Chapter 10
Recruitment of Study Participants

Often the most difficult task in a clinical trial involves obtaining sufficient study participants within a reasonable time. Time is a critical factor for both scientific and logistical reasons. From a scientific viewpoint, there is an optimal window of time within which a clinical trial can and should be completed. Changes in medical practice, including introduction of new treatment options, may make the trial outdated before it is completed. Other investigators may answer the questions sooner. In terms of logistics, the longer recruitment extends beyond the initially allotted recruitment periods, the greater the pressure becomes to meet the goal. Lagging recruitment will also reduce the statistical power of the trial. Selective recruitment of a lower proportion of eligible participants may increase the non-representative nature of the sample. Costs increase, frustration and discouragement often follow. The primary reasons for recruitment failure include overly optimistic expectations, failure to start on time, inadequate planning, and insufficient effort.

Approaches to recruitment of participants will vary depending on the type and size of the trial, the length of time available, the setting (hospital, physician's office, community), whether the trial is single- or multicenter, and many other factors. Because of the broad spectrum of possibilities, this chapter summarizes concepts and general methods rather than elaborating on specific techniques. Emphasis is placed on anticipating and preventing problems. This chapter addresses plans for the recruitment effort, common recruitment problems, major recruitment strategies and sources, use of electronic health records for screening, and monitoring of recruitment.

Fundamental Point

Successful recruitment depends on developing a careful plan with multiple strategies, maintaining flexibility, establishing interim goals, preparing to devote the necessary effort, and obtaining the sample size in a timely fashion.

L.M. Friedman et al., *Fundamentals of Clinical Trials*,
DOI 10.1007/978-3-319-18539-2_10

Considerations Before Participant Enrollment

Selection of Study Sample

In Chap. 4, we define the study population as "the subset of the population with the condition or characteristics of interest defined by the eligibility criteria." The group of participants actually recruited into the trial, i.e., the study sample, is a selection from this study population. Those enrolled into a trial do not represent a random sample of those eligible for enrollment. Eligible individuals who volunteer to participate in a randomized trial may be different from eligible non-participants (see below). The impact of this potential selection bias on the results of a trial is not well understood. A better understanding of the factors that influence either willingness or unwillingness to participate in a research project can be very helpful in the planning of recruitment efforts.

The public is generally willing to participate in clinical trials [1]. A survey of around 1,000 Americans conducted in May 2013 showed that 64% would "take part in a clinical trial if I was asked by someone I trust." Yet only about 15% of Americans report that they have participated in a clinical trial. In this survey, lack of trust was the major barrier to participation in trials. When asked to rate factors involved with decision to volunteer, nearly 70% reported reputation of the people or institution conducting the research and whether medical bills resulting from injury from the study would be covered as very important factors. Opportunity to possibly improve one's own health was noted as very important for 61%, privacy and confidentiality issues for 53%, and opportunity to improve health of others for 50%. Complementary information was reported in a review of 14 studies through 2001 that had addressed the question—What reasons do people give for participating and not participating in clinical trials [2]? The answers came from 2,189 participants and 6,498 who declined. The variability was large, but trial participants gave as their major reason for participating potential health benefit (45%), physician influence (27%), and potential benefit to others (18%). Less commonly mentioned reasons given by participants in other studies included a desire to learn more about their condition, get free and better care, encouragement by family members and friends, favorable impression of and trust in clinical staff, and even to help promote the investigators' careers [3–6].

Several reasons for declining participation in research projects have also been reported. In the Emergency Care Research Institute (ECRI) survey [2], the major general reasons for not participating were inconvenience (25%), concern over experimentation (20%), potential lack of health benefit (19%), and physician influence (14%). Many patients also lacked interest and preferred to stay with their own physicians. In another survey, fear was given as a major reason by half of those declining participation and the use of a placebo by almost one-quarter [6].

Logistical issues are sometimes given—demands on time, conflicts with other commitments, and problems with travel/transportation and parking. Barriers to participation in cancer trials include concerns with the trial setting, a dislike of randomization, presence of a placebo or no-treatment group, and potential adverse effects [7].

Common Recruitment Problems

The published experience from recruitment of participants into clinical trials through 1995 is nicely summarized in a literature review and annotated bibliography [8]. Over 4,000 titles were identified and 91 articles considered useful for formulation of recruitment strategies in clinical trials are annotated. The review focuses on experiences recruiting diverse populations such as ethnic minorities, women, and the elderly. Also discussed are successful recruitment approaches, which include use of registries, occupational sites, direct mailing, and use of media. The article highlights the value of pilot studies, projecting and monitoring recruitment, and the use of data tracking systems. Many of these issues are covered in more detail later in this chapter.

