START Standard Operating Procedures

Study Overview

Name of study: Stanford Accelerated Recovery Trial (START)

Enrollment Goals:

Total N = 560 patients

Start Date:

IRB approved January 26, 2010

Stanford Cancer Center approved March 19, 2010

NIH Certificate of Confidentiality: January 26, 2010 – January 31, 2021

Patient Endpoint Definition: The endpoint for efficacy analyses is five consecutive reports of zero reported pain and five consecutive reports of zero opioid use. The endpoint is defined as the first date of these reports. Patients will continue to receive phone calls until they, in addition to meeting the endpoint as defined above, have stated they consider themselves recovered from surgery.

START Standard Operating Procedures

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Education and Training

Research Staff

All research team members will perform the responsibilities as outlined by the delegation of authority log. Human Subjects Training and HIPAA training will occur as required by Stanford Policy. Additionally, all team members will receive a copy of this document, the Lab Policy Manual, and will be trained directly by the Principal Investigator (PI) on the purpose of the study and their responsibilities. Research staff will be trained on Informed Consent, Phone Screening, and Case Report Form Completion by the research manager, who will monitor appropriate conduct and form completion on an ongoing basis, in collaboration with the PI and study monitor. Recruitment and patient contact will first be conducted under the direct supervision of the PI, until he deems the research team member capable of carrying on responsibilities independently. Research team meetings will occur frequently with the PI to ensure ongoing understanding by study staff and to address any concerns.

Clinic Staff

The Principal Investigator will speak directly with all participating surgeons and pre-operative clinic staff to inform them of the purpose of the research and the process for recruitment and patient referrals. Referring physicians will be informed of the study design such that they are aware of what medication their patients may be receiving, and the schedule of medication administration.

A form will be placed in the patient's chart and at the foot of their bed specifying that they are enrolled in the trial and to contact the study team prior to giving Gabapentin.

Recruitment

Recruitment may take place via one of three methods:

Clinical staff referral

Surgeons, anesthesiologists, or clinical care staff may ask a patient if they are interested in speaking with a member of the research team. With the patient's permission, the staff may forward the patients name and contact information to research staff.

Preoperative clinic:

All patients at the Stanford Surgical Admissions Unit (SAU), and pre-surgical appointments for eligible surgeries with participating surgeons fill out sheet asking whether they are interested in speaking with a member of the research team regarding research. (*Ok to contact ad.doc)* This form is integrated into the patient's regular appointment paperwork and is returned to the front desk staff.

Forms get picked up daily from the clinic(s) by the research assistant or coordinator. Alternatively, the research coordinator or PI may be present in the SAU or pre-surgical appointment clinic to receive the

form or get verbal permission from the clinic staff, and speak with the patient immediately per information in Screening section.

Patients not spoken with during the appointment are contacted that night by the research coordinator or physician for screening and to discuss the study

CT.gov posting

The START clinical trial is posted on the Stanford Clinical Trial site, which is uploaded to clinicaltrials.gov. Site status is listed as "enrolling by invitation". Interested patients may contact the study team at the contact information provided, but will only be considered for inclusion if they are receiving an eligible surgery at Stanford Hospital and Clinics.

Screening

Patients undergoing the following surgeries with the designated surgeons will be considered for inclusion. These are chosen for the appropriateness of the intervention in the context of the surgery, and the willingness of the surgeon to refer eligible patients.

Carpal Tunnel – Chang, Hentz, Curtin, Ladd, Sen, McAdams, Yao

Hand/Other – Chang, Hentz, Curtin, Ladd, Sen, McAdams, Yao

Foot – Dragoo, Hunt

Lumpectomy – Dirbas

Mastectomy – Dirbas (including bilateral matestectomy)

Shoulder – Cheung, Costouros, Dragoo, Fanton, McAdams, Safran, Vaughn, Yao, Abrams

Total Knee Replacement – Goodman, Huddleston, Maloney, Giori (including revisions, including bilateral knees), Chu, Fanton, McAdams, Safran, Vaughn, Abrams

Total Hip Replacement – Goodman, Huddleston, Giori (including revisions), Safran, Vaughn, Abrams

Thoracotomy – Whyte, Shrager, Merrit, Hoang

Trigger Finger – Chang, Hentz, Curtin, Ladd, Sen, McAdams, Yao

VATS – Whyte, Shrager, Merritt, Hoang

Patient will first be given a description of the study as per the approved phone screen to assess interest and answer any questions.

Patients who are interested in participating will have eligibility assessed. Initial screening will take place with approved phone screen either on the phone or via an in-person interview during the patient's pre-

operative appointment. Eligibility will be determined by the research coordinator and PI, who will complete an eligibility checklist up to 3 days prior to surgery and confirm no changes in medical status with the patient on day of surgery.

