

Design and conduct issues in surgical clinical trials

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Abstract

The design and conduct of surgical clinical trials present unique challenges to the investigator that are not encountered in drug studies. Using the Veterans Affairs Cooperative Studies Program Hernia Trial as a case study, this article explores the potential problems and solutions. © 2004 Excerpta Medica Inc. All rights reserved.

In 1995, the American College of Surgeons (ACS) identified the opportunity to study a new technique's application to a well-established procedure (laparoscopic inguinal herniorrhaphy). A new collaborative effort among the ACS, Northwestern University, agencies within the National Institutes of Health (NIH), and the Veterans Affairs Cooperative Studies Program resulted in funding for 2 studies. The first study compared open mesh and laparoscopic herniorrhaphy and was funded by the Veterans Affairs Cooperative Studies program in 1998 [1]; the second study, compared "watchful waiting" with open mesh repair and was funded by the Agency for Healthcare Research and Quality (AHRQ) in 1999 [2]. Analysis of the design and conduct of the open versus laparoscopic hernia trial provides important information on issues, such as site selection, standardization of operative procedures, patient selection and enrollment, reporting of adverse events, and patient retention.

Case study

Definition of end points

All variables, including the primary end point, must be well defined. Death as an end point is easy to define and use, but the cause of death may be more difficult to ascertain. If death is not the outcome of interest, the outcome and how it is to be measured must be well defined in the study design. For the Veterans Affairs study, we postulated that surgeons

would not change practice based on better patient-centered outcomes (pain, return to activities) unless the recurrence rates were similar between the groups. Through focus groups of surgeons, we determined that a minimum clinically meaningful difference in recurrence rates was 3%, so we designed the study to enroll enough patients to show a 3% difference between the groups in recurrence rates. None of the secondary outcomes required as large a sample size to find meaningful results. Once the primary outcome was determined, we had to determine how recurrence would be measured. Although many patients would want a second operation, we did not want to make that a requirement to "prove" recurrence. Because there is no "gold standard" to determine recurrence outside of a second operation, we agreed that examination by 2 independent surgeons or confirmation of the recurrence with ultrasound would be sufficient if the patient did not want to have a repair procedure.

In the watchful-waiting trial, the primary outcome was more difficult to define because it could not be recurrence in both arms. Therefore, after many hours of deliberation and a resubmission of the grant proposal, we decided on a composite outcome: pain or discomfort interfering with usual activities and a physical component summary score on the 36-item short form (SF-36) health survey.

Site selection

Participating site selection must be based on several factors. First and foremost, the investigators at the site must have clinical equipoise about the question to be answered with the study. If the surgeons have strong opinions about which technique is better, selection bias can occur. The sites should also have enough volume to meet enrollment targets.

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In the case of a trial comparing 2 surgical techniques, a volume of at least twice that needed for target enrollment is needed. In the hernia trial, 3,518 of 4,769 (74%) of screened patients met the eligibility criteria. Of the 3,518 who met the criteria, 2,164 (62%) gave written informed consent to participate [3]. For most trials, subject enrollment is much more difficult. In particular, if the treatment arms are very different, recruitment between 10% and 25% of eligible patients should be expected. It is important to take into account the personality of the principal investigator (PI) and the nurse or research assistant at the site because it can affect the ability to recruit patients.

Standardization of procedures

If the trial includes a surgical procedure, the procedure will need to be standardized to the fullest extent possible. Videotapes and written descriptions should be agreed on at an initial meeting (which may or may not include a laboratory session). All surgeons participating, including resident surgeons, should review the written/videotaped procedures, both before performing their first few surgeries and at regular intervals. For the hernia trial, videotapes of the standardized procedures were available through the ACS video library [1]. Large-print versions of the operative technique were posted at the scrub sinks for review just before each procedure. Checklists to be completed at the end of each procedure should be developed. As many operative variables as possible should be standardized. They should also be recorded, preferably by the nurse or research assistant in real time. Review of operations by way of reading a sample or all of the dictated operative reports close to the time of the operation can reveal deviations from the standardized procedures that need to be corrected.

