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A study design to assess the safety and efficacy of on-pump versus off-pump coronary bypass grafting: the ROOBY trial

Dimitri Novitzky[a], A Laurie Shroyer[b], Joseph F Collins[c], Gerald O McDonald[d], John Lucke[e], Brack Hattler[b], Elizabeth Kozora[b], Douglas D Bradham[c], Janet Baltz[b] and Frederick L Grover[b] for the VA #517 Randomized On/Off Bypass (ROOBY) Study Group

Background Since the late 1960s, coronary artery bypass graft (CABG-only) procedures were traditionally performed using a heart-lung machine on an arrested heart (on-pump). Over the past decade, an increasing number CABG-only procedures were performed on a beating heart (off-pump). Advocates of the off-pump approach expect to reduce many of the adverse side effects related to using the heart-lung machine, while advocates for the on-pump procedure raise concerns related to graft patency rates and long-term event-free survival for the off-pump technique.

Purpose The U.S. Department of Veteran Affairs (VA) Cooperative Studies Program funded a randomized, multicenter clinical trial comparing the clinical and resource-related outcomes following on-pump versus off-pump techniques for veterans undergoing a non-emergent CABG-only procedure. The planning committee was faced with several critically important challenges to assure feasibility of study costs and required sample size; generalizability to non-VA surgical practices; and comparability of clinically meaningful results. These challenges are discussed.

Methods This study is a prospective, randomized, multicenter, single blinded (patient) clinical trial that compares on-pump and off-pump techniques for veterans requiring non-emergent CABG-only procedures. There will be 2200 patients randomized at 17 VA Medical Centers when the five-year recruitment period ends on 15 April 2007. There are two primary objectives: a short-term objective to assess the immediate impact of the two techniques on 30-day mortality/morbidity and a long-term objective to assess one-year mortality/morbidity. Major secondary outcomes are one-year graft patency rates and change in neuropsychological assessments from baseline to one year. All patients are assessed at 30 days post-surgery or discharge from the hospital, whichever is latest, and at one-year post-surgery.

Results During planning, several key issues had to be decided. These included 1) choosing primary objectives: a short-term (30-day) and a long-term (one-year) objective were chosen; 2) choosing primary outcome measures: composite measures were selected to ensure sufficient end-points; 3) standardization of surgical techniques: minimal standardization required but guidelines and continuing discussions on both techniques provided; 4) establishing criteria for surgeons and residents for participation: surgeons required to have completed 20 off-pump procedures prior to doing study procedures and residents, in presence of study surgeon, capable of doing either procedure; 5) identifying metrics of cognitive dysfunction sensitive to treatment: a neuropshychologist hired who centrally

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monitors cognitive functioning testing; and 6) blinding participants of surgical procedure: attempt to blind participants.

Limitations Areas of concern are whether all surgeons sufficiently experienced on the off-pump procedure, should residents have been allowed to do study surgeries, should techniques have been standardized more and were the best neurocognitive tests selected.

Conclusion The study design presented allows for a balanced and fair assessment of the on-pump and off-pump CABG procedures across a diversity of clinical outcomes and resource use metrics. Its results have the potential to influence clinical cardiac surgical practice in the future. *Clinical Trials* 2007; **4**: 81–91. http://ctj.sagepub.com

Introduction

According to the American Heart Association's [AHA] 2005 update, 13 million Americans have coronary artery disease (CAD) [1]. The AHA 2005 report indicates that cardiovascular disease is the number one killer in the United States each year, representing 38.0% of all deaths. Adverse events related to cardiovascular disease include but are not limited to: death, myocardial infarction, stroke, and/or angina symptoms. There is a wide range of adverse impacts that CAD may have upon any individual's health status including premature permanent disability.

Common therapeutic approaches for CAD patients include medical therapy, percutaneous coronary interventions (PCI), coronary artery bypass graft (CABG-only) procedures and combined CABG/PCI procedures. According to AHA data for 2002, there were 1 204 000 PCIs and 515 000 CABG-only procedures performed [1] with the CABG-only procedure estimated at $69 853/case. CABG-only procedures represent a high-volume and high-cost CAD patient treatment alternative.