Inclusion criteria

1. Age 18-75*
2. Undergoing a scheduled surgery
3. English speaking
4. Ability and willingness to complete questionnaires or use palm pilot

*Patients undergoing a thoracotomy must be between the ages of 18 and 73

Exclusion Criteria

1. Known kidney disease
2. On gabapentin or (pregabalin) lyrica already
3. Cognitive impairment
4. Previous history of excessive sedation or adverse reaction to gabapentin (not it was tried but ineffective for nerve pain)
5. Coexisting chronic pain >4/10 disorder in area other than surgical target
6. Plan to move out of state
7. Condition that would in judgment of team member make patient likely to be lost to follow up
8. Elevated Suicidality as assessed by an answer of 2 or greater on question 9 of the Beck Depression Inventory assessing suicidal thoughts.
9. Known pregnancy
10. Current symptoms of ataxia, dizziness, or sedation
11. Narrow angle glaucoma
12. Severe respiratory insufficiency (ie severe emphysema or chronic obstructive pulmonary disease)
13. History of gastric bypass surgery and obstructive sleep apnea requiring CPAP

Patient Enrollment

Eligible and interested patients:

Informed consent may be obtained in one of three ways: over the phone, at an already scheduled pre-operative visit, or at a newly scheduled lab visit.

Phone consent - the research team member will mail, fax, or email a .pdf of the approved consent form to the patient. The patient will call the research team member once the consent form is received, or the research coordinator or PI will call the patient to confirm receipt of the consent document. The coordinator or PI will obtain informed consent from the participant, who will bring the signed document with them on the day of surgery. Coordinator or PI will verify signatures and sign the researcher signature line at that time.

In-person consent – if the patient is returning to Stanford for an already scheduled pre-operative appointment, the coordinator or PI may meet the patient before or after this

appointment. Alternatively, the patient may choose to make a separate visit to the lab for the consenting process. The coordinator or PI will obtain informed consent at that time.

See Data Management section for storage of consent forms as well as how to send a copy to medical records.

Patient not interested or ineligible:

Participants who are ineligible or not interested in proceeding with the clinical trial will be offered enrollment in an observational only arm in which no intervention is given, but patients complete the same baseline pre-operative questionnaire packet, and are followed longitudinally with the same questionnaires. Informed consent for the observational only arm will proceed in the same manner as the full trial using the appropriate, approved consent form

Patients who are not interested in the clinical trial component or the observational component or unable to participate in either arm due to eligibility concerns will be asked to provide basic de-identified demographic information to allow comparison with participating patients using the Anonymous Data Form.doc. This may be obtained through discussion with the patient him/herself or by accessing the patient's medical record. Patients will also be asked the reason they chose not to participate.

Patient Welcome Packet

Once patients are consented to participate, they will be given the START welcome packet, which will include: pre-surgical assessment packet (see below), START information sheet, Flowchart for Patients, Post-surgical medication reminders, a copy of their consent form, psychological services brochure, and a business card for the study with study staff contact information. For patients who consented over the phone, this packet will be mailed with the consent form to facilitate the consent process and so that the patient may have these materials immediately once enrollment is complete.

Database Registration

Once a patient has enrolled in the trial, s/he will be entered into the SNAPL central database under Protocol "START", Project "Gabapentin Trial" or "Observational Only".

The research coordinator or assistant will register the patient in the Cancer Center Oncore Database accessed online. All patients must be entered in the Cancer Center's Oncore database within 30 days of enrollment. Patients are registered under protocol VAR0054. Use the Oncore instruction guide found in the START Admin folder on the server.

Pre-Surgical Assessment

Baseline Questionnaire Packet:

After enrollment, patients will complete a pre-surgical questionnaire packet. Pre-surgical assessment questionnaires are documented below:

1. Contact and surgical information
2. Demographics form
3. MC-SDS -- Marlowe-Crowne Social Desirability Scale
4. BIS -- Barratt Impulsivity Scale
5. PTSD and addiction questions
6. BDI -- Beck Depression Inventory
7. PCL-C -- PTSD CheckList, Civilian Version
8. STAI -- State-Trait Anxiety Inventory
9. Pain Outcomes Questionnaire
10. ASI Drug and Alcohol Section
11. ORT- PDUQp Trait Questions
12. Menstrual Cycle Questions
13. Euroqol

Packets will be returned to the study staff on the day of surgery.

Pre-surgical Reminder Call

Study nurse will call the patient the night before surgery to confirm surgery time the following day, review any eligibility information, and remind the patient to bring the baseline questionnaire packet.

Day of Surgery Assessment

Checklist CRF will be completed documenting day of surgery steps and post-surgical days1-3 steps. Study staff will meet the patient prior to surgery to collect the questionnaire packet, collect the consent form if not already obtained, confirm eligibility checklist has been completed up to 3 days prior to surgery and verbally confirm with patient that no changes to health or medical status have occurred since then, and begin randomization.