A review from the United Kingdom of 114 clinical trials that recruited participants between 1994 and 2002 explored the factors related to good and poor recruitment [9]. Approximately one-third of all trials met their original recruitment goal within the proposed time frame while approximately half had to be extended. Among those failing to make the original target, one half revised the goals. About 40% of all trials did not initiate recruitment as planned, mostly due to staffing and logistical issues. Almost two-thirds of the trials acknowledged early recruitment problems. More than half of the reviewed trials, a remarkably high number, had a formal pilot study that led to changes in the recruitment approach for the main trial. The written trial materials were revised, the trial design altered, the recruitment target changed, the number of sites increased, and/or the inclusion criteria broadened.

A systematic review of recruitment methods identified 37 trials describing four broad categories of recruitment strategies: novel trial designs (including different consent strategies), recruiter interventions (including training), incentives, and provision of trial information to potential participants [10]. Strategies that increased recruitment rates included increasing awareness of the health problem being studied, educational sessions, health questionnaires, and monetary incentives. A study using semistructured investigator interviews in the Palliative Care Research Cooperative Group identified five effective recruitment strategies: systematic screening of patient lists or records, messaging to patients to make research relevant, flexible protocols to account for patient needs, clinical champion support, and involvement in the cooperative group [11]. There is little published information on cost-effectiveness of interventions to improve recruitment, although one review of ten studies found that directly contacting potential participants seemed to be an efficient strategy [12].

Electronic health records, combined with programming to systematically screen for eligible participants, provide an important tool for certain trials. A single-center study showed that when an automated electronic health record alert system was put into place in clinics to identify patients for a trial of type II diabetes, referral rates increased by tenfold and enrollment rate by twofold [13]. An electronic screening tool was effective, and it performed particularly well in excluding ineligible patients

at Columbia University for the National Institutes of Health (NIH)-sponsored Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial [14]. A hybrid approach of electronic screening coordinated with paper screening forms was successful in the Veterans Affairs VA-STRIDE trial to recruit patients for a physical activity intervention [15].

A review of the challenges and opportunities of use of electronic health records to support clinical trial enrollment identifies regulatory issues such as use of screening information preparatory to research and barriers related to desire to approach a patient's treating doctor before approaching the patient directly [16]. An overarching goal is to use electronic systems to better integrate clinical trials into clinical practice. An example of success is the Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE) trial, where all interventional hospitals (and cardiologists) in Sweden agreed to approach all eligible patients for enrollment using the national registry platform for randomization and data collection [17]. During the recruitment period (see Fig. 5.1), 59.7% of all the patients presenting with ST segment elevation myocardial infarction and referred for percutaneous coronary intervention and 76.9% of all the patients potentially eligible for enrollment in Sweden and Iceland were included in the trial, at a low per-patient cost. Not only did this remarkably high participant capture allow the trial enrollment to be completed in 2 years and 9 months, but it enhanced generalizability of the results.

But it is more typical that even when carefully planned and perfectly executed, recruitment may still proceed slowly. Investigators should always expect problems to occur, despite their best efforts. Most of the problems are predictable but a few may be completely unforeseen. In one multicenter study, there were reports of murders of inpatients at the hospital adjacent to the study clinic. It is hardly surprising that attendance at the clinic fell sharply.

Overestimation of eligible participants is a common reason for recruitment difficulties. A group of Finnish investigators [18] conducted a retrospective chart review. The typical eligibility criteria for clinical trials of patients with gastric ulcer were applied to 400 patients hospitalized with that diagnosis. Only 29% met the eligibility criteria but almost all deaths and serious complications such as gastric bleeding, perforation, and stenosis during the first 5–7 years occurred among those who would have been ineligible. Clearly, the testing of H_2–blockers or other compounds for the prevention of long-term complication of gastric ulcer in low-risk participants should not be generalized to the entire ulcer population. Troubling in this report is the evidence that the eligibility criteria can have such a dramatic effect on the event rates in those qualifying for participation.

Reliance on physician referrals is common and often problematic. Usually this technique results in very few eligible participants. In 2005, a survey of 7,000 physicians reported that only 31% of them had ever referred a patient to a clinical trial [6]. In one multicenter trial an investigator invited internists and cardiologists from a large metropolitan area to a meeting. He described the study, its importance, and his need to recruit men who had had a myocardial infarction. Each of the physicians stood up and promised to contribute one or more participants.

One hundred fifty participants were pledged; only five were ultimately referred. Despite this, such pleas may be worthwhile because they make the professional community aware of a study and its purpose. Investigators who stay in close contact with physicians in a community and form a referral network have more success in obtaining cooperation and support.

When recruitment becomes difficult, one possible outcome is that an investigator will begin to loosely interpret entry criteria or will deliberately change data to enroll otherwise ineligible participants or even "enroll" fictitious subjects. Unfortunately, this issue is not merely theoretical. Such practices have occurred, to a limited extent, in more than one trial [19–21]. The best way to avoid the problem is to make it clear that this type of infraction harms both the study and the participants, and that neither science nor the investigators are served well by such practices. An announced program of random record audits by an independent person or group during the trial may serve as a deterrent.

