Department of Veterans Affairs Cooperative Studies Program Network of Dedicated Enrollment Sites Implications for Surgical Trials

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**IMPORTANCE** Surgical clinical trials have played a critical role in shaping clinical practice, yet their launch and conduct remain challenging. Innovative approaches to carrying out such studies can not only help transform how trials produce definitive evidence but also move the field toward increased participation in trials.

**OBJECTIVE** To review a recently launched pilot program aimed at enhancing patient enrollment and improving surgical trial operations at individual sites and nationally.

**SETTING AND PARTICIPANTS** After a solicitation to create a national network focused on making the conduct of clinical trials more efficient, 10 Department of Veterans Affairs (VA) sites were selected. These sites, collectively called the Cooperative Studies Program (CSP) Network of Dedicated Enrollment Sites (NODES), were evaluated with regard to their previous participation in CSP multisite trials, the strength of the local clinical research environment, and presentation of innovative plans to coordinate and enhance the operations of local CSP studies and share best practices with other centers. Node accountability was also emphasized and involved metrics that tracked productivity and efficiency.

**RESULTS** Building from available CSP experience in a range of clinical trials, including ones involving surgical interventions, NODES provides VA surgeons with resources for facilitating timely study initiation, determining patient availability, and addressing enrollment barriers. Such resources are particularly important for surgical studies, which often face challenges in patient recruitment and retention. In addition, NODES can maintain qualified and trained personnel at sites to support surgeons with limited time to fulfill the numerous administrative and regulatory responsibilities that often fall to the investigators.

**CONCLUSIONS AND RELEVANCE** The VA’s approach to enhancing trial efficiency may reinvigorate interest in surgical trials by offering a redesigned cooperative framework that builds on a core of high-yield sites and could mitigate traditional limitations of surgical trials.


T
here are significant challenges associated with orchestrating multicenter randomized clinical trials in surgery.\textsuperscript{1,2} Difficulties occur at the trial launch stage and during study conduct. Recruiting study sites, establishing the necessary infrastructure at these sites (eg, hiring coordinators and securing office space), and obtaining institutional review board approvals can significantly delay study start-up. A recent review of surgical and nonsurgical cancer trials funded by the National Cancer Institute found that the time to launch by the National Cancer Institute found that the time to launch a new trial was more than 2½ years and increasing.3 In many trials, problems in patient enrollment necessitate extending the study, which, in turn, requires additional resources and delays the reporting of trial results.\textsuperscript{4} Some studies are stopped prematurely because of difficulty in recruitment;\textsuperscript{5} for example, most trials of surgical ablation for atrial fibrillation were terminated because of lack of enrollment. Other problems that occur during study conduct include study staff turnover and inadequate follow-up of study patients.

Clinical equipoise is an essential factor in the willingness of physicians to enroll their patients in trials. Ensuring surgical equipoise is not an easy proposition and, traditionally, the culture of surgical research has not always embraced clinical trials. Some trials may involve different medical disciplines, and disagreement may arise over identifying suitable patients for the study, which...
requires creating equipoise across disciplines and forging multidisciplinary cooperation in referring patients to and enrolling them in clinical trials. For example, enrollment in a trial of transurethral resection of the prostate vs watchful waiting in men with moderate symptoms of benign prostatic hyperplasia required the cooperation of urologists and primary care physicians. Similarly, successful enrollment in a trial of coronary artery bypass grafts vs percutaneous coronary angioplasty with drug-eluting stents was predicated on cooperation between cardiothoracic surgeons and cardiac interventionists.

The mounting regulatory obligations associated with research and the diminished opportunities for funding are realities facing any investigator contemplating research. At the same time, the explosion in the knowledge base underlying medicine and the development of new drugs, procedures, surgical instruments, and devices make it even more pressing than ever before to conduct trials that can determine what is best for our patients.