Tissue Collection

Patients who are undergoing spinal anesthesia as part of routine care will have a Cerebrospinal Fluid sample obtained if they consent to do so. Prior to the injection of spinal anesthesia, a sample of CSF not to exceed 20ml will be captured by the anesthesiologist placing the spinal anesthesia line. Sample will be collected into an eppendorf tube and delivered to CTRU for processing according to the following instructions:

1. For patients who consented to CSF sample collection, collect one cryovial of sample
2. Label cryovial with pre-printed label and print: cryovial label number (1684-3 digit number starting from 001 – 01), date of collection, time of collection
3. Inform CTRU lab director Ben Varasteh (varasteh@stanford.edu) of an incoming sample
4. Complete the CTU Accession Form – put both START participant ID and cryovial label information on the accession form, keep a copy in the patient folder.
5. Deliver sample on ice to the CTRU at 800 Welch Road

6. CTRU will process and store the samples until we transfer them to HIMC for long-term storage and analysis

Genetic sample

All patients will be asked to provide a saliva sample for genetic analysis through protocol 9435. Patients will be consented separately and participation in START is not contingent on any participation in the genetics study. Participation can occur at any time throughout the START trial after the baseline packet has been received.

Randomization

Patients will be randomized after eligibility has been confirmed and checklist completed. Research coordinator will deliver a prescription form signed by the PI to the OR pharmacy.

Randomization will be pre-generated using the R program. See "START Randomization Readme.docx" for detailed instructions on using the program.

Randomization will occur using blocked, stratified randomization by surgery and surgeon.

Randomization will be pre-generated onto logsheets to be provided to OR pharmacy; One log sheet will be generated per combination of surgeon/surgery, with surgery to be color-coded for ease of differentiation/use. When the pharmacist receives a prescription, s/he will find the appropriate log based on surgery and surgeon for that patient and will fill in the next empty line of the log sheet, which will indicate which medication the patient is to be prescribed. The pharmacist will place the patient's sticker on a START Randomization Card and indicate which medication was prescribed. This will be placed in a sealed envelope and put in a "completed cards" box. Study staff will pick up the sealed envelopes weekly and store in the lab – these will remain in the sealed envelopes until the end of the study unless a safety issue requires un-blinding. Medication Logs will be maintained in a binder in the OR Pharmacy.

Intervention

Patient receives medication from the study nurse, who picks it up from the OR pharmacy. Study team member will document time at which patient received pre-operative medication. Normal standard of care and medications will not be affected by study participation. If dose is given before the patient is in a bed, the study nurse will stay with the patient for observation until s/he is in a bed.

Based on blinded randomization, patient receives:

Preoperative Medication:

4 capsules of 300mg Gabapentin (1200 mg total) OR 3 capsules of inactive placebo plus 1 capsule of active placebo (0.5mg Lorazepam)

Post-operative Medication:

2 capsules of 300mg Gabapentin three times a day (6 total capsules, 1800mg total daily dose) OR 2 capsules of inactive placebo three times a day (6 total capsules) continued for 72 hours post-surgery (10 total doses/20 total capsules over the 72 hour period)Doses will be administered under the default EPIC TID option of 0600, 1400, and 2200. Medication administration will start on the day of surgery at the soonest timepoint (eg 1400 if surgery ends at 1200), or the next day if surgery ends past the tid timepoint that day (eg 0600 the following day if surgery ends at 2300). Medication is stored in the tower pixis.

If the patient is not assigned a bed by 4pm, study nurse will pick up the medication directly from the OR pharmacy and deliver it to the floor once the patient is bedded for storage in the tower pixis.

If patients are discharged before the 72 hour period ends, they will be given the remainder of their capsules to take at home. They will also be given a pill dispenser and instructions for taking the medication. This will be dictated in a note in EPIC to the nurses, and patients will be instructed to ask the nurse for the remainder of their study medication from their medication bin upon discharge. The research team member will confirm this process with the patient and nurse.

Medication Adjustment for Side Effects

Participants who experience significant sedation, as assessed by a dizziness or sedation rating of 7 or greater on the side effect assessment form, patient dosage will be reduced by half (1 capsule of 300mg Gabapentin three times a day for a total dosage of 900mg daily, OR 1 capsule of inactive placebo three times a day). An investigational study help order ("INV Study Drug Help Order") will be placed in EPIC with instructions to the pharmacy to reduce the dose. Research team member will follow-up with a page to the pharmacist on call. Research team member will pick up a new medication bottle label from the pharmacy, and will remove the extra pills from the medication bottle for disposal.

Patients who have been discharged will be assessed over the phone and given instructions for dose adjustment verbally.

If, at next assessment, patient dizziness or sedation remains at 7 or greater on side effect assessment scale, medication administration is stopped.

