

4. Manzotti M, Dell'Orto P, Maisonneuve P, Zurrida S, Mazzarol G, Viale G. Reverse transcription-polymerase chain reaction assay for multiple mRNA markers in the detection of breast cancer metastases in sentinel lymph nodes. *Int J Cancer*. 2001;95:307-312.
5. de Boer M, van Deurzen CH, van Dijk JA, et al. Micrometastases or isolated tumor cells and the outcome of breast cancer. *N Engl J Med*. 2009;361:653-663.
6. Cote R, Giuliano E, Hawes D, et al. ACOSOG Z0010: a multicenter prognostic study of sentinel node (SN) and bone marrow (BM) micrometastases in women with clinical T1/T2 N0 M0 breast cancer (abstract CRA504). *J Clin Oncol*. 2010; 28:18s.

Advocate Involvement in I-SPY 2

Jane Perlmutter, PhD, MBA

I am a breast cancer survivor and advocate who has become involved in work to improve treatment for patients with this dreaded disease. I am especially interested in innovative clinical trial designs that can accelerate the pace of progress. Given my professional experience in experimental design and statistics, and my work as a patient representative for the Cancer and Leukemia Group B cooperative group and the Translational Breast Cancer Research Consortium, I was invited to participate in planning the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 (I-SPY 2) trial at its outset, even before we had a sponsor or a specific trial design. As planning proceeded, there was considerable outreach to additional advocates, and many became involved, as discussed below. In this editorial, I will discuss the use of advocates in I-SPY 2 and the value they add. First, however, I will briefly provide an overview of I-SPY 2.

I-SPY 2 is currently enrolling patients with locally advanced breast cancer who will be randomized to receive neoadjuvant treatment with either standard chemotherapy alone or with an investigational agent that is based on the patient's biomarker profile.^{1,2} Many aspects of I-SPY 2 are highly innovative, including its 1) design (Bayesian, adaptive); 2) inclusion of up to 10 investigational agents produced by multiple companies; 3) treatment of patients on the basis of their tumor profiles; 4) open access to data; and 4) sponsorship by the Foundation of the National Institutes of Health

Biomarkers Consortium,³ partnering with QuantumLeap Healthcare Collaborative.⁴ The goal of I-SPY 2 is to rapidly and efficiently identify investigational agents that are likely to succeed in phase 3 clinical trials, along with information about which patients each agent will help.

I-SPY 2 is especially exciting to me because it represents a new paradigm for phase 2 assessment of investigational agents. In fact, it is a process for continually learning about pipeline drugs rather than a clinical trial. This process should lead to more rapid and personalized drug development.

PRINCIPLES OF ADVOCACY AND THE INVOLVEMENT OF ADVOCATES IN I-SPY 2

During the past 20 years advocates have been involved in cancer clinical trials by, for example, participating in cancer cooperative groups and providing support for the accrual of patients to trials.^{5,6} I-SPY 2 “pushes the envelope” with respect to advocate involvement. Although the trial's advocate activities have been attempted before, I-SPY 2 involves more advocates in a greater variety of ways than previous trials.

Clarifying Goals of Advocate Involvement.—While involving advocates in cancer research is becoming increasingly common, the goals of these collaborations are often unclear and may differ between investigators and advocates. As discussed elsewhere, we believe that advocates contribute to clinical trials by 1) sensitizing researchers to issues that influence patient recruitment, retention, and satisfaction; 2) providing a consumer perspective on ethical issues; 3) focusing on toxicities as well as benefits; 4) encouraging quality-of-life add-ons; 5) encouraging collaboration across

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disciplines and among stakeholders, adding a personal face and sense of urgency to research efforts; and 6) increasing public understanding of science.

Maximizing advocate contributions requires selecting appropriate advocates and providing them with appropriate training and educational opportunities. These were priorities in I-SPY 2.

Selecting Appropriate Advocates.—Given the large number of breast cancer advocates interested in contributing to clinical research, and the desire of the I-SPY 2 principal investigators to engage advocates, we were intentionally inclusive when recruiting advocates for I-SPY 2. We encouraged involvement from both experienced and novice advocates, geographically and ethnically diverse advocates, and advocates with a variety of advocacy affiliations. Some interested advocates—almost 200—have limited time but are kept informed through regular email updates and an advocate website. Others—about 40—who were interested in more involvement have been engaged in either short-term projects (eg, reviewing and contributing to the informed consent forms or other patient materials) or ongoing groups (eg, participating in conference calls as part of scientific working groups or investigator briefings).

