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Subcutaneous Sumatriptan for the Treatment of Post-Craniotomy Pain (SUPS Trial): Protocol for a Randomised Double-Blinded Placebo Controlled Trial

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Scientific Title

Subcutaneous Sumatriptan for the Treatment of Post-Craniotomy Pain (SUPS Trial): Protocol for a Randomised Double-Blinded Placebo Controlled Trial

Acronym:

SUPS Trial

Lay Title:

Subcutaneous Sumatriptan use for Treatment of Post-Neurosurgical Pain

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Abstract

Introduction

Post-craniotomy pain protocols utilise opioids, which are considered suboptimal analgesia following this procedure. Multimodal analgesia components are sparse. Our null hypothesis states that sumatriptan is not different to placebo in addition to usual intravenous opioids, for the treatment of acute post-craniotomy pain. craniotomy pain.

Methods and analysis

This is a prospective single centre randomised double-blinded placebo-controlled phase 3 clinical trial comparing subcutaneous sumatriptan injection in the recovery area with placebo for the treatment of post-craniotomy pain. Eligible adult patients (18 years and older) undergoing craniotomy will be identified pre-operatively. Both patient groups will receive a subcutaneous injection at a point where recovery-nursing staff would initiate the usual intravenous opioid analgesia as per standardised pain management protocol. In both groups, further pain management will be followed by the usual intravenous opioid administration. Primary outcome will consist of the difference in pain experienced by the two groups of patients in recovery area 60 minutes after the study drug administration. Post-craniotomy pain will be measured at regular intervals using the Visual Analogue Scale (VAS) in recovery area. The minimal clinically important difference of 10 mm on the VAS between the two groups will be considered as statistically significant. We will include selected clinical and patient reported outcomes as secondary endpoints. Univariate regression will be conducted on each one of the clinically plausible potential confounders. We will enrol a total 136 patients, with the study duration of 2 years. This trial will commence recruitment on the 1st of July, 2019.

Ethics and dissemination

This trial protocol has achieved approval by the Austin Health Research Committee, HREC/17/Austin/596. This trial was prospectively registered with Australian New Zealand Clinical Trials Registry on the 10/05/2018 with a unique trial identifier U1111-1209-9072 and registration Number ACTRN12618000793213P. Findings of this study will be disseminated in peer reviewed academic journals.

Keywords

Craniotomy; Post-operative Pain; Analgesia; Sumatriptan; Visual Analogue Scale;

Strengths and Weaknesses of the Trial

- To our knowledge SUPS Trial (Subcutaneous Sumatriptan use for Treatment of Post-Craniotomy Pain) is the first randomised placebo-controlled double-blinded trial investigating the effectiveness of subcutaneous sumatriptan in the treatment of post-craniotomy pain.

- This is a novel scientific hypothesis testing the utility of a ubiquitous anti-migraine medication for a post-operative indication in this Phase 3 Clinical Trial.

- Ethical structure of the trial allowing for gold standard placebo use in analgesic therapy in addition to usual treatment, allowing for blinding of patients and investigators.

- Utilisation of validated pain measurement scale in the form of Visual Analogue Scale (VAS), the timing of which has been tailored to fit the pharmacokinetic properties of injectable subcutaneous sumatriptan.

- Involvement of hospital pharmacy in the randomisation sequence generation, with point of care allocation of randomisation envelopes allowing for blinding of investigators, patients and staff whilst maximising allocation efficiency.

Introduction

Post-craniotomy pain is often under-estimated and under-treated. Both acute and chronic post craniotomy surgical pain and headaches have been found to be common and significant clinical phenomena (1). In a recent study by Mordhorst et al, 55% of patients had moderate to severe postoperative pain in the first 24 hours following craniotomy (2). In-hospital poorly controlled pain confers a significant morbid burden. It has been correlated with poor medium and long-term postoperative outcomes, including anxiety, depression, poor rehabilitation and development of chronic pain (3). Risk factors for increased acute post-craniotomy pain include female gender and surgical site of the incision. Opioids are still the mainstay of post-operative craniotomy pain management (4). Effective opioid analgesia administration for the purposes of post-craniotomy pain relief can reduce the clinician's ability to monitor consciousness and result in decreased respiration with subsequent hypercarbia.

There is presently a limited scope for multi-modal analgesia, due to lack of suitable medication components for this type of surgery (5). Ketamine and tramadol exhibit an unfavourable side-effect profile in relation to this type of surgery, with the adverse effect profile of both drugs including seizure risk. The use of non-steroidal anti-inflammatory agents has been restricted in neurosurgery due to their anti-platelet effects. In prior well-designed studies, intravenous parecoxib at skin closure was found to be ineffective at ameliorating post-craniotomy pain (6). Paracetamol has been found to modestly decrease post-operative pain scores but not the post-operative opioid consumption (7). There is a need for further clinical trials in order to improve and optimise multimodal post craniotomy pain management in the short and longer term (2)(8).

Sumatriptan is a widely used drug, licensed for the treatment of migraines and cluster headache (9) (10). There have been reports of its effectiveness for the treatment of medical conditions other than the ones already approved of by the relevant governing bodies. Sumatriptan has shown a promising therapeutic profile in patients suffering from trigeminal neuralgia in selected clinical studies (11). In a recent trial of Sumatriptan use in mini-craniotomy for decompression of trigeminal nerve, it was found to likely be as effective as the standard treatment modality when patient reported outcome measures were evaluated (12). Sumatriptan use improved Quality of Recovery Scores 40 in patients undergoing mini-craniotomy for trigeminal nerve decompression (13). Further reviews have included sumatriptan in their reports of its effectiveness as a component of multimodal analgesia in the treatment of acute and chronic post-craniotomy pain (14). There are reports of the effectiveness of sumatriptan in analgesia regimens following vestibular schwannoma surgery (15).

Sumatriptan is available in the oral immediate release form as well as the subcutaneous injection form. The medication penetrates the blood-brain barrier poorly, which is indicative of its peripheral mode of action. In terms of its pharmacodynamics profile, sumatriptan is a specific vascular 5-hydroxytryptamine-$1_{B\text{-}D}$ ($5HT1_{B\text{-}D}$) receptor agonist with no effect at other 5HT receptor (5HT2-5HT7) subtypes (9). The vascular 5HT1 receptor is found predominantly in cranial blood vessels and mediates large cerebral artery and dural vessel vasoconstriction. Sumatriptan interacts with the trigemino-vascular system in two distinct ways: through direct vessel constriction by its highly selective agonist activity at $5HT1_{B\text{-}D;}$ it may also affect the modulation of the release of various inflammatory neuropeptides, including CGRP(11)

(16). Calcitonin Gene related Peptide (CGRP) is a pro-inflammatory neuropeptide released from trigeminal ganglia cells in migraine conditions (17). Pharmacotherapy with sumatriptan can both reduce CGRP release as well as the CGRP transcription. Prior studies have implicated CGRP in decreasing the pro-inflammatory state (18). Some of the newer studies have brought into question the exact mechanism of CGRP activity (17). Subcutaneous Sumatriptan reaches its peak effect 6-20 minutes after administration. In controlled studies with sumatriptan injection, the most common adverse reaction with greater than 2% risk of events, were injection site reactions, tingling, warm/hot sensations and burning sensation. Other very rare side effects include reports of adverse cardiac events as well as cerebrovascular events. In a number of cases, it appears that cerebrovascular events were primary. It is therefore very rare for sumatriptan to cause these complications with an incidence of less than one percent.

Immediate post-craniotomy pain is multifaceted, due to responses from injury of the skin, muscles, and leptomeninges including the dura. The pain is usually described as a throbbing pulsating headache (4). Sources of postcraniotomy pain include tissue injury (scalp, cranial muscles soft tissue, and dura mater) and nerve disruption, traction, entrapment, and compression (19). The somatic component of the pain occurs due to the surgical incision and reflection of pericranial muscles and soft tissues of the scalp (4). Skull base surgeries employing suboccipital and subtemporal approaches produce higher degree of postoperative pain Meningeal irritation also contributes to postsurgical pain. Nevertheless, it is the amount of tissue damage rather than the location of the surgery, which determines the intensity of post-craniotomy pain. Greater amount of tissue injury generates higher intensity of postoperative pain. Although the brain itself is not innervated, dura matter and the meninges, are rich in blood supply and pain receptors. Much of the post-craniotomy pain is contributed by the irritation of the dura and the meninges (4). We are hypothesizing that in surgical cases of breaching the dura and leptomeninges, sumatriptan would exhibit the anti CGRP-effect and therefore contribute to decreasing the activation of the trigemino-vascular system.

Our null hypothesis states that sumatriptan is not different to placebo in addition to usual intravenous opioids, for the treatment of acute post-craniotomy pain. The alternative hypothesis states that sumatriptan is superior to placebo in addition to usual intravenous opioids, for the treatment of acute post-craniotomy pain. Our objective is to improve the available multimodal analgesic options for the treatment of post-craniotomy pain. Our primary outcome is centered around the measurement of post-operative pain score on Visual Analogue Scale (VAS: at 60 minutes). As a surrogate measurement of pain, we aim to measure the total opioids consumed and ancillary analgesics in both groups at similar points in time, in the recovery area and up to 24 hours post-operatively. We aim to measure satisfaction scores using Quality of Recovery 40 scores at 24 hours (13). We will follow up the patients at the intermediate time point of 30 days postoperatively.

Methods

Trial Design

The Sumatriptan for Post-craniotomy Pain Clinical Trial is designed as a randomised, placebo-controlled, anaesthetist, surgeon, patient and nurse blinded clinical study. This is a single centre study undertaken at the Austin Health main hospital campus (as outlined in trial registration details). Study will be undertaken during the perioperative period. Process of recruitment will begin in the neurosurgical and anaesthesia clinics. Patient consent will be signed preoperatively, either in the preadmission clinic or in the preoperative area prior to delivering care in the pre-anaesthetic area. The actual intervention will be

administered post-operatively in recovery during the pain management process. The primary endpoint of postoperative pain will be measured using the Visual Analogue Scale (VAS). Randomization will be performed as a block randomization with a 1:1 ratio. The study drug will be administered at the usual point of the patient needing analgesia in recovery – when the patient complains of mild-moderate pain or gives a Numerical Rating Score pain of at least 4/10. The initial subcutaneous sumatriptan injection will be compared with an initial placebo injection. The ongoing pain management would be standardised use of iv opioids as per recovery protocol in both groups. The spirit figure (**Figure 1**) demonstrates the schedule of patient review, consent, enrolment, interventions and assessments in this trial. The timeline of patient involvement is illustrated in **Figure 2.**

Study registration

This Protocol, Patient Information Consent Form as outlined in the PICF/person responsible PICF, as well as all other supporting documentation have been reviewed by the Austin Health Ethics Committee with respect to scientific content and compliance with applicable research and human subjects' regulations. This trial protocol has achieved approval by the Austin Health Research Committee, reference HREC/17/Austin/596. This trial has been prospectively registered with Australian New Zealand Clinical Trials Registry with a unique trial identifier U1111-1209-9072 (20). The Principal Investigators will make safety and progress reports to the HREC at the Austin Health at least annually and within three months of the study completion or termination.

Inclusion and Exclusion criteria

Patients who are at least 18 years old and who are undergoing craniotomy will be included in the study. Patients will need to be fully autonomous and able to give a valid consent for surgery and this particular study, or have mild underlying cognitive impairment only with the consent being given by the next of kin. Patients with any of the criteria listed in Table 1 will be excluded.

The exclusion criteria for this trial have been designed to maximise patient safety, while accurately reflecting the available scientific body of knowledge on sumatriptan (9).

Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with subcutaneous sumatriptan, and some have resulted in fatalities (9). This may have occurred due to erroneous prescription of sumatriptan for non-migrainous conditions. Cerebrovascular surgery may very rarely result in adverse events such as cerebral haemorrhage or stroke. We undertook a further safety review in the light of this being a phase 3 clinical drug trial. We located one study demonstrating an average increase of 6 +/- 5 mmHg increase in systolic arterial blood pressure, after administration of 100 mg of oral Sumatriptan. The clinical significance of this finding in terms of potential adverse effects is uncertain (21). In healthy volunteers (N = 18), a study evaluating the effects of sumatriptan on peripheral arterial reactivity failed to detect a clinically significant increase in peripheral resistance (9). In an initial large cohort study of 130 411 migraine sufferers by Valentgas et al, there was no association found between triptan use and risk of stroke (22). An increased overall risk of atypical stroke was found in the population prone to migraines, unrelated to any medication used.

The risk of stroke with the use of Sumatriptan, both secondary to ischemic or haemorrhagic cerebrovascular event is deemed to be and quoted at less than one percent. We have incorporated these quantifiable figures into our Patient Information Consent Form (PICF). This information is identical to the level of risk, which is quoted in the FDA prescribing information (9). As per FDA, Sumatriptan in contraindicated in patients with cerebrovascular disorders. we have excluded the patients undergoing cerebrovascular surgery from participating in this trial.

Figure 1 Standard Protocol Items; Recommendations for Interventional Trials (SPIRIT) figure. The schedule of enrolment interventions and assessments in the study

	Study Period						
	Enrolment	**Allocation**	**Post-allocation**				**Close-out**
Time point	**-T1**		**T1**	**T2**	**T3**	**T4**	
Enrol							
Eligibility screen							
Informed consent	Neurosurgical clinics						
Allocation		Point of care-recovery					
Interventions							
Subcutanous Sumatriptan Or Placebo			**Post-operative admin in recovery**				
Assessments		**Recovery area**	**30 mins post admin**	**60 mins post admin**	**Completion Recovery stay**	**24 hours post**	**Follow up At 1 month**
VAS Pain Score (0-10)		**X**	**X**	**X**			
NRS Pain Score (0-10)		**X**	**X**	**X**	**X**	**X**	**X**
Total Opiod Consumption				**X**	**X**		
Quality of Recovery Index						**X**	

Patient Satisfaction Yes or No							**X**

Figure 2. Participant Timeline

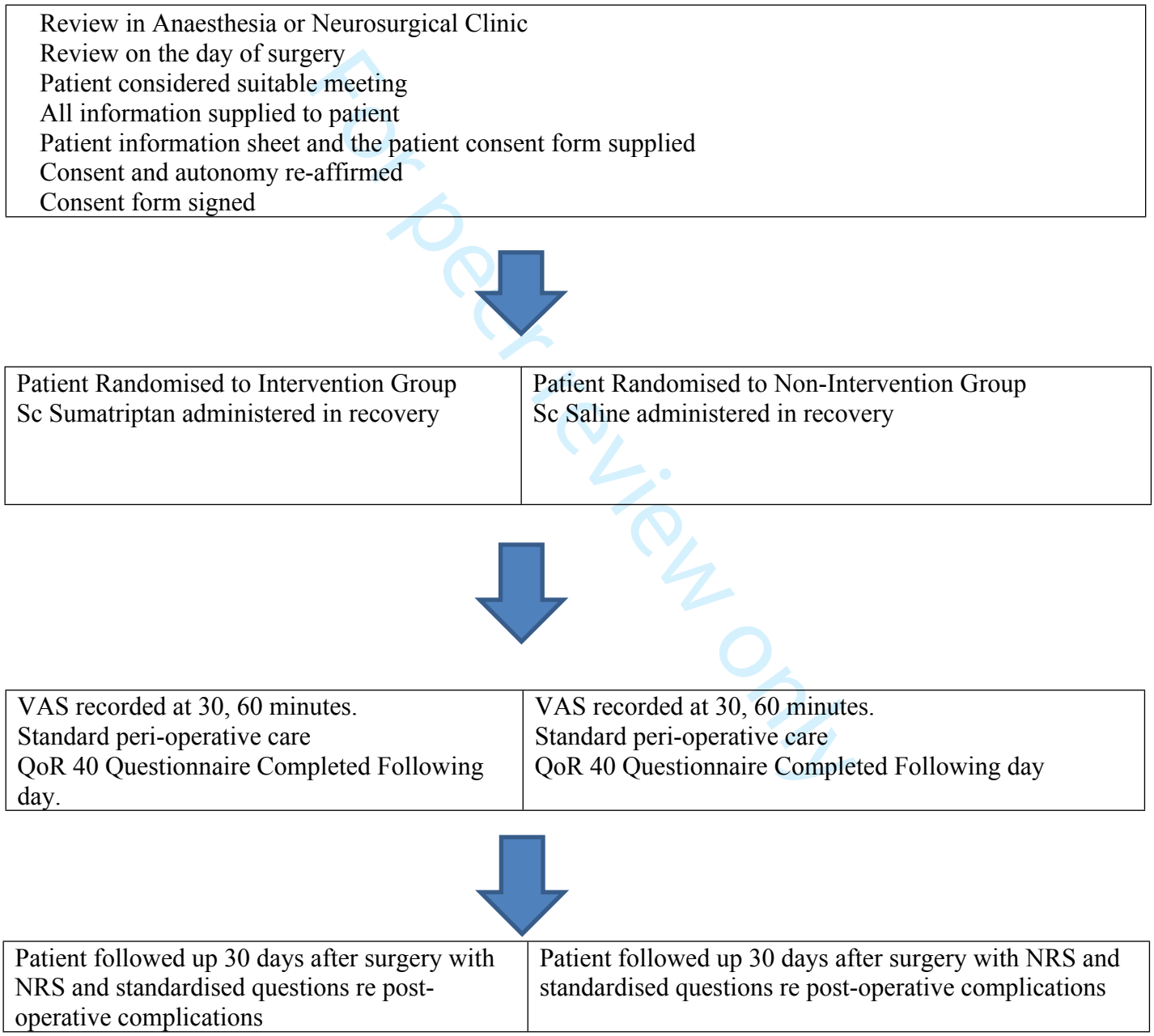

Table 1 Study Exclusion Criteria

Not autonomous, or have mild underlying cognitive impairment only, with the consent being withheld by the next of kin
Craniotomy for cerebrovascular surgery (i.e. cerebral aneurysm or arteriovenous malformation)
Previous Ischemic or Haemorrhagic CVA
Unstable Angina or Previous AMI
Severe hepatic impairment
Uncontrolled Hypertension
Previous sensitivity to Sumatriptan
Current Treatment with MAOI's
Emergency Re-do Craniotomy