Since the 1960s, CABG procedures have been performed using cardiopulmonary bypass (CPB) with cardioplegic arrest [2–4]. Over the past several years there has been a great deal of attention given to performing CABG without CPB (off-pump). Advocates for the approach claim that it will reduce many of the adverse side effects, morbidity, and mortality associated with the use of the CPB machine [5–10]. On the other hand, the off-pump technique has been questioned related to concerns that it is technically more difficult to perform precise coronary anastomoses in a field that is not totally still and bloodless, that new graft patency rates may be not as good, and that long-term results (eg, graft occlusion and restenosis rates) probably will be less favorable than with on-pump procedures [11–14].

Since the peer-reviewed literature suggested that technical equipoise exists between the on-pump and off-pump procedures and that use of the off-pump procedure has grown to about 20% of CABG-only procedures with in the U.S. Department of Veterans Affairs (VA), the VA funded the Randomized On/Off Bypass (ROOBY) trial. To facilitate future similar trials, this article discusses the design challenges faced by the study's planning committee and presents the trial's final study design.

Overview of ROOBY trial

The ROOBY trial is a prospective, randomized, multicenter, single-blinded (patient) study that compares on-pump and off-pump techniques for veterans requiring non-emergent CABG-only procedures. Funding was initiated in October 2001, with patient recruitment beginning in April 2002. Given a five-year recruitment period and a one-year patient follow-up, the study is scheduled to be completed by April 2008. There will be 2200 CABG-only patients randomized to either the on-pump or off-pump procedure at 17 VA Medical Centers.

The study has two primary objectives. The short-term objective is to assess the immediate impact of the two surgical techniques on early clinical outcomes (a 30-day mortality/morbidity composite). The long-term objective is to assess a one-year mortality/morbidity composite for the two procedures. The major secondary hypotheses concern the completeness of revascularization and the graft patency/stenosis rates. A cardiac catheterization is completed on all available patients at one year and submitted to a central reading laboratory where it is read in a blinded fashion. Other secondary objectives are in the domains of 1) change in neuropsychological assessments from baseline to one-year, 2) traditional clinical operative assessments (ie, 30-day and one-year mortality, 30-day individual morbidities), 3) disease-specific and general health related quality of life, 4) system resource use, and 5) cost effectiveness.

After preliminary consultation and screening with a potential participant's clinical team, the participating site's research nurse approaches each non-emergent patient scheduled for a CABG-only procedure to discuss the study. After providing the participant adequate time to read the documents and to ask any questions, the research nurse obtains

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informed consent and collects all of the baseline assessments. Randomization to either the on-pump or the off-pump technique, stratified by study surgeon, occurs at the time of the operation. After surgery, perioperative and discharge assessments are conducted at 30 days or discharge from the hospital, whichever is latest. Patients receive phone calls every two months until 12 months post-surgery, when they are seen at clinic.

Unique challenges of surgical trials

Unlike FDA drug, device or biologics trials, the design and conduct of surgical interventional trials require standardized interventions with flexibility for individual surgeon discretion in specific aspects. Given that surgeons tend to evolve their surgical approaches based on their training and historical experiences, there were several unique challenges to be addressed in the ROOBY trial. During the study planning process, the Planning Committee was required to resolve several critically important issues.

Objective(s)/outcome(s)

In planning the ROOBY trial during 2000, the first challenge raised was the primary objective(s) for the study. Up to that time, no randomized controlled trials of off-pump procedures had been published. The literature contained a number of reports of surgical experience with the technique in up to 700 patients [15–24], mostly from South America and Europe. Types of patients selected for the procedure and outcomes of 30-day mortality and morbidity (traditional cardiac surgery outcome measures) were reported. Mortality statistics compared favorably to on-pump statistics, however, there were reports of some off-pump patients with recurrent angina symptoms over the course of the months following surgery [15,21]. This was thought to be related to incomplete revascularization of the heart. By 1996, retrospective comparisons of on-pump and off-pump cohorts began to appear in the literature [16–19,21]. Again using traditional 30-day mortality and morbidity measures, the off-pump procedure was found to be safe with non-statistically significant mixed results in mortality. Morbidity was equivalent or lower, with sicker patients appearing to benefit most from the off-pump procedure. Myocardial infarction within 30 days of surgery, indicating failure of a graft or incomplete revascularization, showed equivalent or better results in most but not all trials. Blood usage, ventilator time and overall length of stay appeared to be better in most studies with mixed degrees of benefit. Because longitudinal studies of coronary artery bypass surgery (on-pump) had been done, it is known that a certain percentage of grafts will fail over time, with greater failure in vein conduits as compared to arterial conduits [12]. Therefore, surgeons warned that the survival benefit of the procedure has not been demonstrated. Few studies through 2000 followed off-pump patients beyond six months.