Planning

In the planning stage of a trial, an investigator needs to evaluate the likelihood of obtaining sufficient study participants within the allotted time. This planning effort entails obtaining realistic estimates of the number of available potential participants meeting the study entry criteria. However, in the United States, access to available patient data from paper and electronic medical records requires compliance with the Health Insurance Portability and Accountability Act (HIPAA) and similar regulations apply in many other countries. Access can be granted but many community practices do not have such a mechanism in place and tend to be reluctant to release patient information. Even if those restrictions are overcome, census tract data or hospital and physician records may be out of date, incomplete, or incorrect. Information about current use of drugs or frequency of surgical procedures may not reflect what will occur in the future, when the trial is actually conducted. Records may not give sufficient—or even accurate—details about potential participants to determine the impact of all exclusion criteria. Clearly, available data certainly do not reflect the willingness of people to enroll in the trial or comply with the intervention.

After initial record review, an investigator may find it necessary to expand the population base by increasing the geographical catchment area, canvassing additional hospitals, relaxing one or more of the study entrance criteria, increasing the planned recruitment time, or any combination of these. The preliminary survey of participant sources should be as thorough as possible, since these determinations are better made before, rather than after, a study begins.

Investigator and study coordinator commitment is key to success. Since lack of trust is a major barrier to patient agreement to participate, a strategy for effective communication from the treating physician to the patient about the relevance and importance of the study is critical. A concern is that investigators keep adding new

trials to those they already have committed to. Trials with higher payments seem to get more attention. The investigator also needs strong support from his institution and colleagues. Other investigators in the same institution or at nearby institutions may compete for similar participants. Since participants should generally not be in more than one trial at a time, competing studies may decrease the likelihood that the investigator will meet his recruitment goal. Competition for participants may necessitate reappraising the feasibility of conducting the study at a particular site.

Announcements of the trial should precede initiation of recruitment. The courtesy of informing area health professionals about the trial in advance can facilitate cooperation, reduce opposition, and avoid local physicians' surprise at first hearing about the study from their patients rather than from the investigator. Talks to local professional groups are critical, but these and any notices regarding a trial should indicate whether the investigator is simply notifying physicians about the study or is actively seeking their assistance in recruiting participants.

Planning also involves setting up a clinic structure for recruitment with interested and involved co-investigators, an experienced and organized coordinator in charge of recruitment, and other staff required for and dedicated to the operations. A close working relationship between the clinic staff and investigators, with regular clinic meetings, is crucial from the very beginning to enrollment of the last participant. Careful planning and clear delineation of staff responsibilities are essential features of well-performing recruitment units.

Recruitment in most trials is curvilinear, particularly in multicenter trials, with a gradual acceleration of enrollment as centers start up and refine successful strategies for enrollment. But the calculation of a sample size estimate typically assumes a constant rate of enrollment. A slow start can reduce the statistical power of the trial by reducing the average participant follow-up time. Thus, ideally, recruitment should begin no later than the first day of the designated recruitment period. As important as the best planning is, commitment and willingness by everyone to spend a considerable amount of time in the recruitment effort are equally important. Just as investigators usually overestimate the number of participants available, they often underestimate the time and effort needed to recruit. Investigators must accommodate themselves to the schedules of potential participants, many of whom work. Thus, recruitment is often done on weekends and evenings, as well as during usual working hours.

The need for multiple recruitment strategies has been well documented [22, 23]. The first randomization should take place on the first day of the identified recruitment period. Therefore, if there is a lengthy prerandomization screening period, adjustments in the timing of the first randomization should be made. Because it is difficult to know which strategies will be productive, it is important to monitor effort and yield of the various strategies. A successful strategy in one setting does not guarantee success in another. The value of multiple approaches is illustrated by one large study in which the investigator identified possible participants and wrote letters to them, inviting them to participate. He received a poor response until his study was featured on local radio and television news. The media coverage had apparently "legitimized" the study, as well as primed the community for acceptance of the trial.

Contingency plans must be available in case recruitment lags. Experience has shown that recruitment yields, in general, are much lower than anticipated. Thus, the identified sources needed to be much larger than the recruitment goals. Hence, additional sources of potential study participants should be kept in reserve. Approval from hospital staff, large group practices, managed care organizations, corporation directors, or others controlling large numbers of potential participants often takes considerable time. Waiting until recruitment problems appear before initiating such approval can lead to weeks or months of inaction and delay. Therefore, it is advisable to make plans to use other sources before the study gets underway. If they are not needed, little is lost except for additional time used in planning. Most of the time these reserves will prove useful.