Patient selection and enrollment

When considering inclusion and exclusion criteria, the investigator should consider that the more restrictive the criteria, the harder it will be to recruit to the study, and the harder it will be to generalize the results. If the criteria are too broad, a significant finding might not be detected because the patients are too different from each another. Certain populations are in categories that require special review, such as children and prisoners. If the primary outcome to be assessed is not death, it is important to be sure to exclude patients who will not live long enough to assess the primary outcome. For instance, in the hernia study, we did not include patients who had a life expectancy of <2 years because our primary outcome measure was recurrence at 2 years. If the primary outcome is not death, the outcome and how it is to be measured must be defined carefully. Furthermore, to assess the outcome, it is essential to be able to find the patients. Therefore, those who will be inaccessible at the time of the outcome should not be enrolled. This is of particular importance if the population has any propensity to

incarceration, because special considerations exist for prisoners participating in clinical trials. Consider including a decision about whether to contact relatives or other resources in the event that the patient giving informed consent for the study cannot be found; it is a violation of privacy to make such contacts without the patient's explicit permission. Consider asking the patient for a contact person who will remain stable throughout the period of study (again, this should be explicit in the written consent).

Most clinical trials set enrollment targets and develop policies for sites with underenrollment or overenrollment. A reasonable policy for underenrollment is to place a site on probation if its enrollment is <75% of target. The site would be given a certain period of time to improve or risk losing support (eg, salary support for a nurse or assistant) or being terminated as a study site. When considering withdrawing a site after enrollment has started, the decision-making process will be directed by the number of patients already enrolled at that site and case management considerations. During the hernia trial, the status of a nurse at a particular site was reduced to half time. The salary gained from this was then distributed to 2 sites that were the highest recruiters. There can also be problems with overrecruitment. If a site accounts for a large proportion of the subjects, the results can be biased by the intricacies present at that site, creating problems with generalizability. The appropriate institutional review boards (IRBs) must be notified when overenrollment occurs.

Reporting adverse events

We developed guidelines for reporting serious adverse events to both the Hines Human Subjects Committee and the individual IRBs. A serious adverse event is any adverse event or reaction that results in (1) death; (2) a life-threatening experience (in the view of the investigator, one that places the subject at immediate risk of death from the event or reaction as it occurred); (3) inpatient hospitalization; (4) persistent or significant disability/incapacity; (5) congenital anomaly/birth defect; or (6) any other conditions that, based on medical judgment, may jeopardize the subject and require medical or surgical treatment to prevent any of the above measures. Specifically, we sent a copy of our serious adverse event reporting policy to each site IRB. Within the policy, we set forward our procedures for which events required reporting to local and central IRBs and in what time frame (Table 1). This provided guidance to the investigators on what to report immediately. Whenever there was a question, we chose to overreport to all entities rather than to underreport.

An end points adjudication committee can be very helpful in providing an unbiased opinion about outcomes and their relation to the intervention/study. Our end points committee reviewed each death and life-threatening complication to determine whether the cause of death was correct or

Table 1
Serious adverse event reporting guidelines

Event	Forward immediately to chair* and local IRB	Chair to disseminate immediately*
Death	Yes	Yes
Life-threatening event	Yes	Yes
Additional surgery for hernia repair after recurrence	Yes	No
ER visit not resulting in admission	No	No
Urinary retention resolved within 24 hr	No	No
Urinary retention requiring admission or not resolved within 24 hr	Yes	No
Hematoma requiring operation for evacuation	Yes	No
Hematoma or seroma requiring aspiration in clinic	No	No
Admission to hospital during course of study not related to operation	No	No
23-hr telemetry monitoring after operation to rule out MI. Patient did not have MI and is discharged the next morning.	No	No
Hospitalization for preexisting condition not related to the operation	No	No
Recurrence of the hernia	No	No
Admission to hospital before operation (but after randomization) for medical problems unrelated to the hernia	No	No
Delayed extubation after general anesthesia (patient extubated successfully after a couple of hours and sent home)	No	No

ER = emergency room; MI = myocardial infarction.