Randomisation and Study Intervention

Blocked randomisation will be used to assign recruited participants to one of the two study groups- placebo or blinded therapeutic treatment group. Randomisation will be accomplished by the clinical research pharmacist using a sequence of computer-generated random numbers. Randomisation envelopes will be available at the point of care interface (operating theatre). Patients who actually require post-operative analgesic therapy to be administered will complete enrolment in the study at the point of care. This design has been chosen to maximise the efficiency of patient enrolment into the study. All preoperative and intraoperative care will be at the discretion of the treating team and will be in-line with the current best practice institutional principles for intra-cranial surgery. Participants will be randomly assigned to either control or experimental group with a 1:1 allocation ratio in permuted random blocks, as per a pharmacy generated randomisation schedule. Allocation concealment will be ensured, as the randomisation code will not be revealed until the patient is enrolled in the trial. From a scientific perspective, we do not plan to stratify our sample. We plan to deal with potential confounders through a univariate analysis and subsequent covariate multivariable logistic regression.

Randomisation envelopes will be made available only prior to the commencement of the study. Patients will be randomised at the point of care in order to maximise efficiency. The allocation sequence will be restricted and only available to the pharmacy randomisation staff, thereby ensuring the blinding of investigators. The implementation in the recovery stages will be completely independent of the randomisation group – and therefore both the assessor (recovery nursing staff) of the VAS scores and patients will be completely blinded. In the event of a report of a severe adverse event, Data Safety Monitoring Board will be notified and decision made on emergency un-blinding. Intervention in the Group A, the group receiving the Sc Sumatriptan will be initiated by the recovery staff at the point at which they would normally give the intravenous (iv) opioid protocol for pain. Criteria for administration of the study drug would be equivalent to the criteria for the administration of the usual therapy of the recovery intravenous opioid analgesia: Numerical Rating Scores (NRS) indicating mild-moderate pain or a 4-6 pain on a scale from 0-10, as self- reported by the patient (23). It is at this point that the patient

would be randomised in the study, and the randomisation envelope acquired. We have aimed to ensure the efficacy of trial enrolment, through point of care randomisation.

If the patient has been randomised to group A, the recovery nurse would be asked to collect the syringe from BOX A and administer the medication in a usual subcutaneous fashion. If the patient has been randomised to group B, the recovery nurse would be asked to collect the syringe from BOX B and administer the medication in a usual subcutaneous fashion. The relevant anaesthetic nurse will subsequently assess the NRS scores as per iv. opiod protocol i.e. every 5 minutes. If the standard protocol criteria for opioid administration are met during the subsequent assessment, patient will receive the usual iv opioid protocol. All patients will receive usual high standard routine post-operative care. The only additional assessments in recovery area would be those using the Visual Analogue Scale (VAS) scores prior to drug administration, at 30 and 60 minutes post study drug administration. The dose selected for use in this trial by the principal investigators is 6mg subcutaneously as a single injection. Our reasoning for choosing this dosing schedule includes that this is the recommended initial dose by the Australian register of Therapeutic Goods (ARTG). Most of the treatment effect is achieved from a single subcutaneous dose of Sumatriptan (9). Albeit potentially therapeutically inferior, there is an established modality for the treatment of post-surgical pain in the form of opioids. Following the initial single dose injection of subcutaneous sumatriptan, patients in both groups will be treated in the recovery area in a usual manner with an intravenous post-operative analgesia regime.
Criteria for discontinuation of the trial in individual patients include:
-Persistent GCS less than 12 in recovery.
-Significant surgical concern re potential intra-operative adverse features: potential intraoperative cerebrovascular accident;
Study protocol adherence reminders will be made on on-going basis with the recovery nursing staff. There will be regular brief monthly reminders at the nursing education sessions.

Study Outcomes and Their Measures
Primary Endpoints
Our primary objective is to determine if subcutaneous sumatriptan is superior to placebo, in addition to usual intravenous opiod in the management of post-craniotomy pain as measured using Visual Analogue Scores (VAS) 60 minutes after study drug administration. The primary outcome measure chosen was Visual Analogue Score (VAS) at 60 mins after placebo or subcutaneous Sumatriptan administration. From a pharmacokinetic perspective, the time from subcutaneous injection to peak concentration is 6-20 mins. Due to the potential for post-operative impairment of cognitive function, affecting the accurate measurement of pain, VAS result at 60 mins has been chosen as the primary outcome.

Secondary Endpoints
Visual Analogue Scale score at 30 minutes post sumatriptan administration has been chosen to coincide with the peak pharmacokinetic effect of sumatriptan post administration. We will analyse the VAS at 30 mins pain outcome, and compare and contrast this measure to our primary outcome.
As a surrogate measure of pain, we will be assessing the total opioid consumption both in the recovery area and post-operatively at 24 hours. Patient satisfaction at the phone interview 30 days post-oerpativley will be measured with a simple yes or no binary outcome. Any potential adverse events will be documented at 30, 60 minutes and the following day on the data collection sheet. Data on all and any adverse events will be collected by the study investigators, and initially analysed qualitatively.

Table 2 Secondary endpoints

Visual Analogue Scale scores 30 minutes post-operatively.
Numerical Rating Scale scores 24 hours post-operatively.
Total recovery area post-operative opioid consumption.
Total 24 hour post-operative opioid consumption
Quality of Recovery Scores 40, 24 hours post-operatively (day1).
Total hospital length of stay.
Patient satisfaction 30 days post-operatively
NRS pain score 30 days post-operatively.

Sample Size Calculation

Our sample size calculation was based on the primary outcome and the significant difference of 10 mm basis points in pain measurement on the Visual Analogue Scale. A recent article in British Journal of Anaesthesia outlined that Minimal Clinically Important Difference to patients is equivalent to 10 mm (24). We have therefore chosen this value as significant difference between the treatment and placebo group. We used STATA 13 program to calculate the sample size. With monitoring overall VAS scores in recovery postoperatively, the mean value was found to be 73 with a wide standard deviation. In an article by Jones et all, the mean VAS scores in recovery for post craniotomy patients, the VAS was found to be 34 (25). With a range of conflicting research, the median point for VAS was determined to be 50 mm. We have defined the 10 mm difference in VAS scores between the two groups as clinically significant and statistically significant. If we observe a pain reduction of 10 mm down to 40 mm, we would therefore be likely to accept our scientific hypothesis and reject the null hypothesis.

Table 3 Statistical Measures

Continuous summary outcome	Mean and standard deviation
The outcome	Visual Analogue Scale (VAS) scores 60 minutes after study drug administration
The values assumed for outcomes in Each group	Mean VAS for Control Group 50 mm(5 cm) Mean VAS for the Experimental Group 40mm(4cm)
The statistical test	T-test comparing two independent means of continuous outcomes
Alpha error	Two-tailed P value < 0.05
Power	0.8
The calculated sample size per group, Both assuming no loss of data	64 per group

Due to the potential for loss to follow up and missing data, we plan to enrol additional patients to a total of 136. Interim analysis will be conducted at the halfway point of the trial to assess for any differences between the groups. Unless there is overwhelming evidence with a difference in the effect of $p<0.05$, we plan to continue with the trial completion.

Statistical Analysis Plan

The intervention arm will be compared against the control for all primary analysis. Descriptive statistics (mean (SD) or median (IQR)) will be used for continuous variables. Normal data distribution will be confirmed through a histogram validation and Shapiro-Wilks test. We plan to use the student's T-test to compare the means of different groups for the continuous outcome of pain scores. Quantitative variables (continuous outcomes) will be compared using the Student's t-test or Mann-Whitney U-test to compare independent means. When indicated, a one-way repeated measures ANOVA will be performed. Categorical variables will be presented as absolute frequencies and percentage and compared between the two groups using the X^2 or Fisher exact test. The odds ratio (OR) will be calculated with its 95% confidence interval for the categorical post-operative outcome variables. A Bonferroni correction will be applied for multiple comparisons. We will use the Bonferroni method to appropriately adjust the overall significance for multiple primary and secondary outcomes as needed.

For subgroup analysis, we will use regression methods with appropriate interaction terms. Multivariable regression will be based on logistic regression for binary outcomes and linear regression for continuous outcomes. P values will be reported to four decimal places with p-values less than 0.001 reported as $p<0.001$. STATA 13^r will be used for statistical analysis. For all tests, we will use 2-sided p-values with alpha<0.05 level of significance. There may be a number of patient-related or anaesthesia technique related confounders, which may affect the outcome in this study (Table 5). We will conduct a univariate regression analysis on the significance of each one of these parameters. With any of the above parameters demonstrating a two-tailed p value of less than <0.1, they would be entered in a multi-variable regression model for each one of the primary and secondary outcomes. This strategy would be employed in order to assess any significant contribution of these factors on the primary and secondary outcomes of interest. Data collected from all randomised participants regardless of protocol adherence will be assessed on an intention to treat basis and analysed accordingly. Therefore, any patients who have withdrawn or been lost to follow up will be managed on an intention to treat basis. Should any patients withdraw, we will report reasons for doing so and compare the reasons qualitatively. Analysis of harms will be limited to participants who received the intervention.

Table 4 Summary of methods of analysis for each variable

Variable/ outcome	Scientific Hypothesis	Outcome measure	methods of analysis
Primary -VAS at 60 mins	Improvement with Sumatriptan due to improved Post-op Pain Management	Continuous VAS measure scale 0-100 mm	Comparison between 2 groups T-test
Secondary -VAS at 30 mins	Improvement	Continuous VAS measure scale 0-100 mm	Comparison between 2 groups T-test
-total opiod consumption 24 hours post-op	Improvement	Continuous standardised mcq measure	Comparison between 2 groups T-test
-improvement in QOR scores at 24 hrs	Improvement	Continous QOR score	Comparison between 2 groups T-test
Patient satisfaction -yes or no	Improvement	Categorical	Chi-squared or Fisher's exact test
Subgroup analysis			Regression Methods with appropriate interaction terms
-female vs male	Gender affects pain measure.		
-supratentorial vs infratentorial	Pain scores affected by site of craniotomy		
-emergency vs elective craniotomy	Pain scores affected by urgency of the case		

Table 5
Potentially confounding clinical parameters

Demographic parameters	Age
	Weight/BMI
	Gender
Underlying Clinical Conditions	Patient given history of migraine or headache of any variety
	Chronic analgesic consumption other than opioid
	Chronic opioid consumption
Intraoperative techniques	Intra-operative intravenous paracetamol
	Total intra-operative amount of remifentanil administered
	Total intraoperative opioid administered (excluding remifentanil)
	Intraoperative anaesthetic technique, volatile or TIVA
	Local anaesthetic scalp infilatraiton or scalp blocks

Recruitment
The allocated time for this study is 24 months in order to meet the demands for the enrolment of 136 patients. We plan to inform the anaesthesia and neurosurgical clinics of the study where the initial patient contact is made. The research team will monitor the lists in advance and make early contact with eligible patients. Subsequently, the research team will meet the patients and discuss the informed consent. The subjects will be approached by both study investigators, and medical staff familiar with the study.

Data Collection, Management and Analysis
Data will be collected from the standard anaesthesia chart. Numerical Rating Scores (NRS) will be documented as per protocol in the recovery charts. The Visual Analogue Scores(VAS) will be also be documented in the recovery section of the anaesthesia chart. Quality of Recovery (QoR) 40 questionnaires will be completed by patients the following day and filed in the notes by the attending nursing staff. Data on all adverse events during the first 24 hours will be collected. In the sumatriptan for post-surgical pain trial, all data will be entered electronically. Data will be entered in a coded de-identified manner with re-identifiable codes stored in separate file. This will be done at the Austin Health, where the data originated. Participant files are to be stored in numerical order and stored in a

secure and accessible place and manner. Participant files will be maintained in digital password protected storage for 15 years as required by regulation after completion of the study.

Safety Monitoring

Our Data Safety Monitoring Board (DSMB) is independent of the study organisers. During the period of recruitment to the study, interim analysis after 50 percent recruitment will be supplied to the DSMB. DSMB will review whether the active intervention has been proven with the analysis of primary outcome and analyse the total number of adverse events documented. All adverse events occurring after entry into the study and until hospital discharge will be recorded. An adverse event that meets the criteria for a serious adverse event (SAE) between study enrolment and hospital discharge will be reported to the local Data Safety and Monitoring Board (DSMB). DSMB will review the event(s) in an unbiased fashion and make an appropriate report to the sponsor (Austin Health) and Austin Health Human Research Ethics Committee. Life threatening conditions (that is, immediate risk of death); severe or permanent disability, prolonged hospitalization or a significant hazard will all be reportable to the Data Safety Monitoring Board.

Discussion

Significance

To our knowledge, the SUPS trial is the first trial to evaluate the utility and effectiveness of subcutaneous sumatriptan as a component of multimodal analgesic regime for the management of post-craniotomy pain. Primary study outcome is measured using the tools that have good validity and reliability for measurement of pain. The advantages of VAS are that there is good evidence for responsiveness, validity, test–retest reliability (26) (27). In studies attempting to validate the NRS, the VAS is used as the gold standard clinical measurement (28). The NRS is considered to have overall lower precision than VAS in the peri-operative setting and it may therefore negatively bias the outcome of the study. In addition to this, the VAS is considered easier to administer in patients with any verbal difficulties (28).

This study has been designed as a placebo controlled superiority trial. The trial would therefore not require the participants to forgo treatment they would otherwise receive. In this case, there are compelling methodological reasons to determine the efficacy of the intervention, and the patients who receive the initial placebo intervention will not be subject to any risk of serious or irreversible harm (29). Furthermore, the follow-up at a 30-day time-point may provide insight into the effects of study intervention on intermediate perception of pain. If the benefits proposed by our study are substantiated, this can have a significant impact on post-craniotomy multimodal analgesic patient care.

Limitations

Analgesic requirements are commonly used as post hoc measures of pain experience (28). whether this Effectiveness of sumatriptan in reducing the opioid dosage at various end-points during the first 24 hours is addressed in the secondary outcomes. We will be recording any adverse events experienced by the patient in the course of the study. However, accurate opioid side effects may be difficult to define and measure secondary to potential confounding by other medical conditions and medications.

No stratification or matching will be performed during the recruitment and conduct stages of the trial. We have identified a significant number of potential clinical confounders. The most efficient and statistically feasible approach to dealing with a high number of potential confounders is in the analysis stages by conducting a univariate analysis. When each parameter demonstrates significance according to pre-determined p level, it will be entered into a multivariable regression model for each primary and secondary outcome of interest. We plan to conduct three distinct subgroup analysis all with strong

biological basis. Our study is underpowered to detect a statistically meaningful difference in these subgroups. However, our analysis will indicate an observed trend in the data.