The ROOBY planning committee's debate centered about the relative importance of short-term versus long-term success. The short-term safety aspects of the surgical procedures themselves were considered of high importance. Although the Planning Committee recognized that short-term endpoints had to be included in the comparison of on-pump and off-pump procedures, the long-term concerns for the off-pump procedure (graft patency) also needed to be addressed. To pragmatically balance both practice and policy implications, the ROOBY planning committee decided that two primary objectives – both a short-term event-free endpoint and a long-term event-free endpoint, were essential to assess overall ROOBY study success. The choice of the primary outcome measures for each objective was critical to both the study's feasibility (sample size considerations) and the acceptability of the results. Composite event-free endpoints were selected based on the mortality and morbidities that were felt to differentiate the two procedures in the literature (eg, short-term morbidities and one-year morbidities) and to assure both safety and durability of study treatments performed.

For the short-term objective, mortality alone was considered. However, the expected mortality from either surgical procedure was expected to be very small ($<3\%$) so that finding a meaningful difference between the treatment groups would require several thousand patients, which was considered impossible to recruit in a reasonable time frame. To have enough events occur to be able to find a meaningful difference with a reasonable sample size, it was decided to use a composite measure comprised of mortality and major morbidities. To select the morbidities to be included in the composite score, the VA's Continuous Improvement in Cardiac Surgery Program (CICSP) [25] surveyed all Chiefs of CT Surgery for VA cardiac surgery programs nation-wide on the 13 morbidities routinely collected in the program. They rated each of these morbidities on whether they would be willing to have the trial terminated early if there was a difference between the treatment groups for the morbidity. Based on their ratings, six major morbidities were added to mortality for the short-term primary outcome measure. These included 1) repeat cardiac surgery, 2) new mechanical support, 3) cardiac arrest requiring cardiopulmonary resuscitation, 4) coma for $\geq$24 hours, 5) stroke, and 6) renal failure requiring dialysis.

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Another concern with the short-term outcome measure was that patients who did poorly after surgery and were still hospitalized more than 30 days after their surgery would not have all of their surgery related complications or deaths reported. Thus, this short-term outcome measure was expanded to be 30 days or discharge from hospital, whichever was latest. While this could be considered a bias for finding more events, we felt that it was more important to determine all direct surgery related morbidities and deaths.

For the long-term objective, several measures were considered. These included mortality, a composite of mortality and morbidities, and one-year graft patency rates. As with the short-term primary measure, mortality alone was too rare to find clinically meaningful differences with a feasible sample size and trial duration. While graft patency was a major concern for the off-pump procedure, it was felt to be a surrogate for safety and durability of study treatments that could be measured more directly. In addition, at the time, there were no good estimates of expected one-year graft patency rates for the on-pump procedure to use in estimating the required sample size. This measure was, therefore, designated as the study's major secondary outcome measure. A composite measure of: 1) death at any time during the one-year postoperative period, 2) myocardial infarction (MI) occurring after 30 days post-study operation or discharge, whichever is latest, and prior to one-year, and 3) a subsequent revascularization procedure (PCI or CABG) during the same time as for MI in # 2) was chosen as the primary outcome. This measure evaluates both safety (mortality and MI) and duration (need for a subsequent revascularization procedure) directly.

The two primary hypotheses evolved to be:

1) *Short-term null hypothesis*: For patients having CABG-only procedures performed, there will be no difference in the short-term composite clinical outcome (30-day death or major morbidity) between patients randomized to the on-pump and off-pump procedures.
2) *Long-term null hypothesis*: For patients undergoing CABG-only procedures, there will be no difference in long-term clinical outcome as measured by one year mortality and/or acute myocardial infarction prior to one-year and/or a subsequent revascularization procedure within one year between patients randomized to the on-pump and off-pump procedures.

To be comprehensive in assessing the relative treatment efficacy, endpoints were added for assessing the one-year coronary completeness of revascularization, as well as evaluating coronary artery-specific graft patency; one-year neuropsychological status; one-year change from baseline in self-report quality of life measures (SF-36V) [26,27]; and one-year change from baseline for disease-related measures (Seattle Angina Questionnaire) [28]; as well as the marginal difference in the resource utilization and cost effectiveness of the on-pump versus off-pump approaches before one-year. Table 1 gives a comprehensive listing of all of the outcome measures.

