Health-Related Quality of Life in Cancer Prevention Clinical Trials

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By Claudette G. Varricchio, DSN, RN, FAAN [2], Julia H. Rowland, PhD [3], Edward L. Trimble, MD, PhD [4], and Robert E. Gore-langton, PhD [5]

Clinical trials of agents to prevent cancer in populations at risk are relatively recent. To date, these consist of a few large population-based studies. Trials in this area focus on the prevention of cancer in individuals with specific predetermined risk profiles. Two large population-based trials have already been launched and have completed accrual. These include the Breast Cancer Prevention Trial (BCPT-1, or National Surgical Adjuvant Breast and Bowel Project [NSABP] P-1 trial) of tamoxifen (Nolvadex) in women at increased risk for breast cancer,[1] and the Prostate Cancer Prevention Trial (PCPT-1, or Southwest Oncology Group [SWOG]-9217) using finasteride (Proscar) as the agent in men at risk for prostate cancer.[2-4]

Clinical Trials Referral Resource is designed to serve as a ready reference for oncologists to help identify clinical trials that might be suitable for their patients. We hope it will also enhance accrual to clinical trials by informing practicing oncologists of ongoing protocols. Currently in the United States less than 10% of eligible adult patients are entered into clinical trials. The result is a delay in answering important therapeutic and scientific questions and disseminating therapeutic advances to the general oncology community.

It should be emphasized that including a specific trial does not imply that it is more important than another trial. Among the criteria for selection are that the trial is addressing an important question and is not expected to close in the immediate future (less than 1 year), and that initial staging or laboratory tests required for patient eligibility are widely practiced and available. Information on other protocols can be accessed via Physician's Data Query (PDQ).*

We emphasize that this is an attempt to encourage referral of patients to these trials. We are specifically not soliciting additional members for the cooperative groups, nor are we suggesting how practicing oncologists should be treating patients who are not in a study.

This month's installment of Clinical Trials Referral Resource is devoted to health-related quality of life issues in cancer prevention trials. For patient entry information, see the individual trials.

Findings from the BCPT-1 are among the first to demonstrate the benefit of a chemopreventive agent in reducing cancer incidence in an otherwise healthy, at-risk population as determined by the Breast Cancer Detection Demonstration Project model, sometimes called the Gail model.[5] In this study, increased risk for breast cancer was defined as age 35 years or greater with histologic evidence of lobular carcinoma in situ or age 35 to 59 years with a minimum projected 5-year probability of invasive breast cancer at least equivalent to that of women 60 years of age. Women aged 60 years or greater were eligible regardless of other breast cancer risk factors. The PCPT-1, although closed to accrual, will continue to follow participants for up to 7 years or until the occurrence of prostate cancer before data will be available for analysis. Risk of prostate cancer in this trial was defined as age 55 years or older, with a prostate-specific antigen (PSA) no greater than 3.0 ng/mL.

Smaller trials are being conducted that target the prevention of second cancers in persons already diagnosed and treated for cancer. Few of these trials, however, include a health-related quality of life (HRQOL) measure. An important component of the large population-based primary prevention studies is the inclusion in the study design of measures to assess the impact of the preventive agent
and knowledge of cancer risk on the participant’s HRQOL. There are several reasons for the small number of population-based cancer prevention trials. Primary among these is the limited number of agents available with properties that prevent or interrupt the carcinogenesis process. In addition, there is heightened concern in such trials about the safety profile of the agents to be used. Because these agents will be given to healthy individuals who do not have cancer, assessment of risk/benefit takes on added importance. Investigators want to be sure that there will be a low incidence of morbidity associated with prolonged exposure to any proposed agent. This risk, in turn, must be balanced against the anticipated efficacy of the drug in reducing cancer incidence or the burden of cancer to society. Finally, prevention trials are very costly to conduct. Because the end point is a rare occurrence of cancer, thousands of subjects must be recruited and followed over long periods of time to show effectiveness. While there has been much discussion of alternative or surrogate end points (eg, specific biomarkers) for the actual occurrence of cancer in these trials, there is no agreement on what valid surrogate end points should be used.

Just as the basic design concerns of prevention trials are different when the context is primary prevention (in healthy at-risk groups) vs secondary prevention (in already diagnosed groups), so too is the approach to HRQOL assessment. Health-related quality of life measures used in the context of primary prevention trials are most commonly standardized or developed for use in healthy populations. Because individuals participating in these studies do not have cancer, and in some cases, may not be at more than age-appropriate risk for disease, use of cancer-specific scales are often of limited value. In these settings, it is important to use instruments that will permit comparison of participants to other healthy samples or those with diverse (noncancer) chronic illnesses. In addition, any measures used must be sensitive to change over time since these trials generally follow participants for several years.

