BMJ Open

COveRs to impRove EsthetiC ouTcome after Surgery for Chronic subdural hemAtoma by buRr hole trepanation (CORRECT-SCAR) – protocol of a single-blinded, randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031375
Article Type:	Protocol
Date Submitted by the Author:	14-May-2019
Complete List of Authors:	Stienen, MN; University Hospital Zurich, Neurosurgery Akeret, Kevin; University Hospital Zurich, Neurosurgery Vasella, Flavio; University Hospital Zurich, Neurosurgery Velz, Julia; UniversitatsSpital Zurich Neurochirurgische Klinik, Jehli, Elisabeth; University Hospital Zurich, Neurosurgery Scheffler, Pierre; University Hospital Zurich, Neurosurgery Voglis, Stefanos; University Hospital Zurich, Neurosurgery Bichsel, Oliver; University Hospital Zurich, Neurosurgery Smoll, Nicolas; University of Newcastle, School of Medicine and Public Health Bozinov, Oliver; University of Zurich, Neurosurgery Regli, Luca; University Hospital Zurich, Neurosurgery Germans, Menno; University Hospital Zurich, Neurosurgery
Keywords:	Chronic subdural hematoma, Esthetic outcome, Patient satisfaction, Burr hole cover, Trepanation, Value-based medicine

COveRs to impRove EsthetiC ouTcome after Surgery for Chronic subdural hemAtoma by buRr hole trepanation (CORRECT-SCAR) – protocol of a single-blinded, randomized controlled trial

Martin N. Stienen[1], MD/FEBNS; Kevin Akeret[1], MD; Flavio Vasella[1], MD; Julia Velz[1], MD; Elisabeth Jehli[1], MSc; Pierre Scheffler[1], MD; Stefanos Voglis[1], MD; Oliver Bichsel[1], MD; Nicolas R. Smoll[2], MBBS; Oliver Bozinov[1], MD; Luca Regli[1], MD; Menno R. Germans[1], MD/PhD; **on behalf of the CORRECT-SCAR study group***

[1]Department of Neurosurgery, University Hospital Zurich, Clinical Neuroscience Center, University of Zurich, Zurich, Switzerland

[2]School of Population and Global Health, University of Melbourne, Melbourne, Australia

***Contributors are listed in the appendix**

Correspondence to:

Martin N. Stienen, MD

Fellow of the European Board of Neurological Surgeons (FEBNS)

Department of Neurosurgery

University Hospital Zurich

Clinical Neuroscience Center

University of Zurich

Frauenklinikstrasse 10

8091 Zurich, Switzerland

Tel: +41 (0)44-255-1111

Email: mnstienen@gmail.com

Previous presentations:

None.

Appendix: Contributors of the "CORRECT-SCAR study group" (persons listed in alphabetical order):

Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland:

– David Bellut, MD

– Sandra F. Dias, MD

– Giuseppe Esposito, MD
– Jorn Fierstra, MD/PhD
– Dilek Könü-Leblebicioglu, MD
– Niklaus Krayenbühl, MD
– Marian C. Neidert, MD
– Markus Oertel, MD
– Carlo Serra, MD
– Lennart H. Stieglitz, MD

Abstract

Introduction: Outcomes rated on impairment scales are satisfactory after burr hole trepanation for chronic subdural hematoma (cSDH). However, the surgery leads to bony defects in the skull with skin depressions above that are frequently considered esthetically unsatisfactory by patients. Those defects could be covered by approved medical devices (burr hole covers), but this is rarely done today. We wish to assess, whether the application of burr hole covers after trepanation for the evacuation of cSDH leads to higher patient satisfaction with the esthetical result at 90 days postoperative, without worsening disability outcomes or increasing the complication rate.

Methods and analysis: This is a prospective, single-blinded, randomized, controlled, investigator initiated clinical trial enrolling eighty adult patients with first-time uni- or bilateral cSDH. The primary outcome is the difference in satisfaction with the esthetic result of the scar, comparing patients allocated to the intervention (burr hole cover) and control (no burr hole cover) group, measured on the Aesthetic Numeric Analogue scale at 90 days postoperative. Secondary outcomes include differences in the rates of skin depression, complications, as well as neurological, disability and health-related quality of life outcomes until 12 months postoperative.

Ethics and dissemination: The institutional review board approved this study on January 29th 2019 under case number BASEC 2018-01180. This study determines, whether a relatively minor modification of a standard surgical procedure can improve patient satisfaction, without worsening functional outcomes or increasing the complication rate. The outcome corresponds to the value-based medicine approach of modern patient-centered medicine.

Trial registration: ClinicalTrials.gov identifier: NCT03755349.

Key words

Burr hole cover; Chronic subdural hematoma; Trepanation; Esthetic outcome; Complications; Scar; Patient satisfaction; Burr hole plate

Article summary – strengths and limitations of this study

- The study might prove that surgeons can positively influence the satisfaction of their patients by a minor and inexpensive technical nuance (adding a burr hole cover before skin closure).
- By randomizing patients with unilateral cSDH into an intervention and control group, the effect of potential confounders should be minimized.
- The inclusion of patients with bilateral cSDH allows studying a completely unbiased effect of burr hole covers on the outcome of interest (as each patient serves as his/her own internal control).
- The 90-day period of the primary endpoint may be too short to detect a difference in outcome (as skin depressions progressively occur over time), but additional 12-month outcome assessment should capture this.

General Information

Protocol title: COveRs to impRove EsthetiC ouTcome after Surgery for Chronic subdural hemAtoma by buRr hole trepanation (CORRECT-SCAR) - a single-blinded, randomized controlled trial

Protocol identifying number: BASEC 2018-01180

Date of acceptance by institutional review board: January 29th 2019

Sponsor: Prof. Luca Regli, MD; Department of Neurosurgery; University Hospital Zurich; Clinical Neuroscience Center; University of Zurich; Frauenklinikstrasse 10; 8091 Zurich, Switzerland; Tel: +41 (0)44-255-1111

Principle investigator(s) responsible for conducting the research:

Priv.-Doz. Dr. Martin N. Stienen, MD/FEBNS; Department of Neurosurgery; University Hospital Zurich; Clinical Neuroscience Center; University of Zurich; Frauenklinikstrasse 10; 8091 Zurich, Switzerland; Tel: +41 (0)44-255-1111; mnstienen@gmail.com

Dr. Menno R. Germans, MD/PhD; Department of Neurosurgery; University Hospital Zurich; Clinical Neuroscience Center; University of Zurich; Frauenklinikstrasse 10; 8091 Zurich, Switzerland; Tel: +41 (0)44-255-1111; menno.germans@usz.ch

Study coordinator: Elisabeth Jehli, MSc; Department of Neurosurgery; University Hospital Zurich; Clinical Neuroscience Center; University of Zurich; Frauenklinikstrasse 10; 8091 Zurich, Switzerland; Tel: +41 (0)44-255-1111; elisabeth.jehli@usz.ch

Funding agency: Stryker European Operations B.V.; Herikerbergweg 110; 1101 CM Amsterdam; The Netherlands

Monitoring agency: Clinical Trials Center (CTC); UniversitätsSpital Zürich; Rämistrasse 100; 8091 Zurich; Switzerland; +41 (0)43-253-0128; CTC-Monitoring@usz.ch

Introduction

Outcome in terms of recovery of impaired neurological function is generally satisfactory after burr hole trepanation for the evacuation of chronic subdural hematoma (cSDH).[1 2] Despite being considered a relative minimally invasive type of surgery, it requires drilling holes in the patient's skull. With progressive hematoma reabsorption during follow-up, patients may develop skin depressions above the burr hole sites (Figure 1).[3 4] Theoretically, burr holes could be covered by approved medical devices (burr hole covers) after cSDH evacuation and prior to closing the wound.

This has not become standard of care, however, and we previously set out to explore the prevalence and relevance of skin depressions, as well as today's pattern of care by conducting a cross-sectional survey-based study among neurosurgeons globally. Analyzing 576 responses from 78 different countries, 76% of neurosurgeons stated that their patients complained about skin depressions after burr hole trepanations more or less frequently. In contrary, only 28% of neurosurgeons currently apply burr hole covers more or less frequently for this indication. Their reluctance was mostly explained by a lack of evidence for any proven benefit, less so for the fear of an increased complication rate, technical difficulties and financial reasons. Around three quarters (78% of neurosurgeons) indicated that they would consider applying burr hole covers for this indication, in case a high-quality trial demonstrated its efficacy and safety (unpublished data, April 2019).

We retrospectively reviewed a series of n=28 cSDH patients (64 burr holes) treated at our department, of which n=11 patients had received a burr hole cover on 14 burr holes at the surgeon's discretion. Applying the Aesthetic Numeric Analogue (ANA) scale to rate the esthetical result of the surgery,[5] patients rated sites where the burr hole was covered more favorably than sites where the burr hole was left uncovered (ANA 9.3±0.74 vs. 7.9±1.0; $p<0.001$).[4] In addition, the rates of skin depression were as low as 7% in the intervention group and as high as 92% in the control group ($p<0.001$). Evidently, the prior results were subject to selection bias, patients were not blinded for the intervention and the study was underpowered to estimate possible group differences in complications.[4] These preliminary findings were a promising starting point for further and more in-depth research, because filling this knowledge gap is likely to affect future management of cSDH patients.

Methods and analysis

Study Goals and Objectives

The CORRECT SCAR trial aims to demonstrate that the placement of burr hole covers on the burr hole sites improves patient satisfaction with the esthetic outcome of the surgical procedure at 3 and 12 months postoperative. It also aims to demonstrate that clinical outcomes (disability, neurological function & health-related quality of life (hrQoL)) remain similar and complication rates (e.g., surgical site infections (SSIs), cSDH recurrences, etc.) are not increased by applying burr hole covers.

The primary objective is to compare mean ANA scores (patient satisfaction with the esthetic result of the surgery) between the intervention and control group at 90 days postoperatively. Secondary/safety objectives are to compare mean ANA scores, rates of skin depression, impairment in activities of daily living (ADLs), disability (modified Rankin scale (mRS)), hrQoL (Euro-Qol (EQ)-5D), neurological status (National Institute of Health Stroke scale (NIHSS)), complications and residual hematoma volume between the intervention and control group at 3 and 12 months postoperative.

Study Design

Prospective, single-blinded, randomized, controlled, investigator initiated clinical trial. The trial is conducted at the University Hospital Zurich, Switzerland. The study will be reported according to the CONSORT guidelines.[6]

Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Patients with first-time cSDH (hypodense, isodense, hyperdense or mixed-type in CT-imaging), scheduled for uni- or bilateral double burr hole trepanation under general anesthesia
- Patient age ≥ 18 years
- Patient non-comatose at time of inclusion (GCS > 8 points)
- Patient able to communicate (in terms of ability to hear, see, speak and understand).

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Patient with recurrent cSDH or previous surgery for cSDH
- Patient with cSDH treated by craniotomy or by single burr hole trepanation
- Patient with cSDH treated in local anesthesia
- Patient unlikely to attend the follow-up (due to reasons of residency, dismal prognosis, etc.)

- Pregnancy
- Known allergy against or incompatibility with Titanium
- Known or suspected non-compliance
- Inability to follow the study procedures, e.g. due to psychological disorders, dementia, etc. of the participant.

Intervention & study groups

A study algorithm can be found in figure 2 and table 1 outlines all visits and procedures.

1. Patients with unilateral cSDH

   All patients randomized into the control group will be treated according to our standard protocol for cSDH evacuation (supplementary digital content 1).

   All patients randomized into the intervention group will be treated according to our standard protocol for cSDH evacuation with one exception: placement of a burr hole cover (UN3 BURR HOLE COVER, 20mm, W/TAB, Item code 53-34520, Stryker®, Kalamazoo, Michigan) that is fixed with 2 screws (UNIII AXS SCREWS, SELF-DRILLING, 1.5 x 4MM, Item code 56-15934, Stryker®, Kalamazoo, Michigan) on both burr holes after evacuation of the hematoma and prior to skin closure.

2. Patients with bilateral cSDH

   Patients with bilateral cSDH serve as their own internal control. They are randomized concerning the intervention or control side, being either the side with larger or smaller hematoma, respectively.

All patients are blinded concerning the study group/side allocation. For application of the burr hole cover, surgeons will be instructed to firmly press the burr hole cover on the burr hole before receiving the screws from the scrub nurse in order to prevent from screws accidently falling into the subdural space. For this purpose, a standard operating procedure (SOP) has been developed (supplementary digital content 2).

