

Patient Participation and Compliance in Cancer Chemoprevention Trials: Issues and Concerns (44176)

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Abstract. Cancer chemoprevention trials have unique characteristics that make the tasks of participant recruitment, enrollment, and long-term adherence to the study protocol and intervention regimen especially difficult. Barriers to patient accrual, long-term participation, and optimal adherence are inherent in clinical trial design and organization, and are frequently associated with the attitudes and behavioral dynamics of physicians and the participants themselves. Attracting racially and ethnically diverse populations to trial participation adds additional problems and considerations. Careful planning early in the design phase of a chemoprevention clinical trial must take into account these numerous issues. Clinical investigators should seek expert advice from a number of health care disciplines to better design chemoprevention protocols that minimize logistic complexity, maximize participant eligibility, simplify data collection, and take into account the complex behavioral dynamics of the clinical trial process.

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Clinical trials are considered the most reliable method for evaluating the efficacy of therapeutic or preventive interventions in human populations (1). Their design and implementation, especially phase III multicenter trials, require careful planning and vigilant monitoring in order to ensure success. Furthermore, trials testing cancer preventive or chemopreventive agents have unique characteristics that must also be addressed (2, 3). In contrast to cancer treatment, cancer chemoprevention is targeted at reducing cancer incidence and usually involves the long-term administration of specific chemically defined agents, such as vitamins or their synthetic analogs, in patients at risk of developing primary or secondary cancers (4, 5). By their nature, these trials usually involve "healthy" participants. This often limits the choice or dose of the chemopreventive agent in order to minimize the level of toxicity that might otherwise be acceptable in a diseased population. Due to the chronic nature of these interventions, long-term adherence to both the intervention and the protocol by trial participants is a major issue (6). Given the relatively low incidence of

cancer—even in populations at high risk—prevention trials with incident cancer as an end point usually require large numbers of participants to identify clinically and statistically significant differences between the treatment and control groups. Given their long duration, large sample size, and the need for extensive data collection, cancer chemoprevention trials can be quite costly. These special characteristics render the already difficult tasks of participant recruitment, enrollment, and long-term adherence to the study protocol and intervention regimen even more trying.

A number of factors contribute to the difficulties mentioned. The intent of this paper is to review some of these factors, touch on issues of patient compliance or adherence with the study protocol and intervention regimen, and briefly discuss special issues that relate to the participation of minority and underserved populations in clinical trials. All of these issues will be discussed in the context of cancer chemoprevention trials.

Barriers to Patient Accrual and Participation in Cancer Chemoprevention Trials

In any trial, complete and efficient recruitment and enrollment of the required number of study participants are essential for a successful outcome (7, 8). A delay in the recruitment process increases both the cost and the duration of the study while reducing the power of the study given the fewer patient-years of observation (7). Clinical trials

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have been terminated when the required number of participants could not be recruited in a reasonable period of time (7), leading to the complete loss of funds expended in the design and start-up phases. Prolonging the recruitment period can also lead to other problems, such as uneven workload for staff, as well as adverse morale effects on both staff and enrolled participants.

Factors inherent in trial design and organization, those related to physicians and health care providers, as well as those associated with the participants themselves all can present barriers in the recruitment and retention processes (8).

Study Design and Organization. Although study-design complexity is dictated by both the intervention agent being studied and the end point being monitored, a trial with simple, straightforward objectives and end points based on a clearly defined rationale and hypothesis has a greater chance of success in achieving its recruitment goals. Within the construct of the established scientific and organizational infrastructure of a multicenter trial, the temptation is great to include numerous ancillary studies and additional biological specimen collections or tests to facilitate exploring a number of secondary hypotheses. Although such studies may be scientifically valid and interesting, one must take into account the impact their added logistic complexity has on the primary goal of the trial, especially the accrual and long-term participation of study subjects. An overly complex trial has been shown to serve as a disincentive for participation to both physicians (9) and patients alike (10). Even in the most simply designed trial, patient eligibility criteria that are overly rigid or excessive can not only limit the applicability of the results but also decrease the number of patients available for enrollment (11, 12). One study found that more than 8% of physicians surveyed believed that many protocols are too rigidly designed (11).

