

Seminar article
Clinical Trials in Urology

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1. Introduction

Urology has developed as a field largely by means of an apprenticeship model. Clinical examination and data interpretation, surgical techniques, approaches, and nuances have all been passed down to trainees and their repetition has generated a “dogma” by which we practice the art of medicine. The field is changing and we now require (or should require) evidence to inform practice. There are many unanswered clinical questions and a substantial need for leadership from the modern urologist to answer them in prospective clinical studies.

Clinical trials in Urology have suffered due to several well-meaning practices: (1) physician bias, (2) “patient preference” often based on physician presentation bias, and (3) poor discipline for practicing evidence based medicine. As a field we must overcome these, put our biases aside and ask/answer questions in a meaningful way. Trials allow us to question the existing “dogma,” establish standards, develop new treatments and move the field forward. But the notion of developing one’s career as a clinical trialist can be daunting. Many questions come to mind and many more will become apparent as trial designs move forward. This special edition of *Urologic Oncology: Seminars and Investigations* will focus on topics relevant to clinical trial design and development. While it is geared toward the new investigator, it provides significant insight into the process and is relevant for any investigator.

The first article by Kukreja et al., covers the organization of a clinical trial for a new investigator. This covers the question, rationale and feasibility, patient cohort, methodology, and collaboration. It provides the combined perspective of a seasoned clinical trialist (IM Thompson), a mid-career trialist (BF Chapin) and a new, Assistant Professor (J Kukreja) who was able to design and complete a clinical

trial in her fellowship and is now carrying forward clinical trials in her early career. It provides a framework and sets the stage for planning, expected roadblocks, and successful execution of study design.

The second article by Winters et al. covers the fundamentals of clinical trial statistical design. Appropriate statistical trial design is the first question a trialist should ask and can often be where a trial idea comes to an end due to unreasonable required patient numbers, power concerns, event rate, required length of follow up or one of many other reasons a trial is labeled as futile before it even begins. The statistician’s input is invaluable to the trialist and Dr Winters provides an excellent summary on statistical considerations for clinical trials.

Clinical trial design can be an enormous effort and all available areas of interest should be planned for and captured. Secondary outcomes, including quality of life (QOL), patient reported outcomes, and translational correlative studies should be on the short list of items incorporated into the study design. A 3 month improvement in survival may be considered trivial if the treatment requires 6 month to recover from or change the standard of care if the impact on QOL is minimal. Equally important are the biologic correlatives. A negative overall study can still have a major impact on our knowledge of the disease if it provides insight into disease biology. Biomarker development or other means of identification of subsets of patients who benefit from a particular treatment can be determined, it can be even more meaningful than a positive study lacking biospecimens. Drs Gore (QOL) and Meeks (Translational) provide insight into these secondary outcome measures and considerations for early incorporation of stake holders, soon after study conception.

One of my mentors once told me, “a good idea will find the support it needs.” While I have seen truth in this, funding is always a concern when it comes to clinical trials, particularly for the unestablished investigator and even more so for a surgical or treatment based trial without an industry

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partner. The infrastructure, support and cost of medicines, treatments and testing can make a small idea a very costly endeavor. Dr Ryan provides an outline for trial funding sources and options. Covering the in and out of federal resources, industry sponsors, and private sources. As a senior member of SWOG, Dr Ryan has much experience in this arena and provides an excellent synopsis with particular attention to the National Clinical Trials Network.

Our last article in this seminar is a “must read” for any investigator. Long-time cancer survivors and patient advocates, Tony Crispino and Rick Bangs, provide the patient’s perspective on clinical trials. This personalizes the process, identifies considerations a study chair must reflect on, and reminds physicians of the importance of the patient, their fears, their vulnerability and their trust in their doctors that

this whole process is meant to improve their outcomes. This perspective, from the patient’s side, should not be missed.

These articles are by no means a complete clinical trials course, but rather provide the structure and framework from which to start thinking about appropriate trial design beginning with the key elements: (1) the question and 2) the collaborators. Engagement in clinical trial design, development and execution can be one of the most rewarding challenges an investigator can undertake in his/her career. As urologists, we have an opportunity on a daily basis to treat and often cure patients, but by implementing a change of the standard of care or defining disease biology through clinical trials we can multiply this opportunity by the thousands.