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SCORE2 Report 1: Techniques to Optimize Recruitment in Phase III Clinical Trials of Patients with Central Retinal Vein Occlusion

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Abstract

PURPOSE—To investigate recruitment rates of patients with central retinal vein occlusion (CRVO) into phase III clinical trials evaluating intravitreal pharmacotherapy for treatment of macular edema in the United States, describe recruitment techniques in the Study of COmparative Treatments for REtinal Vein Occlusion 2 (SCORE2), and assess which SCORE2 recruitment techniques were most useful to principal investigators and clinical coordinators.

DESIGN—Retrospective survey within a randomized clinical trial.

METHODS—Recruitment rates of the Standard Care versus COrticosteroid for REtinal Vein Occlusion (SCORE)-CRVO trial, CRUISE Study and SCORE2 were calculated. Techniques employed to facilitate recruitment in SCORE2 are described, and a survey was sent to the principal investigator and primary clinical coordinator of each SCORE2 site to assess the usefulness of recruitment techniques.

RESULTS—In SCORE2, the recruitment rate of 0.39 participants/month/site was higher than in SCORE-CRVO (0.10 participants/month/site) and CRUISE (0.23 participants/month/site). For study design factors in SCORE2, investigators and coordinators rated provision of standard of care treatments to all study participants as having a major positive impact on recruitment. A monthly e-newsletter to site staff and communication by physician members of the SCORE2 Executive Committee to sites upon each randomization were perceived as effective means to help site staff focus on recruitment.

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CONCLUSIONS—The SCORE2 recruitment rate compares favorably to previous clinical trials investigating intravitreal pharmacotherapy for treatment of CRVO-associated macular edema. Study design factors, methods of communication with sites and recruitment techniques implemented in SCORE2 were well received by investigators and coordinators and may be helpful in future clinical trials.

INTRODUCTION

Timely recruitment of a sufficient number of study participants to achieve the target sample size represents one of the most challenging aspects of a clinical trial. The American clinical pharmacologist Louis Lasagna observed that, when a clinical trial commences, the supply of suitable patients becomes a fraction of what it was assumed to be prior to the commencement of the trial.^{1,2} Lasagna's Law refers to the observation that the number of patients available for entering a clinical trial falls markedly at study initiation and rises markedly after study completion.^{1,2} Muench's Third Law states that, in order to be realistic, the number of cases promised in any clinical study must be divided by a factor of at least 10.³ Potential reasons for overestimation of patient availability for clinical trials may include such factors as restrictive clinical trial eligibility criteria, high refusal rates among eligible patients, and insufficient or ineffective resources to approach eligible patients.

Slow recruitment into the Standard Care versus COrticosteroid for REtinal Vein Occlusion (SCORE)-CRVO trial prompted a downward revision of the target sample size,⁴ and prompted the trial's leadership to implement several techniques designed to optimize patient recruitment into the Study of COmparative Treatments for REtinal Vein Occlusion 2 (SCORE2).⁵ The current study was designed to investigate recruitment rates of patients with central retinal vein occlusion (CRVO) into phase III clinical trials investigating intravitreal pharmacotherapy for treatment of macular edema in the United States, to describe methods of communication with sites and recruitment techniques in the Study of COmparative Treatments for REtinal Vein Occlusion 2 (SCORE2), and to investigate which of these activities were most useful to SCORE2 site principal investigators and clinical coordinators.

METHODS

SCORE2 is a multicenter, prospective, randomized, clinical trial designed to determine if bevacizumab is non-inferior to aflibercept for the treatment of decreased vision due to macular edema associated with CRVO. The SCORE2 protocol and informed consent were approved prior to participant enrollment by the respective clinical center institutional review boards or a centralized institutional review board (Chesapeake IRB, Columbia, MD).

Study participant recruitment rates of all phase III clinical trials investigating intravitreal pharmacotherapy for the treatment of decreased vision due to macular edema associated with CRVO and conducted solely at clinical sites in the United States (US) were calculated based on information provided in the publications of these studies (total number of study participants recruited, dates of enrollment, number of clinical sites). Clinical trials included in the current study are the SCORE-CRVO,⁴ SCORE2, and CRUISE⁵ trials. The GENEVA Study⁶ is not included since it was not conducted solely at sites in the US (it was conducted

at 167 sites in 24 countries throughout the world) and included patients with CRVO and patients with branch retinal vein occlusion (BRVO). The COPERNICUS⁷ and GALILEO⁸ trials are not included because they were not conducted solely at sites in the US (the GALILEO trial was conducted across 63 sites in Europe and the Asian-Pacific region while the COPERNICUS trial was conducted at 70 sites in the United States, Canada, India, Israel, Argentina, and Colombia).