The actual process of informed consent can also serve as an impediment to patient acceptance of a clinical trial (12). Informed consent is meant to provide the prospective participant with a clear understanding of the personal benefits, the risks, the logistic requirements of participation (follow-up visits, venipuncture, etc.), study-related costs, and the length of time expected for their participation (13). In many instances, adequate time is not allocated for the patient to absorb and understand the document. In the case of the overly complex trial described above, the necessary detail included in the informed consent document can overwhelm the patient, leading to a further lack of understanding and to anxiety and, perhaps, to premature refusal to participate in the trial. Indeed, it is known that in many cases, patients remember or understand little of what they agree to during the consent process (14). In one study of volunteers in an anti-inflammatory drug trial, two-thirds of the participants did not remember being informed of the potential risks of taking the medication (15). It has been shown that patients often view the informed consent document as

overly legalistic and deliberately fail to read it because they feel it intrudes on the physician-patient relationship (16).

The informed consent process should be looked upon not only as an ethical and legal requirement, but as a time to establish a dialogue with the patient regarding his or her participation as part of the study team. A clearer understanding of how patients' participation integrates with the goals of the study may decrease the chance of their dropping out and improve long-term study attrition. Given the altruistic motivations apparent in many study participants surveyed (15, 17-20), it may be beneficial to emphasize, early in the process of recruitment, the potential participants' contribution to medical knowledge and the help their participation might provide to others (14).

Physicians/Health-Care Providers. Within the medical institution conducting clinical research, the decision by physicians not to enroll otherwise eligible patients onto protocol has been identified as a leading reason for inadequate accrual (11, 21). In this setting, the physician serves as a "gatekeeper" to study entry and must decide whether entering a patient into a trial is justified (12). Physician behavior in this regard can be influenced by a number of factors. For example, in a survey conducted among 244 oncologists at a major cancer center, physicians stated that the inconvenience to patients, excessive physician time requirements, and lack of support for follow-up all serve as major impediments to enrolling patients in available clinical trials (11). Physicians also fear that trial participation may interfere with the physician-patient relationship. In traditional medicine, the physician has taken the active role in medical decision making and informs the patient of what they feel he or she needs to know (10). Although most physicians agree with the required process of informed consent, many feel that informed consent forms provide more information than the patient needs. By its nature, the informed consent process acknowledges the uncertainty about the effectiveness of a specific therapy (16). Indeed, resolving this question is the major purpose of the trial. However, some physicians are uncomfortable with communicating this uncertainty to the patient and fear that it may undermine their authority (22). They fear it could be construed by the patient as a lack of knowledge on the part of the physician, leading to a loss of confidence and a compromised physician-patient relationship.

If a physician does not believe in the scientific objectives of a clinical protocol, one can expect little enthusiasm on the part of the physician for enrolling his or her patients in the trial. In fact, the physician's philosophy about patient care can serve as a major barrier to including his or her patient in a clinical trial (22). A physician whose primary allegiance is to the individual patient and not to the aggregate or that of future patients will be less likely to suggest trial enrollment to his or her patients (22). To be an effective clinical investigator, the physician must integrate the role of primary-care provider with that of research scientist (23). If the trial is to be successful, it is critical that the physician

not only agree with the scientific objectives but also adhere to the long-term medical and data follow-up requirements of the study design (10). As mentioned earlier, the complexity of clinical trial design has been cited by many physicians as a barrier to participation. Even if a physician believes in the scientific objectives of a clinical investigation, an overly complex protocol that attempts to answer too many questions and requires extensive collection of both data and biologic specimens can discourage participation. A recent study conducted among oncologists in Norway indicated that the two most important factors in the investigator's design to enroll patients in a trial were the scientific aim of the study and the simplicity of the trial protocol (9).

Another important barrier related to protocol participation is what many physicians see as lack of equitable compensation for their work. It is estimated that, on average, a physician can spend as long as 4 hr evaluating a patient prior to trial enrollment, even for those patients who are ultimately never randomized (10). At the present time, reimbursement for physician's fees, laboratory tests, and other diagnostic procedures is not covered by the federal government or many insurance companies.