Ethics and Dissemination

The structure of our study necessitates that sometimes the study recruiters and investigators will also be the treating clinicians. Patients will always be given information that describes the proposed research as well as the form for withdrawal of consent. When reasonable to do so, patients will be invited back to the clinic to ask any further questions around the trial and consent process. A genuine scientific question has been posed which has the potential to improve future pain management in this group. Patients will be informed through a detailed consent process that they will not achieve any additional clinical care by participating in the study nor will they come to any harm by refusing to participate. The potential undue influence is therefore minimised through the principles of fully informed patient consent, equal care and clinical equipoise (29). There will be no additional invasive investigations occurring in the study participants, decreasing the risk of inconvenience and patient harm. Protecting potentially vulnerable adults with mild cognitive impairment, who are eligible to participate in the study is vitally important. The investigators believe that it is a scientific necessity to enrol this population in -order to avoid selection bias in the study population. Decision making capacity (DMC) of this subset of patients would have been evaluated in order to ensure validity of the surgical consent process. Equivalent decision-making capacity will be transferred to participation in the study.

Any modifications to the protocol which may impact the conduct of the study, the patient outcomes or have the ability to influence the safety of the patient, changes to the study objectives, study design or patient population will be communicated to the Austin Health Ethics Committee. Permission will be sought to modify the protocol prior to any significant changes.

Conclusion

Post-craniotomy pain management consists of opioids with limited multimodal analgesic therapeutic options. We have delineated a phase 3 Clinical Trial utilising a frequently administered anti-migraine drug sumatriptan in its injectable subcutaneous form in the setting of post-craniotomy pain management. Subcutaneous Sumatriptan use for Treatment of Post-Craniotomy Pain is a single centre randomised double-blinded placebo-controlled superiority trial. Primary outcome is a visual analogue score rating. 60 minutes after drug administration. Secondary outcomes consist of VAS rating 30 minutes following the study drug administration as well as total 24 hour post-operative opioid administration. With the design and conduct of this phase 3 clinical trial we intend to expand the evidence base of post-craniotomy analgesia management.

Trial Status

This trial will be recruiting from the 1st of July 2019. The trial is planned to run for 2 years. This trial protocol has achieved approval by the Austin Health Research Committee, reference HREC/17/Austin/596. This trial was prospectively registered with Australian New Zealand Clinical Trials Registry on the 10/05/2018 with a unique trial identifier U1111-1209-9072 and registration Number ACTRN12618000793213P.

Abbreviations:

5-HT (5-hydroxytryptamine), VAS (Visual Analogue Score), NRS (Numerical Rating Score), CGRP (Calcitonin Gene Related Polypeptide).

Author's contributions

Dr Ana Licina reviewed the scientific literature and contributed to the original protocol.
Dr Jeremy Russell contributed the original scientific hypothesis and the original protocol.
Dr Andrew Silvers contributed to the original protocol.
Dr Xin Jin reviewed the scientific literature and contributed to the original protocol
Dr Jason Denny reviewed the scientific literature and contributed to the manuscript.

Funding statement

This research received no specific grant from any funding agency in commercial or not-for profit sectors.
This trial has obtained internal funding from the Austin Neurosurgical Research Fund.

Competing Interests

Dr Ana Licina has no relevant financial or non-financial interests to disclose.
Dr Jeremy Russell has no relevant financial or non-financial interests to disclose.
Dr Andrew Silvers has no relevant financial or non-financial interests to disclose.
Dr Xin Jin has no relevant financial or non-financial interests to disclose.
Dr Jason Denny has no relevant financial or non-financial interests to disclose.

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AUSTIN HEALTH HUMAN RESEARCH ETHICS COMMITTEE

ETHICAL APPROVAL

Dr Ana Licina,
Austin Health

18 September 2018

Dear Dr Ana Licina,

HREC Reference Number [AU RED HREC reference number]: HREC/17/Austin/596

Austin Health SITE REFERENCE Number: DT 17/596

Project Title: Subcutaneous Sumatriptan use for Post-Craniotomy Pain, Randomised Double Blind Placebo Controlled Trial Acronym: SUPS Trial.

I am pleased to advise that the above project has **received ethical approval** from the Austin Health Human Research Ethics Committee (HREC). The HREC confirms that your proposal meets the requirements of the National Statement on Ethical Conduct in Human Research (2007). This HREC is organised and operates in accordance with the National Health and Medical Research Council's (NHRMC) National Statement on Ethical Conduct in Human Research (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

HREC Approval Date: 18 September 2018

Ethical approval for this project applies at the following sites:

Site
Austin Health

Approved Documents:

The following documents have been reviewed and approved:

Document	Version	Date
HREA (AU/1/2282314)	1.3	24/11/2017
VSM	2	20/02/2018
Protocol	1.6	10/08/2018

PICF	1.3	11/02/2018
Person Responsible ICF	1.3	11/02/2018
Form for withdrawal – Participant	-	-
Form for withdrawal – Person Responsible	-	-
CRF	1.2	-
Data Collection From	-	-
Consumer Medicine Information – Sumatriptan succinate	2.0	2003
Statistical Analysis Plan	-	-

Governance Authorisation:

Governance Authorisation is required at each site participating in the study before the research project can commence at that site.

You are required to provide a copy of this HREC approval letter to the principal investigator for each site covered by this ethics approval for inclusion in the site-specific assessment application.

Conditions of Ethics Approval:

- You are required to submit to the HREC:
  - An Annual Progress Report (that covers all sites listed on approval) for the duration of the project. This report is due on the anniversary of HREC approval. Continuation of ethics approval is contingent on submission of an annual report, due within one month of the approval anniversary. Failure to comply with this requirement may result in suspension of the project by the HREC.
  - A comprehensive Final Report upon completion of the project.
- Submit to the reviewing HREC for approval any proposed amendments to the project including any proposed changes to the Protocol, Participant Information and Consent Form/s and the Investigator Brochure.
- Notify the reviewing HREC of any adverse events that have a material impact on the conduct of the research in accordance with the NHMRC Position Statement: *Monitoring and reporting of safety for clinical trials involving therapeutic products November 2016*.
- Notify the reviewing HREC of your inability to continue as Coordinating Principal Investigator.
- Notify the reviewing HREC of the failure to commence the study within 12 months of the HREC approval date or if a decision is taken to end the study at any of the sites prior to the expected date of completion.
- Notify the reviewing HREC of any matters, which may affect the conduct of the project.

The HREC may conduct an audit of the project at any time.

Yours sincerely,

Priyanka Sathe
Research Ethics Officer, Office for Research, Austin Health, Level 8 HSB.
Phone: +61 3 9496 4090;
E-mail: Priyanka.sathe@Austin.org.au
Web: http://www.austin.org.au/researchethics

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Informed Consent form for Patients undergoing Craniotomy who are invited to participate in research on use of Sumatriptan to improve post-operative pain control.

Interventional Study-Adult providing own consent form

The title of this project is:

Subcutaneous Sumatriptan for Post-Craniotomy Pain- A Randomized Double-blind Placebo Controlled Clinical Trial

Short title: Subcutaneous Sumatriptan for Post-Craniotomy Pain

PICF Version: 1.2 Date 11/2/2018

Project Sponsor

Austin Health

Principal Investigators

Dr Jeremy Russell

Dr Dean Cowie

Dr Ana Licina

Co-ordinating Principal Investigator

Dr Ana Licina

Name of Organization/Location where recruitment will occur

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This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

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What does my participation involve?

1.Introduction

You are invited to take part in this research project. This is because you have *a neurosurgical condition requiring an operation (Craniotomy)*. The research project is testing a new treatment for *the improvement of pain control after your surgery.* The new treatment is called *Sumatriptan, a medication which is otherwise well-established in migraine pain management*.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

• Understand what you have read

• Consent to take part in the research project

• Consent to have the tests and treatments that are described

• Consent to the use of your personal and health information as described.

2. Purpose of the research

Craniotomy is a type of surgery which involves operating on the brain and its structures. It is is a relatively common procedure to undergo. The post-operative pain management is not as optimal/good as we would like it to be. The drugs that we use currently cause a lot of drowsiness and are not always ideal for treatment of the headache.

Sumatriptan is approved in Australia to treat migranious headache. However, it is not approved to treat post-operative pain in neurosurgery. Therefore, it is an experimental treatment for the Post-operative pain in this situation. This means that it must be tested to see if it is an effective treatment in Post-operative pain.

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The reason we are doing this research is to find out if subcutaneous Sumatriptan is better than standard opioid therapy for post-surgical headache and pain. If you choose to participate in this study, you may receive Sumatriptan in addition to usual opioid analgesia.

This research has been initiated by the study doctors, Dr Russell, Dr Licina and Dr Cowie.

3.What does participation in this research involve?

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random). You have a one in two chance of receiving the study drug.

You will be participating in a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving. However, in certain circumstances your study doctor can find out which treatment you are receiving.Because we do not know if Sumatriptan is better than the currently available pain relief for treating pain after head surgery, we need to compare the two. To do this, we will put people taking part in this research into two groups. The groups are selected by chance, as if by tossing a coin. This research involves a single injection under your skin with a very small needle to help treat the pain while you are recovering after your surgery in the recovery area. Participants in one group will be given the test drug followed by the standard opioid analgesia. Participants in the other group will be given the placebo followed by standard pain pathway only. A placebo is a medication with no active ingredients or a procedure without any medical benefit. It looks like the real thing but is not. Importantly, which-ever group you belong to, you will also be treated with **standard intravenous pain relief**

It is important that neither you nor we know which of the two drugs you are given. This information will be in our files, but we will not look at these files until after the research is finished. This is the best way we have for testing without being influenced by what we think or hope might happen. We will then compare which of the two has the best results. 'If you find that the drug we are testing does not stop your pain and it is very uncomfortable for you, we can use the rescue medicine to make you more comfortable. The medicine that we will use is called Fentanyl/Morphine/Oxycodone and it has been proven to control pain'.

The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the drug is doing, we will find out which drug you are getting and make changes. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers.

When you arrive in the recovery area, the nursing staff will monitor all your vital signs and pain scores. If you have enrolled in the study and you have measurable pain, you will be given subcutaneous injection of the test drug or a placebo. It's a small thin needle which injects the contents just under your skin. You will be asked about you pain relief regularly. If 5 minutes later, you have ongoing pain, which ever study group you are in, you will be administered intravenous pain relief. At 30 minutes we will ask you to look at the ruler from 0-100 mm and tell us at what level your pain is. At 60 minutes we will ask you to look at the ruler from 0-100 mm and tell us at what level your pain

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is. There may be a break between treatments so that the first drugs are cleared from your body before you start the new treatment.

There will be a Quality of Recovery brief survey on how you are recovering. We will ask you to fill this in. One month after your admission you will get a follow up call to assess your progress.

Blood samples taken will only be the routine ones and there will be no additional investigations required if you choose to participate.

There are minimal time-commitments expected of you during this study. You will be administered the subcutaneous injection in recovery during which time it is standard and expected to administer pain relief to patients as needed. Subsequently if you participate in the study, you pain will be more thoroughly assessed during your stay. There will be no additional time commitments during this period.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

4.What do I have to do?

We are inviting all adults who have a craniotomy (head surgery for a range of conditions) to participate in the research on the use of the well-known migraine drug for treatment of post-surgical pain. There are no changes or restrictions to any of your usual activities

5.Other relevant information about this research project

A total of 136 people will be participating in this trial. The Austin Health is the primary site where this research is being done. We hope to obtain information in order to improve post-cranitomy pain management in the future.

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive during the surgery and afterwards, will continue and nothing will change. If you choose not to participate in this research project, you will be offered routine pain relief after the surgery. You can change your mind and stop participating later if you choose to.

6.Do I have to take part in this research?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

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Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with *Austin Health]*.

7. What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; these include *the standard* opiod analgesia regime which is routinely in use after this type of surgery. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8.What are the possible benefits of taking part?

There will be no clear benefit to you from your participation in this research.

9.What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

As already mentioned, this drug can have some unwanted effects. In controlled studies with sumatriptan injection, the most common adverse reaction with greater than 2% risk of events, were injection site reactions, tingling, warm/hot sensations, burning sensation, feeling of heaviness, pressure sensation, feeling of tightness, numbness, feeling strange, tight feeling in head, flushing, tightness in chest, discomfort in nasal cavity/sinuses, jaw discomfort, dizziness/vertigo, drowsiness/sedation and headache.

Other very rare side effects include:

-reports of adverse cardiac events, including myocardial infarction, coronary vasospasm, life threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of sumatriptan, Considering the widespread use of sumatriptan in patients with migraines, the incidence of these events is very low.

-cerebral haemorrhage, subarachnoid haemorrhage, stroke and other cerebrovascular events have been reported in patients treated with subcutaneous sumatriptan. In a number of cases, it appears that

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cerebrovascular events occurred independently of any drug being given. It is therefore very rare for sumatriptan to cause these complications with a frequency of less than one percent.

While the possibility of the side effects occurring is very low, you should still be aware that they may occur. We will try to decrease the chances of this event occurring, but if something unexpected happens, we will provide you with immediate review and all supportive treatment.

The risk of problems from anaesthesia increases for patients who are having more major surgery, those with medical problems and those that require difficult anaesthetic procedures. If you have any concerns about these issues, you should discuss them with the study team.

10. What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

11. Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

12. What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing. If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data

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collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

13. Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The drug/treatment/device being shown not to be effective
- The drug/treatment/device being shown to work and not need further testing

14. What happens when the research project ends?

On the completion of the research project, you will receive a phone call to inform you of the findings. Please let us know if you do not wish for this to occur.

Part II: How is the research project being conducted?

15. What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this health service for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Austin Health, as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

De-identified information from this project may be used in future related research. It will not identify you, nor will it be traceable to any personal information you provide. In 15 years time, we may offer the study information to a database/registry. The information will not be identifiable nor traceable to you. It may help future researchers and patients to icorporate this data in further rstudies.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you

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cannot be identified, except with your permission. Information about your participation in this research project will be recorded in your health records.

In accordance with relevant Australian and Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project *and for the future research described in Section 14* that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

16. Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, freeof charge, as a public servant in any Australian public hospital.

16. Who is organising and funding the research?

This research project is being conducted by Dr Jeremy Russell and Dr Ana Licina.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

17. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Austin Health. This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

18. Further information and who to contact?

For all clinical complaints and enquiries please contact:

Name	*Dr Ana Licina*
Position	*VMO in Anaesthesia*
Telephone	*0458490244*
Email	*Ana.licina@austin.org.au*

Local HREC Office contact (Single Site - Research Governance Officer)

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Name	*Austin Health Human Research Ethics Committee*
Telephone	*03 9496 4090*
Email	*ethics@austin.org.au*

Consent Form - *Adult providing own consent*

Title: Subcutaneous Sumatriptan for Post-Craniotomy Pain- A Randomized Double-blind Placebo Controlled Clinical Trial

Protocol Number: 1.2

Project Sponsor: Austin Health

Principal Investigators: Dr Jeremy Russell, Dr Ana Licina

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

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Under certain circumstances (see Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 at 4.8.9*) a witness* to informed consent is required.*

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/

Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	10
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	16
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	nil
Sample size	7a	How sample size was determined	13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	14
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10,11,12,13

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	2
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a –potential adverse effects 3/4
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant multiplicity of analyses	21
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	20
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	8
Protocol	24	Where the full trial protocol can be accessed, if available	This is the protocol
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	25

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org

Dear Editor,

We thank the BMJ Open for reviewing our manuscript. Below, we also address the points raised by the reviewers. We submit the revised manuscript taking into account the pertinent reviewer points. We have also clarified the presentation of some of the scientific concepts in our revised manuscript.

Significant Changes we have incorporated into the Revised Manuscript:

- This trial was initially designed as a placebo controlled superiority trial. We have looked more carefully into this and our trial meets the statistical criteria of a superiority trial. As such, we specify that this is a superiority trial.
- We have streamlined the verbal expression of our null hypothesis for future clarity of readership.
- We specify our Primary outcome as Visual Analogue Scale score at 60 mins after study drug administration.
- We have streamlined the strengths and weaknesses statement. We consider the pharmacy involvement a strength of the trial as it will allow for point of care enrolment and therefore maximise trial efficiency.

