considered a crossover (belongs to the IR group).
- In case of intervention failure (e.g. not being able to insert subdural drain, intended or unintended drain removal before 36h), the patient is not considered a crossover.

Primary outcome measure

Our primary outcome measure is the rate of reoperations of ipsilateral CSDHs within 6 months.

Indication for reoperation and reoperation technique

The decision to proceed to reoperation is made by the treating neurosurgeon and will be made by the same indications as the primary operation (i.e. symptom recurrence or insufficient resolution of clinical symptoms correlating to imaging findings [CT or MR imaging] of CSDH). All reoperations will be conducted according to the current standard (i.e. burr-hole with irrigation and subdural drain placement). In case of recurrence requiring reoperation, unblinding will not occur automatically, only in cases when the neurosurgery team treating the patient considers this information necessarily for optimal care of the patient.

Secondary outcome measures

The study is not powered for secondary outcome measure comparisons and these outcomes (analyses) will be considered exploratory. The secondary outcomes include:

1. Modified Rankin Scale at 6 months after operation
2. Mortality within 6 months of operation
3. Duration of the operation
4. Hospital length of stay (index hospital and need for further care)
5. CSDH volume reduction at 2 months after operation

Safety endpoints

Safety endpoints within 6-months of operation, including the number and severity of adverse events (AE) and procedure related adverse events (PRAE). Adverse events are categorized as serious adverse events (SAE) and minor adverse events (MAE). Procedure related (severe and minor) adverse events will be reported separately.

SAE are defined as any inappropriate medical occurrence or effect that results in death, is life-threatening, requires hospitalization or prolongation of an existing inpatient hospitalization, results in persistent or significant disability or incapacity, or is another important medical event.

- Life-threatening in the definition of SAE refers to an event when the patient was at risk of death at the time of the event and does not refer to an event where the event might have hypothetically caused death. Prolonged hospitalization due to delayed transfer will not be considered an AE or SAE.

  Examples of SAEs are death, acute myocardial infarction, pulmonary embolism, systemic infection, acute cerebral infarction (PRAE), intracranial infection (PRAE), epileptic seizures (PRAE) and acute postoperative intracranial haematoma (PRAE).

MAE are defined as clinically mild manifestations, referent to that the patient might be aware of the event or symptom but the event or symptom is easily tolerated by the patient.

- Examples of MAEs are local wound infection manageable with oral antibiotics (PRAE), abnormal skin bleeding from the wound (PRAE), other local infection manageable with oral antibiotics and deep venous thrombosis not causing pulmonary embolism.

Follow-up

The follow-up period is 6 months. We will arrange a clinical outpatient follow-up visit for all patients at 4–8 weeks postoperatively (6 weeks ±2 weeks). Before that, a postoperative brain CT will be performed. If the patient was preoperatively using any form of antithrombotic medication, the medication is not routinely restarted without reasonable clinical indication before the control brain CT. All recurrences requiring surgery within 6 months and complications within 6 months will be recorded. At 6 months, functional outcome (mRS) will be assessed by a FINISH study group member by phone interview. Further, for each patient, mortality will be verified through the Finnish Official Cause-of-Death Statistics at 6 months. This statutory register is virtually 100% complete because each death, its associated official death-certificate, and the corresponding person information in the Finnish computerized population register are cross-checked.

Sample size

The trial is designed to ascertain whether drain without irrigation is non-inferior to drain with irrigation, with the rate of reoperations of ipsilateral CSDHs within 6 months as the primary outcome. We based the standard rate of reoperations (9.6%) on the results from a recent Cochrane review that reported the recurrence rates after CSDH evacuation followed by subdural drainage in six RCTs with more than 30 patients per treatment arm [2]. This yielded a maximum allowed margin of 9.0% to achieve non-inferiority. Following a consensus meeting with the trial investigators, the non-inferiority margin was lowered to 7.5%. Thus, with a non-inferiority margin of 7.5%, a 2.5% level of statistical significance (alpha = 0.025) and an 80% power (beta = 0.20), we will need 243 patients per study group [20]. Accounting for a drop-out rate of 10%, required group size increases to 270 per study group. Accordingly, we set the recruitment target at 540 patients.