Primary Outcome and Follow-Up

For the primary outcome, patient satisfaction with the esthetic results of the scar is determined using a patient-rated outcome measure (PROM), the ANA scale,[5] ranging from 0 (dissatisfied) – 10 (very satisfied), at 90 days postoperative. The outcome is assessed by mailed questionnaire and collected by a study coordinator.

Secondary Outcomes

- Patient satisfaction with the esthetic result of the scar, determined by the ANA scale, at 12 months postoperatively (mailed questionnaire, collected by a study coordinator).

- Impairment in ADLs (e.g., when hairdressing, combing, washing, etc.), rated as "yes" vs. "no", at 90 days and 12 months postoperative (mailed questionnaire, collected by a study coordinator).
- Rate of skin depression, rated as "yes" vs. "no", at 90 days and 12 months postoperative (mailed questionnaire, collected by a study coordinator).
- Disability, determined by the mRS (ranging from 0 (no disability) to 6 (dead)) at 90 days.
- HrQoL, determined by the EQ-5D (allowing the calculation of both the EQ-5D index that ranges from -0.074 (worst hrQoL) – 1.00 (best hrQoL) using European norms and the EQ-5D VAS (ranging from 0 (worst hrQoL) – 100 mm (best hrQoL)), at 90 days and 12 months postoperative (mailed questionnaire, collected by a study coordinator).
- Neurological outcome, determined by the NIHSS (ranging from 0 (no neurological deficit) – 42 (severe neurological deficit)), at 90 days.
- Home time, as surrogate marker of disability,[7] at 90 days and 12 months.

Further safety-outcomes are assessed:

- Intra- and postoperative complications up to 90 days and 12 months, in particular cSDH recurrence and SSIs.
- Residual cSDH volume in ccm^3, absolute (ccm^3) and relative (%) cSDH clearance at 90 days postoperative (measured by two neuroradiologists independently, otherwise not involved in the project, using volumetric analysis).

Patient and Public Involvement

Other than recruiting patients admitted to our hospital, it is not intended to involve patients and the public in the design, conduct and reporting of this research.

Ethics and dissemination

Despite the generally favorable risk profile and outcome of burr hole trepanation for cSDH, skin depressions may occur weeks and months after hematoma reabsorption.[3 4] These are frequently considered esthetically unsatisfactory by patients and may lead to functional restrictions, e.g. when combing, hairdressing or washing. In own clinical experience, patients reported being stared-at for these skin depressions, evoking feelings of astonishment and aversion from both family members and strangers. With an increasing number of senior citizens in good physical/mental health and leading active social lives, the esthetic aspect of

outcome gains new importance. Today's elderly patients do no longer content themselves with a basic surgical procedure, but – as informed customers – expect optimal surgical results topped with an excellent service.[8]

In theory, burr hole covers represent an effective, easy-to-apply and relatively inexpensive solution to prevent cosmetically and functionally unfavorable skin depressions.[4] Our survey has clearly demonstrated that – in order to improve the acceptance of this technical nuance – its efficiency needs to be demonstrated first (unpublished data, April 2019). Moreover, as the intervention is unlikely to improve any "hard outcome" such as disability or survival, more data should substantiate its safety.

We consider a prospective, randomized, blinded and controlled study design optimal to prove a causal relationship between the study intervention and outcome. A clear strength of this study is that patients with bilateral cSDH can be included and serve as their own internal controls. Any retrospective approach to the study question, or applying the burr hole cover in a prospective fashion and comparing it to a (historical) control group is not possible, as the outcome of interest (ANA scale) has not been established in patients before, as well as for the likelihood of selection bias. The study aim corresponds to the value-based medicine approach of modern patient-centered medicine.

Trial Status

The study has started enrolling patients on January 29th 2019.

Safety Considerations

Burr hole covers are applied according to a SOP (supplementary digital content 2) and the medical device is approved for the studied application. All device deficiencies, (severe) adverse events ((S)AEs) and (severe) adverse device effects ((S)ADEs) are systematically recorded. The Clinical Trials Center (CTC) of the University of Zurich externally monitors the trial.

Follow-up

Participating patients are followed up to 12 months postoperative.

Unblinding

Maintenance of trial treatment randomization codes will be done by the electronic data capturing system (run by the CTC Zurich), using a built-in tool for randomization. Breaking codes is not allowed. Unblinding (and revealing a participant's allocated intervention)

towards the patient is permissible only if the trial is suspended, prematurely terminated due to security concerns or completed.

Data Managements and Statistical Analysis

The data is hosted by the CTC, University of Zurich. Electronic case report forms (eCRFs) are implemented. All data are stored on a server in a dedicated database. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission.

Handling of missing data

First, the risk of missing data will be minimized by regular data reviews, also with an intention to identify at risk patients for lack of follow-up data. Even though the effect of skin depression is likely more pronounced at 12 months, compared to 90 days postoperative, we intentionally chose to select the 90-day time point as primary outcome in order to minimize drop-out. Contingency plans foresee home/rehabilitation visits by study personnel to obtain otherwise missing data in patients who cannot show up for the planned 90-day or 12-month follow-up.[9] Patients who die during the study interval (or cannot be evaluated as aphasic or in too poor clinical condition) and in whom for this reason the primary endpoint cannot be obtained will be recorded as not assessable for the primary outcome. Sensitivity analyses will be performed for this study.

If, despite the above-mentioned mechanisms, missing data is present we use the following protocol: First, mechanisms of missing data are assessed. If the data are deemed missing at random, and there is <10-15% of patients with time point missing data, then case deletion will be used (and additional patients will be recruited). Second, if the missing data mechanism is not at random, multiple imputation will be performed, a well-accepted method for intention to treat analysis in RCT with missing outcome data.[9 10]

Determination of sample size

Based on an expected mean satisfaction score of 9/10 on the ANA in the intervention and 7/10 on the ANA in the control group, n=37 patients need to be randomized in each study arm in order to find a statistically significant difference in the primary outcome with alpha set at 0.05, a power of 80% and an estimated standard deviation of 3.[4] Based on a total sample size of 2x37=74, with an estimated dropout rate of 10%, we plan to include n=80 patients in total.

Methods used to minimize bias

A computerized randomization tool, provided by the electronic data capturing system, is used with the only strata being uni- or bilateral cSDH. The random allocation sequence is generated by the CTC, University of Zurich. Study physicians conduct patient enrollment and randomization after basic patient data has been entered into eCRFs. Due to the randomization process, patients with unilateral cSDH are likely to be well balanced for most important parameters that could potentially influence the primary outcome. In patients with bilateral cSDH, each patient serves as his/her own control, which minimizes the risk of bias (=setting of a n-of-1 clinical trial).[11]

Patients with unilateral cSDH will be randomized in a 1:1 fashion into the intervention or control group, respectively. Patients with bilateral cSDH will be randomized in a 1:1 fashion concerning the intervention side, being either the side with more or lesser hematoma size (Figure 2).

Patients will be blinded for allocation to the study group/side, but surgeons will not be. Patients will not be aware of the study group/side, since the operation takes place under general anesthesia. The fact that patients are blinded for the study group allocation will be mentioned in the discharge letter (in order to inform the family physician), and the neurosurgical team of nurses and physicians will also be informed not to "unblind" the patient.

The primary endpoint and most of the secondary endpoints will be determined by mailed questionnaires. This way, the patient will not be influenced by the presence of the physician when judging on satisfaction with the esthetical result of the surgery. In addition, all data is collected by a dedicated study coordinator (E.J.), who is not involved in the patient care (=independent outcome assessment).

Primary analysis

The main analysis will be according to the intention to treat (ITT) protocol. An as-treated analysis will be performed, additionally.

Satisfaction on the ANA scale for both the frontal and parietal scar are measured separately, but a mean satisfaction score is built by adding the values and dividing the sum by two. For analysis of the primary outcome the results obtained in the intervention group (unilateral cSDH) and on the intervention side (bilateral cSDH) will be combined and compared to the combined results obtained in the control group and on the control side. As the dependent variable is a quantitative variable on an interval scale, a rank-sum test is appropriate to analyze group differences. Even though no formal minimum clinically important difference (MCID) of the ANA-scale has been determined, we powered the study to

detect an in-between group difference in outcome of two points, as – abstracted from the numeric rating scale for pain (also ranging between 0 – 10) – a change of two points is considered to be well above the MCID,[12] therefore resulting in a clinically meaningful improvement for the patient.

Subgroup analyses will be made for patients with bald heads vs. patients with scalp hear, male vs. female patients, patients < 60 years vs. ⩾ 60 years and for patients with bilateral cSDH.

Secondary analyses

As the remaining secondary outcomes are not side-specific but reflect the condition of the patient as a whole, the remaining secondary analyses will compare results obtained in patients with unilateral cSDH randomized into either the intervention or control group.

As the safety outcomes are specific for the incision site and side, for the safety analyses the results obtained in the intervention group and on the intervention side will be combined and compared to the combined results obtained in the control group and on the controlled side.

For the outcomes that are quantitative (hrQoL on the EQ-5D) student's t-tests or rank-sum tests will be applied, depending on normally distributed data or not. For the outcomes that are categorical (type of impairment with ADLs, disability on the mRS, neurological outcome on the NIHSS, complications on the CDG) descriptive analyses and chi-square tests will be applied. For the outcomes that are binary (impairment with ADLs, skin depression, etc.) logistic regression analysis will be performed, calculating the odds ratio (OR) and 95% confidence intervals (CIs).

Interim analyses

Once data of 50 patients with completed 90-day follow-up data has been collected, the primary endpoint and the safety analyses will be performed.

Quality Assurance

The study is conducted in accordance with good clinical practice (GCP) guidelines. All source data is accessible for monitoring, audits and inspections. Authorities have the right to perform inspections and on-site auditing. External monitoring will be performed by the CTC, University of Zurich, as detailed in a monitoring plan including pre-study, site initiation, routine monitoring and close-out visits, considering local infrastructure, completeness of

documents, patient safety, adherence to the study protocol, data quality entered into the eCRFs and the trial master file.

Progress of patient inclusion and data completeness is continuously (at least once every two weeks) checked by a study coordinator (E.J.).

Expected Outcomes of the Study

The study will shed more light on the question, whether patient satisfaction with the esthetic result of the surgical procedure can be improved by adding burr hole covers on the burr holes after trepanation for cSDH. An improvement in patient satisfaction would likely be conferred through the decreased prevalence of skin depressions, as a strong difference in prevalence of skin depressions was previously found in two retrospective studies.[3 4] The study will moreover allow to understand better, whether the application of burr hole covers increases the risks of complications, e.g. cSDH recurrence or SSIs. Results of the study are likely to affect future management of cSDH patients.

Duration of the project

Recruitment is expected to be completed by the end of January 2021, with final follow-up collected until January 2022. Publication of the final results is expected around six months after last patient out.

Project management

The principle investigators (M.N.S. & M.R.G.) are responsible for patient inclusion, quality of data collection and adhesion to the protocol. They are supported by a team of site investigators, a dedicated study coordinator (E.J.), the monitoring staff and the sponsor (L.R.).

Ethics

The study protocol has been approved by the local IRB on January 29th 2019 (BASEC 2018-01180) and registered on http://www.clinicaltrials.gov with the identifier: NCT03755349. All patients and/or next-of-kin will give written informed consent.

Tables

Table 1: Tabular listing of schedule of events and assessments and procedures of the study. ADLs = activities of daily living; ANA = Aesthetic Numeric Analogue scale; CDG = Clavien-Dindo grading scale; CT = computed tomography; EQ-5D = EuroQol 5 D health questionnaire; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale.

Study Periods	Before surgery	Surgery	Discharge from hospital	90-day Follow-up	12-month Follow-up
Visit	1	2	3	4	5
Time (days)	0 (-7 – 0)	0	5 (3 – 14)	90 (±10)	365 (±30)
Patient Information and Informed Consent	x		(x)	(x)	
Demographics	x				
Medical History	x				
In- /Exclusion Criteria	x				
Physical Examination	x		x	x	
Laboratory Examinations					
Quick/INR/PTT		x			
Thrombocyte count		x			
Randomization	x				
Other examinations (CT-Scan)	x		x	x	
Hematoma volume	x		x	x	
Administer Medical Device (burr hole covers and screws)		x			
Primary outcome					
Patient satisfaction (ANA)				x	x
Secondary outcomes					
Impairment in ADLs				x	x
Skin depression				x	x
HrQoL (EQ-5D)	x			x	x
Disability (mRS)	x		x	x	
Neurological status (NIHSS)	x		x	x	
Complications (CDG)			x	x	x
Adverse Events	x	x	x	x [B]	x

Figure legends

Figure 1: Example of skin depression above the burr holes in a male patient in his late 80's, about two years following frontal and parietal burr hole trepanation for the evacuation of a large chronic subdural hematoma. The photo was taken with his permission and at this time he continued to lead an active life. Upon inquiry, he and his wife confirmed feeling troubled by the well-visible and stigmatizing skin depressions.