If data concerning recruitment of potential participants to a particular type of trial are scanty, a pilot or feasibility study may be worthwhile. Pilot studies can provide valuable information on optimal participant sources, recruitment techniques, and estimates of yield. In a trial of elderly people, the question arose whether those in their 70s or 80s would volunteer and actively participate in a long-term, placebo-controlled trial. Before implementing a costly full-scale trial, a pilot study was conducted to answer these and other questions [24]. The study not only showed that the elderly were willing participants, but also provided information on recruitment techniques. The success of the pilot led to a full-scale trial.

Recruitment Sources

The sources for recruitment depend on the features of the study population; sick people versus well, hospitalized versus not, or acute versus chronic illness. For example, enrollment of acutely ill hospitalized patients can only be conducted in an acute care setting, while enrollment of healthy asymptomatic individuals with certain characteristics or risk factors requires a community-based screening program. Following the introduction of the HIPAA and other privacy regulations, readily available sources for recruitment have changed. Identification of potential participants through review of electronic health records requires active involvement of those patients' own physicians. Thus, focus has shifted to direct participant appeal.

Direct invitation to study participants is an attractive approach, since it avoids many confidentiality issues. Solicitation may be done through mass media, wide dissemination of leaflets advertising the trial, or participation by the investigator in health fairs. None of these methods is foolproof. The yield is often unpredictable and seems to depend predominantly on the skill with which the approach is made and the size and kind of audience it reaches. One success story featured a distinguished investigator in a large city who managed to appear on a local television station's evening news show. Following this single 5-min appeal, thousands of people volunteered for the screening program. Experience, however, has shown that most individuals who respond to a media campaign are not eligible for the trial.

The recruitment into the Systolic Hypertension in the Elderly Program (SHEP) was a major undertaking [25]. A total of almost 450,000 potential participants were contacted in order to enroll 4,736 (1.1%). One of the major recruitment approaches in SHEP was mass mailings. A total of 3.4 million letters were sent by 14 of the SHEP clinics and the overall response rate was 4.3%. Names were obtained from the Departments of Motor Vehicles, voter registration lists, health maintenance organizations, health insurance companies, AARP, and others. Endorsement was obtained from these organizations and groups; many of them issued the invitations on their own letterheads. Each mailing included a letter of invitation, a standard brochure describing SHEP, and a self-addressed stamped return postcard. Experience showed that the response rates varied by mailing list source. It was also clear that clinics with experienced recruitment staff did better than the others.

A U.S. survey of 620 previous trial participants asked where they first learned about the trials [6]. Media the most common answer, was given by 30%, but 26% said the internet. Web-based strategies seem to be growing in importance, although the yield appears to vary by type of trial. Only 14% in the survey first learned of the trial via physician referral.

Participants may also be approached through a third party. For instance, local chapters of patient organizations may be willing to refer members. Another approach is through physician referrals. To draw physicians' attention to a particular study, an investigator may send letters, make telephone calls, present at professional society meetings, publish notices in professional journals, or exhibit at scientific conferences. The hope is that these physicians will identify potential participants and either notify the investigator or have the potential participant contact the investigator. As noted earlier, this usually yields few participants. To overcome the problem with physician referral, sponsors are offering financial incentives to referring physicians. The value of this practice has not been properly evaluated, but it has raised ethical issues concerning conflict of interest, disclosure to potential participants, and implications for the informed consent process [26].

The recruitment targets have to be adjusted if special subgroups of the population are being recruited. In response to a relative paucity of clinical trial data on women and minorities, the U.S. Congress in 1995 directed the NIH to establish guidelines for inclusion of these groups in clinical research. The charge to the Director of the NIH to "ensure that the trial is designed and carried out in a manner sufficient to provide valid analysis of whether the variables being studied in the trial affect women and members of minority groups, as the case may be, differently than other subjects in the trial" has major implications depending on the interpretation of the term "valid analysis" [27].

To document a similar effect, beneficial or harmful, separately for both men and women and separately for various racial/ethnic groups could increase the sample size by a factor ranging from 4 to 16. The sample size will grow considerably more if the investigator seeks to detect differences in response among the subgroups. We support adequate representation of women and minorities in clinical trials, but suggest that the primary scientific question being posed be the main determinant of the composition of the study population and the sample size. When the effort is made, successful enrollment of women and minorities can be accomplished. An example is the Selenium and Vitamin E Cancer Prevention Trial [28].

An increasingly common approach to meeting the need for large sample sizes in multicenter trials with mortality and major event response variables has been to establish clinical centers internationally [29]. This experience has been positive and the number of participants enrolled by such centers often exceeds those in the country of the study's origin. The success in recruitment may, however, come at a cost. Trial findings may differ among countries (see also Chap. 21). Possible reasons include differences in the baseline characteristics of the study population, in the practice of medicine as a reflection of the quality of care, research traditions, and socioeconomic and other factors [30, 31]. O'Shea and Califf analyzed the international differences in cardiovascular trials and reported important differences in participant characteristics, concurrent therapies, coronary revascularizations, length of hospital stay, and clinical outcomes in the U.S. and elsewhere [32]. Importantly, they pointed out that, in general, the differing event rates would not be expected to affect the relative effects of a treatment. But there are examples of possible differences in treatment effects according to enrollment within versus outside the U.S., including less benefit of beta blockers in heart failure [33] and of ticagrelor following acute coronary syndromes [34]. The authors of a review of 657 abstracts from trials of acupuncture and other interventions concluded that some countries published unusually high proportions of positive results [35]. Possible explanations include publication biases, level of care, and differences in study populations.