Standardization of surgical technique

Another planning committee question focused on what degree of standardization should be established for the two surgical techniques being studied? The committee debated how, in a multisite trial, to balance the need for uniformity and consistency and to eliminate confounders, with the need to allow surgeon-specific variability on issues other than the use of the on-pump versus off-pump procedural requirements. On the one hand, the procedure had to be defined well enough in the protocol so that surgeons were taking a generally acceptable, but similar, approach to their operative technique. On the other, the protocol could not be so rigid as to be impractical and not generalizable to real world surgical practice where variations occur in surgical technique. Descriptions of surgical technique from the literature, including stabilization devices for off-pump, were considered in the context of surgical experience of the primary investigators [15–24]. Among the range of possible surgical approaches, median sternotomy, the safest, most widely used approach, was mandated. Monitoring of patients during the surgery was standardized to assure that equivalent information was available for patient management. Because variations occur in heparinization for the procedures and evidence existed for a pro-coagulant effect in off-pump [29], anticoagulation was standardized to that required for on-pump surgery.

Guidelines and discussions on the surgical techniques were provided to the study surgeons on both techniques, but the surgeons were given much flexibility and use of discretion to ensure that their choice of technique would ensure that patient safety concerns came first. Considerable detail on specific technical details was built into data collection to allow exploration of various techniques and their impact on fine details of the outcomes. For the on-pump group, it was decided that the CPB machine would be used in a 'standard fashion' for each participating surgeon and institution. For the off-pump technique, no CPB machine would be used, but one would be on stand-by in case it was needed. The key aspects for both the on-pump and off-pump procedures include 1) exposure, 2) motionless and bloodless surgical

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Table 1 Outcome measures

I. Primary Outcome Measures
- A. Short-Term Primary Outcome Measure
  A composite measure of 1) death, 2) repeat cardiac surgery, 3) new mechanical support, 4) cardiac arrest requiring cardiopulmonary resuscitation, 5) coma for ≥24 hours, 6) stroke, or 7) renal failure requiring dialysis occurring either in-hospital or within 30 days of surgery, whichever is latest.
- B. Long-Term Primary Outcome Measure
  A composite measure of:
  1. Mortality during one year postsurgery.
  2. Acute myocardial infarction after 30 days postsurgery or discharge from hospital, whichever is latest, and prior to or at one year postsurgery.
  3. Any revascularization procedure after 30 days postsurgery or discharge from hospital, whichever is latest, and prior to or at one year postsurgery.

II. Major Secondary Outcome Measures *(baseline and one-year)*
- A. Number of planned grafts (by anatomic regions of the heart)
- B. Number of grafts actually performed (by anatomic regions of the heart)
- C. Fitzgibbon Patency Class [41] by graft source and site
- D. Most severe stenosis (%) by graft source and site
- E. New >70% lesion within 1 cm of anastomoses by graft source and site

III. Secondary Outcome Measures (baseline and one-year)
- A. Neuropsychological Measures
  1. Wechsler Memory Scale-Third Edition (WMS-III), Logical Memory Test I and II [23]
  2. WMS-III Faces I and II [23]
  3. Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Span Subtest [23]
  4. WAIS-III Digit Symbol Subtest [23]
  5. Trial Making Test [24]
  6. Clock Drawing [25, 26]
- B. Traditional Clinical Measures
  1. 30 days or prior to discharge, whichever is latest, mortality
  2. One year survival rate
  3. 30-day or prior to discharge, whichever is latest, morbidities individually
     a. the six morbidities included in short-term primary outcome measure
     b. Perioperataive myocardial infarction
     c. Reoperation for bleeding
     d. On ventilator >48 hours
     e. Endocarditis
     f. Mediastinitis
     g. Tracheostomy
  4. Individual Items of Long-Term Primary Outcome Measure
- C. Quality of Life Assessments *(baseline, three months and one-year)*
  1. Health Related–SF36V from Veterans Health Survey Project [20,21]
     a. Physical Component Summary
     b. Mental Component Summary
  2. Disease Related Health Status – Seattle Angina Questionnaire [22]
- D. System Resource Use
  1. Inpatient Hospital Resource Use
     a. Operating room time
     b. Blood product utilization
     c. Postoperative extubation and reintubation times
     d. ICU length of stay
     e. Pre- and postoperative length of stay
  2. Readmission within 30 days postdischarge
- E. An economics sub-study, will document several outcomes, if the one intervention is shown to be more effective:
  1. Relative cost of the two interventions (cost of production).
  2. Relative differences in healthcare impact in use and expenses during the surgical admission, and the first 30 days, (immediate-term outcomes).
  3. Relative differences in healthcare consequences (ie, use and expenses) during the first year post-surgery (short-term outcomes).
  4. Relative net cost impact, which offset the cost of production with any healthcare cost savings achieved.
  5. Relative and incremental average cost-effectiveness.