An on-line survey of communication methods and recruitment techniques was constructed and emailed to the SCORE2 principal investigator and primary clinical coordinator at each of the 75 SCORE2 clinical sites that completed study requirements to participate in recruitment, including sites that did not randomize any SCORE2 participants. One SCORE2 clinical site had withdrawn early in the recruitment period and, therefore, was not administered the survey. Response to the site survey on recruitment techniques was good, with 69 of the 75 sites (92%) submitting at least one survey, for a total of 99 surveys submitted. The survey was completed by 65 of 75 (87%) primary clinic coordinators and 34 of 75 (45%) principal investigators. The survey asked questions about the perceived impact of specific study design factors on the site's ability to recruit using a 5-point Likert scale "1-Major hindrance", "2-Minor hindrance", "3-No impact", "4-Minor positive impact", and "5-Major positive impact". The survey also focused on recruitment tools and communication methods to aid recruitment, and within each of these domains, the questions fell into natural pairs: (1) utility of the tool or communication based on whether or not it was used or site staff recalled receiving; and (2) perceived helpfulness of the tool or communication with responses on a 5-point Likert scale covering "Not at all", "Slightly", "Moderately", "Considerably", and "Extremely." For analysis, both members of the pair of questions were combined together, so that responses follow a rank order from "Did not use it" to "Used it, and extremely helpful".

Mostly descriptive analyses are presented, with t-tests and chi-square tests for some comparisons. All analyses and interpretations should be viewed as exploratory in nature.

SCORE2 is registered on <http://www.clinicaltrials.gov> (identifier: NCT01969708).

RESULTS

In SCORE-CRVO, 271 patients were enrolled from 66 clinical sites over 40 months, between November 2004 and February 2008, for an average recruitment rate of 6.7 patients per month (0.10 participants/month/site). In CRUISE, 392 patients were recruited from 95 clinical centers over 18 months, between July 2007 and December 2008, for an average recruitment rate of 21.7 patients per month (0.23 participants/month/site). In SCORE2, 360 patients were enrolled from 66 clinical sites over 14 months, between September 2014 and November 2015, for an average recruitment rate of 25.7 patients per month (0.39 participants/month/site).

Communication methods and recruitment techniques employed in SCORE2 were aimed at study investigators, coordinators, and potential participants to help meet enrollment goals. Engagement of investigators through conference calls and webinars took place during trial

planning, soliciting feedback on trial design that focused not only on the scientific aspects of the study but also operational characteristics that would facilitate recruitment. Four study design features were included in the survey for feedback from the site principal investigator and clinical coordinator as to the impact of that particular trial design feature on the site's ability to recruit, as displayed in Table 1. All four of the study design features were felt by principal investigators and clinical coordinators to be important based on mean scores between 4 (minor positive impact) to 5 (major positive impact). In particular, both the site principal investigators and the coordinators perceived that all study participants receiving standard of care treatments, with absence of an untreated control arm, was positively impactful for recruitment, with 85% of principal investigators and 79% of coordinators noting this factor as having a major positive impact on recruitment.

A number of recruitment aids were made accessible to site staff at the outset of SCORE2 on the study website, including a patient brochure in English and Spanish to help patients better understand SCORE2, a SCORE2 Power Point presentation to allow investigators to lecture locally about SCORE2 and thus increase eligible referrals to their clinical site, and a physician referral letter template made available to clinical site investigators to allow them to send letters to local eye care providers to refer potential eligible patients. Figure 1 shows the responses from the principal investigators and primary clinical coordinators; in general, the Power Point presentation, referral letter, and Spanish patient brochure were not used. The English patient brochure was noted to be used approximately 50% of the time, with 13 principal investigators (38%) and 26 clinical coordinators (40%) rating it moderately, considerably, or extremely helpful.

Communication by the Executive Committee (EC) and the Data Coordinating Center (DCC) was another major focus during recruitment. These included the SCOREBOARD, a monthly e-SCORE2 newsletter designed to keep SCORE2 site staff informed about study progress and provide information about upcoming timelines and events, and a SCORE2 icon for Apple and Android smartphones which provided site staff quick access to SCORE2 inclusion and exclusion criteria and the ability to communicate directly with an ophthalmologist on the SCORE2 EC and the DCC for both time-sensitive and non-time sensitive issues. Figure 2 shows the responses, which notes the mostly favorable ratings regarding the SCOREBOARD; this e-newsletter was recalled being received and very useful, with 26 principal investigators (76%) and 56 clinical coordinators (86%) rating it moderately, considerably, or extremely helpful. The SCORE2 icon for Apple and Android smartphones was not widely taken advantage of in SCORE2, with 28 principal investigators (82%) and 54 clinical coordinators (83%) not using it.