Having an infrastructure and process in place can help mitigate many of the problems that face the surgical investigator. Over the years, the Veterans Affairs Cooperative Studies Program (CSP) has successfully conducted multiple large-scale clinical trials, including some seminal surgical trials. This established infrastructure includes biostatistical and data processing centers that specialize in the design, conduct, and analysis of trials; expertise in drug and device procurement and management; and facilities for genetic biospecimen collection, storage, and analysis. The CSP also draws on the unparalleled field asset of more than 110 research-capable Department of Veterans Affairs Medical Centers (VAMCs) and their academic affiliates. Recruitment sites for studies are selected from among VAMCs and other collaborating sites that have an appropriate patient population, eligible clinical investigators, and a research environment conducive to achieving study goals. Perhaps most important, these elements are devoted to a common mission of providing the best care possible to the veteran patient population.

Given the many challenges inherent in conducting clinical trials, CSP launched a pilot initiative to enhance study planning, trial implementation, and patient enrollment and improve its operations at trial sites. The Network of Dedicated Enrollment Sites (NODES) is intended to supplement the existing CSP infrastructure by establishing more permanent representation at select clinical facilities tasked with achieving consistency and efficiency in the conduct of trials at the site level. For surgical studies, the ability to achieve these goals is critical if findings are to inform and change practice in a timely manner. Given the rapidity with which surgical techniques and technology are advancing, an inability to provide data on comparative effectiveness further limits the ability of surgeons to take an evidence-based approach to their work. This article outlines the conceptual framework and impetus behind the NODES program, its inception, and its potential effect on surgical trials.
local CSP site investigators and study coordinators. In addition to the node director and manager, a node may incorporate an executive committee consisting of the node leadership and established CSP site investigators. An advisory board consisting of subject-matter experts and leadership figures from the facility is another possible component of a node that can guide it toward accomplishing its mission. The NODES program requires some core elements deemed necessary for achieving initiative goals. However, it simultaneously allows flexibility regarding how other components are executed to promote the diversity of approaches and to better inform the larger network about potentially useful practices that other centers could adopt.

Node Interactions and Outreach

Opportunities exist to incorporate a community advisory board composed of representatives of Veteran Service Organizations and other veterans support groups. Such an approach may be particularly valuable as efforts toward more patient-centered research evolve.17,18 This will help represent the interests of veterans, provide outreach in community settings, and enhance the efforts of the Department of Veterans Affairs to provide the highest-quality health care available while conducting high-quality research.

Node directors will work with the community-based outpatient clinics and other affiliated sites to help publicize studies to veterans treated in each clinic. This “hub-and-spoke” model has been successfully implemented in the clinical operations of many VAMCs and has recently gained traction in their research operations.

Node as Facilitating Interface

All site investigators will report to the node director in addition to working closely with their study’s coordinating centers. The site investigators will continue to be ultimately responsible for their studies but will be accountable to the node director, who will effectively interface with them, CSP, and the local research and development office, to which the site investigator is also accountable.

The node is expected to secure the necessary infrastructure and support for the site investigators to effectively and efficiently conduct their studies. At a facility level, the node leadership, through its working relationship with local regulatory bodies, human resources, credentialing, information technology, and other local departments, will facilitate the smooth running of CSP studies. It is envisioned that a pool of coordinators will be available to be assigned to any studies that need them, ensuring timely hiring of fully trained and facility-credentialled coordinators. In addition to having close and regular communication with local research personnel, nodes will communicate with each other by attending conference calls and meetings with CSP and coordinating centers.

Node Management and Performance

Management plans will focus on putting together well-defined standard operating procedures to ensure a consistent and deliberate operational approach. In addition, a lean business model that reduces waste and inefficiency will enhance throughput and optimize workflow. Improving efficiency and consolidating the resources of the various local CSP studies will probably translate into cost savings.

Workload will be balanced among the coordinators. Redundancy in staffing will be minimized, and it is anticipated that the node will communicate with CSP regarding its actual staffing needs on a global basis rather than on an individual study basis. Indeed, one possibility is for CSP to pay nodes according to the number of patients enrolled as part of a pay-for-performance funding model.