Please note that the second reviewer's main concern (how the study will deal with the confounders) was already addressed in the manuscript. We have outlined a detailed explanation on page 13 of this response. We have also clarified this concept in the manuscript to a greater extent.

Evidence in Support of Rebutting the Reviewer One Comments

Reviewer 1:

"Face-to-face [usually hyphenated] adherence reminders" sounds like an effort to maintain clinical equipoise and protocol adherence for the nursing staff. This should be explained in more detail—how are you verifying that all recovery room nurses are aware of the study and trained on its procedures?"

The trial publication needs to consist of an economy of words, while conveying a clear message to the reader- the number of nursing staff present and involved in regular reminders is beyond the scope of this manuscript for the purpose of trial protocol publication. The manuscript contains a significant amount of detail described about the ongoing study processes. Details on training the nursing staff in the study have been provided in the standard operating procedures.

Reviewer 1

"As a simple example, the primary outcome measure does not match the stated null hypothesis; as described, your study only addresses one question: does SQ sumaT 6 mg reduce post-op pain (presumably head pain, although this is never stated) at 60 minutes in craniotomy patients? Your null hypothesis and overall query, however, seems to address a related and more important question: does the use of SQ sumaT in the immediate post-op period reduce (or eliminate??) the use of opioids after craniotomy? For that question, the primary outcome measure would need to be changed."

Our null hypothesis on page three of the original submission relates to the measurement of post-operative pain and states:

"Our null hypothesis states that sumatriptan in addition to standardised post-operative opioid regimens is non-inferior for the treatment of post-craniotomy pain including both post-operative headache and surgical pain as compared to management with opioids alone."

We have now streamlined our null hypothesis to avoid any possible ambiguity:

"Our null hypothesis states that sumatriptan is not different to placebo in addition to usual intravenous opioids, for the treatment of acute post-craniotomy pain. ". Therefore, our null hypothesis revolves around the alleviation of surgical insult, which is pain.. There is a well-validated scale of measuring pain in the form of Visual Analogue Scale. Our null hypothesis does not address the opioid consumption as a measure of pain. Visual Analogue Scale is a validated measurement tool with high construct and content validity. We are therefore choosing to measure the outcome of interest directly (Pain) with the available measurement tool (VAS). Post-operative opioid consumption is a surrogate measure of pain. In our trial design, opioid consumption has been chosen as a secondary outcome.

And our primary outcome states on page six of the original manuscript:
"To determine if subcutaneous sumatriptan is non-inferior in the management of post-craniotomy pain in patients undergoing craniotomy as measured using Visual Analogue Scores (VAS) 30 minutes after study drug administration."
Please note, we have since denoted out trial as a superiority trial with a VAS at 60 for greater clinical accuracy. We have however after reviewing the primary outcome swapped the VAS 30 to VAS 60 from the secondary outcomes for feasibility reasons. The statistical calculations and assumptions are exactly the same. VAS at 60 minutes after the study drug use will allow patients to be more coherent and appropriate at the time of clinical query. Please note, we have streamlined the primary outcome to the following statement:
"Our primary objective is to determine if subcutaneous sumatriptan is superior to placebo, in addition to usual intravenous opiod in the management of post-craniotomy pain as measured using Visual Analogue Scores (VAS) 60 minutes after study drug administration."

Reviewer 1
"It is not clear that a statistician with experience in clinical trials reviewed this protocol or analysis plan; I highly recommend this be done for this and future trials."
This statement is in contrast to the opinion of reviewer two who felt the study was generally well planned statistically. The trial statistical analysis plan and numbers of patients planned to be recruited were carefully considered during the Human Ethics Research Review (HREC), with the result of trial being approved. As such, our HREC felt confident approving the clinical and statistical feasibility of this trial.

Reviewer 1
"There are many examples of confusing redundancy, e.g., "Lack of evidence-based clinical trials"—either "lack of randomized clinical trials" or "lack of a valid evidence base to guide treatment" would convey the point properly. Similarly, "placebo-controlled trial comparing sumatriptan with placebo" is awkward and redundant."
"VAS scale" is redundant—the last letter stands for "scale" already.
We have now dealt be with this in the editing stage specifically stating:

> "With the design and conduct of this phase 3 clinical trial we intend to expand the evidence base of post-craniotomy analgesia management. "

Reviewer 1
This is not a "phase 3" trial, which is used in drug development or pivotal trials for regulatory agency approval. This could be considered a phase 4 trial (drug already approved) but is more simply a RCT.
Sumatriptan is currently not licensed for the management of post-craniotomy or post-operative pain in Australia or internationally. In the FDA regulations, it is stated that the indications for administration of Sumatriptan are:
-Acute Migraine.
-Cluster Headache.
Phase 3 trials are conducted to confirm and expand on drug safety and effectiveness, to compare the drug to standard therapies for the disease or condition being studied, and to evaluate the overall risks and benefits of the drug. The Food and Drug Administration (FDA) reviews results from Phase 3 trials when considering a drug for approval for a certain indication- sumatriptan is not approved for post-operative pain management. Our trial is comparing the suitability of Sumatriptan with placebo, in addition to the usual intravenous opioids for the treatment of post-craniotomy pain.

Furthermore, Therapeutic Goods and Administration regulatory body in Australia defines a phase 3 trial as:
Phase 3, Therapeutic Confirmatory:

Safety, efficacy or effectiveness:

Phase IIIa:
Determine the therapeutic effect in patient populations for which the drug is eventually intended
Provide a definitive assessment of risk-benefit balance (to support drug registration or change in clinical practice)

As such this would be use of a drug for a new indication and for potential regulatory agency approval. Phase 4 trials are post marketing trials, after a drug has been approved by the regulatory agencies for the proposed indication.
In summary:

- Both Australian TGA and FDA define testing drug safety and effectiveness as phase 3 trials prior to approving the drug for a therapeutic indication.
- Phase 4 trials are conducted post FDA and TGA approval.
- Our HREC has defined this as a phase 3 trial.

Reviewer 1
The abstract should clearly describe subject selection, study dates and duration, and the target enrollment number.
We have expanded our abstract in the revised manuscript in order to deal with this issue. We now state: "Eligible adult patients (18 years and older) undergoing craniotomy will be identified pre-operatively, and consented for the SUPS trial at a single tertiary referral centre." And:
"We will enroll a total 136 patients in total, with the study duration of 2 years. This trial will commence recruitment on the 1st of July, 2019."

Reviewer 1
Nowhere in this protocol do you actually say that VAS will be obtained before drug administration—if that is true (that you don't ask), then this study has essentially no value.
The difference measured in the VAS scores between the two groups will be considered as significant, if greater than 10 mm as confirmed by prior clinical studies by Myles et al. As such the baseline VAS will only be that-baseline VAS, ensuring there is no appreciable difference between the two groups in the pain level experienced at the baseline. The manuscript states that the NRS (Numerical Rating Score) will be obtained. The NRS value is used in order to administer the study medication to patients. It would not be feasible to conduct this study (or administer pain relief without a baseline score). The NRS and VAS are comparable and equivalent in scale, although the VAS is the gold standard. The VAS will also however be obtained.

Reviewer 1
General comments:
Standard HA pain responses include 2HPF, 2HPR
"Nociception" also means "pain report after stimulation" and so is confusing
This study is centered around the post-operative pain experienced by the patient.
Nociception in this case means pain after craniotomy, which was the painful stimulus. The purpose of this study is to analyse the post-craniotomy pain.

All of these comments refer to abstract:

Reviewer 1
NRS of what over 24 hrs?
"Selected patient outcomes"? What?
QoR40—validated? In whom? Citation?
It was simply impossible to accommodate this in the body of the abstract- it would have made the abstract well over 500 words.
Quality of recovery 40 is a validated measurement of recovery post anaesthesia. The economy of words in the abstract does not permit a detailed description. We have inserted the following reference citation in the body of the manuscript:

"Myles P, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a postoperative quality of recovery score: the QoR-40. British Journal of Anaesthesia. 2000;84(1):11-15. "

Reviewer 1
"Histogram dist'n curve analysis" sounds like visual inspection. Student's T-test on which measures?
Further information has been provided in the content of the manuscript.
The economy of words required by the BMJ does not allow us to elaborate on this in the abstract. There are however details given in the Statistical Analysis Plan.

Reviewer 1
Any planned confounds?
The confounds for this study have been deemed to be multiple. It was impossible to include all of them with the word requirement of under 300. Please review the main text body.
.

Reviewer 1
Obtain prior HA Hx? FHx? Other med use?
Post-craniotomy pain is the topic of this manuscript, rather than management of headache. Further details on the potential confounders such as headache have been provided in the main body of the manuscript under the Statistical Analysis Plan. In the revised manuscript, we make a suitable mention of the confounders in the abstract. As there is an economy of words needed in the abstract, we elaborate on the details of the confounders in the body of the manuscript.

Reviewer 1
P.4: many redundancies
pbo use "in the non-tx arm": this is not non-Tx, but blinded drug vs placebo Tx. .
We would be happy to re-phrase this for greater clarity:
"blinded placebo intervention versus drug treatment"

Reviewer 1
"Allowing minimization of bias"—yes, that is the principle behind RCTs, not really necessary to state that here.
Placebo controlled trials in anaesthesia are rare in the analgesic field. We have ensured this trial was ethically sound in order to utilize the placebo arm in the initial instance of providing analgesia. We believe this is a strength of our trial design..

Reviewer 1
VAS vs other PROM: there are other validated scales for acute HA response, i.e. PPMQ-r
"Involvement of hospital pharmacy"—this is how randomization is done, not unique or remarkable for an RCT. If you were using a specific randomization scheme, such as urn randomization, that might be worth comment.
This is a study on post-surgical pain. Hence Visual Analogues Scale is the validated appropriate measure of post-operative pain.
Obtaining enthusiasm and funds for the involvement of a pharmacy can be difficult in a clinical trial. This study was fully initiated by authors, based on clinical equipoise, with no external pharmaceutical funding. As such we feel that having the pharmacy assistance towards ensuring the study was as clinically objective as possible, is of great benefit. Please refer to the CONSORT Statement, section 9 on Randomisation.

Reviewer 1
"Opioids are still the mainstay of post-op craniotomy pain mgt"—clearly true based on experience, but can you provide some data? Even a review of a few 100 consecutive cases at your institution would be helpful.

This is available known scientific information, which has been extensively published on. The clinical need for improved management of pain, rather than the mainstay of opioids has been widely described in clinical literature. Performing an observational study just to demonstrate what is widely known already, is not a wise use of precious health resources.

Reviewer 1
Should also acknowledge that NSAIDs would theoretically be helpful but are generally avoided in this setting due to concerns of antiplatelet effects (although that risk has never actually been tested)
We have mentioned briefly the NSAID's lack of clinical feasibility in this setting in the revised manuscript
There is a lack of clinical feasibility for the perioperative use of non-steroidal anti-inflammatory agents (NSAID) in intracranial surgery. The authors chose not to discuss this specifically in this manuscript.

Reviewer 1
Null hypothesis: if you are adding sumaT, then non-inferiority is not really the question. Question is: will acute sumaT reduce opioid use? Null hypothesis: no change in opioid use.
Our null hypothesis centers around measuring the post-operative pain experienced by the two groups. We therefore choose to use well-validated scale to measure the level of post-operative pain. Our null hypothesis does not involve the opioid use as a surrogate measure of pain.

Reviewer 1
Problem; If your primary outcome measure is simply VAS at 30 mins, then that does not address your primary hypothesis. Primary outcome would need to be opioid use at some number of hours (?1, 2, 4, ?24) after sumaT.
Our null hypothesis focuses on the difference in pain experienced by the two parallel patient groups (the treatment arm and placebo arm). Our null hypothesis does not focus on opioid use. Our secondary outcomes do include the measurement of opioid use post-operatively as a surrogate measure of pain.

Reviewer 1
Head pain is not due to hyperemia; intracranial vessels are also richly innervated as are meninges (not simply dura mater)
In our manuscript we state:
"Immediate post-craniotomy pain is multifaceted due to responses from injury secondary to dural innervation eliciting potential dural hyperemia as well as the nociception originating in the muscle and skin innervation."
Thereby acknowledging the nature of the multifaceted post craniotomy pain.
In order to promote scientific clarity, we have now changed the wording of our scientific hypothesis to convey the equivalent message but in improved terms:
"Immediate post-craniotomy pain is multifaceted, due to responses from injury of the skin, muscles, and leptomeninges including the dura."

Reviewer 1
Non-Australian readers don't know what "TGA" is—please define
TGA= Therapeutic Goods Administration, we have corrected this non-provision of a full title.

Reviewer 1
"*SumaT for TN? Really?* "
As referenced Sumatriptan has been studied for its effectiveness in Trigeminal Neuralgia with promising preliminary results. This was referenced in the manuscript with the following clinical paper.

7.Kanai A, Suzuki A, Osawa S, Hoka S. Sumatriptan Alleviates Pain in Patients With Trigeminal Neuralgia. The Clinical Journal of Pain. 2006;22(8):677-680.

In this well-designed placebo controlled trial, subcutaneous sumatriptan was found to be more effective than subcutaneous normal saline.

Reviewer 1
Need to explain origin, validation of QoR40. Note its use in a differ article
Quality of Recovery Indicator 40 has been validated by the group in Melbourne in 2000 and the article published in British Journal of Anesthesia Myles et al BJA 84. It has been used by multiple other groups in anesthesia for validation. We would be happy to include this reference in the group of references for the manuscript and have done so in the revised work. In addition, we reference the QoR 40 in the manuscript as it was used to assess the patient recovery in the following study.

8.Venkatraghavan L, Li L, Bailey T, Manninen P, Tymianski M. Sumatriptan improves postoperative quality of recovery and reduces postcraniotomy headache after cranial nerve decompression. British Journal of Anaesthesia. 2016;117(1):73-79.

Reviewer 1
Need to review modern migraine pathophysiology; migraine pain has NOTHING TO DO WITH VASODILATION
The pathophysiology of migraine is not the topic of this study. We do cross-reference the pharmacodynamic properties of Sumatriptan, which acts on the selected 5HT receptors with the net effect of large vessel vasoconstriction (although we do not claim that is how sumatriptan exerts its effect in migrainous headache). Our scientific hypothesis partially rests on Sumatriptan blocking the 5HT1 receptors and therefore decreasing the trigemino-vascular activity (page 4 in the manuscript). The complex and somewhat contentious pathophysiological mechanisms of migraine are not the purpose of this manuscript or this clinical trial.

Reviewer 1
CGRP: sterile inflammation in HA is an accepted but unvalidated concept. If it is really "inflammation" then all that should be needed is NSAIDs or steroids; the latter don't work in acute HA.
Many international migraine experts discuss CGRP and inflammation in their latest work on migraine. An article in Lancet published in 2018 by an international migraine expert discusses the role of CGRP at length. NSAD's are amongst the first line therapeutic agents in headache, and therefore clearly there is a role for their use in migrainous headache. However, the topic of this study was not sterile inflammation in migraine. The topic of our study is the potential for CGRP release to be diminished in intracranial surgical injury through therapeutic means.

Reviewer 1.
P.6
""Anaesthetist, surgeon, patient-blinded"—are the nurses not blinded?
In our original manuscript, it is stated on page 9:
"Methods: Assignment of interventions and Randomisation
The SUPS trial is designed as a randomized, controlled, investigator, patient and **nurse** blinded single-center non-inferiority trial with two parallel groups and a primary endpoint of Visual Analogue Score". We have since more accurately designated our study as a superiority trial.
In our original manuscript, it is stated on page 10:
"The implementation in the recovery stages will be completely independent of the randomization group – and therefore both the assessor (recovery nursing staff) of the VAS scores and patients will be completely blinded."

Reviewer 1
Patient and Public Involvement: very confusing—you conducted a blind study of important of post-op pain mgt; have you reported that? Can you not report the results here as part of justification for this protocol?

We direct the reviewer 1 to the BMJ preamble on patient and public involvement policy available on BMJ open website. We have however since removed the preamble on patient and public involvement for the purpose of clarity.