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field, 3) hemodynamic stability, and 4) complete myocardial revascularization. Beyond these minimal requirements, discretion was given to the surgeon as to which anatomic region of the heart should be revascularized first as well as the nature/timing of sewing the distal and anastomotic graft sections during the operative procedure since these are dependent on such factors as a detailed assessment of the coronary angiogram, severity of the coronary occlusions, and a careful assessment of the collateral circulation. For patient safety reasons (eg, calcified aorta, poor exposure, hypotension), surgeons may convert a patient to the non-randomized technique.

Criteria for surgeon/resident participation

Given the off-pump approach was relatively new and not widely adopted at the start of the ROOBY trial, surgeon and/or resident eligibility for participation were challenging topics of debate. A minimal off-pump 'experience' for a surgeon to participate in the ROOBY trial was discussed, as concerns existed that there may be a 'learning curve' associated with performing the off-pump technique. Given historical practice and training program approaches, it was assumed that staff cardiac surgeons at the participating centers would be experienced in the on-pump procedure. However, the relative new entry for the off-pump procedure into the field of cardiac surgery did not assure that all of the staff surgeons (and/or their trainees) would have sufficient expertise in the off-pump procedure to be equivalently technically competent in both surgical approaches. To provide the off-pump procedure an optimal chance of being identified an efficacious approach, it was felt that a minimum number of 20 cases performed off-pump for each study surgeon (with at least three cases where full and complete revascularization had been achieved in all anatomic regions of the heart) had to have been completed prior to study participation.

Interestingly, the more contentious aspect of surgeon participation was whether to insist that all study surgeons had to do both study procedures or to allow some surgeons to do only on-pump cases and others do only the off-pump cases. The argument for the latter case was that the best surgeon for a particular procedure would do that procedure. This approach would also allow more surgeons at a center and more centers across the VA to participate, which would in turn expand the generalizability of the ROOBY trial's enrollment. Since more surgeons would be eligible to participate in the latter case, there would be a larger patient pool for inclusion into the study, which would make patient recruitment easier.

To assure equipoise and that a treatment by surgeon or treatment by center effect was not a confounder, the argument for having surgeons doing both procedures is that it would rule out any biases that surgeon-specific skill levels might have an effect on outcome. At the merit review committee presentation, it was decided that all study participating surgeons must be capable of doing both on-pump and off-pump procedures for any patient randomized. The protocol was then changed to randomize patients within a surgeon within a participating center.

Since many of the potential participating centers were teaching hospitals, there was concern by both the review committee and the site investigators about the role of residents in the study. Because of the potential loss of patients at those sites having residents, it was decided that residents would be allowed to assist the study surgeon or to perform the study procedures under the guidance of the study surgeon. However, if the resident was assisting or performing the surgery, this decision had to be made prior to the randomization so that the resident would have to be capable of doing either type of procedure. This is being monitored to ensure that residents are doing both types of surgery.

Identifying metrics of cognitive dysfunction sensitive to treatment

One of the most compelling reasons to consider using the off-pump technique is to avoid the deleterious effects of bypass on the patient's cognitive function, which has been the subject of a growing body of literature [2,5–10,30–34]. While our primary study outcomes focused first on safety of the procedure, it was felt that completeness of revascularization and graft patency might most appropriately be weighed against cognitive functional status. Studies indicated there might be less neuropsychological impact for off-pump patients in the early postoperative period, but with improvement in cognitive function over time in on-pump patients, the differences in function might equalize over the course of a year [30–34]. Testing for such deficits has been problematic in previous studies. Not only were the best neuropsychological measures under debate, but the quality and standardization of testing has been an issue. While tests used in previous studies were considered, the most appropriate measures of cognitive dysfunction in ROOBY were based on expertise of our clinical neurophysiologist. These measures included: the Logical Memory (LM) subtest from the Wechsler Memory Scales-Third Edition (WMS-III) [35]; the Faces subtest from the WMS-III; The Digit Span subtest from the WMS-III; the Digit Symbol Subtest from the Wechsler Adult Intelligence

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Scale-Third Edition (WAIS-III) [35]; the Trail Making Test, Parts A and B [36]; the Clock Drawing [37, 38]; and the Beck Depression Inventory [39]. To be able to control for baseline differences when calculating baseline to one-year follow-up changes in cognitive status, patient education level, patient effort and a series of 10 medical history questions were captured including neurological history (ie, head injury or other neurological disease), learning disability, substance abuse, current medication use and previous neuropsychological testing.

