Editorial

Unlocking the Keys to Site Activation and Recruitment Success in a Randomized Controlled Trial

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While randomized controlled trials (RCTs) remain the gold standard investigation for determining the effectiveness of various medications or therapeutic approaches to the more optimal management of patients with infectious or noncommunicable diseases, RCTs can be incredibly complex to design and difficult to conduct. By extension, these trials can be extremely costly to recruit and successfully follow adequate numbers of patients to the trial, as well as include representative patient populations for purposes of more broadly generalizing the eventual trial findings.

Two of the most crucial requirements for successfully carrying out and completing an RCT are the initial construction of different hypothetical scenarios to determine how many healthy individuals or patients with a specific disease or condition are needed to be enrolled in the trial and eventually followed on either a short- or long-term basis to find clinically meaningful differences in one's principal study outcomes and, subsequently, to go out into the field, find, and recruit a sufficient number of patients to the proposed trial to satisfy one's predetermined sample size requirements. Moreover, the logistical operations of an RCT need to be performed within the confines of a manageable budget and typically tight timeline for patient enrollment and follow-up in which all too often projected estimates of the number of patients to be enrolled and successfully retained in the trial greatly exceed reality.

In their interesting, relatively novel, and useful article, Demaerschalk et al[1] present data on the selection process involved in recruiting a large number of study sites to the multicenter CREST-2 trial (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trials). Despite the large volume of RCTs conducted annually in the United States and elsewhere, surprisingly little data exist describing the site selection process involved in multicenter RCTs and factors associated with successful, versus less successful, trial site activation and patient enrollment. The findings of this article have direct relevance for trial investigators, project management personnel, and funding agencies.

In this large RCT, which to date has included 147 of the projected 192 trial sites, by the time of this report, 83% (n=122) of the approved sites had received permission to randomize potentially eligible study patients who met the trial's inclusion/exclusion criteria. Over the >1700 clinic-related months of recruitment completed at this time, the 122 sites had randomized a total of 437 patients.

In addition to collecting a variety of information about the patients participating in this trial, data were also collected for purposes of identifying several possible factors that might favorably affect the rapidity by which patients were randomized and patient enrollment could be enhanced. These factors included the specialty of the Principal Investigator, site type, presence of affiliated recruitment sites, membership in StrokeNet, user of a central Institutional Review Board, presence of a full complement of study investigators, annual number of carotid endarterectomy procedures performed, potential to enroll women and minorities, type of study approval sought, and participation and actual performance in the earlier CREST trial. Several study sites were identified through linkage to the National Institute of Neurological Disorders and Stroke–funded StrokeNet network of 25 regional coordinating centers throughout the United States.

As of the first week of January 2017, 3 quarters of participating sites had successfully randomized one or more patients to the comparison trial treatment regimens. For purposes of the present investigation, the time between trial approval by the site selection committee (SSC) of CREST-2, the time between SSC authorization to randomize patients and the actual first patient randomization, and the average number of patients enrolled per site were examined as the key indicators of a trial sites participation and enrollment performance.

In terms of the time interval between being approved as a trial site and authorization to randomize patients by the SSC, one quarter of the approved sites had received authorization to randomize over a nearly 8 month long period, one half by 10 months, and three quarters by 1 year. None of the site and Principal Investigator–related factors examined were significantly associated with the time interval between site approval and authorization to enroll patients into the study; prior participation in the CREST trial was marginally associated with authorization by the SSC to enroll patients into this trial.

Once a trial site was considered appropriate and was given the go ahead to randomize patients, one quarter of the participating 122 sites did so within ≈2 and a half months of trial authorization, one half of the sites had done so by nearly 5 months later, and 3 quarters by 10 months. The only factor that was significantly associated with the time between SSC approval and actual randomization was whether the site

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investigators were seeking approval to participate in one or both of the proposed CREST-2 trials. The CREST-2 protocol included 2 RCTs in which either carotid endarterectomy plus intensive medical management or the receipt of carotid stenting plus intensive medical management were being compared with intensive medical management alone.

In terms of the third of the site performance indicators being examined in this study, namely the average monthly recruitment rate, the type of study site (VA or otherwise), number of carotid angioplasty and stenting procedures performed annually, whether the site was participating in one or both of the concurrent CREST-2 trials, and prior participation in the original CREST trial and performance in that trial was associated with what was considered to be good study recruitment performance.