Reviewer 1
Enrollment: you say "all adults undergoing Craniotomy" but then exclude all having cerebrovascular surgery without justification. Triptans are not, in fact, vasoconstrictors in vivo so this is confusing. Similarly, current Tx with SSRI (misspelled "SSSRI's"), is not justified—the prohibition on combining triptans and SSRIs is ridiculous and not supported by the preponderance of data or clinical experience.
The authors are following the FDA (USA Food and Drug Authority) approved manufacturers guidelines, which state the contraindications to the administration of Sumatriptan. Under section 4.3 in the FDA guidelines it is clearly stated that Sumatriptan in contra-indicated in patients with Cerebrovascular Syndromes. Patients undergoing cerebrovascular surgery are at a higher than usual risk of developing a cerebrovascular syndrome. Under section 5.5 in the FDA guidelines, the risk of Serotonin Syndrome with the use of triptans is outlined. This was discussed under Trial Safety section in the original manuscript. In the revised manuscript, we have included this section with the exclusion criteria for clarity purposes. We have however found further clinical references which in contrast to the FDA statement, do discuss the use of SSRI's in patients taking triptans and deem this safe. As such, we have removed the use of SSRI's from the exclusion criteria.

Reviewer 1
Interventions—
Need to state at what pain level would opiates normally be given? Are other sx considered (nausea or vomiting? Photophobia?)
We have specified this in the manuscript. On page 6, under Interventions section we stated:
"Criteria for administration would be equivalent: NRS Pain Scores indicating mild-moderate pain."

Reviewer 1
NRS pain scale: what is it? 1-3? 1-5? 1-10? If 1-10, what is the definition of "mild to moderate"?
It sounds like the recovery nurse is NOT blinded, which will influence outcome significantly. If NRS routinely obtained every 5 minutes after injection, at what point post-sumaT would opiate be given?
"Once off" is colloquial and confusing—perhaps clear to Aussies but not professional jargon in the US. "Single injection" is adequate.
Intravenous opioid is administered in recovery when patients indicate mild to moderate pain. This is standardised across units and institutions as recommended by the Australian and New Zealand College of Anaesthetists. The numerical value for mild to moderate is 4-7 as per references and standardisation in Australia. We have now specified this to avoid any ambiguity.
The nursing staff are blinded and we have made this statement twice in the manuscript and continue making it in the revised manuscript..
We have changed the once-off statement to a single injection statement in the revised manuscript.

Reviewer 1
ARTG? Please define
ARTG=Australian Register of Therapeutic Goods, this has been defined in the revised manuscript.

Reviewer 1
"Criteria for discontinuation of the trial" should be "study termination for individual patients" HOWEVER, the data should be recorded and reported in the study.
On page 12 of the original manuscript, we stated that data will be analysed on an intention to treat basis:
"Data collected from all randomized participants regardless of protocol adherence will be assessed on an intention to treat basis and analyzed accordingly. Therefore, any patients who have withdrawn or been lost to follow up will be managed on an intention to treat basis."

Reviewer 1

Potential bias by indication: patient exclusion for post-op "potential intra-op CVA" needs to be recorded and reported as well.

As per the attached FDA guidelines, Sumatriptan administration is contraindicated in patients who have had a cerebrovascular accident. We will not be recording any data from this group as it has no relevance to the analgesic efficacy in patients who are eligible to receive Sumatriptan.

Reviewer 1

"Face-to-face [usually hyphenated] adherence reminders" sounds like an effort to maintain clinical equipoise and protocol adherence for the nursing staff. This should be explained in more detail—how are you verifying that all recovery room nurses are aware of the study and trained on its procedures?

Detailed explanation of the mode and method of reminding the nursing staff was beyond the scope of this manuscript.

Reviewer 1

Do you not have per diem ("fill-in") nurses at your hospital? What would they be asked to do?

It is beyond the scope of this manuscript to describe the number of nurses and education sessions provided. These logistical details are dealt with in the standard operating procedures of the trial (SOP's).

Reviewer 1

P.8

Patient satisfaction rated how?

Simple yes or no answer. Therefore, this outcome will be analyzed in a binary fashion.

Reviewer 1

Sample size calculation: enrolling only 8 add'l patients to account for dropout or data loss appears inadequate.

Patients will be randomized at the point of care and data analyzed on the intention to treat basis maximizing the trial economy and efficacy of enrolment. As such, even any dropout will occur only after data on the primary outcome has been collected by the staff.

Reviewer 1

Statement from Dr Gottschalk

P.11

Recruitment: how many craniotomy patients at your institution per year on average?

Methods: here you say "nurse-blinded" but if nurses choose "box A" or "box B" consistently they will NOT, in fact, be blinded—as the study progresses, they will learn which is which.

Feasibility consideration and ability to complete the trial was considered by the Austin health HREC in some detail prior to approving the study. We are a busy unit with approximately 350 craniotomies conducted in 2017 calendar year. With time, it may be obvious which medication group the administered study drug may belong to. As there is equipoise in this scientific hypothesis, there may not be any difference noted between drugs, and as such there may not be any difference between Box A and Box B. Regular pharmacy consults will facilitate potential box changes of the study drug eg confidential swap in the time line as recorded by the pharmacy department and therefore analyzed post study completion on this basis.

Reviewer 1

P.12

"Parametric data distribution" is not a meaningful term

What are the catergorical variables you are measuring?

What are the "secondary binary outcomes? There are yes-no questions here? I didn't see any.

You propose Bonferroni for "multiple primary outcomes" but have said repeatedly there is only one primary outcome.

Parametric data simply refers to normally distributed data for which parametric statistical tests may be employed. The yes or no answer provided by the patient to patient satisfaction question is the binary outcome.

There is only one primary outcome. However, we leave the option in the statistical plan of comparing the merits of VAS score at 30 minutes versus the VAS score at 60 minutes using the Bonferroni correction.

Reviewer 1
P.14
Here you finally state that you will examine confounds like pre-existing migraine but nowhere do you state how you will determine that. Patient-reported Dx migraine (which is always an underestimate)? Is one of the investigators qualified to make a Dx migraine? did you use ICHD-3 criteria?
It is standard practice to discuss statistical analysis and confounding under the "Statistical Analysis Section". We would like to draw the attention of the reviewer to page 12 of the original manuscript where we state that one of the parameters, which we will conduct the univariate analysis on is migraine. The primary problem for which the patients in this group are presenting is intracranial pathology, rather than the treatment of migraine. As such, we are relying on the patient reported measures of migraine. Post-operatively, the major surgical insult of a craniotomy is the usual cause of pain in the post-anaesthesia care unit. It would be novel to consider migraine as a cause of pain after a major insult to the skin, skull and meningeal structure. As such, for the purposes of the trial, self-reported diagnosis of migraine has been deemed adequate.

P.15
You address the "Ethical issue of undue influence" (I.e., coercion) but then fail to demonstrate you have actually done anything about it. You say, in effect, "this is a good question with scientific value, so there is no undue influence". You have described the mind of a surgeon very well but that does not actually satisfy the criteria of equipoise or eliminate the role of coercion.
The study design takes into account the logistics of the real clinical world. There will be other team members involved in care of these patients. Furthermore, the primary investigators make up a small percentage of a lead team of twenty clinicians who are involved in the regular care of Neurosurgical patients at our institution.

Reviewer 1
"I have some hope that this study has not actually begun enrollment, since nowhere do you state what the study period (initial date) will actually be. If it has begun enrollment, some simple modifications to the study assessments and particularly the analysis plan could still be made and greatly improve the value and impact of this trial."
Our trial has not begun enrollment yet, although this is imminent. The administrative issue of funding has been addressed and we are in the process of finalizing this. We have however commented that the trial is planned to last for two years in order to achieve its outcome. This statement was made on page 9 of the original manuscript submission:
"Recruitment
The allocated time for this study is 24 months in order to meet the demands for the enrolment of 136 patients. We plan to inform the anaesthesia and neurosurgical clinics of the study where the initial patient contact is made. We also plan to inform all the anaesthetists and surgeons who are involved in the performance of neurosurgical lists that there is potential for patient enrolment.
We will be commencing recruitment in July 2019 and have specified this in the abstract and content of the revised manuscript:
"We will enrol a total 136 patients in total, with the study duration of 2 years. This trial will commence recruitment on the 1st of July, 2019"

Reviewer Two Response

Reviewer 2
My main concern about this study is that the authors do not plan for control for intraoperative anesthesia or analgesic management. It may be difficult to show a statistically significant effect if care is not taken to control for these variables including intraoperative administration of local anesthetics, opioids and other analgesics which may have a duration of action long before the timepoint of interest (30 min after administration of sumatriptan.) The authors do plan to adjust for this in multivariate analysis however, this will require adjusting for multiple covariates. Furthermore the authors should specify the postoperative analgesic management including opioid and non-opioid analgesics.

This is a valid concern and one that authors had already accounted for in the design of the study and the original manuscript. We do plan to adjust for multiple co-variates as outlined in the Statistics Analysis Plan.
In research studies with numerous potential covariates such as ours, multiple regression using multiple covariate sis the most feasible methods of dealing with this issue. On page 12, we state the following:
"We will conduct a univariate analysis on the significance of the following parameters: 1.Age 2.Weight/BMI 3.Gender 4.Underlying chronic pain conditions(including migraine (Reviewer One)/chronic headache of any variety**)** 5.Underlying chronic analgesic consumption 6.underlying opioid consumption 7.Intra-operative intravenous paracetamol 8. Intra-operative opioid consumption (excluding remifentanil) 9. Total Intra-operative remifentanil dose 10. Intraoperative Technique, Volatile or Total Intravenous Anaesthesia 11. Local Anaesthetic Infiltration or Scalp Blocks. With any of the above parameters demonstrating a two-tailed p value of less than <0.1, they would be entered in a multi-variable logistic regression model. This strategy would be employed in order to assess any significant contribution of these factors on the primary and secondary outcomes of interest."

In summary,
1.Through the univariate analysis we plan to account for each one of these covariates. We plan to conduct a univariate analysis on 11 covariates as clarified in the table below.
2.Where these have been deemed significant through univariate analysis, we plan to enter these multiple covariates into a multiple regression model for each one of the primary and secondary outcomes of interest.
3. Therefore, the impact of **each significant covariate** on the primary and secondary outcomes will be assessed.

Tabulated Univariate Parameters have been included in the revised manuscript for clarity as shown below.

Demographic parameters	Age
	Weight/BMI
	Gender
Underlying Clinical Conditions	Patient given history of migraine or headache of any variety
	Chronic analgesic consumption other than opioid
	Chronic opioid consumption
Intraoperative techniques	Intra-operative intravenous paracetamol
	Total intra-operative amount of remifentanil administered
	Total intraoperative opioid administered

	(excluding remifentanil)
	Intraoperative anaesthetic technique, volatile or TIVA
	Local anaesthetic scalp infiltration or scalp blocks

Response continued:
The postoperative data on ancillary and opioid analgesia is included as one of our secondary outcomes. If the scientific hypothesis is correct, the sumatriptan administration may have the ability to decrease the opioid administration in recovery, and potentially for longer period of time (data on 24 hour analgesic consumption will be collected).

Reviewer 2
The authors state that they plan to perform subgroup analysis for emergent versus elective procedures and for supratentorial versus infratentorial procedures. It is well documented that the nature of postoperative pain is significantly greater for infratentorial procedures. The study will likely not sufficiently powered to detect a significant difference these subgroups. Would also recommend exclusion of emergency procedures as, at least in my experience, patients undergoing emergent procedures are much more likely to remain intubated, and thus one will not be able to assess VAS

The authors had considered the differences in the postoperative analgesia levels of the two groups: namely the supra-tentorial craniotomy and the posterior craniotomy. We plan to analyse this in the subgroup analysis. We are however looking for the trend, whilst being aware of the lack of statistical power in the study to determine a true difference between the two groups. We have elaborated on this in our revised manuscript.

We agree that there may be differences in the analgesic requirements between the supra-tentorial and infra-tentorial craniotomy groups. And although the muscle pain resulting form the posterior craniotomy may be more significant, there is still a significant dural and leptomeningeal breach. As such, if our null hypothesis is incorrect, there should be an improvement in pain in patients having a posterior craniotomy, albeit from a higher baseline of underlying pain proprioception. The minimum clinically important difference of 10 mm on VAS should still occur, whether it is a supra or infra-tentorial craniotomy. We have included a synopsis of this in the revised manuscript.

We agree that the study is underpowered to detect a true difference between the subgroups and will not be making any firm clinical conclusions based on the results of the subgroup analysis. We clarify this issue in the revised manuscript by stating in the discussion that we will only be looking for a subgroup trend.

Advantages of the point of care randomization is that patients will only be randomized once they require analgesia in recovery. To get there, patients need to have been extubated and safely arrive in the usual post-anaesthesia care unit. As such our study will not be affected by patients who remain intubated as they will bypass our recovery area. This is one of the advantages of point of care randomization in this trial.

Reviewer 2
The authors plan to assess postoperative opioid consumption but do not include complications or side effects. Nausea is a significant complication of intracranial surgery (up to 70% of procedures). It would be useful to assess whether there is a difference in postoperative nausea and vomiting with sumatriptan. Other complications such as PACU sedation scores and time to PACU discharge readiness should also be assessed.

In addition to our primary outcome, we have seven secondary outcomes. This is ample for a study this size. Increasing the number of secondary outcomes would increase the type 1 error through too many analyses in a single trial. We agree that it would be interesting to see the rate of nausea in the two groups. For the above

reasons of increasing the likelihood of a false positive finding through multiple analysis, we have chosen not to include nausea as an outcome. Peri-operative nausea as well as other side effects can be confounded by other causative factors, intrinsic patient factors and anaesthesia techniques to name but a few. We have not structured the study to accurately and reliably measure the association of nausea with sumatriptan administration.

We will however be collecting the data on adverse outcomes (including nausea) as outlined on page 6 in our manuscript. “Adverse events will be documented at 30, 60 minutes and the following day on the data collection sheet. ”This will include nausea and ANY adverse effects of Sumatriptan as discussed in the Introduction. We will be collecting the data on other PACU outcomes such as time to discharge readiness. We did not set that as one of our secondary outcomes.

Dr. Dunn Statement
A minor point is that the time-point for assessment of the primary outcome is unclear. Page 8 states primary outcome is assessment if sumatriptan is non inferior VAS at 30 minutes after drug administration; however, on Page 13 table of outcomes states improvement in VAS at 60 min. Which is the primary outcome and which other timepoints will be assessed? What is the duration of action of sumatriptan and will this timepoint be assessed?

We agree. The authors have debated the VAS 30 versus VAS 60 as the primary outcome. The sample size calculations and all considerations are equivalent. With the assessment at VAS 60, patients will have a slightly longer period of time for cognitive recovery. As such score at VAS 60 will be the primary outcome in this study.

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Subcutaneous Sumatriptan for the Treatment of Post-Craniotomy Pain (SUPS Trial): Protocol for a Randomised Double-Blinded Placebo Controlled Trial

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Scientific Title

Subcutaneous Sumatriptan for the Treatment of Post-Craniotomy Pain (SUPS Trial): Protocol for a Randomised Double-Blinded Placebo Controlled Trial

Acronym:

SUPS Trial

Lay Title:

Subcutaneous Sumatriptan use for Treatment of Post-Neurosurgical Pain

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Abstract

Introduction

Post-craniotomy pain protocols utilise opioids, which are considered suboptimal analgesia following this procedure. Multimodal analgesia components are sparse. Our null hypothesis states that sumatriptan is not different to placebo in addition to usual intravenous opioids, for the treatment of acute post-craniotomy pain. craniotomy pain.

Methods and analysis

This is a prospective single centre randomised double-blinded placebo-controlled phase 3 clinical trial comparing subcutaneous sumatriptan injection in the recovery area with placebo for the treatment of post-craniotomy pain. Eligible adult patients (18 years and older) undergoing craniotomy will be identified pre-operatively. Both patient groups will receive a subcutaneous injection at a point where recovery-nursing staff would initiate the usual intravenous opioid analgesia as per standardised pain management protocol. In both groups, further pain management will be followed by the usual intravenous opioid administration. Primary outcome will consist of the difference in pain experienced by the two groups of patients in recovery area 60 minutes after the study drug administration. Post-craniotomy pain will be measured at regular intervals using the Visual Analogue Scale (VAS) in recovery area. The minimal clinically important difference of 10 mm on the VAS between the two groups will be considered as statistically significant. We will include selected clinical and patient reported outcomes as secondary endpoints. Univariate regression will be conducted on each one of the clinically plausible potential confounders. We will enrol a total 136 patients, with the study duration of 2 years. This trial will commence recruitment on the 1st of July, 2019.