One study that examined the concerns of oncologists with patient participation in clinical trials delineated six variables that distinguish the "experimenter" from the "therapist" among the physicians (23). They can be summarized as follows: (i) allegiance to the aggregate versus the individual patient, (ii) belief that patient care is an outgrowth of clinical research versus the reverse, (iii) belief that uncertainty about a specific therapy requires a clinical trial to resolve versus an individual decision by the physician, (iv) reliance on published data versus personal experience, (v) willingness to be peer-evaluated versus preference for nonaccountability, and (vi) an emphasis on the evaluative dimensions of professional actions versus loyalty to medical traditions (21, 23). Obviously, those physicians whose training and beliefs are concordant with the "experimenter" profile will be more likely to refer or enroll their patients into clinical trials.

Patient participation in a clinical trial can be also influenced by the beliefs, experience, and attitudes of the physician referring the patient to a clinical trial (10, 11, 22, 24). Community physicians who may refer a patient must first be aware that appropriate clinical trial protocols are available. Once aware of the clinical trial protocol, they must be reassured that, should they refer a patient, they will not lose contact or control over their follow-up (10). To enhance trust and communication, referring physicians should be provided complete information regarding the intervention regimen, potential adverse reactions, and suggestions for management of toxic reactions they may observe.

Patients/Participants. The reasons for patients' resistance to participation in clinical research are complex. First, one cannot discount the effect of the behavioral dynamics between primary physician and patient in this process. Since patients cannot enroll themselves into clinical

trials, the referring physician's attitude about clinical research impacts directly on the patients' views. Schain has stated that "a patient's expectations about how the physician's behavior is likely to be affected by participation in a clinical trial are likely to motivate trial enrollment and adherence" (22). The power of the physician's influence over a patient's decision to participate in a clinical trial is illustrated in a recent study which evaluated patients' attitudes about enrollment in a trial (20). Of those individuals surveyed who were current or former trial participants, 38% indicated the main reason behind their participation was to comply with their doctor's request (20).

Even after being referred for enrollment by their primary physician and meeting study eligibility criteria, it is estimated that as many as 30% of potential candidates refuse when asked to participate in a clinical trial (21). One factor that has a major influence on patients' willingness to participate is the extent to which patients need control over their health-care decisions (21). Patients desiring a greater role in the making of medical decisions are less likely to volunteer for clinical studies (21). Random assignment to an intervention regimen is not in concordance with the feelings of a patient who believes his or her needs have a high priority and who wants preferential treatment (22). Because of the inherent design aspects of a randomized, double-blind clinical trial, in which neither the patient nor the physician knows the treatment assignment, feedback and discussion of the treatment's effects must wait until the trial is over. Even the decision to stop the trial, although formalized at the outset of the study, is made at the aggregate rather than the personal level. A survey of 60 colorectal cancer patients found that 58% would not agree to participate in a hypothetical clinical trial if found eligible (25). The major reasons given included the desire for more participation in making decisions about their treatment and an aversion to the uncertainty associated with the process of randomization (25).

In addition to maintaining personal autonomy, a broad range of psychosocial factors can also contribute to the decision to participate in a clinical trial. A number of surveys have been conducted to examine the personal motivation and behavioral correlates to the question of participation in clinical trials (14, 15, 17-20, 25-27). A majority found that those individuals who enrolled or would be willing to enroll in a trial were primarily altruistic in their motivation (15, 17-20, 26, 27). As opposed to those who favored personal autonomy and preferential treatment in the medical setting, many of the individuals surveyed indicated gratification with being part of a research effort that would contribute to medical knowledge and possibly help future patients (15, 17-20). Other characteristics related to increased likelihood of participation in a research effort included younger age, higher socioeconomic status, higher education, higher occupational status, and prior experience with a clinical study (17, 18, 27).

Fear of risk, desire for privacy, and lack of family

support are other psychosocial factors that can serve as barriers to participation (21). In addition, patients often have practical concerns when deciding to make a long-term commitment to a study—such as transportation needs, time off from work, waiting time, extra venipunctures and/or invasive procedures, as well as fear and unwillingness to tolerate toxicity (17, 19, 21, 26). This last, of course, is related to the adverse-effect profile of the intervention agent and the health status of the patient.