Productivity and efficiency must be tracked and optimized. A process flow system will enable node investigators to monitor in real time whether they are meeting their enrollment targets for ongoing studies and the progress of new studies in the local approval process. Node accountability is emphasized and involves metrics that track productivity (Table 2).

Discussion

Evidence From Surgical Trials

An eye-opening review of 9 surgical journals in the mid-1990s found that less than 10% of all articles published in these journals reported results from a randomized trial.7 The percentage of multisite surgical trials is even lower. In contrast, more than half the articles were reports of single-institution case series studies. A decade later, Gelinis et al2 reported no
improvement in the low percentage of randomized trials in the surgical literature. Therefore, it is no surprise that the evidence base underlying surgical practice is inadequate. Although the rationale for some surgical treatments is obvious and based on common sense, in some clinical scenarios surgical intervention or a particular surgical approach may not be the clear-cut remedy. In fact, the paucity of rigorous evidence provides ample opportunity to design and conduct studies that can evaluate different facets of surgical care. High-quality data can then be used to inform surgical decision making, thereby improving patient outcomes. Despite ongoing efforts to develop more targeted and personalized therapeutics, most effective therapies for surgical disease are not specifically targeted. Accordingly, a trial of adequate size to show modest but important effects on true clinical outcomes must remain the standard for the evidence on which therapies are based.\(^2\)

**Challenges of Surgical Trials**

Garas et al\(^2\) identified 4 main categories of barriers to surgical trials: researcher, methodology, intervention, and patient related. Those categories are interrelated and apply to clinical trials in general but also encompass some factors unique to surgical trials, including learning curve, masking, standardization of procedure, and potentially risky procedures. Surgical trials can also be expensive to run because they are procedure and device oriented.

Trials of new surgical procedures are supported mostly by the public sector, but it is estimated that only about 10% of public research funding is allocated to clinical trials and other evaluative studies.\(^2\) In the current economic environment, the already limited funding opportunities for clinical research are further reduced. This reality can deter surgical investigators and decrease the number of new surgical trials being funded and argues for enhancing the effectiveness and efficiency of the surgical trials infrastructure. In 2008, a trial of a new device for treating functional mitral regurgitation was terminated prematurely because the sponsor failed to secure necessary funding.\(^2\) Many barriers to conducting surgical trials can be overcome within a framework that caters to the nuances of individual surgical practices and the routine logistical challenges of a clinical trial.

**NODES’ Effect on Surgical Trials**

The NODES program offers a novel approach that can build on the success of CSP. It can help address some of the challenges associated with surgical trials, and it can be particularly useful in the following 8 areas:

1. Resource for education and training in clinical trials: The NODES program provides various interventions to improve study performance at a local and national level (Figure). In particular, the local node provides a great resource regarding the site-specific culture, including the opportunities for and barriers to surgical trial conduct. It can
facilitate discussions among different specialties involved in conducting a trial, manage outreach to community-based organizations, and constitute a repository of regulatory and administrative know-how. Young investigators can receive guidance on designing and planning new trials or get valuable pointers on participating in and running trials.

2. Easing time constraints: Among the barriers NODES may help alleviate are the time and effort spent on administrative and regulatory responsibilities that often fall on the shoulders of the investigator.20 This is particularly relevant for busy surgeons who have little time outside the operating room. Having a node on site will free up the surgeon to participate in enrolling patients in clinical trials, interact with referring physicians, conduct clinical interventions, and oversee patient retention. This translates into more study procedures and better enrollment. The infrastructure is in place so that surgeons can start enrolling patients as soon as a study is locally approved, instead of having to wait for study funding to arrive before hiring and training support staff.