Research team member will document whether dosage has been reduced or stopped on Medication Administration CRF.

Follow-up*

*Note: Details on questionnaire administration in START Questionnaire FlowChart

Post-operative Days 1 to 3

Post-operative day 1 is defined as the day after the surgery started.

Side Effect Assessment Post-operative Days 1 to 3

Research assistant or coordinator will assess side effects on the patients once daily beginning on post-operative day 1. Research assistant or coordinator will ask patient whether each of the listed side effects is present and, if so, for a rating of severity.

Sedation greater than a 7 out of 10, obvious confusion, and obvious neurologic impairment should be brought to the attention of the principal investigator immediately.

Daily Pain and Opioid Questionnaire:

Will be assessed daily by a research team member through interview with the patient.

Medication Administration:

The daily dosage administered to the patient will be documented on the Medication Administration Case Report Form (CRF) by a research team member by verifying information in EPIC. Patients who are discharged prior to completing the 72-hour medication administration period will give this information via phone to a study team member each day. Source of data (patient report or patient chart) will be recorded.

Quality of Recovery-40:

Will be administered to the patient by a research team member on post-operative day 1 only.

Blinding Assessment Form:

Patient will be asked by the research team member which medication they believe they received throughout the study after the last dose is given, no later than the day following the last dose. If the patient is discharged before assessment, it will be assessed at the first follow-up phone call after the last dose is taken, and no later than the day after the last dose is taken.

Discharge Date and Time

Study team member will verify information in EPIC and record it on the START Checklist.

Medical Chart Review

Research team member will review the patient's medical record for information required on case report form. This will be done within 1 week after the date of surgery.

Post-operative Days 3 until Endpoint

Tracking of monthly and additional reports will occur via the tracking log. A patients surgery will be entered into the log, which will populate all subsequent target dates and the log will be kept in the patient binder. These will then be placed on the calendar for mailing. Date of mailing will be recorded, and date the packet is received.

Daily Phone Calls:

After being discharged, the daily report of pain, medication use, and pain interference will be provided over the phone to a member of the study team. Calls will begin in the morning and continue until early

evening. A missed call will be recorded as such. Calls will continue daily for 3 months, when the frequency will reduce to weekly until the 6 month time-point, at which time calls will reduce to a monthly basis.

Monthly Reports:

A more comprehensive report of drug use will occur on a monthly basis by mailing the participant a questionnaire and stamped return-envelope. Alternatively and preferentially, patients will complete the survey via an online REDCap Survey tool. They will be emailed a reminder 3 days prior to survey due-date with instructions to input their StudyID number and survey number.

Survey link:
http://redcapsurvey.stanford.edu/surveys/index.php?hash=ed3d2c21991e3bef5e069713af9fa6ca

Additional Reports:

One month post-surgery, patients will be asked about any use of antibiotics during the post-surgical time period.

Six months post-surgery patients will be mailed a more comprehensive questionnaire packet to assess current mood, pain and functioning, PTSD symptomatology and quality of life. This applies to patients still enrolled in the trial (Active patient) and those that have met endpoint (this 6-month post-enrollment assessment counts as the first of the up-to-once-every-6-months assessments)

One year post-surgery patients will complete an additional PTSD symptom inventory with the PCL.

Six months after opioid use stops, patients will be mailed an anonymous form to survey how opioids were disposed of.

6 months and 2 years after endpoint is met, patients will be mailed a questionnaire packet including the following: BDP, BPI, CDOQ, PCL, Euro-Qol, Daily Pain and opioid use questionnaire.

Patient Withdrawn or Study Completion

If patient is withdrawn from study, is lost to follow-up, or when the patient reaches the study endpoint, a study staff member will document study completion by using *Study Stop Point* CRF.

Patient tracking log will be updated to reflect subsequent mailing dates no longer apply by crossing them out, initialing, and providing the date.

Data Management

Data will be maintained on appropriate case report forms and participant questionnaires. Data will be entered into an electronic format via the teleform system, by which forms are scanned into an electronic format and stored as .txt or .csv files until imported into an electronic database.

Patient Identification Codes

Patients enrolled in the study will be labeled with a code as follows: 3 digit ID number First Initial Last Initial. Example: 001XX

Data Storage

Binders will be stored in locked cabinets.

Screening & Eligibility Forms

Ok-To-Contact Sheets and phone will be maintained in a recruitment & screening binder in the relevant section. A screening log will be maintained electronically documenting which patients were contacted after giving permission on the ok-to-contact form or from a clinic staff member. The following information will be recorded: the patient name, the date the patient was spoken with, the researcher conducting the screening, the screening result (eligible, ineligible, declined to participate and reason), whether the patient was enrolled, and any comments (eg when consent form packet was mailed to the patient).

Eligibility checklist will be stored in the patient binder and a copy stored in the regulatory binder.