Two published reports have dealt specifically with the topic of patient participation in cancer prevention studies (19, 27). One study examined interest in hypothetical trial participation among a random sample of cancer screening clinic attendees (27), while the other solicited perceptions of patients enrolled in a chemoprevention trial on both past and future participation in a clinical study (19). Interestingly, although the characteristics of the two study populations were quite diverse, more than three-quarters of those surveyed in both studies indicated interest in participating in a future cancer prevention trial. Many of the same motivational characteristics and barriers to participation observed among patients in treatment trials were seen in these two studies. In the chemoprevention study, “careful medical follow-up” and “being part of a research effort” were the most frequently cited important benefits of trial participation, while the “amount of time taken to attend clinic” and “side effects” were the most frequently cited unpleasant aspects (19). In the study of patients attending a cancer screening clinic, interest in participating in a future, hypothetical cancer prevention trial was not predicted by the respondents’ perceived health status, current smoking behavior, family history of cancer, frequency of consumption of fruits and vegetables, or whether they were under the care of a physician for a health problem (27).

Compliance/Adherence Issues

Compliance or adherence in a clinical trial can be broadly defined as the cooperation of study participants with both study protocol procedures (such as laboratory tests, questionnaires, follow-up visits) and the prescribed intervention regimen (pill taking or behavior change) (28). Lack of adherence to the intervention regimen and/or the study protocol can threaten the validity of a clinical trial and hinder the evaluation of efficacy to the intervention (29). This is particularly important in chemoprevention trials, where the duration of the follow-up period is usually long and the expected intervention effect is likely to be modest. Noncompliance with the treatment regimen can severely attenuate study power and mean that a greater number of subjects may need to be enrolled in order to detect statistically significant differences (28). Without adjustment or remedy, poor compliance can lead to an underestimate of the effect of the intervention (29).

In any clinical trial, motivating subjects to be compliant is a difficult matter. This is especially so among the healthy or “at-risk” populations usually participating in cancer che-

moprevention trials (28). In many cases, these study participants are older and can be at high risk for noncompliance with both the study intervention and follow-up (30). For example, it is more likely that older participants will be under treatment for chronic illnesses that require maintenance medication. This complicates the mechanics of pill taking, and if a new illness arises during the study, the additional medication required can be an overwhelming burden on study participation. In addition, gradual health deterioration can prevent participants from following the study protocol. In some instances, especially in a long-term trial, lifestyle changes such as retirement may affect the participants’ ability to attend follow-up appointments (30).

Strategies are available that can improve the likelihood of maintaining optimal participant compliance (28, 30–32). First, one must carefully screen potential participants before enrolling them in a trial. Individuals should be provided with full information on the specifics of the trial regimen and the importance of their full and complete cooperation (31, 32). In this regard, many trials have used patient-friendly “brochures” or pamphlets, written in laymen’s terms, which explain not only the trial objectives but also the methods specific to the conduct of a clinical trial, such as the informed consent process and randomization procedures (30, 33). Once fully informed, individuals should be assessed as to their motivation and ability to participate in the trial (30). Patients who have doubts about their ability to participate fully for the whole duration of the trial should not be enrolled.

It is also important to make some assessment of future compliance prior to randomization. A popular technique to measure objectively the willingness and ability to comply with the intervention regimen is the utilization of a trial “run in” period (30). In this setting, potential participants are told to take placebo medication for a period of one to a few months and their compliance is monitored. If patients fail to take a majority (>80%) of their “medication” or fail to report to follow-up visits, they are not randomized. Screening out poorly motivated patients is crucial to both long-term retention and the trial’s ability to detect differences between the intervention and control groups (31).

The study regimen itself must be made as simple as possible. Compliance declines when a regimen is overly complex and/or of long duration. Intervention regimens should be simplified to within the limits of the pharmacokinetic profile of the intervention agent and the clinical appropriateness of protocol monitoring for safety and efficacy. Where possible, the regimen should be “tailored” to the convenience and lifestyle of the individual study participant (32). Innovative packaging of the study agent into “unit dose” or “calendar packs” has also been shown to be helpful in this regard.