Can findings from low and middle income countries be extrapolated to high income countries and regions and vice versa? It is important that the publications from large international studies address this question by presenting findings by geographic region.

Conduct

Successful recruitment of participants depends not only on proper planning but also on the successful implementation of the plan. Systems should be in place to identify all potential participants from the identified recruitment pool and to screen them for eligibility. For hospital-based studies, logging all admissions to special units, wards, or clinics is invaluable. However, keeping such logs complete can be difficult, especially during evenings or weekends. During such hours, those most dedicated to the study are often not available to ensure accuracy and completeness. Vacation times and illness may also present difficulties in keeping the log up to date. Therefore, frequent quality checks should be made. Participant privacy is also important and is guided by ethics committees, and in the U.S., HIPAA regulations. At what point do the investigators obtain consent? For those who refuse to participate, what happens to the data that had been collected and used to identify them? The answers to this will vary from institution to institution and depend on who is keeping the log and for what reason. Information recorded by code numbers can facilitate privacy. Electronic health records can be used. Electronic medical records

permit software algorithms to search for patient profiles that match a particular protocol and automatically identify for the health care team those eligible for a specific trial. A group at Cincinnati Children's Hospital reported a retrospective study estimating that the electronic health records in the emergency department could be searched with natural language processing, information extraction, and machine learning techniques to reduce screening workload by over 90% for 13 randomly selected, disease-specific trials [36]. However, the broad experience of electronic systems for clinical trial recruitment shows inconsistent evidence of value. The integration of the systems with human workflow may be more important than sophisticated algorithms [37].

For community-based studies, screening large numbers of people is typically a major undertaking especially if the yield is low. Prescreening potential participants by telephone to identify those with major exclusion criteria (e.g., using demographics, medical history) has been employed in many projects. In the Lung Health Study, investigators used prescreening to reduce the number of screening visits to approximately half of those projected [38, 39]. Investigators need to identify the best times to reach the maximum number of potential participants. If they intend to make home visits or hope to contact people by telephone, they should count on working evenings or weekends. Unless potential participants are retired, or investigators plan on contacting people at their jobs (which, depending on the nature of the job, may be difficult), normal working hours may not be productive times. Vacation periods and summers are additional slow periods for recruitment.

The logistics of recruitment may become more difficult when follow-up of enrolled participants occurs while investigators are still recruiting. In long-term studies, the most difficult time is usually towards the end of the recruitment phase when the same staff, space, and equipment may be used simultaneously for participants seen for screening, baseline, and follow-up examinations. Resources can be stretched to the limit and beyond if appropriate planning has not occurred.

The actual mechanics of recruiting participants needs to be established in advance. A smooth clinic operation is beneficial to all parties. Investigators must be certain that necessary staff, facilities, and equipment are available at appropriate times in the proper places. Keeping potential participants waiting is a poor way to earn their confidence.

Investigators and staff need to keep abreast of recruitment efforts. Conducting regular staff meetings and generating regular reports may serve as forums for discussion of yields from various strategies, percent of recruitment goal attained, as well as brainstorming and morale-boosting. These meetings, useful for both single- and multicenter trials, also provide the opportunity to remind everyone about the importance of following the study protocol, including paying careful attention to collection of valid data.

Record keeping of recruitment activities is essential to allow analyses of recruitment yields and costs from the various recruitment strategies. Recruiting large numbers of potential participants requires the creation of timetables, flow charts, and databases to ensure that screening and recruitment proceed smoothly. Such charts should include the number of people to be seen at each step in the

process at a given time, the number and type of personnel and amount of time required to process each participant at each step, and the amount of equipment needed (with an allowance for "down" time). A planned pilot phase is helpful in making these assessments. One positive aspect of slow early recruitment is that the "bugs" in the start-up process can be worked out and necessary modifications made.

Several additional points regarding the conduct of recruitment are worth emphasizing:

First, the success of a technique is unpredictable. What works in one city at one time may not work at the same place at another time or in another city. Therefore, the investigator needs to be flexible and to leave room for modifications.

Second, investigators must maintain good relationships with participants' personal physicians. Physicians disapproving of the study or of the way it is conducted are more likely to urge their patients not to participate.

Third, investigators must respect the families of potential participants. Most participants like to discuss research participation with their family and friends. Investigators should be prepared to spend time reviewing the study with them. If the study requires long-term cooperation from the participant, we encourage such discussions. Anything that increases family support is likely to lead to better recruitment and protocol adherence.