Figure 2: Illustration of the algorithm of the CORRECT-SCAR trial. cSDH = chronic subdural hematoma; CT = computed tomography.

Supplementary digital content

Supplementary digital content 1: Standard protocol for cSDH evacuation.

Supplementary digital content 2: SOP for the application of burr hole covers in the context of cSDH evacuation.

Full references

1. Kolias AG, Chari A, Santarius T, et al. Chronic subdural haematoma: modern management and emerging therapies. Nature reviews. Neurology 2014;**10**(10):570-8 doi: 10.1038/nrneurol.2014.163[published Online First: Epub Date]|.

2. Maldaner N, Sosnova M, Sarnthein J, et al. Burr hole trepanation for chronic subdural hematomas: is surgical education safe? Acta neurochirurgica 2018;**160**(5):901-11 doi: 10.1007/s00701-017-3458-8[published Online First: Epub Date]|.

3. Im TS, Lee YS, Suh SJ, et al. The Efficacy of Titanium Burr Hole Cover for Reconstruction of Skull Defect after Burr Hole Trephination of Chronic Subdural Hematoma. Korean journal of neurotrauma 2014;**10**(2):76-81 doi: 10.13004/kjnt.2014.10.2.76[published Online First: Epub Date]|.

4. Vasella F, Akeret K, Smoll NR, et al. Improving the aesthetic outcome with burr hole cover placement in chronic subdural hematoma evacuation-a retrospective pilot study. Acta neurochirurgica 2018;**160**(11):2129-35 doi: 10.1007/s00701-018-3659-9[published Online First: Epub Date]|.

5. Funk W, Podmelle F, Guiol C, et al. Aesthetic satisfaction scoring - introducing an aesthetic numeric analogue scale (ANA-scale). Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery 2012;**40**(5):439-42 doi: 10.1016/j.jcms.2011.07.018[published Online First: Epub Date]|.

6. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Bmj 2010;**340**:c332 doi: 10.1136/bmj.c332[published Online First: Epub Date]|.

7. Stienen MN, Smoll NR, Fung C, et al. Home-Time as a Surrogate Marker for Functional Outcome After Aneurysmal Subarachnoid Hemorrhage. Stroke 2018;**49**:3081-84

8. Stienen MN, Serra C, Stieglitz LH, et al. UniversitatsSpital Zurich: 80 years of neurosurgical patient care in Switzerland. Acta neurochirurgica 2017 doi: 10.1007/s00701-017-3357-z[published Online First: Epub Date]|.

9. Kang H. The prevention and handling of the missing data. Korean journal of anesthesiology 2013;**64**(5):402-6 doi: 10.4097/kjae.2013.64.5.402[published Online First: Epub Date]|.

10. White IR, Horton NJ, Carpenter J, et al. Strategy for intention to treat analysis in randomised trials with missing outcome data. Bmj 2011;**342**:d40 doi: 10.1136/bmj.d40[published Online First: Epub Date]|.

11. Lillie EO, Patay B, Diamant J, et al. The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? Personalized medicine 2011;**8**(2):161-73 doi: 10.2217/pme.11.7[published Online First: Epub Date]|.

12. Gautschi OP, Stienen MN, Corniola MV, et al. Assessment of the Minimum Clinically Important Difference in the Timed Up and Go Test After Surgery for Lumbar Degenerative Disc Disease. Neurosurgery 2017;**80**(3):380-85 doi: 10.1227/NEU.0000000000001320[published Online First: Epub Date]|.

Authors' contributions:

Those persons listed as authors on the manuscript have made substantial contributions to the conception or design of the work, are currently involved in acquiring, analyzing, or interpreting the data for the work. They all have been active in drafting or revising the study protocol for important intellectual content, which is basis of the current article. All authors have approved the final version to be published. They agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In detail: MNS, KA, FV, JV, EJ, PS, SV, OB, NRS, OLB, LR and MRG designed the study, are local (principle) investigators or other key persons. MNS acquired the funding. MNS reviewed the literature and drafted the manuscript. KA, FV, JV, EJ, PS, SV, OB, NRS, OLB, LR and MRG contributed to drafting of the manuscript. All authors read and approved the final manuscript.

Funding Statement:

This research is financed and conducted by the Department of Neurosurgery, University Hospital Zurich, Switzerland. It is financially supported by the Stryker company, after careful and independent review of the study protocol. The funding source is not involved and does not influence the data collection, measurements, interpretation, or drafting of the manuscript.

Competing interests statement:

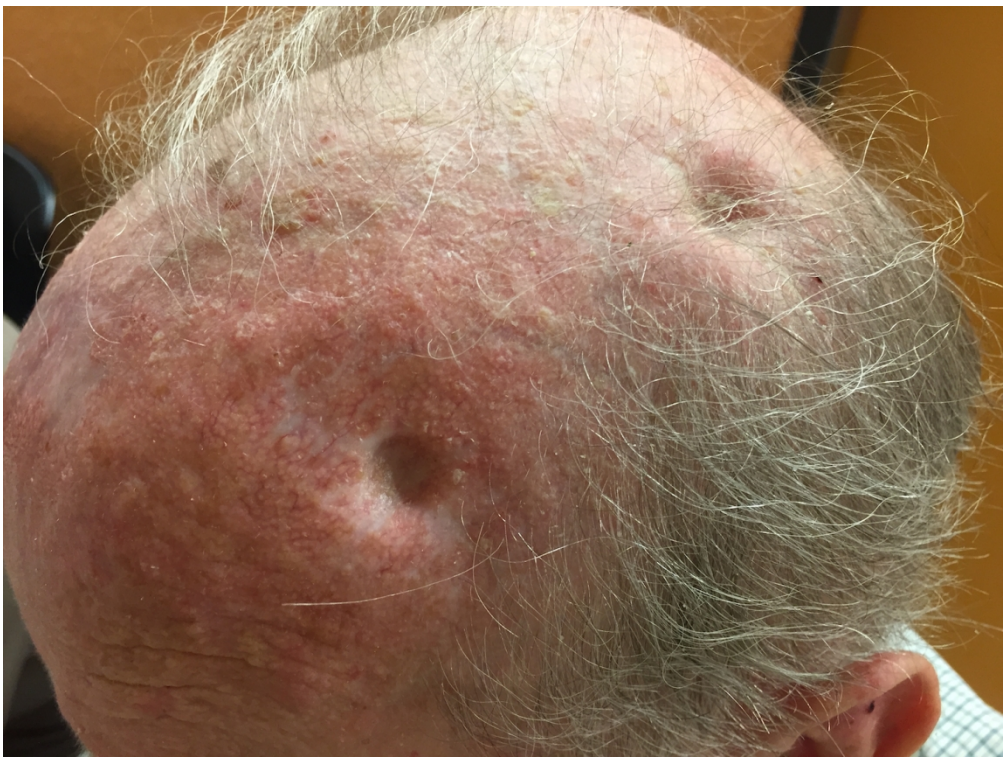
All authors declare that they have nothing to disclose and no conflicts of interest.

Data availability statement:

Individual patient data (IPD), study protocol, statistical analysis plan (SAP) and analytic code will be made available on reasonable request, once the results are published and if approved by the institutional review board (KEK-ZH).

Word count:

3079 for article text (excluding references)



Example of skin depression above the burr holes in a male patient in his late 80's, about two years following frontal and parietal burr hole trepanation for the evacuation of a large chronic subdural hematoma. The photo was taken with his permission and at this time he continued to lead an active life. Upon inquiry, he and his wife confirmed feeling troubled by the well-visible and stigmatizing skin depressions.

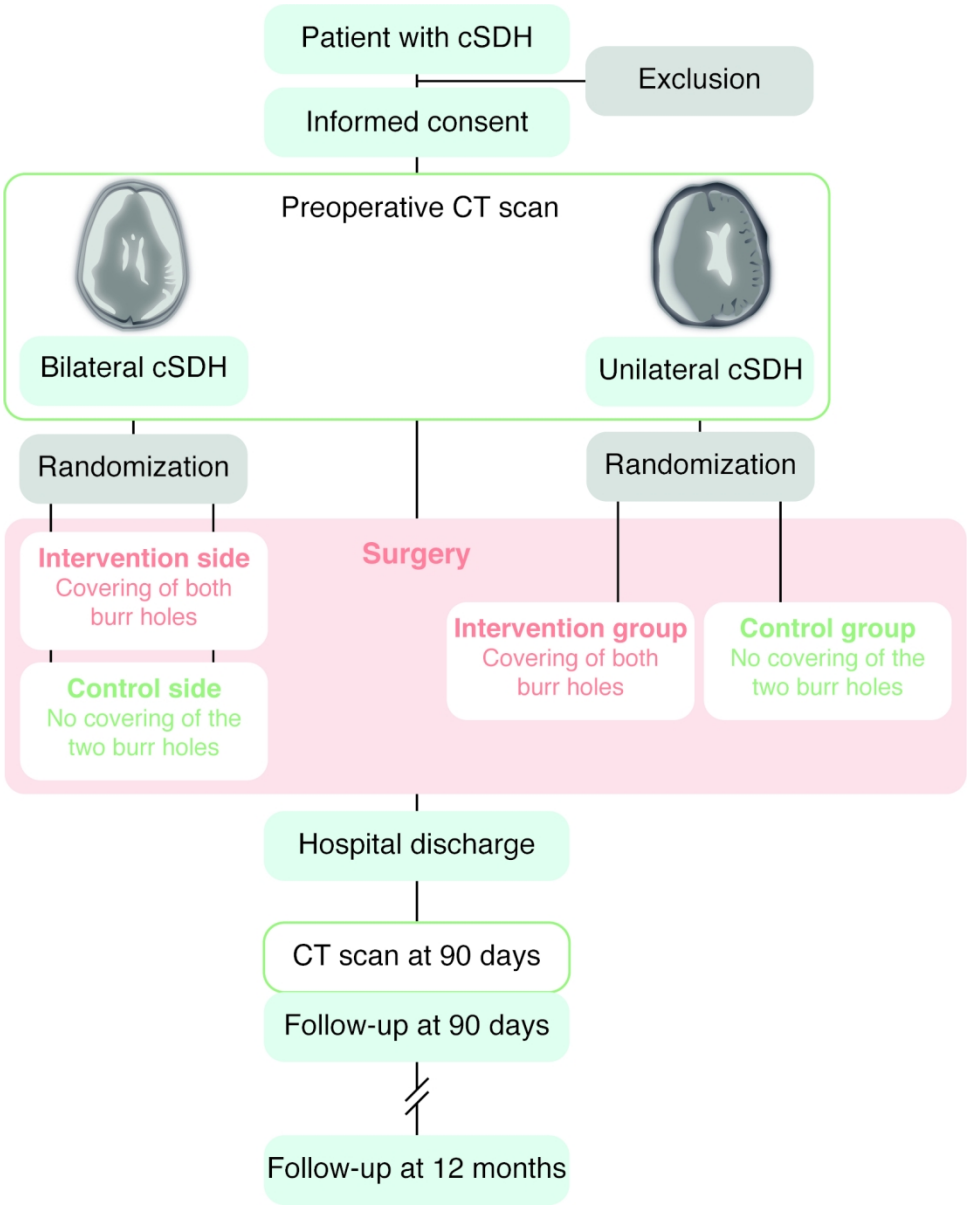


Illustration of the algorithm of the CORRECT-SCAR trial. cSDH = chronic subdural hematoma; CT = computed tomography.

UniversitätsSpital Zürich

STANDARD OPERATING PROCEDURE

Application of burr-hole covers after trepanation of chronic subdural hematoma

Surgical Procedure in general

The procedure is described for one-sided burr-hole trepanation – but can likewise be applied for bilateral trepanations – of chronic subdural hematomas (cSDH).