Case Report Forms

All original case report forms and patient questionnaires will be stored in participant's individual folder.

Consent Forms

Consent forms will be stored in a separate binder. Each consent form will be labeled in the upper right corner with subject ID number. Enrollment logs are generated via the SNAPL Central Database.

A copy of the consent form will also be sent to Medical Records for storage in the patient's chart; this will have the patient's MRN sticker on each page and mailed to: HIMS, room HC032, MC5200

Case Report Form Scoring

Daily Pain and Opioid Use Form

The daily pain and opioid use values will be recorded on the Consolidated BPI CRF. Use the data dictionary on the second worksheet for proper scoring. Data entered into REDCap once the patient completes the study or is withdrawn.

Composite Drug and Opioid Questionnaire

See CDOQ Scoring Manual for instructions. Data is entered directly by the participant into the REDCap survey, sent through the REDCap system each month (email initiated by a member of the study team per the CDOQ email instructions document).

Patient Adherence

Adherence to intervention will be recorded on the Medication Administration Record CRF. Patients have been discharged prior to the 72-hour post-operative medication administration period will have adherence measured by self-report. A study team member will meet with the patient prior to discharge to instruct on how to take the post-operative medication dosages. Instructions will be repeated by phone each day and patients will give a report, to the best of their ability, on the number of doses they took and the timing.

Measures to promote adherence:

Ensuring patient understanding of study expectations:

Knowledgeable and receptive staff: Staff education plan above ensures competent description of the study process and expectations. Staff are selected for the ability to communicate study expectations and process clearly and engage the patient in the process.

Providing a Welcome Packet with study information and easily found contact information for study staff.

Dispensing pill dispenser for patients who need to continue post-operative dosage at home

Exclude those likely to be noncompliant (eg imminent plans to move out of the area)

Follow-up phone calls are entirely the burden of study-staff – patients do not need to contact the research team

Developing a personal relationship with the patient

Friendly staff: Staff are also selected for their interpersonal skills and ability to engage the patient in a friendly conversation.

Birthday and holiday cards are sent to the patient periodically

Send a quarterly newsletter to patients via email citing current enrollment and study progress

Adverse Event Reporting

Adverse events will be monitored daily while the patient is receiving medication during post-operative days 1 to 3 on the Side Effect CRF (See Side Effect Assessment). Adverse events will be reported to the IRB and Stanford Cancer Center Data Safety and Monitoring Committee annually.

Serious adverse events (SAEs) are defined according to the FDA as any adverse drug experience that results in any of the following outcomes:

- Life-threatening
- Death
- Hospitalization/prolongation of hospitalization
- Congenital anomaly
- Persistent or significant disability/incapacity
- Required intervention to prevent permanent impairment/damage

An unanticipated problem is defined as unexpected (not in the consent form or package insert, or unexpected in its severity or frequency), harmful, and related (probably caused by the research drug).

A major protocol deviation or violation includes any procedure that differs from the IRB approved protocol that was intended to eliminate an immediate hazard to the participant, was harmful, or is possible serious or continue non-compliance by a study staff member.

Serious adverse events, unanticipated problems, and major protocol deviations will be communicated by the study staff to the PI immediately. All events will be communicated to the Cancer Center Trials Office (CCTO) using the adverse event communication form within 5 days of the PI learning of the event. A description of the event will be included. The CCTO will submit this information to the IRB.

All minor protocol deviations (those that do not meet the definition of a major deviation and do not affect the interpretation or outcome of the study) will be reported to the CCTO annually.

Medication Ordering

Medication will be ordered through Los Altos Pharmacy and delivered to the Stanford Hospital research pharmacy by a research team member. Gabapentin will be compounded in 300mg capsules. Matched placebo capsules will be prepared by the compounding pharmacist; active placebo capsules will contain 0.5mg Lorazepam. Stanford Hospital research pharmacy will control dispensation and logging of medication.

Trial Monitoring

Adverse Events, Serious Adverse Events, Unanticipated Problems, and Protocol Deviations will be monitored on a continual basis and reported per information in the Adverse Events section.

Patient Adherence will be monitored as described in the relevant section.

The PI will hold regular staff meetings at least twice monthly to assess study team member understanding of responsibilities as per the Education section.

Additional ongoing monitoring will occur as detailed below. Results will be recorded on START Monitoring CRF. The PI will review and sign-off on the results and any suggested resolutions.

The first 10 patients will have case report forms and consent forms reviewed for accuracy and completion immediately after enrollment and entry into the follow-up period. After the first ten patients, case report forms and consent forms will be evaluated for completeness every 50 patients, or every 3 months, whichever is sooner. A monitoring results report will be sent to the entire study team and results will be discussed at the subsequent study team meeting. Ongoing issues with data completion will be addressed with the individual team member and re-training may occur as necessary.