Ethics and dissemination

This trial protocol has achieved approval by the Austin Health Research Committee, HREC/17/Austin/596. This trial was prospectively registered with Australian New Zealand Clinical Trials Registry on the 10/05/2018 with a unique trial identifier U1111-1209-9072 and registration Number ACTRN12618000793213P. Findings of this study will be disseminated in peer reviewed academic journals.

Keywords

Craniotomy; Post-operative Pain; Analgesia; Sumatriptan; Visual Analogue Scale;

Strengths and Weaknesses of the Trial

- To our knowledge SUPS Trial (Subcutaneous Sumatriptan use for Treatment of Post-Craniotomy Pain) is the first randomised placebo-controlled double-blinded trial investigating the effectiveness of subcutaneous sumatriptan in the treatment of post-craniotomy pain.
- This is a novel scientific hypothesis testing the utility of a ubiquitous anti-migraine medication for a post-operative indication in this Phase 3 Clinical Trial.
- Ethical structure of the trial allowing for gold standard placebo use in analgesic therapy in addition to usual treatment, allowing for blinding of patients and investigators.
- Utilisation of validated pain measurement scale in the form of Visual Analogue Scale (VAS), the timing of which has been tailored to fit the pharmacokinetic properties of injectable subcutaneous sumatriptan.
- Involvement of hospital pharmacy in the randomisation sequence generation, with point of care allocation of randomisation envelopes allowing for blinding of investigators, patients and staff whilst maximising allocation efficiency.

Introduction

Post-craniotomy pain is often under-estimated and under-treated. Both acute and chronic post craniotomy surgical pain and headaches have been found to be common and significant clinical phenomena (1). In a recent study by Mordhorst et al, 55% of patients had moderate to severe postoperative pain in the first 24 hours following craniotomy (2). In-hospital poorly controlled pain confers a significant morbid burden. It has been correlated with poor medium and long-term postoperative outcomes, including anxiety, depression, poor rehabilitation and development of chronic pain (3). Risk factors for increased acute post-craniotomy pain include female gender and surgical site of the incision. Opioids are still the mainstay of post-operative craniotomy pain management (4). Effective opioid analgesia administration for the purposes of post-craniotomy pain relief can reduce the clinician's ability to monitor consciousness and result in decreased respiration with subsequent hypercarbia.

There is presently a limited scope for multi-modal analgesia, due to lack of suitable medication components for this type of surgery (5). Ketamine and tramadol exhibit an unfavourable side-effect profile in relation to this type of surgery, with the adverse effect profile of both drugs including seizure risk. The use of non-steroidal anti-inflammatory agents has been restricted in neurosurgery due to their anti-platelet effects. In prior well-designed studies, intravenous parecoxib at skin closure was found to be ineffective at ameliorating post-craniotomy pain (6). Paracetamol has been found to modestly decrease post-operative pain scores but not the post-operative opioid consumption (7). There is a need for further clinical trials in order to improve and optimise multimodal post craniotomy pain management in the short and longer term (2)(8).

Sumatriptan is a widely used drug, licensed for the treatment of migraines and cluster headache (9) (10). There have been reports of its effectiveness for the treatment of medical conditions other than the ones already approved of by the relevant governing bodies. Sumatriptan has shown a promising therapeutic profile in patients suffering from trigeminal neuralgia in selected clinical studies (11). In a recent trial of Sumatriptan use in mini-craniotomy for decompression of trigeminal nerve, it was found to likely be as effective as the standard treatment modality when patient reported outcome measures were evaluated (12). Sumatriptan use improved Quality of Recovery Scores 40 in patients undergoing mini-craniotomy for trigeminal nerve decompression (13). Further reviews have included sumatriptan in their reports of its effectiveness as a component of multimodal analgesia in the treatment of acute and chronic post-craniotomy pain (14). There are reports of the effectiveness of sumatriptan in analgesia regimens following vestibular schwannoma surgery (15).

Sumatriptan is available in the oral immediate release form as well as the subcutaneous injection form. The medication penetrates the blood-brain barrier poorly, which is indicative of its peripheral mode of action. In terms of its pharmacodynamics profile, sumatriptan is a specific vascular 5-hydroxytryptamine-$1_{B\text{-}D}$ ($5HT1_{B\text{-}D}$) receptor agonist with no effect at other 5HT receptor (5HT2-5HT7) subtypes (9). The vascular 5HT1 receptor is found predominantly in cranial blood vessels and mediates large cerebral artery and dural vessel vasoconstriction. Sumatriptan interacts with the trigemino-vascular system in two distinct ways: through direct vessel constriction by its highly selective agonist activity at $5HT1_{B\text{-}D;}$ it may also affect the modulation of the release of various inflammatory neuropeptides, including CGRP(11) (16). Calcitonin Gene related Peptide (CGRP) is a pro-inflammatory neuropeptide released from trigeminal ganglia cells in migraine conditions (17). Pharmacotherapy with sumatriptan can both reduce CGRP release as well as the CGRP transcription. Prior studies have implicated CGRP in decreasing the pro-inflammatory state (18). Some of the newer studies have brought into question the exact mechanism of CGRP activity (17). Subcutaneous Sumatriptan reaches its peak effect 6-20 minutes after administration. In controlled studies with sumatriptan injection, the most common adverse reaction with greater than 2% risk of events, were injection site reactions, tingling, warm/hot sensations and burning sensation. Other very rare side effects include reports of adverse cardiac events as well as cerebrovascular events. In a number of cases, it appears that cerebrovascular events were primary. It is therefore very rare for sumatriptan to cause these complications with an incidence of less than one percent.

Immediate post-craniotomy pain is multifaceted, due to responses from injury of the skin, muscles, and leptomeninges including the dura. The pain is usually described as a throbbing pulsating headache (4). Sources of postcraniotomy pain include tissue injury (scalp, cranial muscles soft tissue, and dura mater) and nerve disruption, traction, entrapment, and compression (19). The somatic component of the pain occurs due to the surgical incision and reflection of pericranial muscles and soft tissues of the scalp (4). Skull base surgeries employing suboccipital and subtemporal approaches produce higher degree of postoperative pain Meningeal irritation also contributes to postsurgical pain. Nevertheless, it is the amount of tissue damage rather than the location of the surgery, which determines the intensity of post-craniotomy pain. Greater amount of tissue injury generates higher intensity of postoperative pain. Although the brain itself is not innervated, dura matter and the meninges, are rich in blood supply and pain receptors. Much of the post-craniotomy pain is contributed by the irritation of the dura and the meninges (4). We are hypothesizing that in surgical cases of breaching the dura and leptomeninges, sumatriptan would exhibit the anti CGRP-effect and therefore contribute to decreasing the activation of the trigemino-vascular system.

Our null hypothesis states that sumatriptan is not different to placebo in addition to usual intravenous opioids, for the treatment of acute post-craniotomy pain. The alternative hypothesis states that sumatriptan is superior to placebo in addition to usual intravenous opioids, for the treatment of acute post-craniotomy pain. Our objective is to improve the available multimodal analgesic options for the treatment of post-craniotomy pain. Our primary outcome is centered around the measurement of post-operative pain score on Visual Analogue Scale (VAS: at 60 minutes). As a surrogate measurement of pain, we aim to measure the total opioids consumed and ancillary analgesics in both groups at similar points in time, in the recovery area and up to 24 hours post-operatively. We aim to measure satisfaction scores using Quality of Recovery 40 scores at 24 hours (13). We will follow up the patients at the intermediate time point of 30 days postoperatively.

Methods

Trial Design

The Sumatriptan for Post-craniotomy Pain Clinical Trial is designed as a randomised, placebo-controlled, anaesthetist, surgeon, patient and nurse blinded clinical study. This is a single centre study undertaken at the Austin Health main hospital campus (as outlined in trial registration details). Study will be undertaken during the perioperative period. Process of recruitment will begin in the neurosurgical and anaesthesia clinics. Patient consent will be signed preoperatively, either in the preadmission clinic or in the preoperative area prior to delivering care in the pre-anaesthetic area. The actual intervention will be administered post-operatively in recovery during the pain management process. The primary endpoint of postoperative pain will be measured using the Visual Analogue Scale (VAS). Randomization will be performed as a block randomization with a 1:1 ratio. The study drug will be administered at the usual point of the patient needing analgesia in recovery – when the patient complains of mild-moderate pain or gives a Numerical Rating Score pain of at least 4/10. The initial subcutaneous sumatriptan injection will be compared with an initial placebo injection. The ongoing pain management would be standardised use of iv opioids as per recovery protocol in both groups. The spirit figure (**Figure 1**) demonstrates the schedule of patient review, consent, enrolment, interventions and assessments in this trial. The timeline of patient involvement is illustrated in **Figure 2.**

Study registration

This Protocol, Patient Information Consent Form as outlined in the PICF/person responsible PICF, as well as all other supporting documentation have been reviewed by the Austin Health Ethics Committee with respect to scientific content and compliance with applicable research and human subjects' regulations. This trial protocol has achieved approval by the Austin Health Research Committee, reference HREC/17/Austin/596. This trial has been prospectively registered with Australian New Zealand Clinical Trials Registry with a unique trial identifier U1111-1209-9072 (20). The Principal Investigators will make safety and progress reports to the HREC at the Austin Health at least annually and within three months of the study completion or termination.

Patient and Public Involvement

Patients, patient advisors and public were not involved in the development of the research question or in the design of the study. Patient involvement in the study includes completing the patient reported outcome measures postoperatively in the form of questionnaires QoR40. Results will be disseminated to participants at the completion of the study.

Inclusion and Exclusion criteria

Patients who are at least 18 years old and who are undergoing craniotomy will be included in the study. Patients will need to be fully autonomous and able to give a valid consent for surgery and this particular study, or have mild underlying cognitive impairment only with the consent being given by the next of kin. Patients with any of the criteria listed in Table 1 will be excluded.

The exclusion criteria for this trial have been designed to maximise patient safety, while accurately reflecting the available scientific body of knowledge on sumatriptan (9).

Cerebral haemorrhage, subarachnoid haemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with subcutaneous sumatriptan, and some have resulted in fatalities (9). This may have occurred due to erroneous prescription of sumatriptan for non-migrainous conditions. Cerebrovascular surgery may very rarely result in adverse events such as cerebral haemorrhage or stroke. We undertook a further safety review in the light of this being a phase 3 clinical drug trial. We located one study demonstrating an average increase of 6 +/- 5 mmHg in systolic arterial blood pressure, after administration of 100 mg of oral Sumatriptan. The clinical significance of this finding in terms of potential adverse effects is uncertain (21). In healthy volunteers (N = 18), a study evaluating the effects of sumatriptan on peripheral arterial reactivity failed to detect a clinically significant increase in peripheral resistance (9). In an initial large cohort study of 130 411 migraine sufferers by Valentgas et al, there was no association found between triptan use and risk of stroke (22). An increased overall risk of atypical stroke was found in the population prone to migraines, unrelated to any medication used.

The risk of stroke with the use of Sumatriptan, both secondary to ischemic or haemorrhagic cerebrovascular event is deemed to be and quoted at less than one percent. We have incorporated these quantifiable figures into our Patient Information Consent Form (PICF). This information is identical to the level of risk, which is quoted in the FDA prescribing information (9). As per FDA, Sumatriptan in contraindicated in patients with cerebrovascular disorders. we have excluded the patients undergoing cerebrovascular surgery from participating in this trial.

Table 1 Study Exclusion Criteria

Not autonomous, or have mild underlying cognitive impairment only, with the consent being withheld by the next of kin
Craniotomy for cerebrovascular surgery (i.e. cerebral aneurysm or arteriovenous malformation)
Previous Ischemic or Haemorrhagic CVA
Unstable Angina or Previous AMI
Severe hepatic impairment
Uncontrolled Hypertension
Previous sensitivity to Sumatriptan
Current Treatment with MAOI's
Emergency Re-do Craniotomy

Randomisation and Study Intervention

Blocked randomisation will be used to assign recruited participants to one of the two study groups- placebo or blinded therapeutic treatment group. Randomisation will be accomplished by the clinical research pharmacist using a sequence of computer-generated random numbers. Randomisation envelopes

will be available at the point of care interface (operating theatre). Patients who actually require post-operative analgesic therapy to be administered will complete enrolment in the study at the point of care. This design has been chosen to maximise the efficiency of patient enrolment into the study. All preoperative and intraoperative care will be at the discretion of the treating team and will be in-line with the current best practice institutional principles for intra-cranial surgery. Participants will be randomly assigned to either control or experimental group with a 1:1 allocation ratio in permuted random blocks, as per a pharmacy generated randomisation schedule. Allocation concealment will be ensured, as the randomisation code will not be revealed until the patient is enrolled in the trial. From a scientific perspective, we do not plan to stratify our sample. We plan to deal with potential confounders through a univariate analysis and subsequent covariate multivariable logistic regression.

Randomisation envelopes will be made available only prior to the commencement of the study. Patients will be randomised at the point of care in order to maximise efficiency. The allocation sequence will be restricted and only available to the pharmacy randomisation staff, thereby ensuring the blinding of investigators. The implementation in the recovery stages will be completely independent of the randomisation group – and therefore both the assessor (recovery nursing staff) of the VAS scores and patients will be completely blinded. In the event of a report of a severe adverse event, Data Safety Monitoring Board will be notified and decision made on emergency un-blinding. Intervention in the Group A, the group receiving the SC Sumatriptan will be initiated by the recovery staff at the point at which they would normally give the intravenous (iv) opioid protocol for pain. Criteria for administration of the study drug would be equivalent to the criteria for the administration of the usual therapy of the recovery intravenous opioid analgesia: Numerical Rating Scores (NRS) indicating mild-moderate pain or a 4-6 pain on a scale from 0-10, as self- reported by the patient (23). It is at this point that the patient would be randomised in the study, and the randomisation envelope acquired. We have aimed to ensure the efficacy of trial enrolment, through point of care randomisation.

If the patient has been randomised to group A, the recovery nurse would be asked to collect the syringe from BOX A and administer the medication in a usual subcutaneous fashion. If the patient has been randomised to group B, the recovery nurse would be asked to collect the syringe from BOX B and administer the medication in a usual subcutaneous fashion. The relevant anaesthetic nurse will subsequently assess the NRS scores as per iv. opioid protocol i.e. every 5 minutes. If the standard protocol criteria for opioid administration are met during the subsequent assessment, patient will receive the usual iv opioid protocol. All patients will receive usual high standard routine post-operative care. The only additional assessments in recovery area would be those using the Visual Analogue Scale (VAS) scores prior to drug administration, at 30 and 60 minutes post study drug administration. The dose selected for use in this trial by the principal investigators is 6mg subcutaneously as a single injection. Our reasoning for choosing this dosing schedule includes that this is the recommended initial dose by the Australian register of Therapeutic Goods (ARTG). Most of the treatment effect is achieved from a single subcutaneous dose of Sumatriptan (9). Albeit potentially therapeutically inferior, there is an established modality for the treatment of post-surgical pain in the form of opioids. Following the initial single dose injection of subcutaneous sumatriptan, patients in both groups will be treated in the recovery area in a usual manner with an intravenous post-operative analgesia regime.

Criteria for discontinuation of the trial in individual patients include:

-Persistent GCS less than 12 in recovery.

-Significant surgical concern re potential intra-operative adverse features: potential intraoperative cerebrovascular accident;

Study protocol adherence reminders will be made on on-going basis with the recovery nursing staff. There will be regular brief monthly reminders at the nursing education sessions.

Study Outcomes and Their Measures

Primary Endpoints

Our primary objective is to determine if subcutaneous sumatriptan is superior to placebo, in addition to usual intravenous opioid in the management of post-craniotomy pain as measured using Visual Analogue Scores (VAS) 60 minutes after study drug administration. The primary outcome measure chosen was Visual Analogue Score (VAS) at 60 mins after placebo or subcutaneous Sumatriptan administration. From a pharmacokinetic perspective, the time from subcutaneous injection to peak concentration is 6-20 mins. Due to the potential for post-operative impairment of cognitive function, affecting the accurate measurement of pain, VAS result at 60 mins has been chosen as the primary outcome.