1. The procedure is usually performed under general anesthesia.
2. The head is rotated about 80° towards the contralateral side and positioned on a ring-shaped gel cushion.
3. The hair is shaved for 5x2 cm in the region of anticipated incisions.
4. No infiltration of the skin (with saline or local anesthesia).
5. Skin incisions, each one frontal and parietal, about 35 mm in length.
6. Double burr-hole trepanation with the 14-mm trepan.
7. The frontal burr-hole is usually placed at the junction of the superior temporal line and the coronal suture (stephanion), while the posterior burr-hole is usually placed in the region of the parietal eminence.
8. After trepanation and dural opening, the hematoma is evacuated by repeated irrigation with warmed saline solution until reflux is limpid.
9. Per operated side, a subperiostal drain is placed.
10. The burr-hole cover is now placed and secured with 2 screws, according to the protocol below.
11. The subdural space is filled with warmed saline solution in order to prevent from trapped air inside the skull.
12. The skin is closed by tight subcutaneous sutures and staples on the skin (one staple for each 3 mm incision length).
13. For bilateral cSDH, the procedure is repeated on the contralateral side

Application of the burr-hole cover

The following steps must be taken to prevent from patient injury during application of the burr-hole cover and its fixation with screws. Of note, we usually place the subperiostal drain before placement of the burr-hole covers, but for demonstration purpose the following pictures were made without the drain (it can gently be pushed aside for the burr-hole cover placement).

1. For each burr-hole that is to be covered, one burr-hole cover (UN3 BURR HOLE COVER, 20mm, W/TAB, Item code 53-34520, Stryker®, Kalamazoo, Michigan; Figures 1 & 2) is applied.

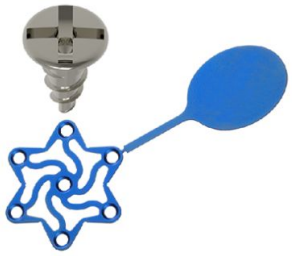


Figure 1: UN3 BURR HOLE COVER, 20mm (Stryker®, Kalamazoo, Michigan) with magnified UNIII AXS SCREWS, SELF-DRILLING, 1.5 x 4MM (Stryker®, Kalamazoo, Michigan).

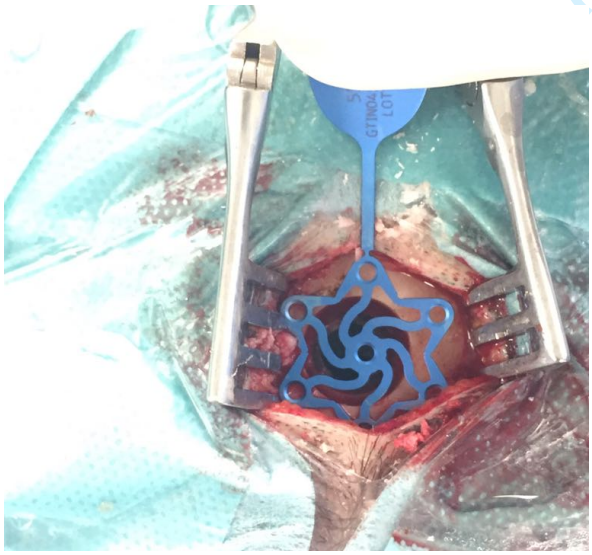


Figure 2: Image demonstrating the placement of UN3 BURR HOLE COVER, 20mm (Stryker®, Kalamazoo, Michigan) in situ.

2. The burr-hole cover is firmly pressed to the patient skull with the finger, making sure that the burr-hole is completely covered and no items such as screws can fall into the subdural space (Figure 3).

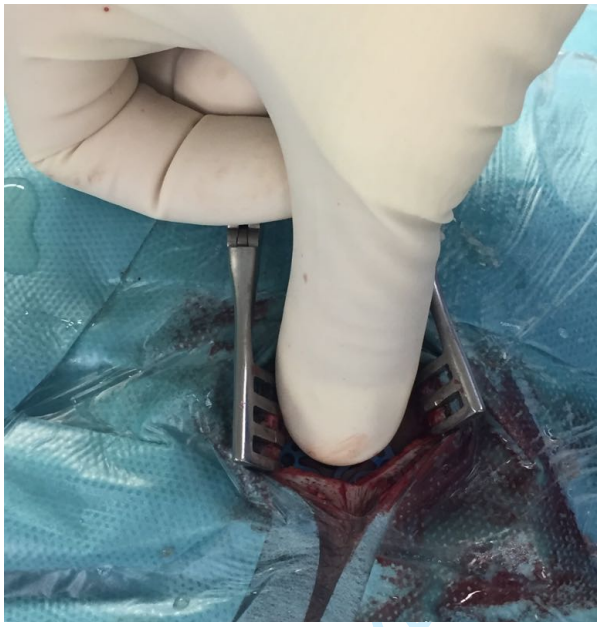


Figure 3: Image demonstrating how the burr-hole cover is positioned over the burr-hole, using a finger to hold the position.

3. Only when the burr-hole is completely covered, the surgeon receives the first screw (UNIII AXS SCREWS, SELF-DRILLING, 1.5 x 4MM, Item code 56-15934, Stryker®, Kalamazoo, Michigan) and applies it in any given screw hole of the burr-hole cover (Figure 4).

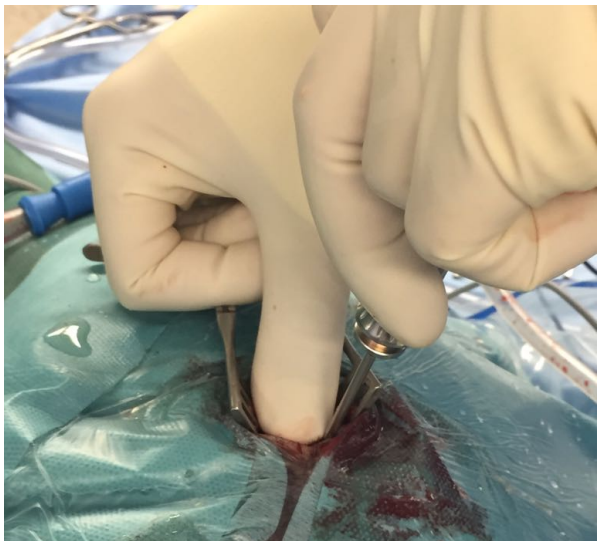


Figure 4: Image demonstrating how the screw should be applied, with the surgeon making sure that the burr-hole cover covers the burr-hole completely.

4. Only after double-checking that the burr-hole is still completely covered and while continuing to press it onto the patient skull, the surgeon receives the second screw (UNIII AXS SCREWS, SELF-DRILLING, 1.5 x 4MM, Item code 56-15934, Stryker®, Kalamazoo, Michigan) and applies it in the screw hole on the most opposite side (Figure 5).

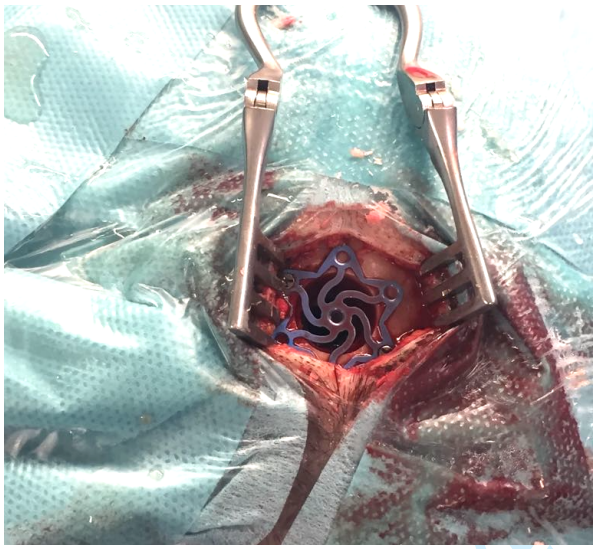


Figure 5: Image demonstrating the application of the second screw in the most opposite screw hole of the burr-hole cover.

Authors:
Martin N. Stienen, Menno R. Germans, Julia Velz, Flavio Vasella, Luca Regli
Department of Neurosurgery, University Hospital Zurich, Switzerland

Standard protocol for chronic subdural hematoma (cSDH) evacuation

All symptomatic patients, particularly those with large cSDH (maximal axial diameter > 15mm or relevant midline shift (MLS)) or presenting in reduced vigilance (GCS < 15) are usually operated within 24 hours. Coagulation parameters are checked routinely prior to surgery. Surgery for patients under anti-aggregation or anticoagulation is delayed until blood clotting and thrombus functions is restored, whenever possible, under close monitoring. Our departmental protocol aims at maintaining platelets at >100 x 10^9/dl and an international normalized ratio (INR) of <1.4. Coagulation abnormalities are actively reversed preoperatively with prothrombin complex concentrate or fresh frozen plasma, if urgent surgery is required. Antiplatelet medication is stopped 5–7 days prior to surgery; if urgent surgery is required, one jumbo unit of platelet concentrate is administered immediately preoperative.

We usually perform double burr-hole trepanation (20mm) per side under general anesthesia. The patient is placed in supine position with the head rotated about 80° towards the contralateral side and positioned on a ring-shaped gel cushion. If necessary, the hair is shaved for 5 x 2 cm in the region of anticipated incisions. Two skin incisions per side, each 35 mm in length, are required. A 14-mm trepan is used for both burr holes. The frontal burr hole is usually placed at the junction of the superior temporal line and the coronal suture (stephanion), while the posterior burr hole is usually placed in the region of the parietal eminence. In case of significant bilateral hematoma, trepanation is performed on both sides. After trepanation and dural opening, the hematoma is evacuated by repeated irrigation with warmed saline solution until reflux is limpid. There is little doubt that placing a drain after hematoma evacuation can significantly reduce the recurrence rate in cSDH. Whether placing the drain in the superiostal or subdural space is superior has not been proven so far, but we prefer subperiostal drains for the better safety profile. The skin is closed by tight subcutaneous sutures and staples on the surface. For bilateral cSDH the procedure is repeated on the contralateral side.

Postoperatively, patients remain immobilized and flat in supine position for 48 hours until the drain is removed. In absence of residual deficits, patients are discharged from postoperative day three on. We routinely perform outpatient follow-up visits with cranial computed

tomography (CT) scan at 6 and 12 weeks postoperatively. Follow-up is continued on an individual basis afterwards.

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **- YES**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **- YES**
	2b	All items from the World Health Organization Trial Registration Data Set **- YES**
Protocol version	3	Date and version identifier **- YES**
Funding	4	Sources and types of financial, material, and other support **- YES**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **- YES**
	5b	Name and contact information for the trial sponsor **- YES**
	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 **- YES**
	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) **- YES**
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 **- YES**
	6b	Explanation for choice of comparators **- YES**
Objectives	7	Specific objectives or hypotheses **- YES**

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) **- YES**
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 **- YES**
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) **- YES**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **- YES**
	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) **- YES**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **- YES**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **– NOT APPLICABLE**
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 **- YES**
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) **– YES – FIGURE 2 & 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 **- YES**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **- YES**
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 **- YES**
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 **- YES**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **- YES**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **- YES**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **- YES**
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 **- YES**
	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 **- YES**
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 **- YES**
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 **- YES**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **- YES**
	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) **- YES**

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 **- YES**
	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 **- YES**
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 **- YES**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **- YES**

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **- YES**
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) **- YES**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **- YES**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **– NOT APPLICABLE**
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 **- YES**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **- YES**
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 **– NOT APPLICABLE – DATA ACCESS REGULATED BY ELECTRONIC GCP-CONFORM DATABASE**
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 **– NOT APPLICABLE**

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 **- YES**
	31b	Authorship eligibility guidelines and any intended use of professional writers **- YES**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **– THIS PROTOCOL IS PUBLISHED OPEN ACCESS IN BMJ Open, IF ACCEPTED**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **– NOT HELPFUL TO MOST READERS, AS IN GERMAN LANGUAGE**
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 **- NOT APPLICABLE**

*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.