SCORE2 physician leadership was also actively involved in recruitment by sending congratulatory/motivating emails to site investigators and coordinators upon site activation and upon each randomization, and communicating with the principal investigator of any site when a time period (guidelines developed by study leadership) lapsed without any randomizations in order to assess enrollment efforts and discuss enrollment barriers that SCORE2 leadership may address to try to help with recruitment at the site. Figure 3 shows the responses to the survey specific to communication to sites at time of randomization among sites with at least one randomization, which were mostly positive with 20 of 29

principal investigators (69%) and 32 of 58 clinical coordinators (55%) rating it moderately, considerably, or extremely helpful. Among sites receiving a communication at time of slow requirement, 13 of 33 principal investigators (39%) and 22 of 64 clinical coordinators (34%) rated this communication moderately or considerably helpful.

Additional analyses were performed on the site data to better understand the survey data and its impact on recruitment. Sites with either the principal investigator or clinical coordinator responding to the survey (n=69) randomized significantly more participants (mean =5.1 participants/site) than sites (n=6) with no responders (mean=1.3 participants/site; $p=0.002$ based on a t-test). Therefore, the experience reported from this survey mostly reflects those sites that were more successful in randomizing participants.

No association was identified between the use or non-use of a recruitment aid or communication resource (Power Point presentation, referral letter, patient brochure [English or Spanish], or SCORE2 Icon for smartphones) and the number of participants the site randomized (all p-values > 0.14 based on t-tests). We also investigated whether or not the principal investigator and clinical coordinator agreed or disagreed with whether a recruitment aid or a communication method was used or recalled at the site. Although there was not strict concordance between the answers given by the principal investigator and clinical coordinator at each site to each of these questions, discordances were not significant by chi-squared tests (all p-values > 0.19).

Beyond the site survey, we investigated other factors that may be related to the number of participants a site recruited. One factor was whether the number of participants randomized per site differed by whether the site was a private practice (n=55) or academic (n=20) site, with academic sites defined as those with an institutional facilities and administrative (indirect) rate negotiated with the National Institutes of Health. Recognizing that sites had differing lengths of time to recruitment, we calculated the enrollment risk time (time from site activation to overall trial-level enrollment cessation) for each site, and divided this into the number enrolled to get enrolled per risk-month. Enrollment risk months varied greatly across sites, from 4.92 to 14.09 (mean=11.94). The number enrolled per risk month was 0.45 for private practice sites, which is almost twice that of academic sites (0.24; $p=0.005$ based on a t-test). We also investigated whether site recruitment was related to the number of investigators at a site. The number of investigators noted on the site's Form FDA 1572 ranged from 1 to 16 per site, with 3 being most common (24% of sites). The correlation between number of investigators and number of participants recruited is not significant ($r = 0.13$, $p = 0.25$).

DISCUSSION

The SCORE2 recruitment rate compares favorably to previous clinical trials conducted in the US investigating intravitreal pharmacotherapy for treatment of CRVO-associated macular edema. Patient recruitment into clinical trials is impacted by design considerations such as patient eligibility criteria, whether patients may be randomized on the same day as screening, and whether all study arms receive active treatment; whether concurrent trials

compete for the same types of participants; and advent of competing treatments during recruitment. In addition, activities can be implemented within trials to optimize recruitment.

All four study design features (Table 1) included in the survey were rated by site principal investigators and clinical coordinators as having had a major positive impact on recruitment. SCORE2 leadership engaged investigators through conference calls and webinars during trial planning; this permitted investigators to voice opinions regarding scientific and operational issues and facilitated inclusion of study design features favorable to patient recruitment. In addition, inclusion of investigators in trial planning provided investigators with a sense of study ownership which may have increased their enthusiasm with respect to study participation and patient recruitment. Some of the design features identified as having had a major positive impact on patient recruitment may be relatively specific to SCORE2 (e.g. eligibility criteria allowing for prior use of anti-VEGF treatment) and may have limited generalizability to other clinical trials. However, engaging investigators in trial planning, provision of study drug, all participants receiving standard of care treatments with no untreated control arm, and ability to screen and randomize patients on the same day may represent study design features which may help facilitate patient recruitment in other clinical trials. It is important to consider factors impacting recruitment during the trial design phase in order to optimize the ability of the trial to achieve timely patient recruitment of the target sample size.