The relationship between the physician and patient or the patient and the “study team” is critically important in maintaining participant adherence to both the intervention and the protocol (31). The long duration of most chemo-

prevention trials requires that the investigator, study coordinator, or some member of the study team make frequent contact with participants to provide positive reinforcement and feedback (30, 31). Stevens *et al.* stressed the importance of a good clinical study coordinator in this regard (30). An enthusiastic coordinator, who is both knowledgeable and supportive of the study as well as familiar and empathetic with each participant, is invaluable in maintaining long-term adherence, especially to protocol follow-up visits. For example, coordinators can use a variety of techniques, such as mailing postcard appointment reminders and providing toll-free telephone numbers, to maintain contact with study participants and inspire commitment to the study protocol. On a more personal level, taking the time to send out birthday and holiday cards to participants also builds rapport between the participant and the study team. Centrally distributed newsletters discussing study progress and topics suggested by coordinators and participants are also helpful in reinforcing study commitment and building a sense of taking part in an important research effort.

Given the altruistic motivation of most study participants, emphasizing allegiance to the study can be helpful in maintaining long-term compliance (30). Undue attention to the intervention agent under study can encourage the study participant to obtain the intervention on their own ("drop in" to the treatment group) possibly threatening the validity of the study (30). This is especially true in a chemoprevention trial where the intervention may be a vitamin or mineral that may be available in some form to the general public. It is better to focus on the role the participant is playing as part of the research team and how their participation is contributing to the advancement of medical knowledge.

Other Issues

In recent years, the issue of including ethnically diverse populations as sources for clinical trial participants has attracted much attention. In the past, the profile of the "typical" clinical trial participant included white race, high level of education, middle to upper middle class socioeconomic status, and male gender. Broadening this profile to include more women and subjects from diverse racial, cultural, and socioeconomic groups is a subject of current debate and has recently been reviewed (34–38). The topic has engendered discussions with political, economic, and sociological ramifications, most of which are beyond the scope of this paper. Issues of scientific validity versus representativeness aside, it is fair to say that, in the current environment, one must strive to be inclusive as possible in recruiting patients from diverse populations to clinical trials. This may be particularly important in cancer chemoprevention trials, given the higher cancer incidence and mortality experienced by certain races and ethnic groups in the United States (36).

In approaching this issue, one must first recognize the complexity inherent in the concepts of race and ethnicity and the need to adequately define "minority" populations before patient recruitment begins. In order to be more ef-

fective in both recruiting and maintaining the participation of "minorities," clinical trials forms, protocol procedures, and study management should be designed to recognize the needs of diverse ethnic groups. Multicenter trials should strive to include research clinics that primarily serve minority populations. Health professionals from minority backgrounds should be encouraged to participate in clinical research both as referring physicians and study investigators (38). Social, medical, and religious organizations which have the trust of the community should be sought as collaborators in the process of study recruitment in underserved areas (37, 38). On a societal level, the lack of adequate health insurance and access to appropriate medical care for large segments of the population certainly have a major impact on this problem. Hopefully, sensitivity to ethnocultural differences in planning and design of clinical trials along with reforms of our current system of health care will allow the dismantling of the cultural and economic barriers to greater participation of minority populations in clinical trials (36).

Conclusion

Careful planning early in the design phase of a chemoprevention clinical trial must take into account the numerous issues related to both patient participation and compliance that are outlined here. To avoid the pitfalls inherent in the design and implementation of a project as daunting as a multicenter cancer chemoprevention trial, one should enlist research study team members from several disciplines, including clinicians, biostatisticians, epidemiologists, behavioral scientists, and health educators. With such expert advice, one can better design protocols that minimize logistic complexity, maximize participant eligibility, simplify data collection, and take into account the complex behavioral dynamics of the clinical trial process. The collective experience of clinical scientists in developing effective techniques to optimally recruit and retain study participants can, if properly documented in the scientific literature, make the path easier for future researchers.

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