COMMENTARY

Defining "Success" in Recruitment of Underrepresented Populations to Cancer Clinical Trials

Moving Toward a More Consistent Approach

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Although medically underserved groups bear a heavy burden of cancer disease and governmental agencies have required inclusion of minorities and women in cancer clinical trials since 1993, many of these groups are underrepresented in cancer prevention or treatment clinical trials. To assess and enhance recruitment of underrepresented populations into cancer-related clinical trials, investigators and governmental agencies need consistent measurement approaches for recruitment that can be applied to diverse settings where trials are conducted. We conducted a systematic review to evaluate what measurement approaches were used to evaluate the success of recruitment of underrepresented groups into cancer prevention or treatment trials, and whether these recruitment goals were stated a priori. Only two articles reported an a priori recruitment goal. The recruitment measurement approaches varied considerably, with no consistent standard, especially for individual trials. By using the empiric evidence from this review in conjunction with the National Institutes of Health (NIH) guidelines, we constructed a framework for choosing consistent a priori recruitment goals for underrepresented groups based on the research question and study location. Using consistent measurement approaches for underrepresented groups will improve comparability of recruitment strategies across trials, improve equity in distribution of benefits and burdens of cancer-related clinical trials, and may improve applicability of trial results to multiple populations. ***Cancer* 2006;106: 1197–204.** © *2006 American Cancer Society.*

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The US healthcare system has marked disparities in cancer incidence, prevention, and treatment that differ by age, gender, race/ethnicity, and socioeconomic status.[1,2] Medically underserved groups bear a heavy burden of cancer disease,[3,4] and many of these groups are underrepresented in clinical trials aimed at the prevention or treatment of cancer.[5] This constitutes an additional kind of disparity by leading to inequities in the sharing of benefits and risks of cancer-related clinical trials, and potentially reduces generalizability of trial results to underrepresented populations. Consequently, since 1993 the National Institutes of Health (NIH) has required that all sponsored clinical trials ensure that women and members of minorities be included in all human subjects research.[6] More than a decade later, certain populations are still underrepresented in cancer-related clinical trials, including racial and ethnic minorities, older adults, adolescents, rural populations, and individuals of low socioeconomic status (SES).[7] Increasing representation of these groups may be an important component of improving evidence-based health services to these populations.

To assess and enhance recruitment of underrepresented populations into cancer-related clinical trials, investigators and governmental agencies need specific measurement approaches for recruitment success that can be applied to diverse settings where trials are conducted. The NIH gives investigators guidelines on when to include minorities and women into clinical trials based on prior scientific knowledge of known or potential differences by race, ethnicity, or gender.[8] However, these guidelines do not consistently delineate which specific measurement approaches to use when an investigator designs recruitment to a study. Without consistent measurement approaches for recruitment of underrepresented groups in given situations, investigators will not be able to determine which recruitment strategies are most effective for targeted populations.

Purpose

To address these issues, we conducted a systematic review to determine: 1) what measurement approaches have been used to evaluate the success of strategies for recruiting underrepresented populations into cancer prevention and treatment trials, and 2) to determine whether goals for recruitment of underrepresented populations into these cancer-related clinical trials were stated a priori. We then use these data to discuss the challenges to choosing an a priori definition of recruitment success as well as to evaluate the strengths and limitations of the reported measurement approaches. By using the empiric evidence from our previous review along with NIH guidelines and existing theory, we propose a more consistent approach to choosing a recruitment goal for underrepresented groups based on the research question and the study location.

Methods of Literature Review

The methods of this systematic review are reported in detail elsewhere.[9] Briefly, we searched for English language articles published before January 2005 using search terms such as "accrual," "minority," "recruitment," and "cancer" in MedLine and other electronic databases. We also conducted a hand search of 34 relevant journals from January 2003 through July 2004. Articles were included that contained original data discussing strategies for recruiting underrepresented groups to a cancer-related clinical trial, or review articles presenting data on recruitment of underrepresented groups to multiple cancer-related clinical trials. Underrepresented groups were defined as racial and ethnic minorities, older adults, adolescents, rural populations, and individuals of low SES based on a review of cancer trials by Sateren et al.[7] Articles were excluded if they were: not in English, not human data, not original data, a meeting abstract only, not addressing cancer treatment or prevention, not reporting recruitment to a controlled trial, not reporting results for an underrepresented group, or not relevant to the study question.

On a standardized data abstraction form, we grouped the measurement approaches for recruitment success of underrepresented groups into five categories: 1) no definition provided; 2) researcher-established proportion of a population from an underrepresented group (e.g., based on statistical power, convenience, data from prior studies, and data from an available comparison group); 3) disease-specific proportion of a population from an underrepresented group (e.g., proportion of a population from an underrepresented group *with any cancer or a specific type of cancer*); 4) geographic proportion of a population from an underrepresented group (e.g., proportion of the US population from an underrepresented group); and 5) institution-specific proportion of a population from an underrepresented group (e.g., proportion of patients seen in a specific cancer center that are in an underrepresented group). A primary reviewer abstracted data from each article using a standardized data abstraction form, and a second reviewer checked these data for accuracy and completeness. Disagreements in abstraction were resolved by adjudication between reviewers.