BMJ Open

COveRs to impRove EsthetiC ouTcome after Surgery for Chronic subdural hemAtoma by buRr hole trepanation (CORRECT-SCAR) – protocol of a Swiss single-blinded, randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031375.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Oct-2019
Complete List of Authors:	Stienen, MN; University Hospital Zurich, Neurosurgery Akeret, Kevin; University Hospital Zurich, Neurosurgery Vasella, Flavio; University Hospital Zurich, Neurosurgery Velz, Julia; UniversitatsSpital Zurich Neurochirurgische Klinik, Jehli, Elisabeth; University Hospital Zurich, Neurosurgery Scheffler, Pierre; University Hospital Zurich, Neurosurgery Voglis, Stefanos; University Hospital Zurich, Neurosurgery Bichsel, Oliver; University Hospital Zurich, Neurosurgery Smoll, Nicolas; University of Newcastle, School of Medicine and Public Health Bozinov, Oliver; University of Zurich, Neurosurgery Regli, Luca; University Hospital Zurich, Neurosurgery Germans, Menno; University Hospital Zurich, Neurosurgery
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Geriatric medicine, Neurology, Surgery
Keywords:	Chronic subdural hematoma, Esthetic outcome, Patient satisfaction, Burr hole cover, Trepanation, Value-based medicine

COveRs to impRove EsthetiC ouTcome after Surgery for Chronic subdural hemAtoma by buRr hole trepanation (CORRECT-SCAR) – protocol of a Swiss single-blinded, randomized controlled trial

Martin N. Stienen[1], MD/FEBNS; Kevin Akeret[1], MD; Flavio Vasella[1], MD; Julia Velz[1], MD; Elisabeth Jehli[1], MSc; Pierre Scheffler[1], MD; Stefanos Voglis[1], MD; Oliver Bichsel[1], MD; Nicolas R. Smoll[2], MBBS; Oliver Bozinov[1], MD; Luca Regli[1], MD; Menno R. Germans[1], MD/PhD; **on behalf of the CORRECT-SCAR study group***

[1]Department of Neurosurgery, University Hospital Zurich, Clinical Neuroscience Center, University of Zurich, Zurich, Switzerland

[2]School of Population and Global Health, University of Melbourne, Melbourne, Australia

Correspondence to:

Martin N. Stienen, MD

Fellow of the European Board of Neurological Surgeons (FEBNS)

Department of Neurosurgery

University Hospital Zurich

Clinical Neuroscience Center

University of Zurich

Frauenklinikstrasse 10

8091 Zurich, Switzerland

Tel: +41 (0)44-255-1111

Email: mnstienen@gmail.com

Previous presentations:

None.

***Contributors of the "CORRECT-SCAR study group" (persons listed in alphabetical order):**

Department of Neurosurgery, University Hospital Zurich, Zurich, Switzerland:

– David Bellut, MD

– Sandra F. Dias, MD

– Giuseppe Esposito, MD

– Jorn Fierstra, MD/PhD

– Dilek Könü-Leblebicioglu, MD

– Niklaus Krayenbühl, MD

– Marian C. Neidert, MD

– Markus Oertel, MD

– Carlo Serra, MD

– Lennart H. Stieglitz, MD

Abstract

Introduction: Outcomes rated on impairment scales are satisfactory after burr hole trepanation for chronic subdural hematoma (cSDH). However, the surgery leads to bony defects in the skull with skin depressions above that are frequently considered esthetically unsatisfactory by patients. Those defects could be covered by approved medical devices (burr hole covers), but this is rarely done today. We wish to assess, whether the application of burr hole covers after trepanation for the evacuation of cSDH leads to higher patient satisfaction with the esthetical result at 90 days postoperative, without worsening disability outcomes or increasing the complication rate.

Methods and analysis: This is a prospective, single-blinded, randomized, controlled, investigator initiated clinical trial enrolling eighty adult patients with first-time uni- or bilateral cSDH in Switzerland. The primary outcome is the difference in satisfaction with the esthetic result of the scar, comparing patients allocated to the intervention (burr hole cover) and control (no burr hole cover) group, measured on the Aesthetic Numeric Analogue scale at 90 days postoperative. Secondary outcomes include differences in the rates of skin depression, complications, as well as neurological, disability and health-related quality of life outcomes until 12 months postoperative.

Ethics and dissemination: The institutional review board (Kantonale Ethikkommission Zürich) approved this study on January 29th 2019 under case number BASEC 2018-01180. This study determines, whether a relatively minor modification of a standard surgical procedure can improve patient satisfaction, without worsening functional outcomes or increasing the complication rate. The outcome corresponds to the value-based medicine approach of modern patient-centered medicine. Results will be published in peer-reviewed journals and electronic patient data will be safely stored for 15 years.

Trial registration: ClinicalTrials.gov identifier: NCT03755349.

Key words

Burr hole cover; Chronic subdural hematoma; Trepanation; Esthetic outcome; Complications; Scar; Patient satisfaction; Burr hole plate

Article summary – strengths and limitations of this study

- The study might prove that surgeons can positively influence the satisfaction of their patients by a minor and inexpensive technical nuance (adding a burr hole cover before skin closure).
- By randomizing patients with unilateral cSDH into an intervention and control group, the effect of potential confounders should be minimized.
- The inclusion of patients with bilateral cSDH allows studying a completely unbiased effect of burr hole covers on the outcome of interest (as each patient serves as his/her own internal control).
- The 90-day period of the primary endpoint may be too short to detect a difference in outcome (as skin depressions progressively occur over time), but additional 12-month outcome assessment should capture this.

General Information

Protocol title: COveRs to impRove EsthetiC ouTcome after Surgery for Chronic subdural hemAtoma by buRr hole trepanation (CORRECT-SCAR) - a single-blinded, randomized controlled trial

Protocol identifying number: BASEC 2018-01180

Date of acceptance by institutional review board: January 29th 2019

Sponsor: Prof. Luca Regli, MD; Department of Neurosurgery; University Hospital Zurich; Clinical Neuroscience Center; University of Zurich; Frauenklinikstrasse 10; 8091 Zurich, Switzerland; Tel: +41 (0)44-255-1111

Principle investigator(s) responsible for conducting the research:

Priv.-Doz. Dr. Martin N. Stienen, MD/FEBNS; Department of Neurosurgery; University Hospital Zurich; Clinical Neuroscience Center; University of Zurich; Frauenklinikstrasse 10; 8091 Zurich, Switzerland; Tel: +41 (0)44-255-1111; mnstienen@gmail.com

Dr. Menno R. Germans, MD/PhD; Department of Neurosurgery; University Hospital Zurich; Clinical Neuroscience Center; University of Zurich; Frauenklinikstrasse 10; 8091 Zurich, Switzerland; Tel: +41 (0)44-255-1111; menno.germans@usz.ch

Study coordinator: Elisabeth Jehli, MSc; Department of Neurosurgery; University Hospital Zurich; Clinical Neuroscience Center; University of Zurich; Frauenklinikstrasse 10; 8091 Zurich, Switzerland; Tel: +41 (0)44-255-1111; elisabeth.jehli@usz.ch

Funding agency: Stryker European Operations B.V.; Herikerbergweg 110; 1101 CM Amsterdam; The Netherlands

Monitoring agency: Clinical Trials Center (CTC); UniversitätsSpital Zürich; Rämistrasse 100; 8091 Zurich; Switzerland; +41 (0)43-253-0128; CTC-Monitoring@usz.ch

Introduction

Outcome in terms of recovery of impaired neurological function is generally satisfactory after burr hole trepanation for the evacuation of chronic subdural hematoma (cSDH).[1 2] Despite being considered a relative minimally invasive type of surgery, it requires drilling holes in the patient's skull. With progressive hematoma reabsorption during follow-up, patients may develop skin depressions above the burr hole sites (Figure 1).[3 4] Theoretically, burr holes could be covered by approved medical devices (burr hole covers) after cSDH evacuation and prior to closing the wound.

This has not become standard of care, however, and we previously set out to explore the prevalence and relevance of skin depressions, as well as today's pattern of care by conducting a cross-sectional survey-based study among neurosurgeons globally. Analyzing 576 responses from 78 different countries, 76% of neurosurgeons stated that their patients complained about skin depressions after burr hole trepanations more or less frequently.[5] In contrary, only 28% of neurosurgeons currently apply burr hole covers more or less frequently for this indication. Their reluctance was mostly explained by a lack of evidence for any proven benefit, less so for the fear of an increased complication rate, technical difficulties and financial reasons. Around three quarters (78% of neurosurgeons) indicated that they would consider applying burr hole covers for this indication, in case a high-quality trial demonstrated its efficacy and safety.[5]

We retrospectively reviewed a series of n=28 cSDH patients (64 burr holes) treated at our department, of which n=11 patients had received a burr hole cover on 14 burr holes at the surgeon's discretion. Applying the Aesthetic Numeric Analogue (ANA) scale to rate the esthetical result of the surgery,[6] patients rated sites where the burr hole was covered more favorably than sites where the burr hole was left uncovered (ANA 9.3±0.74 vs. 7.9±1.0; $p<0.001$).[4] In addition, the rates of skin depression were as low as 7% in the intervention group and as high as 92% in the control group ($p<0.001$). Evidently, the prior results were subject to selection bias, patients were not blinded for the intervention and the study was underpowered to estimate possible group differences in complications.[4] These preliminary findings were a promising starting point for further and more in-depth research, because filling this knowledge gap is likely to affect future management of cSDH patients.

Methods and analysis

Study Goals and Objectives

The CORRECT SCAR trial aims to demonstrate that the placement of burr hole covers on the burr hole sites improves patient satisfaction with the esthetic outcome of the surgical procedure

at 3 and 12 months postoperative. It also aims to demonstrate that clinical outcomes (disability, neurological function & health-related quality of life (hrQoL)) remain similar and complication rates (e.g., surgical site infections (SSIs), cSDH recurrences, etc.) are not increased by applying burr hole covers.

The primary objective is to compare mean ANA scores (patient satisfaction with the esthetic result of the surgery) between the intervention and control group at 90 days postoperatively. Secondary/safety objectives are to compare mean ANA scores, rates of skin depression, impairment in activities of daily living (ADLs), disability (modified Rankin scale (mRS)), hrQoL (Euro-Qol (EQ)-5D), neurological status (National Institute of Health Stroke scale (NIHSS)), complications and residual hematoma volume between the intervention and control group at 3 and 12 months postoperative.

Study Design

Prospective, single-blinded, randomized, controlled, investigator initiated clinical trial. The trial is conducted at the University Hospital Zurich, Switzerland. The study will be reported according to the CONSORT guidelines.[7]

Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Patients with first-time cSDH (hypodense, isodense, hyperdense or mixed-type in CT-imaging), scheduled for uni- or bilateral double burr hole trepanation under general anesthesia
- Patient age ≥ 18 years
- Patient non-comatose at time of inclusion (GCS > 8 points)
- Patient able to communicate (in terms of ability to hear, see, speak and understand).

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

- Patient with recurrent cSDH or previous surgery for cSDH
- Patient with cSDH treated by craniotomy or by single burr hole trepanation
- Patient with cSDH treated in local anesthesia
- Patient unlikely to attend the follow-up (due to reasons of residency, dismal prognosis, etc.)
- Pregnancy
- Known allergy against or incompatibility with Titanium

- Known or suspected non-compliance
- Inability to follow the study procedures, e.g. due to psychological disorders, dementia, etc. of the participant.

Intervention & study groups

A study algorithm can be found in figure 2 and table 1 outlines all visits and procedures.

1. Patients with unilateral cSDH

   All patients randomized into the control group will be treated according to our standard protocol for cSDH evacuation (supplementary digital content 1).

   All patients randomized into the intervention group will be treated according to our standard protocol for cSDH evacuation with one exception: placement of a burr hole cover (UN3 BURR HOLE COVER, 20mm, W/TAB, Item code 53-34520, Stryker®, Kalamazoo, Michigan) that is fixed with 2 screws (UNIII AXS SCREWS, SELF-DRILLING, 1.5 x 4MM, Item code 56-15934, Stryker®, Kalamazoo, Michigan) on both burr holes after evacuation of the hematoma and prior to skin closure.
2. Patients with bilateral cSDH

   Patients with bilateral cSDH serve as their own internal control. They are randomized concerning the intervention or control side, being either the side with larger or smaller hematoma, respectively.

All patients are blinded concerning the study group/side allocation. For application of the burr hole cover, surgeons will be instructed to firmly press the burr hole cover on the burr hole before receiving the screws from the scrub nurse in order to prevent from screws accidently falling into the subdural space. For this purpose, a standard operating procedure (SOP) has been developed (supplementary digital content 2). No dexamethasone is applied to surgical candidates who are enrolled into this trial.

Primary Outcome and Follow-Up

For the primary outcome, patient satisfaction with the esthetic results of the scar is determined using a patient-rated outcome measure (PROM), the ANA scale,[6] ranging from 0 (dissatisfied) – 10 (very satisfied), at 90 days postoperative. The outcome is assessed by mailed questionnaire and collected by a study coordinator.

Secondary Outcomes

- Patient satisfaction with the esthetic result of the scar, determined by the ANA scale, at 12 months postoperatively (mailed questionnaire, collected by a study coordinator).

- Impairment in ADLs (e.g., when hairdressing, combing, washing, etc.), rated as "yes" vs. "no", at 90 days and 12 months postoperative (mailed questionnaire, collected by a study coordinator).
- Rate of skin depression, rated as "yes" vs. "no", at 90 days and 12 months postoperative (mailed questionnaire, collected by a study coordinator).
- Disability, determined by the mRS (ranging from 0 (no disability) to 6 (dead)) at 90 days.
- HrQoL, determined by the EQ-5D (allowing the calculation of both the EQ-5D index that ranges from -0.074 (worst hrQoL) – 1.00 (best hrQoL) using European norms and the EQ-5D VAS (ranging from 0 (worst hrQoL) – 100 mm (best hrQoL)), at 90 days and 12 months postoperative (mailed questionnaire, collected by a study coordinator).
- Neurological outcome, determined by the NIHSS (ranging from 0 (no neurological deficit) – 42 (severe neurological deficit)), at 90 days.
- Home time, as surrogate marker of disability,[8] at 90 days and 12 months.