Fourth, recruiting should not be overly aggressive. While encouragement is necessary, excessive efforts to convince, or "arm twist" people to participate could prove harmful in the long run, in addition to raising ethical concerns. One might argue that excessive salesmanship is unethical. Those reluctant to join may be more likely to abandon the study later or be poor adherers to study interventions after randomization. Effective work on adherence begins during the recruitment phase.

Fifth, the recruitment success is closely associated with the level of commitment and effectiveness of communication of the investigator and the study coordinator.

Sixth, electronic health records and social media provide important opportunities to use electronic data and communication for certain types of trials.

Monitoring

Successful trial recruitment often depends on establishing short-term and long-term recruitment goals. The investigator should record these goals and make every effort to achieve them. Since lagging recruitment commonly results from a slow start, timely establishment of initial goals is crucial. The investigator should be ready to randomize participants on the first official day of study opening.

The use of weekly and/or monthly interim goals in a long-term study orients the investigator and staff to the short-term recruitment needs of the study. These goals can serve as indicators for lagging recruitment and may help avoid a grossly uneven recruitment pace. Inasmuch as participant follow-up is usually done at regular intervals, uneven recruitment results in periods of peak and slack during the

follow-up phase. This threatens effective use of staff time and equipment. Of course, establishing a goal in itself does not guarantee timely participant recruitment. The goals need to be realistic and the investigator must make the commitment to meet each interim goal.

The reasons for falling behind the recruitment goal(s) should be determined. In a multicenter clinical trial, valuable insight can be obtained by comparing results and experiences from different centers. Those clinical sites with the best recruitment performance can serve as role models for other sites, which should be encouraged to incorporate other successful techniques into their recruitment schemes. Multicenter studies require a central office to oversee recruitment, compare enrollment results, facilitate communication among sites, and lend support and encouragement. Frequent feedback to the centers by means of tables and graphs, which show the actual recruitment compared with originally projected goals, are useful tools. Examples are shown in the following figures and table. Figure 10.1 shows the progress of an investigator who started participant recruitment on schedule and maintained a good pace during the recruitment period. The investigator and clinic staff accurately assessed participant sources and demonstrated a commitment to enrolling participants in a relatively even fashion. Figure 10.2 shows the record of an investigator who started slowly, but later improved. However, considerable effort was required to compensate for the poor start. Clinic efforts included expanding the base from which participants were recruited and increasing the time spent in enrollment. Even if the clinic eventually catches up, the person-years of exposure to the intervention has been reduced which may affect event rates and trial power. In contrast, as seen in Fig. 10.3, the investigator started slowly and was never able to improve his performance. This center was dropped from a multicenter study because it could not

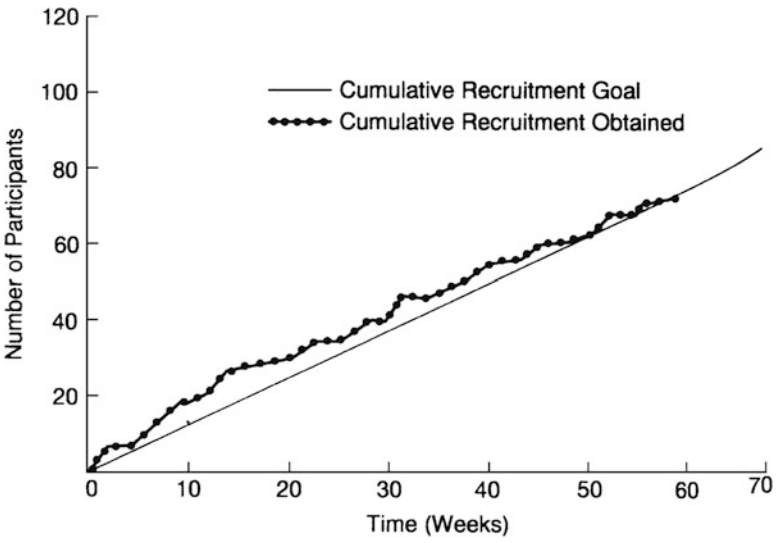

Fig. 10.1 Participant recruitment in clinic that consistently performed at goal rate