These preliminary results, based on >400 patients enrolled to date out of a projected total of nearly 2500 eligible and consenting patients to be included in the 2 trials in CREST-2, provide insights into the time course from the time of initial site selection to actual patient randomization and some of the site, as well as investigator, factors associated with early site start-up and patient enrollment.

In the investigators review of the scientific literature, they found an extremely limited literature to compare the present findings with, and they identified 2 nonstroke-related trials that examined a limited set of predictors of actual trial performance. Irrespective of the lack of a published literature in this area, the present data suggest that both the times from site activation to randomization and the time from authorization to randomize to actual randomization are relatively long and need to be considered in advance by individuals planning an RCT. Moreover, it is important to a priori understand the factors that may be associated with rapid or slow site activation to keep the projected number and flow of patients to be recruited to the trial on track.

Of note, the trials that have provided data in these important areas were either medical- or surgical-type trials. No data have been systematically reported from behavioral intervention trials, which may be less complicated to set up and obtain regulatory approval for as compared with medical or surgical therapy-type trials in which different factors may be associated with rapid or slow site activation and patient enrollment.

For example, in our recently completed feasibility-clustered randomized trial, which evaluated a storytelling method for improving hypertension control among adults with hypertension from 4 rural communities in Hung Yen province of Vietnam (funded by the National Institutes of Health/Fogarty International Center), the time from site selection to the beginning of the trial (intervention development phase) was 3 months; this time interval included obtaining necessary regulatory approval, organizing workshops in the participating communities, and training study personnel in the delivery of the standardized intervention and collection of data from trial participants.[2] The time interval from authorization to randomize adult patients with hypertension to actual trial participation was ≈6 weeks, which included the screening and enrolling of eligible patients.

In our population-based trial, we used a sampling frame of all adult community members. Community residents who were ≥50 years were randomly selected for hypertension screening; if these individuals satisfied the study eligibility criteria, they were invited to participate in our trial. By using these population sampling frames, rather than approaching hypertensive patients at nearby clinics, we could facilitate trial recruitment because a considerable proportion of the adult population in Vietnam has hypertension. As a result of this collective effort and boots on the ground, we were able to successfully recruit >50% of the target sample size (160 patients versus 100 patients based on our original sample size estimates).

The results of our successfully completed lifestyle intervention trial may not, however, reflect the general situation in other behavioral intervention trials. This is because the site activation and patient enrollment time frames may vary by the type of intervention to be used, conditions under which the trial is being conducted, community contacts, and study setting. In a similar vein, the results presented about the recruitment process in the CREST-2 trial may not be broadly generalizable to other stroke prevention trials, especially when well-characterized enrollment sites, as in StrokeNet, may be included. StrokeNet is a network of 25 regional coordinating centers that has been designed to maximize efficiencies of high quality, multicenter, RCTs among patients with stroke (though participation in StrokeNet was associated with slower participant recruitment in the present investigation).

Irrespective of these findings, more studies in different content areas and study settings are needed to more fully understand the factors associated with successful trial site recruitment, activation, and the timely randomization of patients to various study intervention approaches. These data remain needed for purposes of developing and implementing different intervention strategies to optimize the trial's overall time frame and the time needed to successfully recruit the targeted study population and follow these individuals for the development of prespecified trial end points. Collection of these data can advance the present state of the art in terms of providing information that can be used to enhance the cost and scientific efficiencies of future RCTs and translate the acquired knowledge to the more optimal care and outcomes of patients with different disease conditions.

Disclosures

None.

References

1. Demaerschalk BM, Brown, RD Jr, Roubin GS, Howard VJ, Cesko E, Barrett KM, et al. Factors associated with time to site activation, randomization, and enrollment performance in a stroke prevention trial. *Stroke* 2017;48:XX–XX. doi: 10.1161/STROKEAHA.117.016976.
2. Nguyen HL, Allison JJ, Ha DA, Chiriboga G, Ly HN, Tran HT, et al. Culturally adaptive storytelling intervention versus didactic intervention to improve hypertension control in Vietnam: a cluster-randomized controlled feasibility trial. *Pilot Feasibility Stud*. 2017;3:22. doi: 10.1186/s40814-017-0136-9.

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