TABLE 1
Studies of Measurement Approaches Used to Evaluate Recruitment Success of Underrepresented Populations into Cancer Prevention and Treatment Trials

Study results	No. (%)	References
A priori recruitment goals	2 (7.1)	17, 37
Categories of recruitment success definitions reported		
Researcher-set proportion of underrepresented group	14 (50.0)	10–24
Power to detect differences	0 (0.0)	None
Convenience	7 (25.0)	10, 11, 16, 17, 19, 20, 24
Data from prior studies	3 (10.7)	13, 14, 17
Data from an available comparison group	7 (25.0)	12, 13, 15, 18, 21–23
Disease-specific proportion of underrepresented group	12 (42.9)	12, 21, 22, 25–34
Geographic proportion of underrepresented group	4 (14.3)	12, 35–37
National geographic proportion	3 (10.7)	12, 36, 37
Local geographic proportion	1 (3.6)	35
Institution-specific proportion of underrepresented group	1 (3.6)	38
Underrepresented groups		
Older adults	16 (57.1)	11, 12, 14, 16, 17, 20–23, 26–29, 31, 32, 34
African Americans	15 (53.6)	11–14, 18,24–26, 31, 32, 34–38
Latino/Hispanics	8 (28.6)	10–12, 18, 25, 32, 35, 36
Asian/Pacific Islanders	3 (10.7)	22, 32, 36
Rural	2 (7.1)	15, 17
American Indian/Alaskan Native	1 (3.7)	36
Low socioeconomic status	1 (3.7)	19
Adolescents	1 (3.7)	30
Cancer prevention trials	9 (32.1)	10, 11, 13, 14, 16, 19, 24, 35, 37
Cancer treatment trials	16 (57.1)	12, 15, 17, 18, 20, 21, 23, 25–29, 32, 34, 36, 38
Both cancer prevention and treatment trials	3 (10.7)	22, 30, 31

Measurement Approaches for Recruitment Success Reported in the Literature

Our search yielded 28 studies that reported on recruitment success of underrepresented groups into cancer-related clinical trials (Table 1). Authors reported recruitment success differently across studies. The majority of studies defined success in recruiting underrepresented groups as a researcher-established proportion[10–24] or a disease-specific proportion.[12,21,22,25–34] The remainder of the studies defined recruitment success as a geographic proportion[12,35–37] or an institution-specific proportion.[38] Three studies reported more than one recruitment measurement approach.[12,21,22] Of note, articles that retrospectively reviewed multiple cancer trials mainly reported recruitment success of underrepresented groups in terms of disease-specific proportions,[12,21,22,25–30,32,34] whereas articles of individual trials mainly reported recruitment success in terms of researcher-established proportions.[10,11,13,14,16,17,19,20,24,38]

With respect to specific underrepresented groups, recruitment success was reported mostly for older adult,[11,12,14,16,17,20–23,26–29,31,32,34] African American,[11–14,18,24–26,31,32,34–38] and Latino/Hispanic populations.[10–12,18,25,32,35,36] Few studies reported recruitment success for Asian/Pacific Islander,[22,32,36] rural,[15,17] American Indian/Alaskan Native,[36] low SES,[19] or adolescent populations.[30]

Was a Recruitment Goal Set A Priori?

Of the 28 articles that discussed recruitment of underrepresented groups, 16 were retrospective reviews that combined recruitment data from multiple cancer trials.[12,18,20–23,25–30,32,34,36,38] This leaves 12 articles that reported recruitment success of underrepresented groups for recruitment strategies used in individual cancer trials.[10,11,13–17,19,24,31,35,37] Only two of these 12 articles reported having a recruitment goal for an underrepresented group a priori.[17,37]

Maurer et al.[17] conducted a study to evaluate changes in patterns of care for specific cancers by setting up a rural hospital consortium as a single Cancer and Leukemia Group B (CALGB) affiliate. A secondary aim was to compare rural accrual into cancer clinical trials to accrual at other CALGB sites. They set an a priori recruitment goal of having at least 22% of the rural study population be eligible for a cancer trial. This recruitment goal was based on a study by Hunter et al.[34] that reported results of rural recruitment to cancer-related trials for the Community Clinical Oncology Program (CCOP). Whereas Maurer et al.[17] met this researcher-established goal for eligible rural par-

ticipants, they were only able to recruit 3.3% of incident cancer cases in this rural population to cancer trials because protocol availability was much lower than expected.

Moinpour et al.[37] conducted the Prostate Cancer and Prevention Trial (PCPT), a randomized controlled trial comparing finasteride to placebo for prevention of prostate cancer in men older than 55 years of age. They set an a priori recruitment goal of having at least 8% of the study population be African American men older than 55 years of age. This was based on the national proportion of African American men older than 55 years old, yet only 4% of the study population ended up being older African American men.

