EDITORIAL The decline and fall of RCTs

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A theme for this issue is data quality. Wehbi and colleagues[1] review the progress made in randomized clinical trials (RCTs) over the last few decades, particularly in prostate cancer. RCTs have increased, although they still represent a small minority of published studies. Encouragingly, almost 50% of the RCTs were led by urologists, and 7% of the RCTs worldwide were from Canada. The authors conclude with a plea for greater efforts to initiate and complete RCTs.

This is laudable. The authors rightly emphasize that a randomization of patients reduces the confounding effects of selection bias. But, despite high hopes for specific initiatives, RCTs (more often than not) fail to answer the question which motivated the original trial. Biology is complex, and gives up its secrets reluctantly. Difficulties of trial design, implementation, patient and disease heterogeneity, changing epidemiology and evolving science confound the best of intentions. For example, the mother of all prostate trials, ERSPC, has not resolved the question of whether screening is warranted (although it has served to focus the discussion and clarify the issues). PLCO tried to answer the same question, but arguably the results have only confused matters. PCPT and REDUCE do not appear to have resolved the question of the preventive benefit of 5-ARIs. Randomized trials of androgen deprivation therapy have left many key questions unanswered about timing of therapy, combination therapy versus monotherapy, the importance of nadir testosterone, etc. The phenomenon, whereby a supposedly definitive trial mainly serves to raise more questions, can be observed in all urology subspecialities, and indeed throughout medicine.

A disturbing trend in the area of RCTs is the change in the mandate and funding of the NCIC Clinical Trials Group. The financial basis for the NCIC CTG national trials was that most cancer centres in the country supported these trials "pro bono" due to low per-case reimbursement. This was the only way the trials could be carried out affordably. Resources were provided by the cancer centres and industry-sponsored trials generated some additional revenue to make up the shortfall. The arrangement worked well for about 30 years, but has become unfeasible due to a reduction in these sources. Cancer centres are no longer willing or can no longer afford to subsidize uneconomic clinical trial operations and the "overage" from industry-sponsored trials diminished. The NCIC CTG, recognizing this, announced that it is moving out of the domain of uneconomic large scale trials, and will, going forward, be a facilitator for pharmaceutical and other funded trials. The NCIC CTG lion has become a pussycat. Lamentably, the opportunity to do large scale trials testing the tough questions in urologic cancer will be reduced for the foreseeable future.

In the current climate, there is still opportunity. Investigator-initiated trials, sponsored by industry, offer a great opportunity to carry out trials of new drugs, or established drugs seeking new indications. Pharmaceutical companies look very favourably on these proposals due to substantially reduced monitoring requirements. I'd encourage all research-oriented urologists to think about interesting drug-related questions answerable with a small-medium size trial, and propose these to potential sponsors. In the context of the controversy over the interpretation of the 2 large screening trials, the publication of the new CUA prostate cancer screening guideline in this issue is a welcome and clear statement in this perennially controversial area.[2] While the controversy is far from closed, this guideline is a major step forward and will be quoted for years to come.

References

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2. Izawa JI, Klotz L, Siemens DR, et al. Prostate cancer screening: Canadian guidelines 2011. *Can Urol Assoc J* 2011;5:235-40; DOI:10.5489/cuaj.11134.