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Letter to the Editor: Defining "Standard of Care"

Re: Rachel F. Dear, Kevin McGeechan, Megan B. Barnet, et al. "Standard Care" in Cancer Clinical Trials: An Analysis of Care Provided to Women in the Control Arms of Breast Cancer Clinical Trials. J Natl Compr Canc Netw 2017;15(9):1131–1139.

I believe the study by Dear et al[1] in the September issue highlights the complexity of how to define "standard care" for the control arm of phase III clinical trials. In reviewing this study, I am assured that analysis of trials within the United States suggests a significantly lower deviation rate than trials conducted outside of the United States. This suggests that we are doing something right with our efforts in developing guidelines and standards, in addition to the vast regulatory oversight placed on clinical trials conducted in our country. Using the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer at only one specific point in time as the "gold standard" may not be the most precise way to measure deviations of standard care, although certainly it provides us with a good starting point.

The authors note that 13% of trials in the United States deviated from standard (11 of 83 trials), but I would have to think that the clinically significant deviations from standard care are probably less, because the definition of "standard care" is a moving target and very complex, particularly if taking into account the extensive knowledge bases of the experts writing these protocols and the amount of time it takes for one protocol to be written, approved, and instituted for accrual. For example, the authors include one US trial in metastatic breast cancer as deviant because the control arm was 75 mg/m^2 of intravenous docetaxel every 21 days, when the corresponding NCCN Guideline at the time (v1.2004) recommended 80 to 100 mg/m^2 every 21 days. However, when we look at the current NCCN Guidelines for Breast Cancer (v2.2017), the recommended dosage is now 60 to 100 mg/m^2 every 21 days. Therefore, the dosage delivered in the control arm was, in fact, what we would currently consider completely acceptable.

This highlights the point that although the NCCN Guidelines for Breast Cancer are updated on average 1 or 2 times per year, there are always new fluxes of information, such that no clinical practice guidelines *can ever* truly reflect available data in real time. Keeping this in mind, I am encouraged by the findings within the US trial cohort.

On the other end of the spectrum are the debates and controversies surrounding trials conducted outside of the United States. In these, the authors report 39% of trials (49 of 127) deviated from standard care (NCCN Guidelines or German Gynecological Oncology Group [AGO] guidelines). One major issue relates to international outsourcing of clinical trials by more Westernized, affluent countries and/or large lucrative pharmaceutical companies to low- or middle-income countries in order to reduce costs and avoid the "red tape" regulatory checks we have in place in the United States. This may, in part, be a factor. One could also discuss the interpretation of "best proven intervention" for the control arm mandated by the Declaration of Helsinki and whether it refers to best care available worldwide or the best care available locally. One could discuss whether guidelines developed in Western countries can even be applicable to countries with limited resources.

So, although the discussion is complex, ultimately probably a little of all of the above apply, we must consider all of these factors and include geographic variations and preferences in practices. Nevertheless, this body of work allows for a starting point for identifying deviations from "standard care" in clinical tri-

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als, and with further investigation into practice patterns over time and regional/geographic practice differences, it may be possible to identify clinically significant deviations that may be detrimental for patients.

Reference

1. Dear RF, McGeechan K, Barnet MG, et al. "Standard care" in cancer clinical trials: an analysis of care provided to women in the control arms of breast cancer clinical trials. J Natl Compr Canc Netw 2017;15:1131–1139.

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Author's Reply to Letter to the Editor: Defining "Standard of Care"

Author's Reply to Meena S. Moran's Letter to the Editor re: Rachel F. Dear, Kevin McGeechan, Megan B. Barnet, et al. "Standard Care" in Cancer Clinical Trials: An Analysis of Care Provided to Women in the Control Arms of Breast Cancer Clinical Trials. J Natl Compr Canc Netw 2017;15(9):1131–1139.

We would like to thank Dr. Moran for her excellent summary of the important issues raised by our paper exploring the quality of the control arm in breast cancer randomized trials. Our premise was that for a trial to validly evaluate a new treatment, it should be compared with the best existing alternative treatment. Researchers have an ethical responsibility to design scientifically sound clinical trials, testing new treatments against the current standard of care, so that the considerable resources—both personal and financial—required by randomized trials are not wasted and can generate valuable evidence to guide future clinical care.

Overall, we found that treatment offered to control groups in 29% of breast cancer clinical trials from 2004 to 2014 failed to meet standards of care as determined by the contemporaneous NCCN Clinical Practice Guidelines in Oncology for Breast Cancer. For trials recruiting outside the United States, we used the German Gynecological Oncology Group (AGO) guidelines.

As highlighted in the letter by Dr. Moran, for trials recruiting inside the United States, 13% deviated from standard care; however, for trials recruiting outside of the United States, this number increased to 39%. This difference highlights the complexities of determining the appropriate control arm for a randomized controlled trial. Although we specifically chose the best available clinical guidelines to determine the standard of care, we acknowledge that this may be a simplistic way to answer this question. It is difficult for clinical guidelines to keep up with the pace of new data from clinical trials. Regional variations in practice are a reality for the reasons well described by Dr. Moran. For example, the AGO guidelines allow either an aromatase inhibitor or tamoxifen for early-stage postmenopausal breast cancer, whereas in the United States, aromatase inhibitors are preferred. Randomized controlled trials support the latter recommendation, but in clinical practice, individual and tumor-related factors mean that either drug may be appropriate given that the absolute differences in effect between them are small.

Although we recognize these complexities, we believe there remains a pressing need to conduct well-designed clinical trials so that we know if the intervention being tested is truly better than an existing standard. To this end, there is an urgent need for guidance regarding how to choose the appropriate control group for randomized trials. Patients who participate in clinical trials deserve nothing less.

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