Data management

All study data will be stored in an eCRF provided by Granitics Inc (Espoo, Finland). Data are entered locally by the local research team. Upon receipt of the data, the FINISH personnel, blinded to the group allocation, will make a visual check of the data and query all missing, implausible and inconsistent data. Hospital patient records will also be utilized to collect missing data and to interpret inconsistent or implausible data. Participant files will be maintained in storage (both in electronic and paper format) at the coordinating centre for a period of 15 years after completion of the study.

Data sharing

Data generated by our study will be made available as soon as possible and will be available upon reasonable request. Data access requests will be reviewed by the FINISH steering group. Requestors will be required to sign a Data Access Agreement. Only anonymized data will be shared.

Statistical analysis

The statistical analysis will be performed both according to intention-to-treat (ITT) and per protocol (PP) principles. We will claim non-inferiority of single burr-hole evacuation without irrigation and subdural drainage only if this outcome is supported both by the ITT and the PP analysis. The ITT analysis will be performed using the full analysis set (FAS), defined as all randomised patients in the groups allocated to by the randomisation.

No exclusions other than caused by missing information will be made. No imputation will take place. The PP analysis will be performed on the subset of FAS that is compliant with the protocol have a completed treatment, available measurements, and neither major protocol violations nor entry criteria violations.

Summary statistics will be presented for both groups. Continuous variables will be presented in terms of mean values or medians with standard deviations and interquartile ranges, respectively. Categorical variables will be presented with relative frequencies in percent.

The results from the statistical analysis will be considered to support a claim of non-inferiority if the upper limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) excludes a difference in the primary endpoint in favour of the irrigation group of more than 7.5%. The centre stratification of the randomisation will be accounted for in the calculation of the confidence interval.

Exploratory analyses of secondary and other binary endpoints will be performed using the Chi-squared test or logistic regression analysis. Continuous outcomes will be analysed using Student's t-test or ANCOVA. Potential effect modifiers (patient age, unilateral versus bilateral CSDH, use of antithrombotic medication, preoperative mRS and preoperative clinical status, haematoma density, haematoma size and presence of membranes on preoperative imaging) will be analysed by including interaction terms in statistical models.

The primary endpoint will be investigated as described above using a confidence interval, which is equivalent to using a non-inferiority test with a one-sided p-value of 0.025 (or a two-sided of 0.05). The statistical testing of other endpoints will also be performed using a two-sided significance level of 0.05. The statistical analysis will be performed using appropriate statistical software packages.

Prior to the statistical analysis, a statistical analysis plan will be finalised and an independent statistician will approve a dataset with sufficient data quality for the statistical analysis. Another statistician blinded to treatment arm will perform the analyses.

Blinded data interpretation

As in previous studies [21,22], we will interpret the results of the trial according to a blinded data interpretation scheme [23]. In brief, an independent statistician will provide the Writing Committee of the FINISH trial with blinded results from the analyses with the groups labelled group A and group B. The Writing Committee will then contemplate the interpretation of the results until a consensus is reached and all alternative interpretations of the findings are agreed upon in writing. Once a consensus is reached, we will record the minutes of this meeting in a document coined “statement of interpretation”, which will be signed by all members of the Writing Committee. Only after reaching this common agreement will the data manager

and independent statistician break the randomisation code and the correct interpretation chosen. A manuscript will then be prepared and finalized for the publication of the results. Detailed minutes of blinded data interpretation meetings will be provided as a supplement to the trial manuscript.