As with many other types of clinical trials, HRQOL questions in these larger, population-based prevention trials can often be answered with a smaller sample size than required for the principal prevention hypotheses. Thus, accrual to the HRQOL component may close before that of the larger study. Moreover, it is often possible for several HRQOL studies, using different subsets of the larger trial, to be run in parallel. For example, in BCPT-1, in addition to information collected on the general HRQOL of participants,[6] ancillary studies exploring participants’ attitudes about the trial and adherence behavior were also conducted.[7-9]

Finally, prevention trials can offer the opportunity to address the effect of behavioral interventions on participants’ HRQOL and behavior. Research on issues related to adherence is one example of this type of research. Because these population-based studies are, by nature, long-term and longitudinal in design, ensuring that individuals not only participate in, but also follow the specified agent dosing across the course of the study is necessary to answer the research question. Measures of the effectiveness of protocol adherence behavior of both participants and providers, and interventions to improve these could help maximize the success of the trial in meeting its aims. At the same time, this information could inform investigators designing new trials about ways to maximize accrual and retention.

Listed below are two large, population-based cancer prevention trials currently sponsored by the Division of Cancer Prevention, National Cancer Institute (NCI). Other NCI-sponsored trials for the prevention of primary or secondary cancers are at various stages of development.

**Breast Cancer**

**Group:** National Surgical Adjuvant Breast and Bowel Project (NSABP)

**Protocol Number:** NSABP-P-2

**Title:** Study of Tamoxifen and Raloxifene (STAR) for the Prevention of Breast Cancer

**Eligibility Criteria:** Postmenopausal women, 35 years of age or older, and with increased risk of developing breast cancer as defined by age > 35 years with histologic diagnosis of lobular carcinoma in situ (LCIS) treated by local excision only or a minimum projected 5-year probability of invasive breast cancer of at least 1.66% (ie, average probability for women 60 years of age), as determined by the Breast Cancer Risk Assessment Profile generated by the NSABP Biostatistical Center. Contact the Group for full eligibility/ineligibility criteria.

**QOL Instruments/End Points:** HRQOL Questionnaire consisting of three self-administered subinstruments: (1) *Medical Outcomes Study Short Form 36 (MOS-SF36)*; Subscales for physical functioning, role functioning-physical, bodily pain, social functioning, mental health, role functioning-emotional, vitality, and general health perceptions. End points include overall health
rating, limitations to physical activities, problems at work or in regular daily activity related to physical health or emotional problems, interference with social activities, pains, and interference with normal work and emotional state. (2) Medical Outcomes Study Sexual Functioning Scales measure lack of sexual interest, difficulty in becoming sexually aroused, unable to relax and enjoy sex, difficulty in having orgasm. (3) Center for Epidemiological Studies Depression Scale (CES-D) evaluates feelings, attitudes, and behaviors including depression, poor appetite, restless sleep, hopefulness, failure in life, happiness or sadness, talkativeness, loneliness, enjoyment of life, crying spells, feeling disliked, feeling that everything was an effort.

P-1 Breast Cancer Prevention Trial Symptom Checklist, Modified (SCL) 43 items addressing symptoms, based on previous B-14 trial and clinical experience of NSABP consultants. Current version is modified and shortened on the basis of information from the P-1 trial.

Contact: Mary Ketner, (412) 330-4624. Additional information on the STAR trial may be obtained on the NCI website at http://cancer.gov/star or from the Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) in English or Spanish. The number for callers using TTY equipment is 1-800-332-8615. NSABP maintains a website for this trial at http://www.nsabp.pitt.edu/star/index.html.

Prostate Cancer

**Group:** Southwest Oncology Group (SWOG)

**Protocol Number:** S0000

**Title:** Selenium and Vitamin E Cancer Prevention Trial (SELECT) for Prostate Cancer

**Eligibility Criteria:** Men age 55 years or older or African-American men age 50 years or older, digital rectal examination deemed not suspicious for prostate cancer, and total PSA < 4.0 ng/mL. Contact the Group for full eligibility/ineligibility criteria.

**QOL Instruments/End Points:**

- **SF-36 Health Survey, Veterans’ version (SF-36V)** The SF-36 instrument was modified for the Veteran’s Administration ambulatory care setting. This included a change from a dichotomous to a five-level response format for the two role-functioning scales. See MOS-SF36 above for end points. The Physical and Mental Component Scale summary scores will provide the outcome variables for treatment comparisons.

- **UNISCALE** A single-item measure of global HRQOL using a visual analog scale (VAS) measure from "lowest quality" to "highest quality."

Contact: Marj Godfrey, Coordinator (210) 677-8808. Additional information on the SELECT trial may be obtained on the NCI website at http://cancer.gov/select or from the Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) in English or Spanish. The number for callers using TTY equipment is 1-800-332-8615. The SWOG maintains a website for this trial at http://www.crab.org/select/.

**References:**


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