Secondary Endpoints

Visual Analogue Scale score at 30 minutes post sumatriptan administration has been chosen to coincide with the peak pharmacokinetic effect of sumatriptan post administration (Table 2). We will analyse the VAS at 30 mins pain outcome, and compare and contrast this measure to our primary outcome.

As a surrogate measure of pain, we will be assessing the total opioid consumption both in the recovery area and post-operatively at 24 hours. Patient satisfaction at the phone interview 30 days post-operatively will be measured with a simple yes or no binary outcome. Any potential adverse events will be documented at 30, 60 minutes and the following day on the data collection sheet. Data on all and any adverse events will be collected by the study investigators, and initially analysed qualitatively.

Table 2 Secondary endpoints

Visual Analogue Scale scores 30 minutes post-operatively.
Numerical Rating Scale scores 24 hours post-operatively.
Total recovery area post-operative opioid consumption.
Total 24-hour post-operative opioid consumption
Quality of Recovery Scores 40, 24 hours post-operatively (day1).
Total hospital length of stay.
Patient satisfaction 30 days post-operatively
NRS pain score 30 days post-operatively.

Sample Size Calculation

Our sample size calculation was based on the primary outcome and the significant difference of 10 mm basis points in pain measurement on the Visual Analogue Scale. A recent article in British Journal of Anaesthesia outlined that Minimal Clinically Important Difference to patients is equivalent to 10 mm (24). We have therefore chosen this value as significant difference between the treatment and placebo group. We used STATA 13 program to calculate the sample size. With monitoring overall VAS scores in recovery postoperatively, the mean value was found to be 73 with a wide standard deviation. In an article by Jones et all, the mean VAS scores in recovery for post craniotomy patients, the VAS was found to be 34 (25). With a range of conflicting research, the median point for VAS was determined to be 50 mm.

We have defined the 10-mm difference in VAS scores between the two groups as clinically significant and statistically significant. If we observe a pain reduction of 10 mm down to 40 mm, we would therefore be likely to accept our scientific hypothesis and reject the null hypothesis (Table 3).

Table 3 Statistical Measures

Continuous summary outcome	Mean and standard deviation
The outcome	Visual Analogue Scale (VAS) scores 60 minutes after study drug administration
The values assumed for outcomes in Each group	Mean VAS for Control Group 50 mm (5 cm) Mean VAS for the Experimental Group 40mm(4cm)
The statistical test	T-test comparing two independent means of continuous outcomes
Alpha error	Two-tailed P value < 0.05
Power	0.8
The calculated sample size per group, Both assuming no loss of data	64 per group

Due to the potential for loss to follow up and missing data, we plan to enrol additional patients to a total of 136. Interim analysis will be conducted at the halfway point of the trial to assess for any differences between the groups. Unless there is overwhelming evidence with a difference in the effect of $p<0.05$, we plan to continue with the trial completion.

Statistical Analysis Plan

The intervention arm will be compared against the control for all primary analysis. Descriptive statistics (mean (SD) or median (IQR) will be used for continuous variables. Normal data distribution will be confirmed through a histogram validation and Shapiro-Wilks test. We plan to use the student's T-test to compare the means of different groups for the continuous outcome of pain scores. Quantitative variables (continuous outcomes) will be compared using the Student's t-test or Mann-Whitney U-test to compare independent means (Table 4). When indicated, a one-way repeated measures ANOVA will be performed. Categorical variables will be presented as absolute frequencies and percentage and compared between the two groups using the X^2 or Fisher exact test. The odds ratio (OR) will be calculated with its 95% confidence interval for the categorical post-operative outcome variables. A Bonferroni correction will be applied for multiple comparisons. We will use the Bonferroni method to appropriately adjust the overall significance for multiple primary and secondary outcomes as needed.

For subgroup analysis, we will use regression methods with appropriate interaction terms. Multivariable regression will be based on logistic regression for binary outcomes and linear regression for continuous outcomes. P values will be reported to four decimal places with p-values less than 0.001 reported as $p<0.001$. STATA 13^r will be used for statistical analysis. For all tests, we will use 2-sided p-values with alpha<0.05 level of significance. There may be a number of patient-related or anaesthesia technique

related confounders, which may affect the outcome in this study (Table 5). We will conduct a univariate regression analysis on the significance of each one of these parameters. With any of the above parameters demonstrating a two-tailed p value of less than <0.1, they would be entered in a multi-variable regression model for each one of the primary and secondary outcomes. This strategy would be employed in order to assess any significant contribution of these factors on the primary and secondary outcomes of interest. Data collected from all randomised participants regardless of protocol adherence will be assessed on an intention to treat basis and analysed accordingly. Therefore, any patients who have withdrawn or been lost to follow up will be managed on an intention to treat basis. Should any patients withdraw, we will report reasons for doing so and compare the reasons qualitatively. Analysis of harms will be limited to participants who received the intervention.

Table 4 Summary of methods of analysis for each variable

Variable/ outcome	Scientific Hypothesis	Outcome measure	methods of analysis
Primary -VAS at 60 mins	Improvement with Sumatriptan due to improved Post-op Pain Management	Continuous VAS measure scale 0-100 mm	Comparison between 2 groups T-test
Secondary -VAS at 30 mins	Improvement	Continuous VAS measure scale 0-100 mm	Comparison between 2 groups T-test
-total opioid consumption 24 hours post-op	Improvement	Continuous standardised mcq measure	Comparison between 2 groups T-test
-improvement in QOR scores at 24 hrs	Improvement	Continuous QOR score	Comparison between 2 groups T-test
Patient satisfaction -yes or no	Improvement	Categorical	Chi-squared or Fisher's exact test
Subgroup analysis			Regression Methods with appropriate interaction terms
-female vs male	Gender affects pain measure.		
-supratentorial vs infratentorial	Pain scores affected by site of craniotomy		
-emergency vs elective craniotomy	Pain scores affected by urgency of the case		

Table 5

Potentially confounding clinical parameters

Demographic parameters	Age
	Weight/BMI
	Gender
Underlying Clinical Conditions	Patient given history of migraine or headache of any variety
	Chronic analgesic consumption other than opioid
	Chronic opioid consumption
Intraoperative techniques	Intra-operative intravenous paracetamol
	Total intra-operative amount of remifentanil administered
	Total intraoperative opioid administered (excluding remifentanil)
	Intraoperative anaesthetic technique, volatile or TIVA
	Local anaesthetic scalp infiltration or scalp blocks

Recruitment

The allocated time for this study is 24 months in order to meet the demands for the enrolment of 136 patients. We plan to inform the anaesthesia and neurosurgical clinics of the study where the initial patient contact is made. The research team will monitor the lists in advance and make early contact with eligible patients. Subsequently, the research team will meet the patients and discuss the informed consent. The subjects will be approached by both study investigators, and medical staff familiar with the study.

Data Collection, Management and Analysis

Data will be collected from the standard anaesthesia chart. Numerical Rating Scores (NRS) will be documented as per protocol in the recovery charts. The Visual Analogue Scores(VAS) will be also be documented in the recovery section of the anaesthesia chart. Quality of Recovery (QoR) 40 questionnaires will be completed by patients the following day and filed in the notes by the attending nursing staff. Data on all adverse events during the first 24 hours will be collected. In the sumatriptan for post-surgical pain trial, all data will be entered electronically. Data will be entered in a coded de-identified manner with re-identifiable codes stored in separate file. This will be done at the Austin Health, where the data originated. Participant files are to be stored in numerical order and stored in a secure and accessible place and manner. Participant files will be maintained in digital password protected storage for 15 years as required by regulation after completion of the study.

Safety Monitoring

Our Data Safety Monitoring Board (DSMB) is independent of the study organisers. During the period of recruitment to the study, interim analysis after 50 percent recruitment will be supplied to the DSMB. DSMB will review whether the active intervention has been proven with the analysis of primary outcome and analyse the total number of adverse events documented. All adverse events occurring after entry into the study and until hospital discharge will be recorded. An adverse event that meets the criteria for a serious adverse event (SAE) between study enrolment and hospital discharge will be reported to the local Data Safety and Monitoring Board (DSMB). DSMB will review the event(s) in an unbiased fashion and make an appropriate report to the sponsor (Austin Health) and Austin Health Human Research Ethics Committee. Life threatening conditions (that is, immediate risk of death); severe or permanent disability, prolonged hospitalization or a significant hazard will all be reportable to the Data Safety Monitoring Board.

Discussion

Significance

To our knowledge, the SUPS trial is the first trial to evaluate the utility and effectiveness of subcutaneous sumatriptan as a component of multimodal analgesic regime for the management of post-craniotomy pain. Primary study outcome is measured using the tools that have good validity and reliability for measurement of pain. The advantages of VAS are that there is good evidence for responsiveness, validity, test–retest reliability (26) (27). In studies attempting to validate the NRS, the VAS is used as the gold standard clinical measurement (28). The NRS is considered to have overall lower precision than VAS in the peri-operative setting and it may therefore negatively bias the outcome of the study. In addition to this, the VAS is considered easier to administer in patients with any verbal difficulties (28).

This study has been designed as a placebo controlled superiority trial. The trial would therefore not require the participants to forgo treatment they would otherwise receive. In this case, there are compelling methodological reasons to determine the efficacy of the intervention, and the patients who receive the initial placebo intervention will not be subject to any risk of serious or irreversible harm (29). Furthermore, the follow-up at a 30-day time-point may provide insight into the effects of study intervention on intermediate perception of pain. If the benefits proposed by our study are substantiated, this can have a significant impact on post-craniotomy multimodal analgesic patient care.

Limitations

Analgesic requirements are commonly used as post hoc measures of pain experience (28). whether this Effectiveness of sumatriptan in reducing the opioid dosage at various end-points during the first 24 hours is addressed in the secondary outcomes. We will be recording any adverse events experienced by the patient in the course of the study. However, accurate opioid side effects may be difficult to define and measure secondary to potential confounding by other medical conditions and medications.

No stratification or matching will be performed during the recruitment and conduct stages of the trial. We have identified a significant number of potential clinical confounders. The most efficient and statistically feasible approach to dealing with a high number of potential confounders is in the analysis stages by conducting a univariate analysis. When each parameter demonstrates significance according to pre-determined p level, it will be entered into a multivariable regression model for each primary and secondary outcome of interest. We plan to conduct three distinct subgroup analysis all with strong biological basis. Our study is underpowered to detect a statistically meaningful difference in these subgroups. However, our analysis will indicate an observed trend in the data.

Ethics and Dissemination

The structure of our study necessitates that sometimes the study recruiters and investigators will also be the treating clinicians. Patients will always be given information that describes the proposed research as well as the form for withdrawal of consent (Supplementary file- Patient Information Consent Form-PICF 1.3). When reasonable to do so, patients will be invited back to the clinic to ask any further questions around the trial and consent process. A genuine scientific question has been posed which has the potential to improve future pain management in this group. Patients will be informed through a detailed consent process that they will not achieve any additional clinical care by participating in the study nor will they come to any harm by refusing to participate. The potential undue influence is therefore minimised through the principles of fully informed patient consent, equal care and clinical equipoise (29). There will be no additional invasive investigations occurring in the study participants, decreasing the risk of inconvenience and patient harm. Protecting potentially vulnerable adults with mild cognitive impairment, who are eligible to participate in the study is vitally important. The investigators believe that it is a scientific necessity to enrol this population in order to avoid selection bias in the study population. Decision making capacity (DMC) of this subset of patients would have been evaluated in order to ensure validity of the surgical consent process. Equivalent decision-making capacity will be transferred to participation in the study.

Any modifications to the protocol which may impact the conduct of the study, the patient outcomes or have the ability to influence the safety of the patient, changes to the study objectives, study design or patient population will be communicated to the Austin Health Ethics Committee. Permission will be sought to modify the protocol prior to any significant changes.

Conclusion

Post-craniotomy pain management consists of opioids with limited multimodal analgesic therapeutic options. We have delineated a phase 3 Clinical Trial utilising a frequently administered anti-migraine drug sumatriptan in its injectable subcutaneous form in the setting of post-craniotomy pain management. Subcutaneous Sumatriptan use for Treatment of Post-Craniotomy Pain is a single centre randomised double-blinded placebo-controlled superiority trial. Primary outcome is a visual analogue score rating. 60 minutes after drug administration. Secondary outcomes consist of VAS rating 30 minutes following the study drug administration as well as total 24 hour post-operative opioid administration. With the design and conduct of this phase 3 clinical trial we intend to expand the evidence base of post-craniotomy analgesia management.

Trial Status

This trial will be recruiting from the 1st of July 2019. The trial is planned to run for 2 years. This trial protocol has achieved approval by the Austin Health Research Committee, reference HREC/17/Austin/596 (Ethics approval- Supplementary file). This trial was prospectively registered with Australian New Zealand Clinical Trials Registry on the 10/05/2018 with a unique trial identifier U1111-1209-9072 and registration Number ACTRN12618000793213P.

Abbreviations:

5-HT (5-hydroxytryptamine), VAS (Visual Analogue Score), NRS (Numerical Rating Score), CGRP (Calcitonin Gene Related Polypeptide).

Data Sharing Statement

Individual participant data that underlie the results, after de-identification (text, tables, figures and appendices) will be available for sharing upon completion of the trial. Other documents available for sharing will include: study protocol and statistical analysis plan. Data will be available beginning 9 months and ending 36 months after study result publication. Data will be shared with investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose. Data will be available for individual participant data meta-analysis. Research proposals should be directed to analicina@hotmail.com. To gain access, data requestors will need to sign a data access agreement. Information regarding submitting proposals and accessing data will be found at https://datadryad.org nine months following the final research outcome publication.

Author's contributions

Dr Ana Licina reviewed the scientific literature and contributed to the original protocol.
Dr Jeremy Russell contributed the original scientific hypothesis and the original protocol.
Dr Andrew Silvers contributed to the original protocol.
Dr Xin Jin reviewed the scientific literature and contributed to the original protocol
Dr Jason Denny reviewed the scientific literature and contributed to the manuscript.

Funding statement

This research received no specific grant from any funding agency in commercial or not-for profit sectors. This trial has obtained internal funding from the Austin Neurosurgical Research Fund.

Competing Interests

Dr Ana Licina has no relevant financial or non-financial interests to disclose.
Dr Jeremy Russell has no relevant financial or non-financial interests to disclose.
Dr Andrew Silvers has no relevant financial or non-financial interests to disclose.
Dr Xin Jin has no relevant financial or non-financial interests to disclose.
Dr Jason Denny has no relevant financial or non-financial interests to disclose.