Further safety-outcomes are assessed:

- Intra- and postoperative complications up to 90 days and 12 months, in particular cSDH recurrence and SSIs.
- Residual cSDH volume in ccm^3, absolute (ccm^3) and relative (%) cSDH clearance at 90 days postoperative (measured by two neuroradiologists independently, otherwise not involved in the project, using volumetric analysis).

Patient and Public Involvement

Other than recruiting patients admitted to our hospital, it is not intended to involve patients and the public in the design, conduct and reporting of this research.

Ethics and dissemination

Despite the generally favorable risk profile and outcome of burr hole trepanation for cSDH, skin depressions may occur weeks and months after hematoma reabsorption.[3 4] These are frequently considered esthetically unsatisfactory by patients and may lead to functional restrictions, e.g. when combing, hairdressing or washing. In own clinical experience, patients reported being stared-at for these skin depressions, evoking feelings of astonishment and aversion from both family members and strangers. With an increasing number of senior citizens in good physical/mental health and leading active social lives, the esthetic aspect of outcome

gains new importance. Today's elderly patients do no longer content themselves with a basic surgical procedure, but – as informed customers – expect optimal surgical results topped with an excellent service.[9]

In theory, burr hole covers represent an effective, easy-to-apply and relatively inexpensive solution to prevent cosmetically and functionally unfavorable skin depressions.[4] Our survey has clearly demonstrated that – in order to improve the acceptance of this technical nuance – its efficiency needs to be demonstrated first (unpublished data, April 2019). Moreover, as the intervention is unlikely to improve any "hard outcome" such as disability or survival, more data should substantiate its safety.

We consider a prospective, randomized, blinded and controlled study design optimal to prove a causal relationship between the study intervention and outcome. A clear strength of this study is that patients with bilateral cSDH can be included and serve as their own internal controls. Any retrospective approach to the study question, or applying the burr hole cover in a prospective fashion and comparing it to a (historical) control group is not possible, as the outcome of interest (ANA scale) has not been established in patients before, as well as for the likelihood of selection bias. The study aim corresponds to the value-based medicine approach of modern patient-centered medicine and results shall be published in peer-reviewed journals.

Trial Status

The study has started enrolling patients on January 29th 2019.

Safety Considerations

Burr hole covers are applied according to a SOP (supplementary digital content 2) and the medical device is approved for the studied application. All device deficiencies, (severe) adverse events ((S)AEs) and (severe) adverse device effects ((S)ADEs) are systematically recorded. The Clinical Trials Center (CTC) of the University of Zurich externally monitors the trial.

Follow-up

Participating patients are followed up to 12 months postoperative.

Unblinding

Maintenance of trial treatment randomization codes will be done by the electronic data capturing system (run by the CTC Zurich), using a built-in tool for randomization. Breaking codes is not allowed. Unblinding (and revealing a participant's allocated intervention) towards

the patient is permissible only if the trial is suspended, prematurely terminated due to security concerns or completed.

Data Managements and Statistical Analysis

The data is hosted by the CTC, University of Zurich. Electronic case report forms (eCRFs) are implemented. All data are stored on a server in a dedicated database. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission. Electronic patient data will be stored for 15 years until trial completion.

Handling of missing data

First, the risk of missing data will be minimized by regular data reviews, also with an intention to identify at risk patients for lack of follow-up data. Even though the effect of skin depression is likely more pronounced at 12 months, compared to 90 days postoperative, we intentionally chose to select the 90-day time point as primary outcome in order to minimize drop-out. Contingency plans foresee home/rehabilitation visits by study personnel to obtain otherwise missing data in patients who cannot show up for the planned 90-day or 12-month follow-up.[10] Patients who die during the study interval (or cannot be evaluated as aphasic or in too poor clinical condition) and in whom for this reason the primary endpoint cannot be obtained will be recorded as not assessable for the primary outcome. Sensitivity analyses will be performed for this study.

If, despite the above-mentioned mechanisms, missing data is present we use the following protocol: First, mechanisms of missing data are assessed. If the data are deemed missing at random, and there is <10-15% of patients with time point missing data, then case deletion will be used (and additional patients will be recruited). Second, if the missing data mechanism is not at random, multiple imputation will be performed, a well-accepted method for intention to treat analysis in RCT with missing outcome data.[10 11]

Determination of sample size

Based on an expected mean satisfaction score of 9/10 on the ANA in the intervention and 7/10 on the ANA in the control group, n=37 patients need to be randomized in each study arm in order to find a statistically significant difference in the primary outcome with alpha set at 0.05, a power of 80% and an estimated standard deviation of 3.[4] Based on a total sample size of 2x37=74, with an estimated dropout rate of 10%, we plan to include n=80 patients in total.

Methods used to minimize bias

A computerized randomization tool, provided by the electronic data capturing system, is used with the only strata being uni- or bilateral cSDH. The random allocation sequence is generated by the CTC, University of Zurich. Study physicians conduct patient enrollment and randomization after basic patient data has been entered into eCRFs. Due to the randomization process, patients with unilateral cSDH are likely to be well balanced for most important parameters that could potentially influence the primary outcome. In patients with bilateral cSDH, each patient serves as his/her own control, which minimizes the risk of bias (=setting similar to that of a n-of-1 clinical trial but without repetitive crossover).[12 13]

Patients with unilateral cSDH will be randomized in a 1:1 fashion into the intervention or control group, respectively. Patients with bilateral cSDH will be randomized in a 1:1 fashion concerning the intervention side, being either the side with more or lesser hematoma size (Figure 2).

Patients will be blinded for allocation to the study group/side, but surgeons will not be. Patients will not be aware of the study group/side, since the operation takes place under general anesthesia. The fact that patients are blinded for the study group allocation will be mentioned in the discharge letter (in order to inform the family physician), and the neurosurgical team of nurses and physicians will also be informed not to "unblind" the patient.

The primary endpoint and most of the secondary endpoints will be determined by mailed questionnaires. This way, the patient will not be influenced by the presence of the physician when judging on satisfaction with the esthetical result of the surgery. In addition, all data is collected by a dedicated study coordinator (E.J.), who is not involved in the patient care (=independent outcome assessment).

Primary analysis

The main analysis will be according to the intention to treat (ITT) protocol. An as-treated analysis will be performed, additionally.

Satisfaction on the ANA scale for both the frontal and parietal scar are measured separately, but a mean satisfaction score is built by adding the values and dividing the sum by two. For analysis of the primary outcome the results obtained in the intervention group (unilateral cSDH) and on the intervention side (bilateral cSDH) will be combined and compared to the combined results obtained in the control group and on the control side. As the dependent variable is a quantitative variable on an interval scale, a rank-sum test is appropriate to analyze group differences. Even though no formal minimum clinically important difference (MCID) of the ANA-scale has been determined, we powered the study to detect an in-between group

difference in outcome of two points, as – abstracted from the numeric rating scale for pain (also ranging between 0 – 10) – a change of two points is considered to be well above the MCID,[14] therefore resulting in a clinically meaningful improvement for the patient.

Subgroup analyses will be made for patients with bald heads vs. patients with scalp hear, male vs. female patients, patients < 60 years vs. ≥ 60 years and for patients with bilateral cSDH.

Secondary analyses

As the remaining secondary outcomes are not side-specific but reflect the condition of the patient as a whole, the remaining secondary analyses will compare results obtained in patients with unilateral cSDH randomized into either the intervention or control group.

As the safety outcomes are specific for the incision site and side, for the safety analyses the results obtained in the intervention group and on the intervention side will be combined and compared to the combined results obtained in the control group and on the controlled side.

For the outcomes that are quantitative (hrQoL on the EQ-5D) student's t-tests or rank-sum tests will be applied, depending on normally distributed data or not. For the outcomes that are categorical (type of impairment with ADLs, disability on the mRS, neurological outcome on the NIHSS, complications on the CDG) descriptive analyses and chi-square tests will be applied. For the outcomes that are binary (impairment with ADLs, skin depression, etc.) logistic regression analysis will be performed, calculating the odds ratio (OR) and 95% confidence intervals (CIs).

Interim analyses

Once data of 50 patients with completed 90-day follow-up data has been collected, the primary endpoint and the safety analyses will be performed.

Quality Assurance

The study is conducted in accordance with good clinical practice (GCP) guidelines. All source data is accessible for monitoring, audits and inspections. Authorities have the right to perform inspections and on-site auditing. External monitoring will be performed by the CTC, University of Zurich, as detailed in a monitoring plan including pre-study, site initiation, routine monitoring and close-out visits, considering local infrastructure, completeness of documents, patient safety, adherence to the study protocol, data quality entered into the eCRFs and the trial master file.

Progress of patient inclusion and data completeness is continuously (at least once every two weeks) checked by a study coordinator (E.J.).

Expected Outcomes of the Study

The study will shed more light on the question, whether patient satisfaction with the esthetic result of the surgical procedure can be improved by adding burr hole covers on the burr holes after trepanation for cSDH. An improvement in patient satisfaction would likely be conferred through the decreased prevalence of skin depressions, as a strong difference in prevalence of skin depressions was previously found in two retrospective studies.[3 4] The study will moreover allow to understand better, whether the application of burr hole covers increases the risks of complications, e.g. cSDH recurrence or SSIs. Results of the study are likely to affect future management of cSDH patients.[5]

Duration of the project

Recruitment is expected to be completed by the end of January 2021, with final follow-up collected until January 2022. Publication of the final results is expected around six months after last patient out.

Project management

The principle investigators (M.N.S. & M.R.G.) are responsible for patient inclusion, quality of data collection and adhesion to the protocol. They are supported by a team of site investigators, a dedicated study coordinator (E.J.), the monitoring staff and the sponsor (L.R.).

Ethics

The study protocol has been approved by the local IRB (Kantonale Ethikkommission Zürich) on January 29th 2019 (BASEC 2018-01180) and registered on http://www.clinicaltrials.gov with the identifier: NCT03755349. All patients and/or next-of-kin will give written informed consent to contributing study physicians. Protocol modifications have to be approved by the local IRB and communicated to trial registries. Authorship for publications will be determined according to the recommendation given by the International Committee of Medical Journal Editors (ICMJE). No use of professional writers is planned.

Tables

Table 1: Tabular listing of schedule of events and assessments and procedures of the study. ADLs = activities of daily living; ANA = Aesthetic Numeric Analogue scale; CDG = Clavien-Dindo grading scale; CT = computed tomography; EQ-5D = EuroQol 5 D health questionnaire; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale.

Study Periods	Before surgery	Surgery	Discharge from hospital	90-day Follow-up	12-month Follow-up
Visit	1	2	3	4	5
Time (days)	0 (-7 – 0)	0	5 (3 – 14)	90 (±10)	365 (±30)
Patient Information and Informed Consent	x		(x)	(x)	
Demographics	x				
Medical History	x				
In- /Exclusion Criteria	x				
Physical Examination	x		x	x	
Laboratory Examinations					
Quick/INR/PTT		x			
Thrombocyte count		x			
Randomization	x				
Other examinations (CT-Scan)	x		x	x	
Hematoma volume	x		x	x	
Administer Medical Device (burr hole covers and screws)		x			
Primary outcome					
Patient satisfaction (ANA)				x	x
Secondary outcomes					
Impairment in ADLs				x	x
Skin depression				x	x
HrQoL (EQ-5D)	x			x	x
Disability (mRS)	x		x	x	
Neurological status (NIHSS)	x		x	x	
Complications (CDG)			x	x	x
Adverse Events	x	x	x	x [B]	x

Figure legends

Figure 1: Example of skin depression above the burr holes in a male patient in his late 80's, about two years following frontal and parietal burr hole trepanation for the evacuation of a large chronic subdural hematoma. The photo was taken with his permission and at this time he continued to lead an active life. Upon inquiry, he and his wife confirmed feeling troubled by the well-visible and stigmatizing skin depressions.

Figure 2: Illustration of the algorithm of the CORRECT-SCAR trial. cSDH = chronic subdural hematoma; CT = computed tomography.

Supplementary digital content

Supplementary digital content 1: Standard protocol for cSDH evacuation.

Supplementary digital content 2: SOP for the application of burr hole covers in the context of cSDH evacuation.