Patient and public involvement

To achieve a more patient-friendly design for our trial, we recruited five patient experts from the European Patients' Academy on Therapeutic Innovation (EUPATI Finland, https://fi.eupati.eu/) while designing the study. They were asked to review the informed consent form and questionnaires of the study. Further, these experts were asked to assess the burden of the intervention, time required to participate in the study, and outcomes all of which they estimated to be reasonable. After the FINISH study is completed, we will deliberate together with EUPATI Finland on how to share the study results with the general public.

Data Safety and Monitoring Committee

Study monitoring is provided by the Clinical Research Institute of Helsinki University Hospital, who will ensure the quality of data collection and trial integrity. The monitoring is performed in accordance with currently valid rules and regulations, Good Clinical Practice (ICH-GCP) and the standardized instructions of the Clinical Research Institute Helsinki University Hospital.

The members of the Data Safety and Monitoring Committee (DSMC) are neurosurgeons independent of the trial and have neither financial nor scientific conflicts of interest with the trial. The DSMC will oversee the interim analyses. The purpose of the interim analysis is safety surveillance. The interim analyses are performed after 50, 100 and 200 patients. No efficacy-related early stopping is planned.

Ethics and dissemination

The study was approved by the institutional review board (IRB) of the Helsinki and Uusimaa Hospital District on November 13, 2019 (HUS/3035/2019 §238, updated 26.2.2020) and duly registered at ClinicalTrials.gov (NCT04203550).

All participating centres will obtain local institutional research approvals for the consent form template, the eCRF and any additional protocol amendments. Any protocol amendment will be communicated to the site investigators, the IRB, trial participants and trial registries as necessary.

Information about the study participants will be kept confidential and will be managed in accordance with the following rules: 1) all study-related information is stored securely at the clinical sites, 2) all possible study participant information in paper form is stored in locked file cabinets and is accessible only to study personnel, 3) all CRFs are identified only by a coded patient number, 4) all records that contain patient names or other identifying information are stored separately from the study records that are identified only by the coded patient number and 5) all local databases are password protected.

The results of the study will be published in an international journal and presented at (inter)national congresses. Trial results will be disseminated to the public in collaboration with EUPATI Finland.

DISCUSSION

To the best of our knowledge, this is the first large scale multicentre RCT comparing intraoperative irrigation with no intraoperative irrigation after burr-hole craniostomy and subdural drain placement for CSDH. The incidence of CSDH in Finland is approximately 18/100,000, reaching as high as 130/100,000 in persons over 80 years old [24]. As a consequence of the ageing population, more frequent use of antithrombotic medication and the improved access to diagnostics in most high-income countries, the incidence of CSDH is expected to increase in the future [25]. The risk of complications following CSDH is rather low, but reducing the risk of recurrence is essential to avoid over-hospitalization of otherwise fragile patients, which could be detrimental [26]. Current studies examining strategies to decrease risk of recurrence include the Swedish study of irrigation-fluid temperature in the evacuation of chronic subdural haematoma (SIC!) [27], the Dutch dexamethasone therapy versus surgery for chronic subdural haematoma (DECSA trial) [28], the British dexamethasone for adult patients with a symptomatic chronic subdural haematoma (Dex-CSDH) trial [29], and two Canadian studies looking at the role of tranexamic acid in the treatment of chronic subdural haematomas (TRACS trial, NCT02568124 [30] and TRACE trial, NCT03280212).

A multicentre RCT that could show a decrease in recurrence rates has the potential to set a new gold standard of therapy, which would influence the treatment of these patients all over the world. If subdural irrigation fails to show any benefit over no irrigation, it would translate to a reduction in the risk of iatrogenic surgical complications and shortened operation times. It may also enable opportunities to develop newer, minimally invasive surgical techniques, including only subdural drain placement. This would not only benefit the individual patient but also health care systems all over the world, considering the sharply increasing incidence of CSDH.