Blinding of study treatment arm until study termination

Given that the patient care team could not be blinded to the patient treatment arm, a single-blind (patient) study was discussed. It was unknown if the clinical care team would be compliant if instructed not to inform the patient or family of the use or non-use of the heart lung machine. Although desirable, the surgeons and cardiologists on the planning committee believed that it was highly unlikely that patients could be kept blinded, particularly once their care was beyond the cardiac surgery program. Given that the primary outcome measures were relatively hard end-points, it was originally decided not to blind the patients to their treatment group. The review committee, however, felt that it was important to attempt to blind the patients even though they admitted that it would be difficult. Maintaining equipoise at the study core laboratories for neuropsychological testing and reading of cardiac catheterization was always considered essential. Therefore, all patient information processed at these laboratories is accomplished in a blinded fashion. A recent meta-analysis [40] indicated that only four of 37 randomized controlled trials on off-pump CABG employed single-blind outcome assessment.

Other design and methods considerations

Patient population

All veterans (including woman and minorities) providing informed consent that require either an elective or stable urgent CABG-only surgical procedure are eligible to be enrolled. Exclusion criteria were kept to a minimum to ensure generalizability without endangering the patients. A number of early off-pump articles note the importance of appropriate patient selection for good outcomes [16–24], however reasons for exclusion varied. Most uniformly accepted the exclusion reasons of small target vessels (with some variation in suggested minimal size) and diffuse disease. Off-pump procedures for redo cardiac surgery and left main disease were controversial. As hemodynamic stability during the procedure is crucial, tolerance for higher risk patients varied across studies. The availability of an exclusion choice for 'Clinical care team has reservations' served as a safety mechanism in the randomization process and a way to identify other common reasons surgeons would systematically or individually exclude patients from the procedure. Emergent and salvage patients were excluded to eliminate likely confounders to the outcomes evaluation. Patients with significant valve disease were excluded to eliminate possible concomitant valve procedures and confounders related to symptoms and functional status. Table 2 lists the trial's detailed exclusion criteria.

Randomization

Randomization is done separately for each study surgeon to ensure that each surgeon is doing about the same number of both study procedures. To ensure that the surgeon for whom a patient's randomization occurs is the one that actually performs that surgery, randomization does not normally occur until the patient is in the operating room suite (ideally just prior to the induction of anesthesia). Even doing this, there have been a few instances where, after randomization, a study surgeon has had to leave for another emergency case and another study surgeon has had to do the case. Randomization is completed by calling the study's Data Coordinating Center's automated telephone randomization system.

Table 2 Exclusion criteria

1) Any patient requiring valve surgery combined with CABG.
2) Patients who are emergent, hemodynamically unstable, or in cardiogenic shock preoperatively.
3) Patients with moderate to severe valvular disease.
4) Patients enrolled in a different therapeutic study (without a special exception approved).
5) Patients with angiographic documentation of a majority of diffusely diseased distal vessels or of small target coronary arteries (<1.1 mm) that the surgical team agrees cannot be bypassed adequately in either arm (or both arms) of the study.
6) After discussion with, and approval from, the Denver VA Medical Center Chairman's office, any patient that the clinical care team has reservations about including in the study [with a clear clinical rationale documented, such as a unique risk-factor profile predisposing to adverse events].
7) Patients with a history of non-compliance with follow-up appointments.
8) Patient-stated preference for one treatment arm over another.
9) Inability or unwillingness to provide informed consent.

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Patient participation

The ROOBY patient's flow through the study is given in Figure 1. Baseline, perioperative and discharge assessments are conducted including details of the surgical procedures, complications, relevant laboratory and diagnostic test evaluations, as well as short-term outcome endpoints. Every two months following surgery until one-year postoperation, the local study research nurse calls the participant to determine whether they are having any problems or have had any study endpoints. Endpoints are also verified and/or obtained through use of various VA databases. These follow-up calls also serve to remind patients that they are still in the study.