Data Safety and Monitoring Board

The Stanford Cancer Center will serve as the DSMB for the trial. Safety will be reviewed according to the CCTO DSMB Standard Operating Procedures.

Case Report Form Completion

Missing data that is available through patient records such as EPIC will be recorded with a notation of such. Data discrepancies will be compared to any source data such as EPIC and corrections made by crossing out the original value, providing the correct value, dating, initialing, and providing a reason for the correction. Missing data or data discrepancies that cannot be resolved by verifying source data will be left as missing.

Consent Form Completion

Consent forms will be evaluated for completeness of all signatures, required initials, and dates. Any missing signatures will be obtained by mailing the patient a copy of the consent form and requesting the signature with the current date. Any missing PI signatures will be obtained and dated with the current date. Patients with missing signatures who are unable, or unwilling, to provide missing signature will be withdrawn from the study and data will not be used.

Electronic Data Verification

Electronic data is entered via the Stanford REDCap system. Patients enter responses directly into the electronic system for monthly CDOQs, unless they specifically request a paper copy. Case Report Forms are entered into REDCap by study staff, after they have completed instructional training and a mock-entry packet that is reviewed by the Research Manager, coordinator, or study monitor.

An additional 10% of data will be randomly verified by study staff prior to data analysis. Verification will occur via visual inspection. Discrepancies will be noted, original source data checked, and the correct value entered. All verified data will be noted with the reviewers initials and date. Corrections will be noted with the date, initials, and reason for correction. Consistent errors will prompt a more comprehensive review of the data at the PIs discretion.

Analysis

All randomized patients will be included in an intention to treat analysis. Patients with 100% compliance will be tested in a per-protocol analysis.

Primary Endpoint

Time to pain resolution, defined as five consecutive days of reported zero out of ten average pain.

Secondary endpoints

Time to opioid cessation, defined by five consecutive days of zero reported opioid use. For patients entering the trial already taking opioid medication, an additional endpoint will include time to return to baseline levels of opioid use.
The proportion of patients continuing on chronic opioids at 6 month and 1 year.
The proportion of patients with continued pain at 6 months and 1 year.
Survival at 1 , 3, and 5 years.
PCL-C Scores at 6 and 12 months.

Background and Demographic Characteristics

Demographic and background information will be summarized with descriptive statistics (mean, standard deviation, percentages, etc.)

Evaluation of Efficacy:

Primary and secondary endpoint will be analyzed using survival analysis or logistic regression stratified by surgery type and surgeon as appropriate. Trial efficacy will be determined by the significance of treatment assignment in the intention to treat analysis.

Methods for handling missing data and non-adherence to protocol:

Primary analysis will be intent to treat. Separate efficacy analysis on those with complete protocol adherence will be done. Subjects dropping out will be censored at the last known data point. Competing events such as a second surgery will be reasons for censoring at the time of the competing event. Missing data will not be imputed.