A major strength of the study is that the five participating centres cover 100% of the Finnish population in terms of provision of neurosurgical care. In Finland, the surgical treatment of CSDH is exclusively carried out in University Hospital clinics, meaning that the follow-up regarding the primary endpoint (recurrence) should be 100%. Also, in a highly digitalized healthcare system (local electronic healthcare databases since the early 2000s and nationwide electronic healthcare database since 2010) where every citizen has a unique personal identification number, the chances for successful follow-up regarding other endpoints is extremely high. A limitation is that it is impossible to blind the treating surgeon in relation to the treatment arm (irrigation or no irrigation). Furthermore, we cannot adjust for subtle differences in surgical technique between surgeons, although all participating centres as a whole perform the surgeries similarly. For example, the normal surgical

technique involves irrigation until the fluid is deemed to be clear. However, in order to ensure a sufficient amount irrigation, we set a minimum threshold of 200 ml (per side).

TRIAL STATUS

The trial started recruiting patients in January 2020 in Helsinki and the other centres will start recruiting during the spring of 2020.

CONTRIBUTORSHIP STATEMENT

Kimmo Lönnrot, Rahul Raj, Christoph Schwartz, Riku Kivisaari, Jarno Satopää, Teemu Luostarinen, Teppo Järvinen and Simo Taimela designed the trial. Pihla Tommiska, Rahul Raj, Christoph Schwartz, Teemu Luostarinen, Jarno Satopää, Simo Taimela, Teppo Järvinen, Janek Frantén, Jonas Ranstam, Jussi Posti, Teemu Luoto, Ville Leinonen, Sami Tetri, Timo Koivisto and Kimmo Lönnrot have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

COMPETING INTERESTS

None

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Footnotes

Trial sponsor: Helsinki University Hospital

Patient consent for publication: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data availability statement: Anonymized data are available on reasonable request.

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Study administration structure

Writing Committee: Pihla Tommiska, Rahul Raj, Christoph Schwartz, Teemu Luostarinen, Jarno Satopää, Simo Taimela, Teppo Järvinen, Jussi Posti, Teemu Luoto, Ville Leinonen, Sami Tetri, Timo Koivisto and Kimmo Lönnrot

Steering Committee: Kimmo Lönnrot (chair), Riku Kivisaari (co-chair), Teemu Luostarinen (co-chair), Rahul Raj, Jussi Posti, Teemu Luoto, Ville Leinonen, Sami Tetri and Timo Koivisto

Methods Centre: Helsinki University Hospital: Rahul Raj (principal investigator), Jarno Satopää (co-principal investigator), Pihla Tommiska (co-principal investigator, data management), Maarit Tuomisto (research coordinator)

Central Adjudication Committee: Kimmo Lönnrot, Riku Kivisaari, Teemu Luostarinen, Rahul Raj, Jussi Posti, Teemu Luoto, Ville Leinonen, Sami Tetri and Timo Koivisto

Data Safety Monitoring Board: Martin Lehecka (MD, PhD, A. Prof, Helsinki University Hospital, Finland), Frederick A. Zeiler (MD, PhD, A. Prof, Rady Faculty of Health Sciences, University of Manitoba, Canada), Jiri Bartek Jr. (MD, Karolinska University Hospital, Stockholm, Sweden)

Table 1: Table of events

Assessment	Baseline	Surgery	48–72h	6 weeks	6 months
Informed consent	X				
Randomisation		X			
Demographics	X				
Antithrombotic medication	X		X	X	X
Neurological symptoms	X		X	X	X
Residence and mobility	X			X	X
Imaging	X			X	
Surgical details		X			
Modified Rankin Scale	X		X	X	X
Survival status					X
Need for ipsilateral CSDH reoperation					X
Adverse events			X	X	X

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	4-6
Protocol version	3	Date and version identifier	footnote
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	20
	5b	Name and contact information for the trial sponsor	23
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20, 23
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14-15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13-14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12, 15-16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17, 24
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13-14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17-18

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10, 15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20, 23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	17-18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	23
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	10

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Additional File 2: Summary of the FINISH trial protocol