* Within 72 hours.

whether the life-threatening complication was truly a life-threatening event, and then whether either was related to the study. The people on this committee provided expertise from surgery, anesthesia, and pathology, but were not otherwise affiliated with the study. About halfway through our recruitment period, the data and safety monitoring board became concerned about safety for the subjects. A particular site had recorded 6 life-threatening complications. All were “hypotension requiring pharmacologic support.” The end points committee reviewed these and discovered a practice at this site of prophylactic phenylephrine drips for patients undergoing spinal anesthesia to prevent hypotension. The complications were determined by the committee to not be life-threatening. We discussed the practice with the site

anesthesiologists and asked them to refrain from this practice for study patients.

Patient retention

At our third annual meeting, we identified problems getting the patients to return for their 2-year visits (Fig. 1). We immediately instituted a retention policy (Table 2). This type of policy should be considered for implementation at the start of the study. Large numbers of dropouts can bias the results of a study and affect the researchers’ ability to detect differences, or the lack thereof. Institution of this policy and close monitoring of follow-up at each site resulted in success in determining our primary outcome (recurrence at 2 years) in 85% of patients.

Publications

As we thought ahead to the end of the study, the need to develop several publications to disseminate the results became apparent. The design of the study was enough to warrant publication [1]. Just after we concluded enrollment, we started discussions about what other publications would be necessary. We wanted to be able to disseminate the major results expediently at the conclusion of the study. We also wanted to seek out a journal with a high impact factor and readership. Once we decided on the venues for publication and presentation, we started writing the main document. A writing group was convened, first by a face-to-face meeting, and then through weekly conference calls. We used Internet resources (eRoom) to facilitate tracking of changes and drafts. As our target submission date neared, we increased the frequency and length of the calls. We developed a publications list that included target dates and journals, and identified which of the executive committee members was taking the lead. We have been successful in writing and editing these manuscripts via conference calls (usually weekly).

Communication and coordination

Paramount to the success of this trial was communication within the sites, within the study group, and with monitoring and funding entities. The PI at each site was instructed to have a weekly meeting with the site nurse coordinator. The site PIs and coordinators were encouraged to publicize the study during the enrollment phase to the primary care clinics and caregivers. The site PIs and coordinators met with the new resident physicians as they rotated onto the service to help them explain the study to the patients. We had regular national conference calls for the executive committee (monthly), site PIs and nurses (monthly), and nurses (weekly). Site PIs were encouraged to have a strong presence in the study. Site PIs called the study chair with any questions and to give timely notification about

Table 2

Retention policy: CSP #456 Retention policy, April 5, 2001

The following policy memo is proposed for CSP #456 to ensure uniform follow-up procedures and SF-36 data:

1. Hines will send out a list of patients who have missed their return visit (3-mo, 1 yr, 2 yr) to the individual sites. (Anita will do this.)
2. On a monthly basis, Hines will send out to the sites lists of upcoming patient appointments. (Anita will do this.)
3. The individual sites will report back to Hines when the patient does not show for his or her appointment. The sites will report back using a 1-page per patient form. This will be faxed to Hines.
4. Hines will make patient travel money available, after the site coordinators have tried, without success, to get the patient to make a return visit. The site will give this information to Hines, and decisions will be made on a case-by-case basis and after attempting to obtain travel funds at the local level. (Contact Anita.)
5. Site coordinators will make phone contact with each patient every 3 mo for the duration of the study.
6. A follow-up chart, by site, will be generated and reviewed during both the Executive Committee conference call and the investigator call each month. (Anita will do this.)
7. For patients who have been “lost” and for whom all efforts to find have been unsuccessful (ie, CPRS, DHCP, etc), communicate this information to Hines and the databases will be searched to try to locate. (Contact Anita or Sheldena.)
8. Patients may be examined for their 2-yr check up by a surgeon remotely if attempts to have the patient examined at the site and/or by a study surgeon are unsuccessful. The site PI will make the initial contact with the outside surgeon for individual patients and a \$50 fee will be paid to the surgeon upon receipt of the follow-up form. The surgeon selected should be a Fellow or Associate Fellow of the American College of Surgeons.
9. When necessary, the PI may travel to the patient’s location or may see patients during off hours.
10. Gifts of appreciation could include enclosing a calling card inside a birthday card as a token of appreciation for patient participation.
11. A certificate of participation will be given to each patient in the study at the 2-yr return visit.
12. Commitment by all involved is an essential part of this policy.