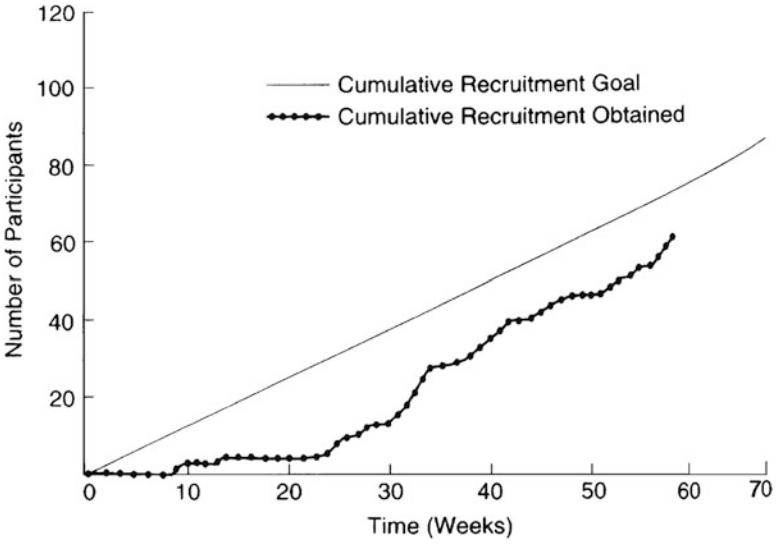

Fig. 10.2 Participant recruitment in a clinic that started slowly and then performed at greater than goal rate

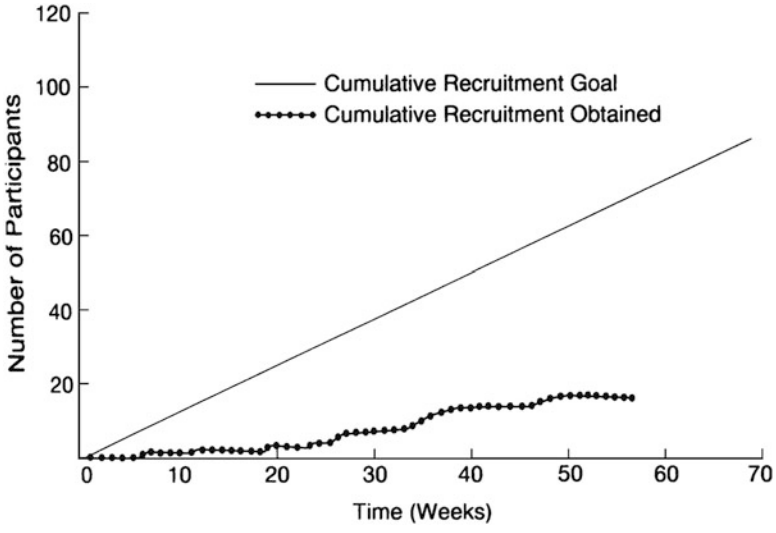

Fig. 10.3 Participant recruitment in a clinic that performed poorly

contribute enough participants to the study to make its continued participation efficient. Figure 10.4 shows enrollment in the TASTE trial [17], an example of a trial that enrolled the majority of eligible patients in an entire country, and even in this highly organized trial, enrollment started gradually and the rate increased over the first few months.

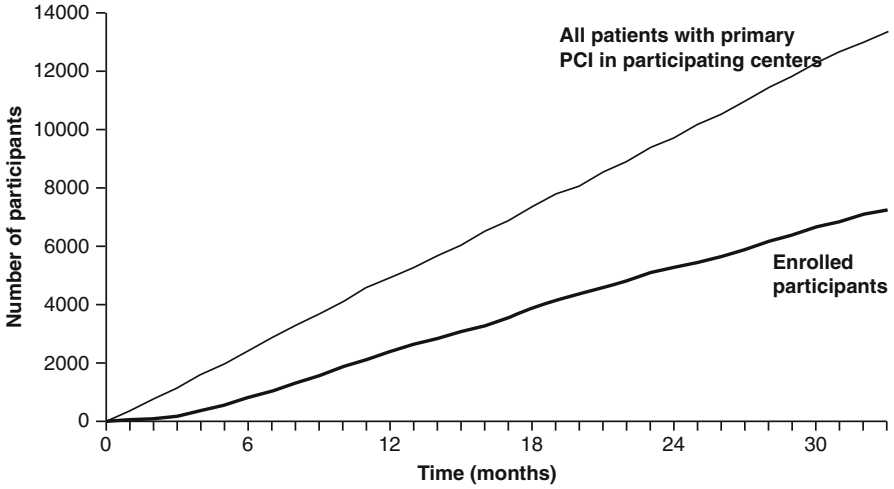

Fig. 10.4 Participant recruitment in the TASTE trial [17] using a national registry for participant identification. PCI = percutaneous coronary intervention

Table 10.1 Weekly recruitment status report by center

Center	(1) Contracted goal	(2) Enrollment this week	(3) Actual enrollment to date	(4) Goal enrollment to date	(5) Actual minus goal	(6) Success rates (3)/(4)	(7) Final projected intake	(8) Final deficit or excess (7)-(1)
A	150	1	50	53.4	−3.4	0.94	140	−10
B	135	1	37	48.0	−11.0	0.77	104	−31
C	150	2	56	53.4	2.6	1.06	157	7

Table used in the Beta-Blocker Heart Attack Trial: Coordinating Center, University of Texas, Houston

Table 10.1 shows goals, actual recruitment, and projected final totals (assuming no change in enrollment pattern) for three centers of a multicenter trial. Such tables are useful to gauge recruitment efforts short-term as well as to project final numbers of participants. The tables and figures should be updated as often as necessary.