Full references

1. Kolias AG, Chari A, Santarius T, et al. Chronic subdural haematoma: modern management and emerging therapies. *Nature reviews Neurology* 2014;10(10):570-8. doi: 10.1038/nrneurol.2014.163
2. Maldaner N, Sosnova M, Sarnthein J, et al. Burr hole trepanation for chronic subdural hematomas: is surgical education safe? *Acta neurochirurgica* 2018;160(5):901-11. doi: 10.1007/s00701-017-3458-8
3. Im TS, Lee YS, Suh SJ, et al. The Efficacy of Titanium Burr Hole Cover for Reconstruction of Skull Defect after Burr Hole Trephination of Chronic Subdural Hematoma. *Korean journal of neurotrauma* 2014;10(2):76-81. doi: 10.13004/kjnt.2014.10.2.76
4. Vasella F, Akeret K, Smoll NR, et al. Improving the aesthetic outcome with burr hole cover placement in chronic subdural hematoma evacuation-a retrospective pilot study. *Acta neurochirurgica* 2018;160(11):2129-35. doi: 10.1007/s00701-018-3659-9
5. Velz J, Vasella F, Akeret K, et al. Patterns of Care: Burr-Hole Cover Application for Chronic Subdural Hematoma Trepanation. *Neurosurg Focus (accepted for publication)* 2019;47(5 (Nov 2019))
6. Funk W, Podmelle F, Guiol C, et al. Aesthetic satisfaction scoring - introducing an aesthetic numeric analogue scale (ANA-scale). *Journal of cranio-maxillo-facial surgery : official publication of the European Association for Cranio-Maxillo-Facial Surgery* 2012;40(5):439-42. doi: 10.1016/j.jcms.2011.07.018
7. Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Bmj* 2010;340:c332. doi: 10.1136/bmj.c332
8. Stienen MN, Smoll NR, Fung C, et al. Home-Time as a Surrogate Marker for Functional Outcome After Aneurysmal Subarachnoid Hemorrhage. *Stroke* 2018;49:3081-84.
9. Stienen MN, Serra C, Stieglitz LH, et al. UniversitatsSpital Zurich: 80 years of neurosurgical patient care in Switzerland. *Acta neurochirurgica* 2017 doi: 10.1007/s00701-017-3357-z
10. Kang H. The prevention and handling of the missing data. *Korean journal of anesthesiology* 2013;64(5):402-6. doi: 10.4097/kjae.2013.64.5.402
11. White IR, Horton NJ, Carpenter J, et al. Strategy for intention to treat analysis in randomised trials with missing outcome data. *Bmj* 2011;342:d40. doi: 10.1136/bmj.d40
12. Lillie EO, Patay B, Diamant J, et al. The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? *Personalized medicine* 2011;8(2):161-73. doi: 10.2217/pme.11.7
13. Kravitz RL, Duan N, and the DEcIDE Methods Center N-of-1 Guidance Panel (Duan N EI, Gabler NB, Kaplan HC, Kravitz RL, Larson EB, Pace WD, Schmid CH, Sim I, Vohra S). AHRQ Publication No. 13(14)-EHC122-EF. Design and Implementation of N-of-1 Trials: A User's Guide. Rockville, MD: Agency for Healthcare Research and Quality 2014.
14. Gautschi OP, Stienen MN, Corniola MV, et al. Assessment of the Minimum Clinically Important Difference in the Timed Up and Go Test After Surgery for Lumbar Degenerative Disc Disease. *Neurosurgery* 2017;80(3):380-85. doi: 10.1227/NEU.0000000000001320

Authors' contributions:

Those persons listed as authors on the manuscript have made substantial contributions to the conception or design of the work, are currently involved in acquiring, analyzing, or interpreting the data for the work. They all have been active in drafting or revising the study protocol for important intellectual content, which is basis of the current article. All authors have approved the final version to be published. They agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In detail: MNS, KA, FV, JV, EJ, PS, SV, OB, NRS, OLB, LR and MRG designed the study, are local (principle) investigators or other key persons. MNS acquired the funding. MNS reviewed the literature and drafted the manuscript. KA, FV, JV, EJ, PS, SV, OB, NRS, OLB, LR and MRG contributed to drafting of the manuscript. All authors read and approved the final manuscript.

Funding Statement:

This research is financed and conducted by the Department of Neurosurgery, University Hospital Zurich, Switzerland. It is financially supported by the Stryker company, after careful and independent review of the study protocol. The funding source is not involved and does not influence the data collection, measurements, interpretation, or drafting of the manuscript.

Competing interests statement:

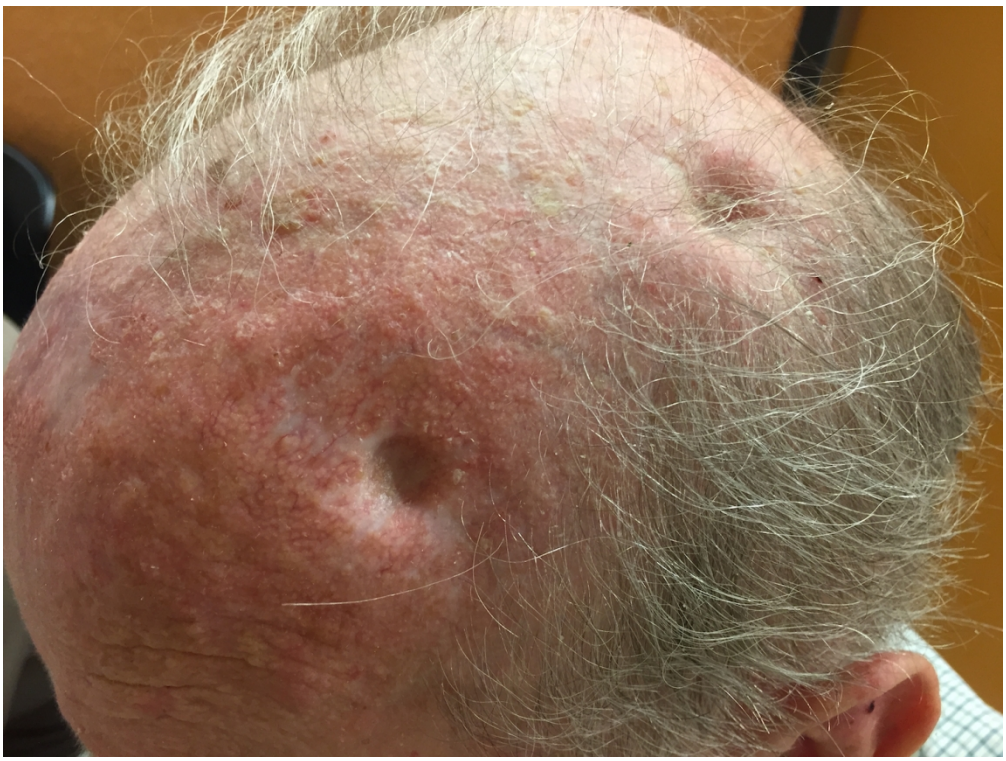
All authors declare that they have nothing to disclose and no conflicts of interest.

Data availability statement:

Individual patient data (IPD), study protocol, statistical analysis plan (SAP) and analytic code will be made available on reasonable request, once the results are published and if approved by the institutional review board (KEK-ZH).

Word count:

3364 for article text (excluding references)



Example of skin depression above the burr holes in a male patient in his late 80's, about two years following frontal and parietal burr hole trepanation for the evacuation of a large chronic subdural hematoma. The photo was taken with his permission and at this time he continued to lead an active life. Upon inquiry, he and his wife confirmed feeling troubled by the well-visible and stigmatizing skin depressions.

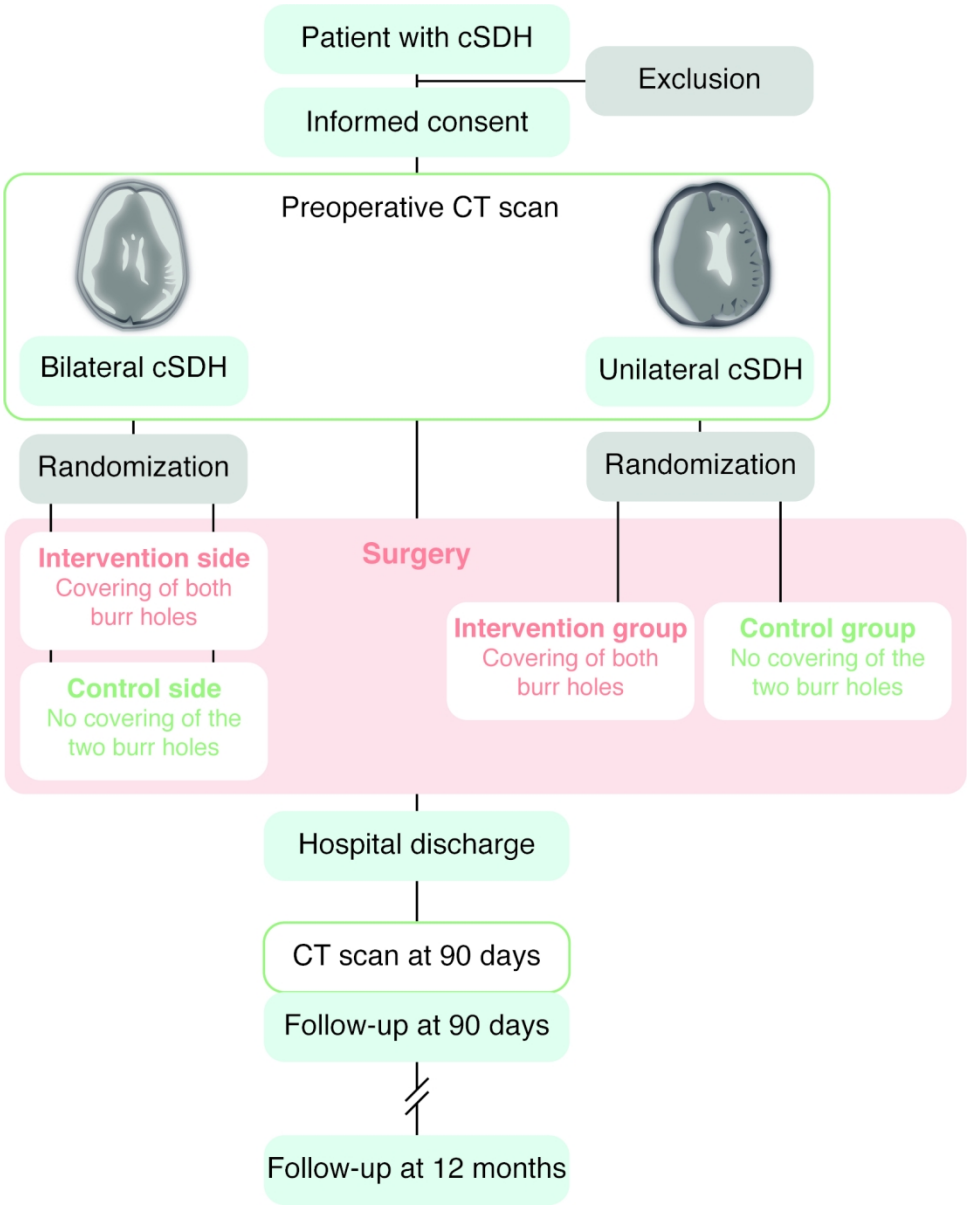


Illustration of the algorithm of the CORRECT-SCAR trial. cSDH = chronic subdural hematoma; CT = computed tomography.

UniversitätsSpital Zürich

STANDARD OPERATING PROCEDURE

Application of burr-hole covers after trepanation of chronic subdural hematoma

Surgical Procedure in general

The procedure is described for one-sided burr-hole trepanation – but can likewise be applied for bilateral trepanations – of chronic subdural hematomas (cSDH).

1. The procedure is usually performed under general anesthesia.
2. The head is rotated about 80° towards the contralateral side and positioned on a ring-shaped gel cushion.
3. The hair is shaved for 5x2 cm in the region of anticipated incisions.
4. No infiltration of the skin (with saline or local anesthesia).
5. Skin incisions, each one frontal and parietal, about 35 mm in length.
6. Double burr-hole trepanation with the 14-mm trepan.
7. The frontal burr-hole is usually placed at the junction of the superior temporal line and the coronal suture (stephanion), while the posterior burr-hole is usually placed in the region of the parietal eminence.
8. After trepanation and dural opening, the hematoma is evacuated by repeated irrigation with warmed saline solution until reflux is limpid.
9. Per operated side, a subperiostal drain is placed.
10. The burr-hole cover is now placed and secured with 2 screws, according to the protocol below.
11. The subdural space is filled with warmed saline solution in order to prevent from trapped air inside the skull.
12. The skin is closed by tight subcutaneous sutures and staples on the skin (one staple for each 3 mm incision length).
13. For bilateral cSDH, the procedure is repeated on the contralateral side

Application of the burr-hole cover

The following steps must be taken to prevent from patient injury during application of the burr-hole cover and its fixation with screws. Of note, we usually place the subperiostal drain before placement of the burr-hole covers, but for demonstration purpose the following pictures were made without the drain (it can gently be pushed aside for the burr-hole cover placement).