CPRS = computerized patient record system; CSP = Cooperative Studies Program; DHCP = decentralized hospital computer program; PI = principal investigator; SF36 = 36-item short form.

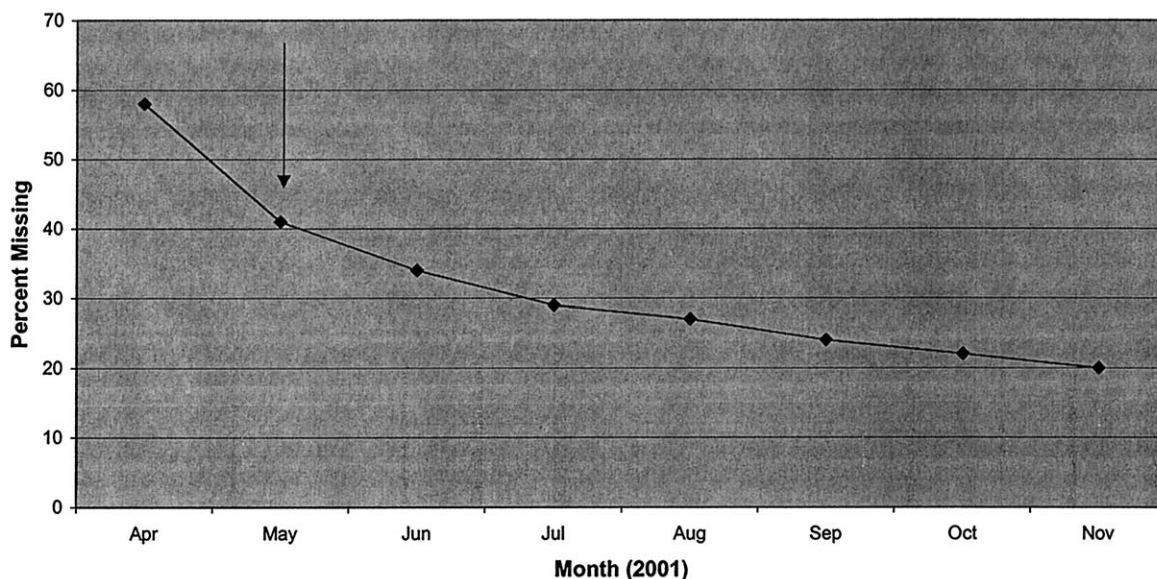


Fig. 1. The 2-year rate of missing visits. The arrow indicates implementation of retention policy.

any potentially serious event. The study chair then was able to notify appropriate entities of the event in real time, rather than waiting for an inquiry.

Conclusion

The Veterans Administration Cooperative Studies Program Hernia Trial was completed successfully [3] and is

considered a landmark trial [4]. Examination of the design and conduct of the trial reveals important points for investigators embarking on the design and implementation of surgical clinical trials. These issues include (1) adequate inclusion and exclusion criteria, (2) precise and measurable outcome variables, (3) standardization of protocols and procedures with methods in place to monitor, (4) anesthesia input early in the design, and (5) monitoring of important, controllable confounding variables. It is most important to keep the

end of the study in mind when making decisions about design, implementation, and changes during the study.

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