Patient self report questionnaires, the SF36V from the Veterans Health Survey Project [26, 27] and Seattle Angina Questionnaire [28], are completed at baseline and one-year. They also are mailed to study participants at three months post-surgery. At the time of the four month telephone call, the nurses encourage patients who have not completed these two self-report measures to complete and submit them. The 10-month follow-up call is used to coordinate the one-year follow-up visits including scheduling the cardiac catheterization and neuropsychological assessments. Pending no clinical contraindications and a separate consent, a cardiac catheterization is performed on patients at the one year clinic visit to assess the change in native vessel and graft patency. Other one-year assessments include the follow-up assessment of neuropsychological status, repeat self-report symptom status and health related quality of life measures, subsequent resource utilization, laboratory studies, EKG, echocardiogram and an assessment of effectiveness of patient blinding. Patients receive a small payment ($50.00) for the expense of returning to the clinic for this one-year follow-up visit.

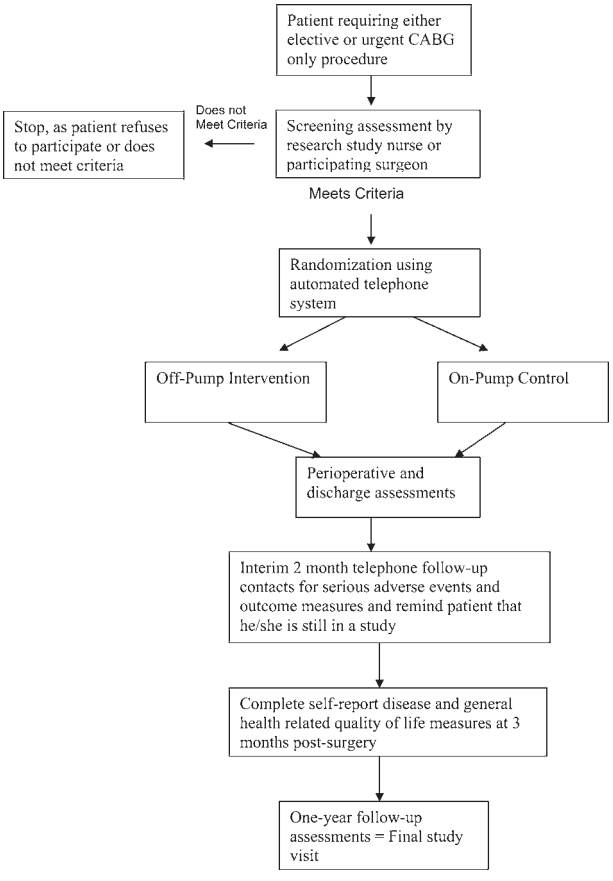

Figure 1 Patient flow in ROOBY trial

Sample size

Sample size was determined for each of the two primary outcome measures separately and the largest of the two was selected for the study. Estimates for the percent of patients expected to have early and one-year clinical outcomes in the control group (on-pump) were based on observed results from the CICSP database at the 26 VA medical centers that had >20 off-pump procedures over a three-year period (1 October 1997 to 30 September 2000) for the early measure and over a 1.5 year period (1 October 1997 to 1 April 1999) for the one-year measure. Differences to be sought between treatment groups were chosen to be clinically meaningful, but still allow for a feasible study, which was considered to be about 2 000 participants.

For the early clinical outcome, the CICSP data indicated that 14% of the on-pump patients could be expected to have an early mortality/morbidity outcome. The planning committee felt that a 30% reduction (14% versus 9.8%) in the off-pump group would be a reasonable and clinically relevant difference to detect. Using this difference, a two-sided continuity-corrected chi-square test with Type I error of 0.05 and power of 0.80, a sample size of 979 patients per group or 1958 total patients was determined. For the one-year clinical outcome measure, the CICSP data indicated that about 8% of the on-pump patients would have such an outcome. For this measure, the planning committee felt that a 40% reduction (8% versus 4.2%) could be detected. While a 40% reduction may seem high, the actual reduction of 3.2 percentage points is fairly small but one that is large enough to be clinically meaningful. Using this expected difference, a two-sided, continuity-corrected chi-square test, Type I error of 0.05, power of 0.80 and a 10% loss rate, a sample size of 1088 patients per group or 2 176 patients was determined. This was raised to 2 200 to allow for a larger than expected loss rate. A four-year enrollment

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period was planned based on 17 centers averaging 2.7 patients enrolled per month. However, due to less than expected recruitment, an extension of up to five years enrollment was sought and approved.

