Where have all the clinical trials gone?

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In this edition of the *Journal*, there are 2 articles that focus on the diagnosis and staging of patients with suspicious lung nodules or lung cancer.^{1,2} Finley and colleagues¹ demonstrate that the use of a localization technique decreases operative time, reduces cost, and limits the number of conversions to thoracotomy compared with no preoperative localization technique. In a multi-institutional effort, Fernandez and colleagues² demonstrate that surgical staging of the mediastinum in radiographically node-negative early-stage lung cancer adds little value. Both articles are accompanied by thoughtful editorials that frame the new knowledge and place it in perspective. Although both articles provide important information, I am more interested in *how* this information was obtained. It is refreshing to note that these articles are investigator-initiated prospective studies; one is a randomized clinical trial (RCT),¹ and the other is a multi-institutional clinical trial.² They each address common clinical problems: pulmonary nodule localization and surgical staging of the mediastinum. These issues are highly relevant to thoracic surgeons and their patients. The studies offer perhaps the best available evidence to date that can be used to guide and augment practice patterns of thoracic surgeons. The authors of these important articles deserve much credit for performing prospective clinical trials; however, their publication reminds us of a serious deficit in academic thoracic surgery: the lack of surgeon-initiated clinical trials.

The Lung Cancer Study Group, initiated in 1977 and funded by the National Institutes of Health/National Cancer Institute, was site visited in 1983 and became a cooperative group in February 1984. It was disbanded in 1989 by the National Cancer Institute despite publishing more than 100 articles and accruing more patients than all other cooperative groups combined during that period.³ During its existence, several important studies were published that established the gold standard for physicians caring for

patients with lung cancer. After a lull of several years, in the 1990s the American College of Surgeons Oncology Group established a thoracic surgery branch, and several important surgeon-led clinical trials were initiated, completed, and published, many of them in the *Journal*. In 2012, there was a reshuffling of the National Institutes of Health-sponsored cooperative groups, which saw the American College of Surgeons Oncology Group, the Cancer and Leukemia Group B, and the North Central Cancer Treatment Group folded into 1 group: the Alliance for Clinical Trials in Oncology. Since then, only a few clinical trials focused on issues relevant to thoracic surgeons and their patients have opened or are under consideration. There are several reasons why RCTs are challenging to initiate and complete. These include the involvement of multiple stakeholders, an excessive regulatory and bureaucracy burden, cost, slow patient accrual, and the need for long periods of follow-up. Moreover, in oncologic cooperative group trials in the United States, more than 30% of all RCTs close early secondary to poor accrual, resulting in the generation of no new knowledge.⁴ Currently, there is little enthusiasm in the thoracic surgical community to attempt to initiate a multi-institutional RCT inclusive of 10 to 50 sites. There is even less money and fewer mechanisms to support such an endeavor. Finally, although no prospective clinical trial, even an RCT, is perfect, as a rule they have significantly more impact on the field than all other methodologies. Despite these sobering facts, we desperately need data to drive discovery and innovation, enhance patient care and safety, and provide value. Some of these data may come from the myriad of articles examining administrative or societal databases, although auditing policies here are very loose and data integrity can be questioned. It is also possible that industry-sponsored trials will step into the breach and generate new knowledge. This has certainly been true in cardiovascular diseases,⁵ although less so in thoracic or congenital heart surgery.

To provide some context for this editorial, I queried the general thoracic surgery articles published in 3 major thoracic surgical journals: *The Annals of Thoracic Surgery*, the *European Journal of Cardio-Thoracic Surgery*, and *The Journal of Thoracic and Cardiovascular Surgery*. The singular question used was how many of the publications were prospective trials and whether any of these were RCTs. I examined only a single year (2013), and the results are shown in Table 1. The locations of these studies were Europe (5), Asia (4), and North America (3). I certainly could have missed 1 or more prospective trials, 1 year does not tell an entire story, and we know that some thoracic surgeon-led clinical trials are published in other journals.

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TABLE 1. Number of general thoracic surgery prospective and randomized clinical trial publications in selected thoracic surgery journals (2013)

No. of GTS publications*	Prospective clinical trial	RCT	Combined
295	7	5	12 (4%)

GTS, General thoracic surgery; RCT, randomized clinical trial. *Excludes "basic science" publications.

Notwithstanding these reasonable concerns, I believe the results support my supposition that there are few thoracic surgeons performing clinical trials.

Perhaps there is another way for thoracic surgeons to ask clinically or biologically relevant questions, design well-controlled studies to test the hypothesis, and then successfully execute the completion of the project. Perhaps we need a more contemporary, less arduous paradigm for thoracic surgeons to reengage with prospective clinical trials. I believe there are opportunities for single institutions to perform high-quality RCTs or prospective trials on important topics. The article by Finley and colleagues¹ from British Columbia proves this point; an appropriately powered RCT was completed in approximately 2 years and is now peer-reviewed and published. However, there are questions that require the inclusion of more patients to address the aims of the study, and these will require more than 1 institution to address. In the article by Fernandez and colleagues,² we see how this is possible, as well as some problems with this approach. These authors completed a prospective clinical trial in approximately 100 patients across 5 institutions, although it took approximately 5 years to complete. Barriers included 5 different institutional review boards, increased bureaucracy, increased cost, and competing clinical trials, among others. Despite these challenges, the study is now published and provides important information on the need, or lack thereof, for surgically staging the mediastinum in high-risk, radiographically node-negative patients with resectable non-small cell lung cancer.

What would be the mechanisms for initiating, funding, analyzing the data, and reporting the results of prospective clinical trials coming from single or selected multiple institutions? The path for a successful launch in-

volves asking the correct question, finding equipoise, being passionate about the project, performing a realistic accrual evaluation, strategizing on the identification of funding streams to support the project, using extant and available institutional resources to defray costs, and, most important, demonstrating thoracic surgeon ownership. I do not know the cost of performing the trials published in this edition of the *Journal*, but I suspect that existing resources (information technology support, research nurses, and biostatisticians) were extensively leveraged to support the trials. Instigating clinical trials requires skill sets that many thoracic surgeons do not possess, and these include writing the clinical trial, performing appropriate power analyses, and appreciating the time commitment necessary for the regulatory elements and data safety monitoring boards. Successfully initiating and completing a clinical trial is hard work. However, all of these challenges are relatively easily addressed by identifying excellent collaborations in biostatistics and epidemiology and by empowering clinical research managers and support staff.

In summary, this suggested approach to reinvigorating thoracic surgeon-led clinical trials is supported by the 2 articles in this issue of the *Journal*. It involves transitioning from the traditional government or industry-subsidized mechanisms of clinical trial initiation and accrual to a more contemporary, grassroots, thoracic surgeon and associated disease management team-led process. The result could be the generation of significantly higher-quality data than what we are publishing, while using a more nimble, less-expensive, and timely platform.

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