The patient brochure in English was the only recruitment aid used by a substantial proportion of respondents. A number of sites did not have large Hispanic populations, which may explain why the English brochure was used more than the Spanish brochure and why the site principal investigators and clinical coordinators perceived the English brochure to be more useful than the Spanish brochure.

The monthly e-newsletter, the SCOREBOARD, and congratulatory/motivating emails from SCORE2 physician leadership to site investigators and coordinators upon site activation and upon each randomization were rated by the majority of investigators and coordinators surveyed as helpful with respect to keeping site staff aware of study progress and keeping sites focused on patient recruitment. Such communications represent relatively inexpensive, high yield communication and recruitment tools that should be considered for future clinical trials. The fact that the SCOREBOARD was applicable to everyone and was sent every month, while the physician communications occurred less frequently depending on recruitment or lack thereof, may explain why the SCOREBOARD was rated somewhat more favorably than the physician communications in the current study. Over eighty percent of investigators and coordinators who responded to the survey reported not using the SCORE2 icon for Apple and Android smartphones. This may be due to the fact that the SCORE2 icon for smartphones was added 3 months after recruitment in SCORE2 had started; in addition, this a relatively new technology that may take some time to adopt. Of note, the few investigators and coordinators who did use the SCORE2 icon for smartphones rated it as being extremely useful. In future clinical trials, the utility and effectiveness of this technology may be increased if the use of such icons were implemented when the clinical trials start and their availability made known from the beginning of the clinical trial.

Private practice sites recruited more efficiently than academic sites. This may be due, at least in part, to the greater administrative burden at academic sites. For example, the investigative team at academic sites is responsible for obtaining institutional review board (IRB) approval for the study protocol and meeting ongoing IRB and regulatory requirements throughout the study while the Data Coordinating Center performs such tasks for the investigative team at private practice sites. Further, the investigative team at academic sites generally has less authority to prioritize a study over other missions in the department (e.g. patient care, teaching) and often needs to share research resources (e.g. clinical coordinator support) with other investigative teams, while private practice researchers generally have more flexibility in prioritizing a study within the practice and generally have more direct authority over allocation of research resources. While an advantage of private practices may be fewer indirect (overhead) costs, some of the reduced indirect costs are simply cost-shifting to the Data Coordinating Center. Despite the reduced efficiency with respect to patient recruitment at academic sites compared with private practice sites, there may be other important reasons for trial sponsors to include academic sites, such as the scientific contributions of academic investigators, and the ability to recruit certain minority and other under-represented (e.g. socioeconomic status) populations who may receive care at academic centers.

In summary, the recruitment rate in SCORE2 compares favorably to previous clinical trials investigating intravitreal pharmacotherapy for treatment of CRVO-associated macular edema. Several trial design features and recruitment techniques implemented in SCORE2 were perceived by investigators and coordinators as helpful with respect to patient recruitment, and may be useful to implement in future clinical trials in order to optimize patient recruitment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Utility and Perceived Usefulness of Recruitment Tools Made Available to Site Staff.

Responses from the principal investigators are displayed in blue and the primary clinical coordinators in red, with the height of each bar representing the percent of responses in each group and the actual number is written above the bar.

Figure 2.
Utility and Perceived Usefulness of Tools To Facilitate Communication with Site Staff

Figure 3.
Utility and Perceived Usefulness of Direct Communication from SCORE2 Leadership on Recruitment

Table 1Perception of Design Factors on a Site's Ability to Recruit in SCORE2^a

	Principal Investigator (N=34)		Clinical Coordinator (N=65)	
	Mean Score	% Noting Major Positive Impact	Mean Score	% Noting Major Positive Impact
Eligibility criteria allowed for prior use of anti-VEGF treatment	4.15	50.0%	3.89	35.4%
SCORE2 supply of study drug	4.53	70.6%	4.68	78.5%
All study participants received standard of care treatments and there was no untreated control arm (e.g., sham injection, observation)	4.76	85.3%	4.62	78.5%
Ability to screen and randomize on one day	4.53	67.7%	4.43	61.5%

^aRanking based on a 5-point scale "1-Major hindrance", "2-Minor hindrance", "3-No impact", "4-Minor positive impact", and "5-Major positive impact".