Analysis plan

Baseline comparability between the two treatment groups will be evaluated with respect to disease characteristics (eg, NYHA functional class, comorbidites), demographics (eg, age, race, gender) and baseline values of self-report measures (eg, SF-36 and Seattle Angina Questionnaire subscales). Chi-square and analysis of variance techniques, as appropriate, will be used for these comparisons. Any variable that appears to be different between the treatment groups ($P < 0.10$) and related to outcome will be considered as a potential covariate. As traditional with randomized controlled trials, the two primary outcome measures will be analyzed as intent-to-treat analyses (ie, patients will be analyzed in the groups that they were randomized to regardless of which surgical procedure they actually received). Subanalyses, however, are preplanned to evaluate the impact of conversions between treatment arms. The primary statistical test for each will be the continuity corrected chi-square test unless a covariate is needed. Then either a Mantel–Haenszel chi-square test or a multivariate logistic modeling approach will be used. Secondary outcome measures will be analyzed appropriately with Wilcoxon (Mann–Whitney) two sample tests used for the major secondary outcome measures, chi-square techniques and life table techniques used for the traditional clinical mortality/morbidity measures, including the one-year primary outcome measure, and analysis of covariance techniques for the quality of life measures.

Study organization

The study is being conducted at 17 VA medical centers. Each center was expected to have at least two surgeons who met the criteria of having performed at least 20 off-pump CABGs. However, two sites only had one qualified participating surgeon, while the others had two or more. Each site has a full-time study-funded nurse coordinator. The Co-Chairperson's offices are located in Denver, CO and Tampa, FL, with the main office for the study coordination being located in Denver. Administrative, biostatistical, economic, and data management support is being provided by the Cooperative Studies Program Coordinating Center (CSPCC) at the Perry Point, MD VA Medical Center. An Executive Committee, composed of the three Co-Chairpersons, the study biostatistician, two participating study surgeons, the heads of the two core laboratories, the study's health economist and two outside consultants, constitutes the primary decision-making body for the study. In addition to monthly conference calls, the Executive Committee meets at the annual Study Group meetings to review study and sites progress and to resolve any study issues that arise.

Two central core laboratories were established at the Denver Co-Chairperson's Office. The first provides central reading of the baseline, interim and one-year follow-up catheterization imagings to determine graft patency/stenosis in a blinded, unbiased fashion. The second core center provides training of study staff on how to conduct the neuropsychological core lab assessments and, by monitoring the site data, to ensure that the nurses continue to properly administer the neuropsychological testing in standardized manner. Finally, this neuropsychological core lab receives the raw study data and provides the CSPCC with the final scored data rated in a blinded, unbiased fashion.

Study approval and ongoing monitoring

Initially, the ROOBY trial was approved by the VA's Cooperative Studies Scientific Merit Review Board at its 10 May 2001 meeting. Prior to it being funded in January 2002, it was also approved by the CSPCC's Human Rights Committee (HRC), a central ethical review committee, and by each participating center's local Institutional Review Board (IRB). The HRC and local IRBs also review the study annually. An independent Data and Safety Monitoring Board (DSMB), reviews study progress at annual meetings and receives study progress reports at six month intervals. The DSMB is comprised of two cardiac surgeons, a cardiologist, an anesthesiologist, a primary care physician, and two clinical trials biostatisticians. Each time it meets, the DSMB makes recommendations to the Director of the VA's Cooperative Studies Program on whether the study should be continued based on study progress and interim outcome analyses and on whether any protocol changes and/or subprotocols proposed by the study investigators should be approved.

Discussion

The ROOBY trial will compare two surgical techniques – on-pump versus off-pump approaches – for performing CABG-only procedures across 17 participating centers. Inherently, surgical-based multicenter studies present a number of challenges that investigators must consider when planning such a study. While no research study design is perfect, the

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ROOBY trial's study design as presented in this manuscript allows for a balanced and fair assessment of the two types of CABG procedures across a diversity of clinical outcome and resource use metrics.

Given the large coordination efforts and high costs involved, it is anticipated that the ROOBY study will be the first (and perhaps only) multicenter prospective, randomized, controlled clinical trial to comprehensively evaluate the relative efficacy of on-pump versus off-pump CABG-only procedures. In view of the one-year cardiac catheterizations performed across 17 VA cardiac surgery centers, ROOBY will uniquely address the recent questions raised related to graft patency, completeness of revascularization and the consequences of incomplete revascularization. Using a comprehensive clinical outcomes assessment, combined with an economic utilization and resources analysis, ROOBY findings have the potential to influence clinical cardiac surgical practice in the future.

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