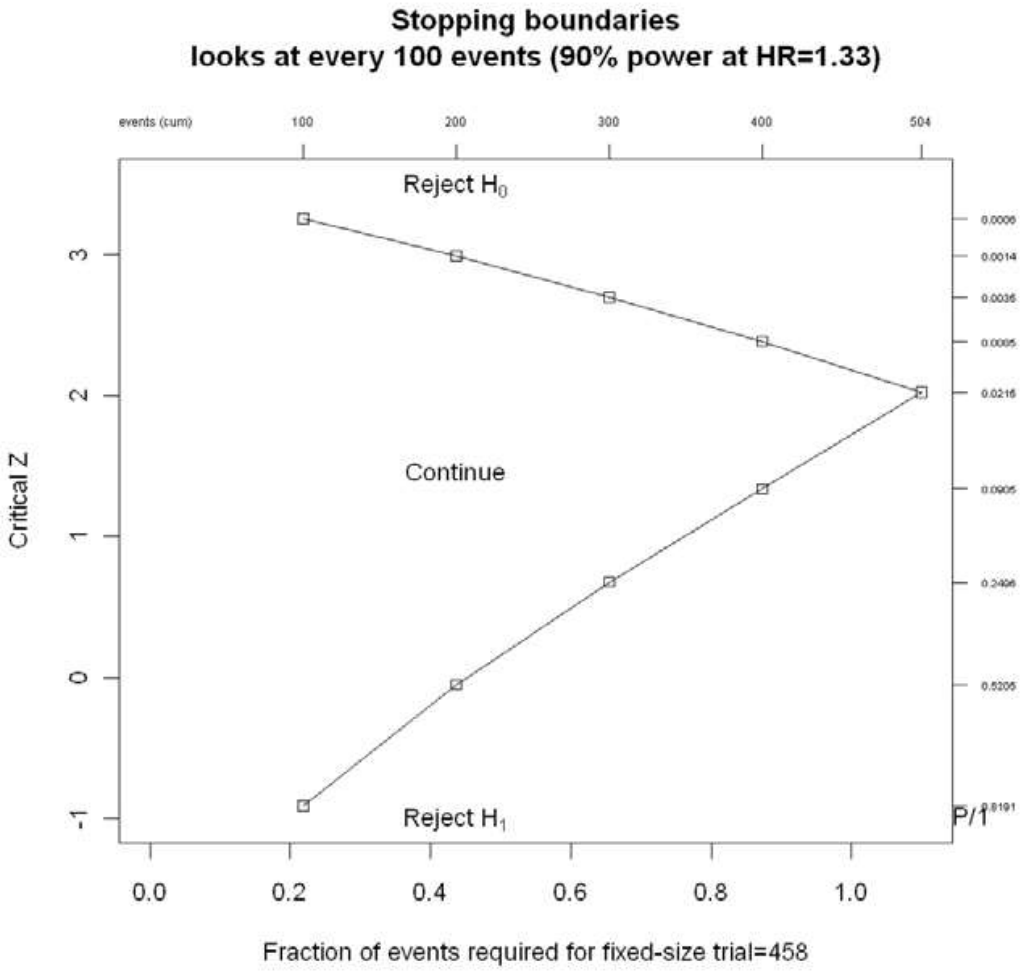
Subgroup Analyses

Subgroup analysis will examine the treatment efficacy in high risk subgroups defined by the presence of PTSD, Depression, High self report of addiction susceptibility. Preplanned subgroup analyses include: Patients with PTSD symptoms at baseline as defined by answering yes to any question on primary care PTSD screen, and patients with BDI scores greater than 13. Analysis will involve comparing single dose versus continued dosing as dichotomous variable and continuous variable of total dose (since a proportion will get only single dose secondary to side effects)

Interim Analyses

Planned interim analysis will be conducted every 100 events using the stopping rules outlined below and the indicated P-values.

Note the p values here are one sided. So the p-value for efficacy on the final analysis will be an overall p=0.043


Stopping boundaries
looks at every 100 events (90% power at HR=1.33)
events (cum)
100
200
300
400
504
Reject H0
Continue
Reject H1
Critical Z
3
2
1
0
-1
0.0
0.2
0.4
0.6
0.8
1.0
P/1
Fraction of events required for fixed-size trial=458

See Also

START Flowcharts

Schedule of Events

Delegation of Authority Log

Composite Drug and Opioid Questionnaire Scoring Manual

REDCap Survey Data Dictionary

Notes on START Calls

Modifications History

9/27/10

Study endpoint – Study Overview page: Patients continue to be called until they consider themselves recovered from surgery – this does not change the study endpoint analysis

Inclusion/Exclusion criterion: Age range increased from 69 years of age to 75 years; Thoracotomy patients only enrolled up to age 73

Inclusion/Exclusion Criterion: Opioid use no longer an exclusion criterion

Secondary Endpoint: Additional endpoint added for patients who enter the trial already taking opioid medications.

10/15/10

Follow-up – Monthly reports: Information regarding use of online REDCap survey included.

Follow-up – Additional Reports: Information regarding questionnaires to be mailed after endpoint is met (6 months and 2 years post-endpoint) is included. See also Schedule of Events.

See Also – Reference to Notes on START Calls.

10/21/10

Follow-up – Blinding assessment form: Clarified time-point at which it is assessed – after last dose, no later than the following day

Intervention: Instructions added for study nurse to stay with patient if the pre-op dose is given before patient is in a bed.

Intervention – postoperative medication: Details regarding storage of medication in pixis and delivery of medication to the floor if patient is bedded after 4pm

Intervention – Medication Adjustment for Side Effects: If adjustment occurs, additional detail added to follow-up with a page to the pharmacist on call. Study team member will also obtain new label for the medication bottle, and will dispose of the extra pills.

Pre-surgical reminder call (new section): information added

11/2/10

Follow-up – Additional Assessments: Clarity provided for what is assessed at 6-months post-enrollment (including for patients who meet endpoint), and at 2-years post-completion.

11/15/10

Screening: Bilateral Knee surgeries now on list of included surgeries

3/7/11 (SOP updated 4/8/11)

Screening: Dr. Maloney included on the list of applicable surgeons

7/15/11

Collection of 6-month post-endpoint packet was not added to the details of the Additional Reports section when initially decided upon (See modification notes 10-15-10) – this is corrected with this version

9/23/2011

If student doesn't reach patient after 2 weeks – give to Deb to call. If Deb can't reach after another week – send patient letter. Continue student calls for 1 final week – after 4 total weeks with no response = lost to follow-up (confirmed with Ian)

Patients who are already taking opioids before surgery can be moved to monthly calls early if they return to baseline levels of opioid use and all other endpoints are met. Calls will be continued until primary endpoint is met (no opioid use) – Needs to be confirmed by Rebecca before moving to Monthly.