In single-center trials, the investigator should also monitor recruitment status at regular and frequent intervals. Review of these data with staff keeps everyone aware of recruitment progress. If recruitment lags, the delay can be noted early, the reasons identified, and appropriate action taken.

Approaches to Lagging Recruitment

We have identified five possible approaches to deal with lagging recruitment, in addition to the strategies to enhance enrollment reviewed above.

The first is to accept a smaller number of participants than originally planned. Doing this is far from ideal as the power of the study will be reduced. In accepting a smaller number of participants than estimated, the investigator must either alter design features such as the primary response variable, or change assumptions about intervention effectiveness and participant adherence. As indicated elsewhere, such changes midway in a trial may be liable to legitimate criticism. Only if the investigator is lucky and discovers that some of the assumptions used in estimating sample size were too pessimistic would this "solution" provide comparable power. There are rare examples of this happening. In a trial of aspirin in people with transient ischemic attacks, aspirin produced a greater effect than initially postulated [40]. Therefore, the less-than-hoped-for number of participants turned out to be adequate.

A second approach is to relax the inclusion criteria. This should be done only if little expectation exists that the study design will suffer. The design can be marred when, as a result of the new type of participants, the control group event rate is altered to such an extent that the estimated sample size is no longer appropriate. Also, the expected response to intervention in the new participants may not be as great as in the original participants. Furthermore, the intervention might have a different effect or have a greater likelihood of being harmful in the new participants than in those originally recruited. The difference in additional participants would not matter if the proportion of participants randomized to each group stayed the same throughout recruitment. However, as indicated in Chap. 6, certain randomization schemes alter that proportion, depending on baseline criteria or study results. Under these circumstances, changing entrance criteria may create imbalances among study arms.

The Coronary Drug Project provides a classic example [41]. Only people with documented Q-wave myocardial infarctions were originally eligible. With enrollment falling behind, the investigators decided to admit participants with non-Q-wave infarctions. Since there was no reason to expect that the action of lipid-lowering agents being studied would be any different in the new group than in the original group and since the lipid-lowering agents were not contraindicated in the new participants, the modification seemed reasonable. However, there was some concern that overall mortality rate would be changed because mortality in people with non-Q-wave infarctions may be less than mortality in people with Q-wave infarctions. Nevertheless, the pressure of recruitment overrode that concern. Possible baseline imbalances did not turn out to be a problem. In this particular study, where the total number of participants was so large (8,341), there was every expectation that randomization would yield comparable groups. If there had been uncertainty regarding this, stratified randomization could have been employed (Chap. 6). Including people with non-Q-wave infarctions may have reduced the power of the study because this group had a lower mortality rate than those with Q-wave infarctions in each of the treatment groups, including the placebo group. However, the treatments were equally ineffective when people with Q-wave infarctions were analyzed separately from people with non-Q-wave infarctions [42].

The third and probably most common approach to recruitment problems is to extend the time for recruitment or, in the case of multicenter studies, to add recruiting centers. Both are the preferred solutions, requiring neither modification of admission criteria nor diminution of power. However, they are also the most costly. Whether the solution of additional time or additional centers is adopted depends on cost, on the logistics of finding and training other high quality centers, and on the need to obtain study results quickly.

A fourth approach to lagging recruitment is "recycling" of potential participants. When a prospective participant just misses meeting the eligibility criteria, the temptation is natural to try to enroll them by repeating a measurement, perhaps under slightly different conditions. Due to variability in a screening test, many investigators argue that it is reasonable to allow one repeat test and give a person interested in the trial a "second chance." In general, this practice should be discouraged. A study is harmed by enrolling persons for whom the intervention might be ineffective or inappropriate. However, in some progressive diseases, waiting a year to recycle a potential participant may prove to be useful.

Instances exist where, in order to enter a drug study, the participant needs to be off all other medication with similar actions. At baseline, participants may be asked whether they have adhered to this requirement. If they have not, the investigator may repeat the instructions and have the participants return in a week for repeat baseline measurements. The entrance criterion checks on a participant's ability to adhere to a protocol and their understanding of instructions. This "second chance" is different from recycling and it is legitimate from a design point of view. However, the second-chance participant, even if he or she passes the repeat baseline measurement, may not be as good a candidate for the study as someone who adhered on the first occasion [43].

The fifth approach of broadening or changing the pre-specified primary response variable is very common, and is discussed in more detail in Chap. 3. Enrollment was slower than expected in the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial [44]. This, combined with a narrowing of entry criteria to exclude patients with diabetes and either proteinuria or hypertension and microalbuminuria for whom benefit was clearly established from other trials, prompted a change in the primary outcome (of death from cardiovascular causes or nonfatal myocardial infarction) to include coronary revascularization, reducing the sample size from 14,100 patients to 8,100.

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