Providing Training and Educational Opportunities.—Appropriate training is needed to maximize the contributions of advocates. Fortunately, there are wonderful opportunities for breast cancer advocates to learn about the relevant science, such as the National Board for Certified Counselors' Project LEAD⁷ programs and the American Association for Cancer Research's Scientist ← → Survivor Program.⁸ More specific project-based education is often also necessary, as is mentorship by experienced advocates and/or staff. In I-SPY 2, we hosted a series of webinars, led by study investigators, that were specifically geared toward advocates and covered a variety of relevant topics (eg, biomarkers, drug development, breast imaging, adaptive trials, and reading and reviewing trial protocols). We also maintain an advocate website that features materials specific to I-SPY 2, as well as general information for cancer research advocates. Finally, our experienced advocates, including me, actively mentor the less experienced advocates.

Assessing Advocate Contributions and Disseminating Results.—Although most cancer research advocates are not professional advocates and work on a volunteer basis, I view their work as part of a maturing discipline. Assessing their work, disseminating the results, and continually improving the processes are important. As described below, we have begun assessing advocate involvement in I-SPY 2 and have already presented 3 posters describing different aspects of our work.⁹⁻¹¹

SUCSESSES AND CHALLENGES OF ADVOCATE INVOLVEMENT IN I-SPY 2

Patient Support Materials and Institutional Review Boards (IRBs).—Approximately 25 advocates expressed interest in reviewing the I-SPY 2 protocol and/or assisting in developing patient support materials. The advocates worked with the I-SPY 2 staff through email and teleconferences, and this effort was quite successful.¹⁰ Prior to the start of these activities, Barbara LeStage, an advocate with many years of experience in cancer cooperative groups, the National Cancer Institute (NCI) Central IRB, and the Directors' Consumer Liaison Group, hosted a teleconference to review the components and goals of the I-SPY 2 protocol and offered tips on reviewing materials and providing useful feedback. She subsequently hosted a number of teleconferences to discuss advocates' reactions to various drafts and consolidate their feedback. Investigators and staff were very receptive to the advocates' input. In addition to considerable wording and formatting changes, other refinements suggested by advocates included the use of a 2-step consent process, travel reimbursement to patients for research-related visits, and foreign language translation of the informed consent document. A similar process involved advocates in reviewing patient support materials, including a brochure, DVD (produced through the generosity of The Safeway Foundation), and patient website.¹² While these materials could certainly be improved, they set a high bar and will be helpful to patients who are considering enrolling in I-SPY 2.

I was disappointed, however, by what happened to the informed consent and patient materials when they reached the IRBs. Many IRBs had concerns about the materials with which I disagreed and which sometimes conflicted with concerns raised by other IRBs. Since each site is using their own specific informed consent documents, patients enrolled in I-SPY 2 at different sites may receive different information presented in different ways. This cannot be in the best interest of patients. Furthermore, the use of several different versions of these documents resulted in the need for additional time and resources to review all of the changes and significantly increased the financial burden associated with translating these documents into foreign languages, given the variations among documents across the study sites.

Engaging Advocates with Investigators.—I-SPY 2 has a formal organizational structure that includes 9 scientific, project management, and data working groups as well as several external advisory groups and committees. Although we assigned both an experienced advocate mentor and a less experienced advocate to each group, and provided

written roles and responsibilities for advocates and working group chairs, many of the groups did not actively engage the advocates. This may have occurred, in part, because some groups held no formal meetings or teleconferences. The lessons I learned from this experience are to focus on the areas in which advocates are most likely to contribute and to put more effort into ensuring that investigators understand the potential of advocate contributions and how best to engage the advocates.

Assessing Advocate Involvement and Disseminating Results.—As discussed above, we are committed to advancing the discipline of cancer research advocacy by assessing and disseminating the results of patient advocate involvement. This is easier said than done. Nevertheless, a group of advocates led by Liz Frank, who has a professional background in assessment, is tackling this challenge. The first success was a survey conducted to assess staff and advocates' experiences while reviewing the trial protocol and patient support materials for I-SPY 2. The results of this survey were presented in a poster session at the 2010 San Antonio Breast Cancer Symposium.¹⁰ We learned that the process was successful but also identified specific strengths and opportunities for improvement. In the future, we plan to assess and report on the impact on patients of this and other advocate initiatives.