10/12/12

PTSD CAPS interviews no longer being conducted – removed from follow-up assessments section, schedule of events, and flowcharts

1/8/13

START-Participant Schedule of Events document updated to reflect events that still occur in the case of a "censored" patient. A patient censored due to a second surgery, or other reason deeming them no longer eligible (eg going out of the country for an extended period of time such that daily data cannot be collected) will have long-term follow-up data collected if applicable endpoints met. This includes: 1-month follow-up question, 6-month packet, opioid disposition form (if opioid endpoint was met before censoring), 1-year post-surgery PCL-C, 6-month post-endpoint packet (if primary endpoint was met before censoring), and 2-year post-endpoint packet (if primary endpoint met before censoring).

3/26/13

Document comprehensively reviewed for accuracy

Screening – Miller removed as applicable surgeon. Dr. Miller's patients will no longer be enrolled in the trial.

Day of Surgery Assessment – Statement about receiving gift card removed; Compensation no longer provided to participants as of 4/20/2012

Data storage – case report forms – clarified to indicate each participant has an individual participant folder in which case report forms are stored

Patient Adherence – Measures to promote Adherence - $25 gift card removed; no longer provided as of 4/20/2012

Case Report Form Scoring – updated to include statements of the use of REDCap for Daily Pain and Opioid use and the CDOQ data.

Trial Monitoring – Electronic Data Verification – updated to remove Teleform system and include information about REDCap system.

4/5/13

Screening – Giori added to list of Total Knee and Total Hip Replacement surgeons (has been one of the participating surgeons since August 2010; Neglected to update SOP at that time)

Screening – Exclusion Criteria: Added gastric bypass surgery and obstructive sleep apnea (have been exclusionary since August 2011; Neglected to update SOP at that time)

Screening: Clarified that eligibility checklist may be completed up to 3 days prior to patient's surgical date, with verbal confirmation of no changes to medical status on the day of surgery

Day of Surgery Assessment: Clarified that eligibility checklist may be completed up to 3 days prior to patient's surgical date, with verbal confirmation of no changes to medical status on the day of surgery

10/29/13

BPI updated with additional question, "In the last 24 hours, have you needed to take your pain medication to help you sleep? (Yes, No)" IRB approval received 11/20/13

4/9/13

Screening – Shoulder, Trigger Finger, Carpal Tunnel, Hand/Other, Foot added to list of surgeries

Screening – Chang, Hentz, Cheung, Chu, Costouros, Curtin, Dragoo, Fanton, Hunt, Ladd, Sen, McAdams, Safran, Vaughn, Yao, Abrams added to list of surgeons

"Total Knee Replacement – Unicompartmental" added to Surgery list in START Log

7/14/14

CIDI-SAM administration paused due to unavailability of computer program for PI; Statement removed from Follow-up section: “Patients still taking opioids at one year post-surgery will also have the CIDI-SAM administered by the PI.”

9/2/14

If student doesn’t reach patient after 3 weeks – send patient letter. Continue student calls for 1 final week – after 4 total weeks with no response = lost to follow-up.

1/27/15

If Student doesn’t reach patient after 1 month – send patient letter. Continue calls for 4 more weeks. After a total of 2 months with no response = lost to follow-up.

Statistical Analysis Modification

5/10/15 Method for imputing scores in the presence of missing responses specified:

To calculate scores for the Marlow-Crowne Social Desirability Scale, Barratt Impulsivity Scale, Beck Depression Inventory-II, PTSD Checklist-Civilian Version, and State and Trait Anxiety Inventory, if less than 20% of responses were missing, the average of the existing responses was imputed for missing responses to calculate the final score. Otherwise, a score was treated as missing.

Specified details of preplanned subgroup analyses:

Preplanned subgroup analyses include: patients with PCL-C score ≥ 25, patients with BDI score ≥ 13, TRAI score ≥ 33, STAI score ≥35, self-perceived likelihood of addiction to pain medicine score >1, and ORT score ≥8.

1/25/16 Added senior statistician review of all analyses.

2/2/16 Added post-hoc subgroup analysis of surgery type.

4/25/16 Noted analysis of serious adverse events and adverse events and participant blinding:

Evaluation of Serious Adverse Events and Adverse Events

The number of serious adverse events and adverse events will be reported along with Chi-square tests to compare the proportion of patients between groups with serious adverse events, at least 1 adverse event, adverse events leading to discontinuation of the trial drug, and specific adverse events assessed during the trial.

Evaluation of Participant Blinding to Treatment

The research team member will ask patients which medication they believe they received throughout the study on post-operative day 3. The proportion of patients correctly guessing their treatment allocation in each group will be compared via a Chi-square test.