3. Striving for surgical equipoise through feedback from the field: The NODES program provides a unique opportunity to obtain center-level perspectives on the design and execution of studies, thus being sensitive to surgeons' needs and preferences. This can enhance surgical equipoise. The surgeon’s buy-in will undoubtedly boost enrollment. For example, input from the field was an important factor in drafting a protocol of a proposed CSP trial to evaluate antiplatelet therapy after cardiac surgery. Surveying the surgeons about the minimum time needed before the safe administration of postoperative antiplatelet therapy helped in identifying a target cutoff with which most surgeons would feel comfortable. The NODES provides the ideal platform to run such surveys and get a reliable and timely response. The final product of all this is surgical trials that are based on good science and have a rigorous core design that is fine-tuned by surgical feedback to ensure that it is realistic and successful.

4. Facilitating enrollment: By helping identify local expertise and site investigators, NODES can ensure timely study initiation and target patient enrollment. This is particularly important for surgical studies that tend to have a limited number of eligible patients per center and face difficulties in patient recruitment and retention. For example, in a CSP trial of the use of the radial artery as a conduit in coronary artery bypass grafting, the target enrollment rate was set at 2 patients per center per month.33 Some centers struggled to reach this target, but other, comparatively sized centers met or exceeded it. The NODES program will enhance enrollment by reviewing pretrial screening logs to ascertain available patient populations at sites, possibly modifying eligibility criteria, developing patient-tailored enrollment materials and template letters to referring physicians, and using regular conference calls with investigators (from various disciplines) to discuss enrollment barriers. Having the NODES in place can help minimize this variation and reduce the risk of study shutdowns due to underenrollment.

5. Space and inventory management: Surgical studies often involve the implantation of devices and prosthetics and may require special procedure-related equipment. Securing and managing storage space and restocking supplies in a timely manner can burden surgeons and research coordinators. The NODES can anticipate and plan for the equipment, space, and supply needs of such studies long before they start. The logistics associated with surgical studies can be optimized, and the local node can negotiate with hospital administration to accommodate study-related needs.

6. Vetting surgical investigators: Because modern surgery is technology oriented and often involves sophisticated and complex operations, it is important to make sure that the surgical investigators who conduct them have the technical expertise to do so. The outcomes of procedures performed by inadequately trained or underskilled surgeons can compromise the validity of the study findings or, more important, have patient-safety implications. For example, trials of surgical revascularization by on-pump vs off-pump techniques have been criticized for including surgeons with suboptimal skill and experience in the off-pump technique.22 The nodes can use their intimate knowledge of local talent and expertise to recommend reliable and qualified surgical investigators.

7. Patient follow-up: One ongoing challenge in trials, including surgical trials, is retention of patients for long-term follow-up. This is particularly important in studies that evaluate durability of certain interventions.23-25 These studies are particularly difficult and expensive to run because of staff turnover and limited reimbursement once active patient accrual is completed. The NODES will provide investigators with the continuity and flexibility to successfully undertake such trials. With a pool of well-trained research coordinators, the workload can be shifted and adjusted to cover the needs of multiple active studies at different stages of their life cycle. For certain trials, the NODES may recommend centralized follow-up of patients, which will reduce the workload of the clinical center staff.