CONCLUSIONS

Now, almost 4 years since I was first approached about becoming involved with I-SPY 2, we are accruing patients from most trial sites. I am as enthusiastic as I was when first approached about the trial because I believe it will significantly improve both patient outcomes and the drug development process.

I am also considerably wiser about the trials and tribulations of getting cancer clinical trials launched, especially any trial as innovative as I-SPY 2. It is widely recognized that we must improve our approach to conducting clinical cancer research.^{13,14} My own priorities would be to 1) increase the use of innovative approaches to designing clinical trials (eg, Bayesian approaches¹⁵) so as to increase the pace of progress; 2) change the IRB process so it focuses on protecting patients rather than institutions and becomes more efficient (eg, assigning a single IRB responsible for all multi-institutional trials); and 3) streamline the contracting process to be faster and encourage data sharing.

With respect to involving advocates in clinical trials, I remain enthusiastic about their potential contributions but also better recognize the need for significant planning, mentoring, and supervising to take full advantage of what they offer. I believe advocacy organizations and groups like the

NCI Office of Advocacy Relations¹⁶ must increase their efforts to better define and nurture research advocacy, with a focus on assessing, sharing, and improving advocate contributions.

References

1. Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clin Pharmacol Ther.* 2009;86:97-100.
2. Winslow RA. New Rx for medicine: fed up with slow drug trials, cancer patients and doctors are testing a fast track to personalized treatments. *Wall Street Journal.* October 2, 2010. http://online.wsj.com/article/SB10001424052748703882404575520190576846812.html?mod=WeekendHeader_Rotator. Accessed December 16, 2010.
3. Baker BM. The role of patient advocates in clinical trials: patient advocacy 101. *Breast Dis Year Bk Q.* 2010;20:362-364.
4. Collyar D. How have patient advocates in the United States benefited cancer research? *Nat Rev Cancer.* 2005;5:73-78.
5. The Biomarkers Consortium. <http://www.biomarkersconsortium.org>. Accessed December 16, 2010.
6. QuantumLeap Healthcare. <http://www.quantumleaphealth.org>. Accessed December 16, 2010.
7. Project LEAD. <http://www.stopbreastcancer.org/learn/project-lead>. Accessed December 16, 2010.
8. American Association for Cancer Research's Scientist ← → Survivor Program. <http://www.aacr.org/home/survivors-advocates/scientistharr/survivor-program.aspx>. Accessed December 16, 2010.
9. I-SPY 2 Team, Buxton M, Davis S, DeMichele A, et al. I-SPY 2 Clinical Trial: Strategies to Achieve Aggressive Accrual Targets. Poster presented at: NCI-ASCO Cancer Trial Accrual Symposium; 2010; Bethesda, MD. http://www.gemini-grp.com/ISPY/Accrual_Poster.pdf. Accessed December 16, 2010.
10. Gemini Group, Perlmutter J, Frank E, LeStage B, et al. I-SPY 2 Clinical Trial: Advocate Involvement in Protocol, Informed Consent and Patient Support Materials Development (Poster P5-07-02). Poster presented at: San Antonio Breast Cancer Symposium; 2010; San Antonio, TX.
11. Gemini Group, Perlmutter J, Parker B, Nixon N, et al. I-SPY 2 Clinical Trial: Telephone Support Provided by Peer Counselors (Poster P2-12-03). Poster presented at: San Antonio Breast Cancer Symposium; 2010; San Antonio, TX. http://www.gemini-grp.com/ISPY/SABCS_NOS.pdf. Accessed December 16, 2010.
12. I-SPY 2 TRIAL. <http://www.ispy2.org>. Accessed December 16, 2010.

13. Doroshow JH, Fine HA, Abbruzzese JL, et al. Restructuring the National Cancer Clinical Trials Enterprise. Report of the Clinical Trials Working Group of the NCI. <http://transformingtrials.cancer.gov/files/ctwg-report.pdf>. Accessed December 16, 2010.
 14. Institute of Medicine. A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program. <http://www.iom.edu/Reports/2010/A-National-Cancer-Clinical-Trials-System-for-the-21st-Century-Reinvigorating-the-NCI-Cooperative.aspx>. Accessed December 16, 2010.
 15. Spiegelhalter DJ, Abrams KR, Myles JP. *Bayesian Approaches to Clinical Trials and Health-Care Evaluation: Statistics in Practice*. Hoboken, NJ: Wiley; 2004.
 16. Advocates in Research Working Group. Background and Summary Recommendations. <http://dclg.cancer.gov/working-groups/involving-advocates>. Accessed December 16, 2010.
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