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT04203550
Date of registration in primary registry	December 18, 2019
Secondary identifying numbers	N/A
Source(s) of monetary or material support	State funding for University-level health research (Helsinki University Hospitals), Finska Läkaresällskapet, Medicinska Understödsföreningen Liv & Hälsa
Primary sponsor	Helsinki University Hospital
Secondary sponsor(s)	N/A
Contact for public queries	Kimmo Lönnrot, MD, PhD; email: *kimmo.lonnrot@hus.fi*; address: Töölö Hospital, Topeliuksenkatu 5, PB 266, 00029 HUS, Finland; phone: +358-50-427-0270
Contact for scientific queries	Kimmo Lönnrot, MD, PhD; email: *kimmo.lonnrot@hus.fi*; address: Töölö Hospital, Topeliuksenkatu 5, PB 266, 00029 HUS, Finland; phone: +358-50-427-0270
Public title	Irrigation or no irrigation for surgery of chronic subdural haematoma (FINISH)
Scientific title	The Finnish study of Intraoperative Irrigation versus drain alone after evacuation of chronic Subdural Haematoma (FINISH): A study protocol for a multicentre randomised controlled trial
Countries of recruitment	Finland
Health condition(s) or problem(s) studied	Chronic subdural haematoma (CSDH)
Intervention(s)	Active comparator: Irrigation (i.e. the subdural space is irrigated by repeated rinsing with body temperature saline solution with a syringe and blunt needle until surgeon considers exudate to be clear. The minimum volume of irrigation is 200 ml per operated side. A subdural drain is inserted 3–5 cm underneath the skull and parallel to it and kept as a passive drain for 48 hours) Experimental: No irrigation (i.e. after a small incision of the dura, a subdural drain is inserted 3–5 cm underneath the skull and parallel to it and kept as a passive drain for 48 hours)

Additional File 2: Summary of the FINISH trial protocol

Data category	Information
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: All Accepts healthy volunteers: No Inclusion criteria: - Patients with a symptomatic unilateral or bilateral CSDH requiring burr-hole evacuation - Predominantly hypodense or isodense on imaging (CT/MRI) - Clinical symptoms correlating with CSDH - Patients with bilaterally operated CSDHs will be treated with the same protocol on both sides and analysed as a single study participant Exclusion criteria: - CSDH requiring surgical treatment other than burr-hole evacuation (e.g. craniotomy) - CSDH in a patient who has a cerebrospinal fluid shunt - Patients who have previously undergone any intracranial surgery - Comatose patients (GCS 8 or lower) with absent motor responses to painful stimuli; decerebrate or decorticate posturing - Patient's postoperative cooperation is suspected to be insufficient for drain usage (i.e. disoriented or semiconscious patient) - Patient has a haematogenic malignancy that has been actively treated within the previous five years - Patient has a central nervous system tumour or malignancy - Patient has an acute infection requiring antibiotic treatment - Patient has a high risk of life-threatening thrombosis (e.g. recent coronary stent, intracranial stent, recent pulmonary embolism, low pressure cardiac valve replacement [mitral- or tricuspid valve replacement]) and discontinuation of antithrombotic medication is not recommended
Study type	Prospective, randomised, controlled, parallel group, non-inferiority trial Allocation: Randomised Intervention model: Parallel assignment Intervention model description: Prospective, randomised, controlled, parallel group, non-inferiority trial Masking: Quadruple (participant, care provider, investigator, outcomes assessor) Primary purpose: Treatment
Date of first enrolment	January 2020

Additional File 2: Summary of the FINISH trial protocol

Data category	Information
Target sample size	540 participants
Recruitment status	Recruiting
Primary outcome(s)	Rate of reoperations of ipsilateral chronic subdural hematoma (time frame: 6 months from randomization)
Key secondary outcomes	Change of Modified Rankin Scale (time frame: 6 months), rate of mortality (time frame: 6 months), duration of operation, hospital length of stay, rate of adverse events (time frame: 6 months), change in volume of CSDH between baseline and 2 months