1. For each burr-hole that is to be covered, one burr-hole cover (UN3 BURR HOLE COVER, 20mm, W/TAB, Item code 53-34520, Stryker®, Kalamazoo, Michigan; Figures 1 & 2) is applied.

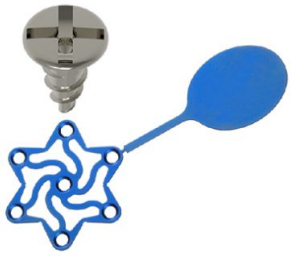


Figure 1: UN3 BURR HOLE COVER, 20mm (Stryker®, Kalamazoo, Michigan) with magnified UNIII AXS SCREWS, SELF-DRILLING, 1.5 x 4MM (Stryker®, Kalamazoo, Michigan).

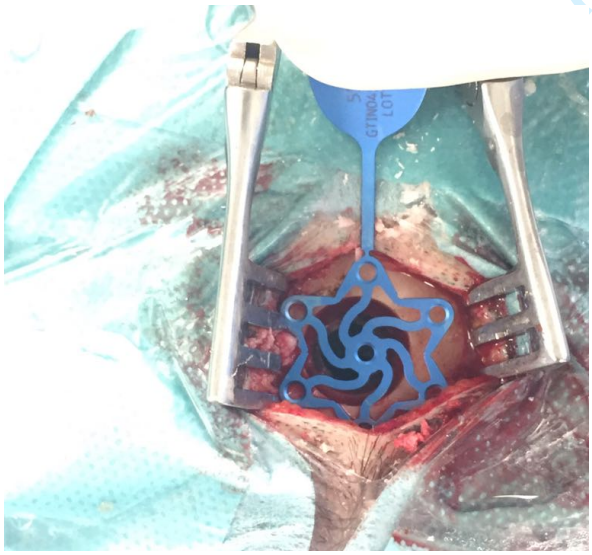


Figure 2: Image demonstrating the placement of UN3 BURR HOLE COVER, 20mm (Stryker®, Kalamazoo, Michigan) in situ.

2. The burr-hole cover is firmly pressed to the patient skull with the finger, making sure that the burr-hole is completely covered and no items such as screws can fall into the subdural space (Figure 3).

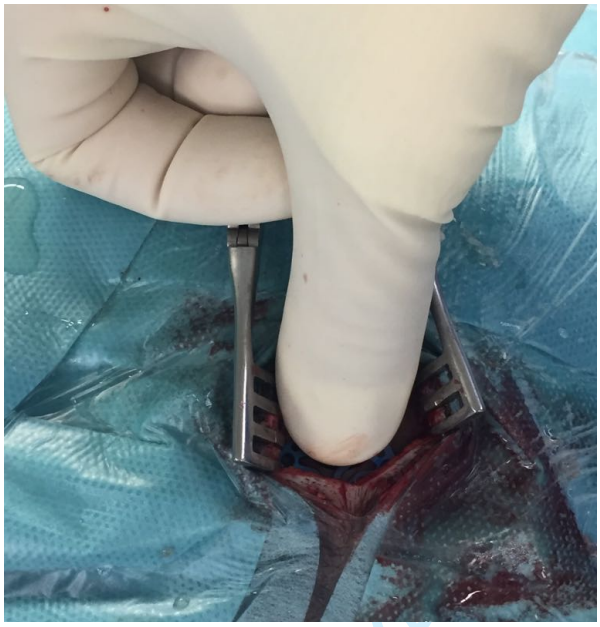


Figure 3: Image demonstrating how the burr-hole cover is positioned over the burr-hole, using a finger to hold the position.

3. Only when the burr-hole is completely covered, the surgeon receives the first screw (UNIII AXS SCREWS, SELF-DRILLING, 1.5 x 4MM, Item code 56-15934, Stryker®, Kalamazoo, Michigan) and applies it in any given screw hole of the burr-hole cover (Figure 4).

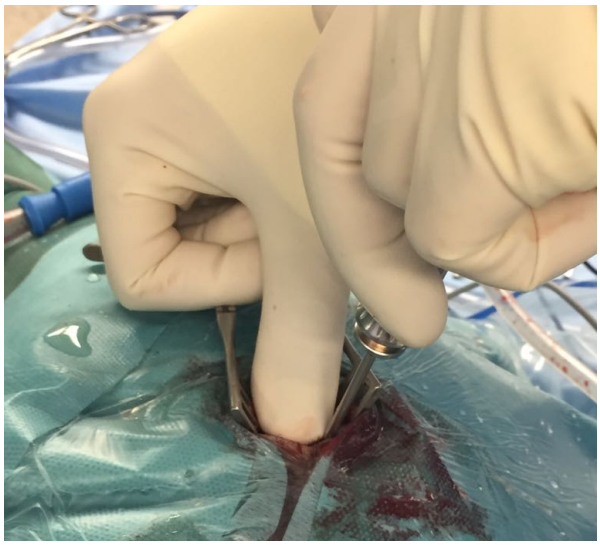


Figure 4: Image demonstrating how the screw should be applied, with the surgeon making sure that the burr-hole cover covers the burr-hole completely.

4. Only after double-checking that the burr-hole is still completely covered and while continuing to press it onto the patient skull, the surgeon receives the second screw (UNIII AXS SCREWS, SELF-DRILLING, 1.5 x 4MM, Item code 56-15934, Stryker®, Kalamazoo, Michigan) and applies it in the screw hole on the most opposite side (Figure 5).

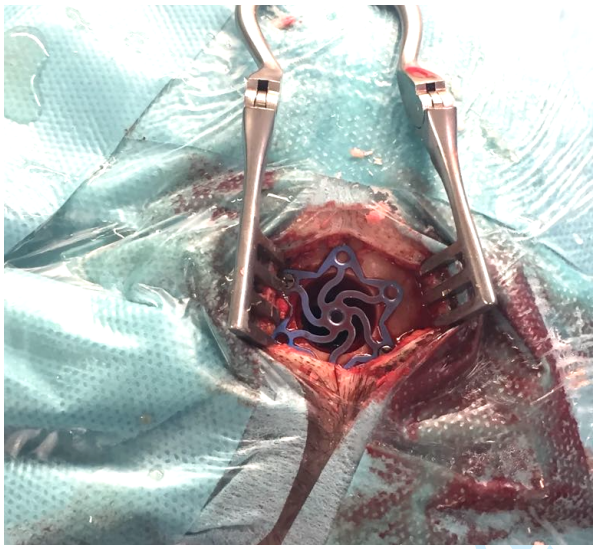


Figure 5: Image demonstrating the application of the second screw in the most opposite screw hole of the burr-hole cover.

Authors:
Martin N. Stienen, Menno R. Germans, Julia Velz, Flavio Vasella, Luca Regli
Department of Neurosurgery, University Hospital Zurich, Switzerland

Standard protocol for chronic subdural hematoma (cSDH) evacuation

All symptomatic patients, particularly those with large cSDH (maximal axial diameter > 15mm or relevant midline shift (MLS)) or presenting in reduced vigilance (GCS < 15) are usually operated within 24 hours. Coagulation parameters are checked routinely prior to surgery. Surgery for patients under anti-aggregation or anticoagulation is delayed until blood clotting and thrombus functions is restored, whenever possible, under close monitoring. Our departmental protocol aims at maintaining platelets at >100 x 10^9/dl and an international normalized ratio (INR) of <1.4. Coagulation abnormalities are actively reversed preoperatively with prothrombin complex concentrate or fresh frozen plasma, if urgent surgery is required. Antiplatelet medication is stopped 5–7 days prior to surgery; if urgent surgery is required, one jumbo unit of platelet concentrate is administered immediately preoperative.

We usually perform double burr-hole trepanation (20mm) per side under general anesthesia. The patient is placed in supine position with the head rotated about 80° towards the contralateral side and positioned on a ring-shaped gel cushion. If necessary, the hair is shaved for 5 x 2 cm in the region of anticipated incisions. Two skin incisions per side, each 35 mm in length, are required. A 14-mm trepan is used for both burr holes. The frontal burr hole is usually placed at the junction of the superior temporal line and the coronal suture (stephanion), while the posterior burr hole is usually placed in the region of the parietal eminence. In case of significant bilateral hematoma, trepanation is performed on both sides. After trepanation and dural opening, the hematoma is evacuated by repeated irrigation with warmed saline solution until reflux is limpid. There is little doubt that placing a drain after hematoma evacuation can significantly reduce the recurrence rate in cSDH. Whether placing the drain in the superiostal or subdural space is superior has not been proven so far, but we prefer subperiostal drains for the better safety profile. The skin is closed by tight subcutaneous sutures and staples on the surface. For bilateral cSDH the procedure is repeated on the contralateral side.

Postoperatively, patients remain immobilized and flat in supine position for 48 hours until the drain is removed. In absence of residual deficits, patients are discharged from postoperative day three on. We routinely perform outpatient follow-up visits with cranial computed

tomography (CT) scan at 6 and 12 weeks postoperatively. Follow-up is continued on an individual basis afterwards.

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
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym **– YES, page 1 ll 1-3**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry **– YES, page 3 line 24**
	2b	All items from the World Health Organization Trial Registration Data Set **– YES, all 20 points are mentioned on various pages of the manuscript**
Protocol version	3	Date and version identifier **– YES, page 5 line 6**
Funding	4	Sources and types of financial, material, and other support **– YES, page 5 ll 26-27 & page 19 ll 15-19**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors **– YES, page 5 ll 10-31**
	5b	Name and contact information for the trial sponsor **– YES, page 5 ll 10-12**
	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 **– YES, page 19 ll 2-13**
	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) **– YES, page 14 ll 18-21**
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 **– YES, page 6 ll 1-30**

	6b	Explanation for choice of comparators **– YES, page 10 ll 10-17**
Objectives	7	Specific objectives or hypotheses **– YES, page 7 ll 1-6**
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) **– YES, page 7 ll 16-18**
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 **– YES, page 7 ll 15 - 18**
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) **– YES, page 7 l 19 – page 8 l 5**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered **– YES, page 8 ll 6 - 25**
	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) **– YES, page 10 ll 30ff**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) **– YES, page 11 ll 9ff**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial **– NOT APPLICABLE**
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 **– YES, page 8 line 26 ff**
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) **– YES – FIGURE 2 & TABLE 1, page 10 line 19 & page 14 ll 14ff**
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 **– YES, page 11 ll 26ff**

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size **– YES, part of the quality assurance – page 13 ll 27ff**

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 **– YES, page 12 ll 2 ff**
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 **– YES, page 12 ll 2 ff**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions **– YES, page 12 ll 2 ff**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how **– YES, page 12 ll 2 ff**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial **– YES, page 10 ll 30ff**

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 **– YES, page 15 table 1**
	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 **– YES, part of quality assurance on page 13 ll 27ff**
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 **– YES, page 11 ll 4-8**

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 **– YES, page 12 line 24 – page 13, line 4**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) **– YES, page 12 ll 5-22**
	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) **– YES, page 11 ll 9-25**
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 **– YES, page 13 ll 27ff**
	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 **– YES, page 13 ll 23-25**
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 **– YES, page 13 ll 8ff**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor **– YES, page 13 ll 27ff**
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval **– YES, page 14 ll 22-26**
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) **– YES, page 14 ll 22ff**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) **- YES, page 14 ll 22ff**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable **– NOT APPLICABLE**

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 **– YES, page 11 ll 4-8**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site **– YES, page 19 ll 21-22**
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 **– NOT APPLICABLE – DATA ACCESS REGULATED BY ELECTRONIC GCP-CONFORM DATABASE contained on page 11 ll 4-8**
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 **– NOT APPLICABLE**
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 **– YES, page 19 ll 24ff, page 10 line 17**
	31b	Authorship eligibility guidelines and any intended use of professional writers **– YES, page 14, ll 27ff**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code **– THIS PROTOCOL IS PUBLISHED OPEN ACCESS IN BMJ Open, IF ACCEPTED. Further information on page 19 ll 24ff**
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates **– NOT HELPFUL TO MOST READERS, AS IN GERMAN LANGUAGE**
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 **- NOT APPLICABLE**

*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.