8. Cutting costs: Expense can be a barrier to running surgical trials that tend to be resource demanding. The NODES will

### Table 2. Proposed Metrics for Node Performance

<table>
<thead>
<tr>
<th>Performance Criterion</th>
<th>Metric</th>
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<tbody>
<tr>
<td>Effectiveness</td>
<td>Time from notification of a new CSP study to designation of a local site investigator; time from notification about a new CSP study to obtaining full regulatory approval; time from full regulatory approval to enrollment of the first patient; time to replace a study coordinator or hire a new one; and enrollment rates, including observed-to-expected enrollment rate for each study</td>
</tr>
<tr>
<td>Efficiency</td>
<td>Patients enrolled per study coordinator FTE</td>
</tr>
<tr>
<td>Quality</td>
<td>No. of citations and protocol deviations</td>
</tr>
<tr>
<td>Stability</td>
<td>Ability to retain staff; rate of staff loss</td>
</tr>
<tr>
<td>Outreach</td>
<td>Percentage of patients from CBOCs and from underenrolled groups</td>
</tr>
<tr>
<td>Academic productivity</td>
<td>No. of publications by node members</td>
</tr>
<tr>
<td>National contribution</td>
<td>Service by node members on various national CSP committees, panels, and initiatives</td>
</tr>
<tr>
<td>Responsiveness</td>
<td>Time to respond to and clear an inquiry by Central Office or Coordinating Centers; timeliness of SAE and AE reporting</td>
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Abbreviations: AE, adverse event; CBOCs, community-based outreach clinics; CSP, Cooperative Studies Program; FTE, full-time employee; SAE, serious AE.
facilitate the efficient design and conduct of trials. Where appropriate, it will suggest the design of large, simple trials that have a limited number of end points and a low per-patient cost. In addition, innovations in informatics offer opportunities to substantially reduce the costs of conducting trials, such as access by the coordinating center to the electronic health records for remote monitoring, integration of the electronic data capture system for clinical trials with the electronic health records to avoid duplicate data entry, and data collection from patients using smartphone applications and tablets. Moreover, regulatory, coordination, and monitoring resources will be consolidated and integrated. Anticipated cost savings can be reinvested by the CSP to further improve its infrastructure and fund additional studies.

**Potential Limitations of the NODES Program**

Focusing attention on NODES sites incurs the risk of overlooking sites that do not belong to NODES but might have the appropriate patient population and physician expertise for certain trials. This disadvantage applies only to the pilot phase of the program and will be ameliorated if the program proves successful and more sites are recruited into it. Another potential limitation is that established investigators at the site level may resist sharing control of research assets, including personnel, with the new local node.

**Conclusions**

The NODES program provides an opportunity to reinvigorate interest in surgical trials by offering a redesigned cooperative framework that builds on a core of high-yield sites. This framework could mitigate the usual limitations of surgical trials and encourage junior investigators to participate in trials. The ultimate goal is to improve the surgical care of our veterans and of patients in general.

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**ARTICLE INFORMATION**

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Network of Dedicated Enrollment Sites: An Attempt to Improve the Randomized Clinical Trial

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The multicenter prospective randomized clinical trial (RCT) is the keystone of clinical research. It is the research format that has the greatest possibility of causing a widespread change in clinical practice, with the change based on scientifically valid data. These studies attempt to avoid the biases of an individual site or investigator, generate larger numbers with an increase in the resultant statistical power, and provide more generalizable results.

However, despite decades of experience with RCTs, there are still significant challenges in their conception, planning, and execution. Collaboration must be obtained between proponents of the various modalities to be compared. These are frequently practitioners of different and sometimes competing medical specialties (e.g., cardiac surgeons and cardiologists). Selection and staffing of participating sites must be accomplished. Finally, adequate numbers of willing research participants must be identified.

The Department of Veterans Affairs (VA), through its Cooperative Studies Program (CSP), has a long history of carrying out high-quality RCTs in surgery as well as in most other medical disciplines. In the past decade alone, studies in such diverse areas as open vs laparoscopic approach to the repair of inguinal hernia, on-pump vs off-pump coronary artery bypass graft procedures, and open vs endovascular repair of abdominal aortic aneurysms have been carried out by VA investigators, with results published in prestigious journals.

Even with the ongoing success of the CSP, leaders of VA research have recognized the persistent difficulties in RCT development and execution already noted. To generate objective data on these issues and begin to develop innovative solutions, the VA instituted the Network of Dedicated Enrollment Sites (NODES) program. In this issue, Bakaee and associates do an excellent job of clearly delineating the problems, and their article should be valuable to anyone interested in developing a multicenter study, whether within the VA or not. However, the real value of the program will be seen if and when solutions to the problems are published. Bakaee et al and their colleagues in the NODES program need to remember a key aspect of the well-designed RCT: the results should be generalizable. They should work to ensure that the solutions generated are not VA-centric but rather applicable to RCTs carried out in any segment of the medical research community. If they are successful, this work will be a major step forward in our ability to design and implement trials that will continue to shape medical and surgical practice.

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REFERENCES