Supplementary Files

Patient Information Consent Form-PICF 1.3
Ethics Approval -20180918 Letter HREC17 Austin596 New Study Ethics Approval

Word Count

Number of words excluding the abstract and references: 5603

Figure Legends:

Figure 1 Standard Protocol Items; Recommendations for Interventional Trials (SPIRIT) figure. The schedule of enrolment interventions and assessments in the study

Figure 2 Participant Timeline

References:

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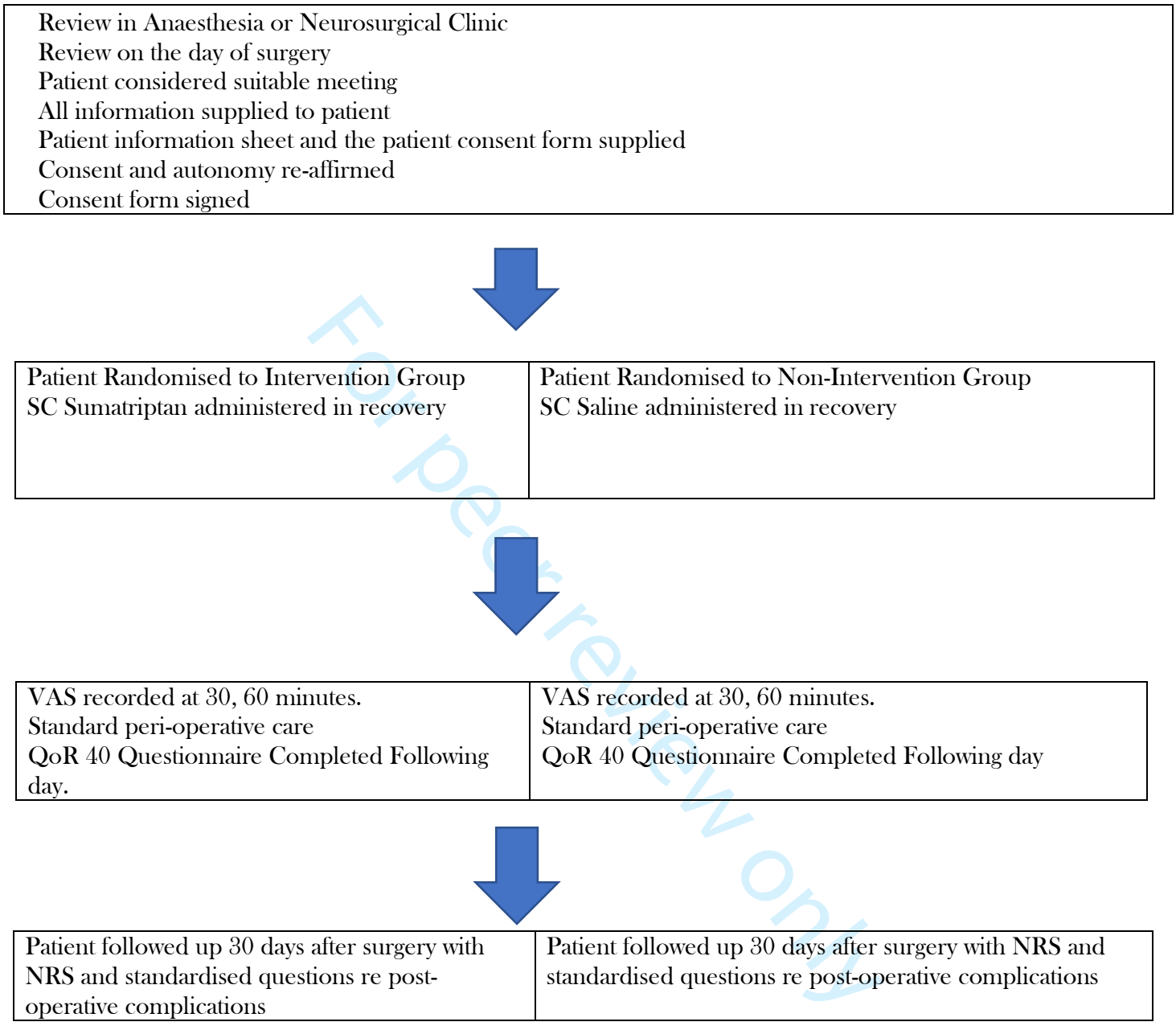
Subcutaneous Sumatriptan Use for the Treatment of Post-Craniotomy Pain
-Randomised Double-Blinded Placebo Controlled Trial

Figure 1 Standard Protocol Items; Recommendations for Interventional Trials (SPIRIT) figure. The schedule of enrolment interventions and assessments in the study

	Study Period						
	Enrolment	Allocation	Post-allocation				Close-out
Time point	-T1		T1	T2	T3	T4	
Enrol							
Eligibility screen							
Informed consent	Neurosurgical clinics						
Allocation		Point of care-recovery					
Interventions							
Subcutaneous Sumatriptan Or Placebo			Post-operative admin in recovery				
Assessments		Recovery area	30 mins post admin	60 mins post admin	Completion Recovery stay	24 hours post	Follow up At 1 month
VAS Pain Score (0-10)		X	X	X			
NRS Pain Score (0-10)		X	X	X	X	X	X
Total Opioid Consumption				X	X		
Quality of Recovery Index						X	
Patient Satisfaction Yes or No							X

Figure 2. Participant Timeline



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AUSTIN HEALTH HUMAN RESEARCH ETHICS COMMITTEE

ETHICAL APPROVAL

Dr Ana Licina,
Austin Health

18 September 2018

Dear Dr Ana Licina,

HREC Reference Number [AU RED HREC reference number]: HREC/17/Austin/596

Austin Health SITE REFERENCE Number: DT 17/596

Project Title: Subcutaneous Sumatriptan use for Post-Craniotomy Pain, Randomised Double Blind Placebo Controlled Trial Acronym: SUPS Trial.

I am pleased to advise that the above project has **received ethical approval** from the Austin Health Human Research Ethics Committee (HREC). The HREC confirms that your proposal meets the requirements of the National Statement on Ethical Conduct in Human Research (2007). This HREC is organised and operates in accordance with the National Health and Medical Research Council's (NHRMC) National Statement on Ethical Conduct in Human Research (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

HREC Approval Date: 18 September 2018

Ethical approval for this project applies at the following sites:

Site
Austin Health

Approved Documents:

The following documents have been reviewed and approved:

Document	Version	Date
HREA (AU/1/2282314)	1.3	24/11/2017
VSM	2	20/02/2018
Protocol	1.6	10/08/2018

PICF	1.3	11/02/2018
Person Responsible ICF	1.3	11/02/2018
Form for withdrawal – Participant	-	-
Form for withdrawal – Person Responsible	-	-
CRF	1.2	-
Data Collection From	-	-
Consumer Medicine Information – Sumatriptan succinate	2.0	2003
Statistical Analysis Plan	-	-

Governance Authorisation:

Governance Authorisation is required at each site participating in the study before the research project can commence at that site.

You are required to provide a copy of this HREC approval letter to the principal investigator for each site covered by this ethics approval for inclusion in the site-specific assessment application.

Conditions of Ethics Approval:

- You are required to submit to the HREC:
  - An Annual Progress Report (that covers all sites listed on approval) for the duration of the project. This report is due on the anniversary of HREC approval. Continuation of ethics approval is contingent on submission of an annual report, due within one month of the approval anniversary. Failure to comply with this requirement may result in suspension of the project by the HREC.
  - A comprehensive Final Report upon completion of the project.
- Submit to the reviewing HREC for approval any proposed amendments to the project including any proposed changes to the Protocol, Participant Information and Consent Form/s and the Investigator Brochure.
- Notify the reviewing HREC of any adverse events that have a material impact on the conduct of the research in accordance with the NHMRC Position Statement: *Monitoring and reporting of safety for clinical trials involving therapeutic products November 2016*.
- Notify the reviewing HREC of your inability to continue as Coordinating Principal Investigator.
- Notify the reviewing HREC of the failure to commence the study within 12 months of the HREC approval date or if a decision is taken to end the study at any of the sites prior to the expected date of completion.
- Notify the reviewing HREC of any matters, which may affect the conduct of the project.

The HREC may conduct an audit of the project at any time.

Yours sincerely,

Priyanka Sathe
Research Ethics Officer, Office for Research, Austin Health, Level 8 HSB.
Phone: +61 3 9496 4090;
E-mail: Priyanka.sathe@Austin.org.au
Web: http://www.austin.org.au/researchethics

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Interventional Study- Adult providing own consent

Informed Consent form for Patients undergoing Craniotomy who are invited to participate in research on use of Sumatriptan to improve post-operative pain control.

Interventional Study-Adult providing own consent form

The title of this project is:

Subcutaneous Sumatriptan for Post-Craniotomy Pain- A Randomized Double-blind Placebo Controlled Clinical Trial

Short title: Subcutaneous Sumatriptan for Post-Craniotomy Pain

PICF Version: 1.2 Date 11/2/2018

Project Sponsor

Austin Health

Principal Investigators

Dr Jeremy Russell

Dr Ana Licina

Co-ordinating Principal Investigator

Dr Ana Licina

Name of Organization/Location where recruitment will occur

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This Informed Consent Form has two parts:

- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

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PART I: Information Sheet

What does my participation involve?

1.Introduction

You are invited to take part in this research project. This is because you have *a neurosurgical condition requiring an operation (Craniotomy).* The research project is testing a new treatment for *the improvement of pain control after your surgery.* The new treatment is called *Sumatriptan, a medication which is otherwise well-established in migraine pain management.*

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

2. Purpose of the research

Craniotomy is a type of surgery which involves operating on the brain and its structures. It is is a relatively common procedure to undergo. The post-operative pain management is not as optimal/good as we would like it to be. The drugs that we use currently cause a lot of drowsiness and are not always ideal for treatment of the headache.

Sumatriptan is approved in Australia to treat migranious headache. However, it is not approved to treat post-operative pain in neurosurgery. Therefore, it is an experimental treatment for the Post-operative pain in this situation. This means that it must be tested to see if it is an effective treatment in Post-operative pain.

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The reason we are doing this research is to find out if subcutaneous Sumatriptan is better than standard opioid therapy for post-surgical headache and pain. If you choose to participate in this study, you may receive Sumatriptan in addition to usual opioid analgesia.

This research has been initiated by the study doctors, Dr Russell, Dr Licina and Dr Cowie.

3.What does participation in this research involve?

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random). You have a one in two chance of receiving the study drug.

You will be participating in a double-blind study. This means that neither you nor your study doctor will know which treatment you are receiving. However, in certain circumstances your study doctor can find out which treatment you are receiving. Because we do not know if Sumatriptan is better than the currently available pain relief for treating pain after head surgery, we need to compare the two. To do this, we will put people taking part in this research into two groups. The groups are selected by chance, as if by tossing a coin. This research involves a single injection under your skin with a very small needle to help treat the pain while you are recovering after your surgery in the recovery area. Participants in one group will be given the test drug followed by the standard opioid analgesia. Participants in the other group will be given the placebo followed by standard pain pathway only. A placebo is a medication with no active ingredients or a procedure without any medical benefit. It looks like the real thing but is not. Importantly, which-ever group you belong to, you will also be treated with **standard intravenous pain relief**

It is important that neither you nor we know which of the two drugs you are given. This information will be in our files, but we will not look at these files until after the research is finished. This is the best way we have for testing without being influenced by what we think or hope might happen. We will then compare which of the two has the best results. 'If you find that the drug we are testing does not stop your pain and it is very uncomfortable for you, we can use the rescue medicine to make you more comfortable. The medicine that we will use is called Fentanyl/Morphine/Oxycodone and it has been proven to control pain'.

The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the drug is doing, we will find out which drug you are getting and make changes. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers.

When you arrive in the recovery area, the nursing staff will monitor all your vital signs and pain scores. If you have enrolled in the study and you have measurable pain, you will be given subcutaneous injection of the test drug or a placebo. It's a small thin needle which injects the contents just under your skin. You will be asked about you pain relief regularly. If 5 minutes later, you have ongoing pain, which ever study group you are in, you will be administered intravenous pain relief. At 30 minutes we will ask you to look at the ruler from 0-100 mm and tell us at what level your pain is. At 60 minutes we will ask you to look at the ruler from 0-100 mm and tell us at what level your pain is. There may be a break

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between treatments so that the first drugs are cleared from your body before you start the new treatment.

There will be a Quality of Recovery brief survey on how you are recovering. We will ask you to fill this in. One month after your admission you will get a follow up call to assess your progress.

Blood samples taken will only be the routine ones and there will be no additional investigations required if you choose to participate.

There are minimal time-commitments expected of you during this study. You will be administered the subcutaneous injection in recovery during which time it is standard and expected to administer pain relief to patients as needed. Subsequently if you participate in the study, you pain will be more thoroughly assessed during your stay. There will be no additional time commitments during this period.

There are no additional costs associated with participating in this research project, nor will you be paid. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

4.What do I have to do?

We are inviting all adults who have a craniotomy (head surgery for a range of conditions) to participate in the research on the use of the well-known migraine drug for treatment of post-surgical pain. There are no changes or restrictions to any of your usual activities

5.Other relevant information about this research project

A total of 136 people will be participating in this trial. The Austin Health is the primary site where this research is being done. We hope to obtain information in order to improve post-cranitomy pain management in the future.

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive during the surgery and afterwards, will continue and nothing will change. If you choose not to participate in this research project, you will be offered routine pain relief after the surgery. You can change your mind and stop participating later if you choose to.

6.Do I have to take part in this research?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with *Austin Health*.

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7. What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; these include *the standard* opioid analgesia regime which is routinely in use after this type of surgery. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8.What are the possible benefits of taking part?

There will be no clear benefit to you from your participation in this research.

9.What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

As already mentioned, this drug can have some unwanted effects. In controlled studies with sumatriptan injection, the most common adverse reaction with greater than 2% risk of events, were injection site reactions, tingling, warm/hot sensations, burning sensation, feeling of heaviness, pressure sensation, feeling of tightness, numbness, feeling strange, tight feeling in head, flushing, tightness in chest, discomfort in nasal cavity/sinuses, jaw discomfort, dizziness/vertigo, drowsiness/sedation and headache.

Other very rare side effects include:

-reports of adverse cardiac events, including myocardial infarction, coronary vasospasm,life threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of sumatriptan, Considering the widespread use of sumatriptan in patients with migraines, the incidence of these events is very low.

-cerebral haemorrhage, subarachnoid haemorrhage, stroke and other cerebrovascular events have been reported in patients treated with subcutaneous sumatriptan. In a number of cases, it appears that cerebrovascular events occurred independently of any drug being given. It is therefore very rare for sumatriptan to cause these complications with a frequency of less than one percent.

While the possibility of the side effects occurring is very low, you should still be aware that they may occur. We will try to decrease the chances of this event occurring, but if something unexpected happens, we will provide you with immediate review and all supportive treatment.

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The risk of problems from anaesthesia increases for patients who are having more major surgery, those with medical problems and those that require difficult anaesthetic procedures. If you have any concerns about these issues, you should discuss them with the study team.

10. What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

11. Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

12. What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing. If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

13. Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

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- Unacceptable side effects
- The drug/treatment/device being shown not to be effective
- The drug/treatment/device being shown to work and not need further testing

14. What happens when the research project ends?

On the completion of the research project, you will receive a phone call to inform you of the findings. Please let us know if you do not wish for this to occur.

Part II: How is the research project being conducted?

15. What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this health service for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Austin Health, as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

De-identified information from this project may be used in future related research. It will not identify you, nor will it be traceable to any personal information you provide. In 15 years time, we may offer the study information to a database/registry. The information will not be identifiable nor traceable to you. It may help future researchers and patients to icorporate this data in further rstudies.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Information about your participation in this research project will be recorded in your health records.

In accordance with relevant Australian and Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project *and for the future research described in Section 14* that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

Austin Health

Place Patient Label Here

Interventional Study- Adult providing own consent

16. Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public servant in any Australian public hospital.

16. Who is organising and funding the research?

This research project is being conducted by Dr Jeremy Russell and Dr Ana Licina.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

17. Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Austin Health. This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

18. Further information and who to contact?

For all clinical complaints and enquiries please contact:

Name	*Dr Ana Licina*
Position	*VMO in Anaesthesia*
Telephone	
Email	*Ana.licina@austin.org.au*

Local HREC Office contact (Single Site - Research Governance Officer)

Name	*Austin Health Human Research Ethics Committee*
Telephone	*03 9496 4090*
Email	*ethics@austin.org.au*

Austin Health

Place Patient Label Here

Interventional Study- Adult providing own consent

Consent Form - *Adult providing own consent*

Title: Subcutaneous Sumatriptan for Post-Craniotomy Pain- A Randomized Double-blind Placebo Controlled Clinical Trial

Protocol Number: 1.2

Project Sponsor: Austin Health

Principal Investigators: Dr Jeremy Russell, Dr Ana Licina

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to *[Name of Institution]* concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Under certain circumstances (see Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 at 4.8.9*) a witness* to informed consent is required.*

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

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Place Patient Label Here

Interventional Study- Adult providing own consent

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/

Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	Footer
Funding	#4	Sources and types of financial, material, and other support	Manuscript 25
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	25

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Austin health 8
Roles and responsibilities: sponsor and funder	#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	10
Roles and responsibilities: committees	#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)	n/a
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	4/5/6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7/12
Objectives	#7	Specific objectives or hypotheses	4/5/6
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, non-inferiority, exploratory)	8
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10

Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
Interventions: modifications	#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)	10/11/12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
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	12
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)	Figure 1and 2
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	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8/9/10
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	10

		interventions	
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	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10/11
Data collection plan	#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	12/14/15
Data collection plan: retention	#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	12/14/15
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	12/14/15
Statistics: outcomes	#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	14
Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and	14

analyses		adjusted analyses)	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12/14
Data monitoring: formal committee	#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	19
Data monitoring: interim analysis	#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	19/20
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19/20
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19/20
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	8
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)	8
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	19

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	19
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	25
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	24
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	12
Dissemination policy: trial results	#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	3
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	25
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	3
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Suppl.
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	n/a