Ten articles discussed recruitment success of underrepresented groups into individual trials without reporting a priori recruitment goals.[10,11,13–16,19,24,31,35] One study by Ford et al.[13] did not state an a priori goal, yet suggested that there was a set goal. Ford et al.[13] conducted a randomized controlled trial evaluating different strategies for recruiting older African American men to the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. They did not report a specific recruitment goal, yet they tested recruitment hypotheses that were declared a priori. They also reported that because of the large numbers of African American men recruited, one needs to look at absolute recruitment differences between recruitment strategies and not just statistically significant differences. This implies an understanding that they would recruit enough participants to be able to detect differences in recruitment arms for older African American men.

Challenges to Choosing an A Priori Definition of Recruitment Success

Practically, many studies may incur substantially increased recruitment costs if they have an a priori mandate to recruit a specified number of patients from underrepresented groups. The disproportionate burden of poverty and lack of insurance that is borne by underrepresented groups such as African Americans and Latino/Hispanic Americans results in these groups receiving a substantial fraction of their cancer care in public hospitals. These 'safety net' institutions are unlikely to have the infrastructure necessary to meet the patient education, regulatory, and data management needs of well-designed clinical trials. Moreover, researchers typically balance competing priorities when determining recruitment goals. These priorities may include: 1) disease-specific requirements (e.g., having equal representation at different stages of a specific type of cancer); 2) participant retention concerns (e.g., investigators may work to accrue participants with decreased barriers to remaining in the study such as participants with reliable transportation); 3) Internal Review Board requirements; and 4) timeline requirements (e.g., recruiting a large enough sample size in a specific time frame).

Social and ethical challenges exist as well. The literature on clinical trial recruitment usually assumes that any differences in recruitment, accrual, or retention in clinical trials represent problems that should be overcome by researchers.[39–42] The term underrepresented itself assumes that there is an accepted proportion of the population that should enroll in cancer clinical trials. However, some differences in recruitment rates may be a reflection of legitimate beliefs and social norms that ought not be overcome, but rather respected. Pushed to an extreme by overzealous recruiters, a priori recruitment goals for underrepresented groups might inadvertently jeopardize the integrity of the informed consent process for underrepresented groups.[43] This could jeopardize the already fragile trust between vulnerable populations and healthcare research institutions.[44,45]

Strengths and Limitations of Recruitment Measurement Approaches

Besides these challenges, one must consider the strengths and limitations of each type of recruitment measurement approach. We suggest that investigators consider four criteria (feasibility, comparability, generalizability, and equity) with regard to each of the recruitment measurement approaches (Table 2).

Researcher-established proportions typically are the most convenient for the investigator conducting the trial. For example, in our review we found that many investigators used the proportion of the study population in an underrepresented group enrolled in their trial as their post-hoc measure of recruitment success. Whereas this is convenient, it may not allow for equitable distribution of benefits and burdens of clinical trials for underrepresented groups. In addition, researcher-established proportions of underrepresented groups lack comparability because no standard recruitment definition exists within this category. This, in turn, may limit the generalizability of the trial results because clinicians will have difficulty determining whether the underrepresented groups in the study populations are truly representative of the patients they see in their own practices. One notable exception is when the investigator conducts a priori power calculations to detect differences between subgroups (as may have been done by Ford et al.,[13] although not explicitly stated). Calculating a priori recruitment goals based on the ability to detect statistical differences between recruitment arms is one type of researcher-established proportion that al-

TABLE 2
Strengths and Limitations of Recruitment Measurement Approaches for Underrepresented Groups

Recruitment success definition categories	Strengths	Limitations	Exceptions
Researcher-established proportion of underrepresented groups	Usually highly feasible	May lack:1) generalizability, 2) comparability across studies, and 3) equitable distribution of benefits and burdens of clinical trials to URGs	A priori power calculations improves comparability and generalizability, but may have worse feasibility
Disease-specific proportion of underrepresented groups	Comparability and generalizability	1) Decreased equity: may lead to oversampling of URGs, and increased risks of cancer clinical trials; 2) May lack feasibility in certain geographic areas	None
Geographic proportion of underrepresented groups			
National geographic proportion	Strong comparability and equity	May lack: generalizability and feasibility	None
Local geographic proportion	Usually highly feasible	May lack: generalizability, comparability, and equity	None
Institution-specific proportion of underrepresented groups	Usually highly feasible	May lack: generalizability, comparability, and equity	None

URG: underrepresented group.

lows for comparability and generalizability of clinical trial results, yet was rarely seen in our review.

Disease-specific proportions are more comparable across studies because they are less variable in their definition than researcher-established proportions. Depending on the cancer burden and number of people in an underrepresented group in a geographic area, investigators may experience practical difficulties in recruiting sufficient numbers of patients from underrepresented groups based on the prevalence or mortality of a specific type of cancer. To improve generalizability and feasibility in this instance, one might choose to use as a measurement approach the proportion of an underrepresented group adjusted for all cancer prevalence or mortality as opposed to using the proportion of underrepresented group adjusted for the prevalence or mortality of a specific type of cancer. Using disease-specific proportions may, in theory, lead to oversampling of underrepresented groups, and thereby decrease equity because these groups will then face increased risks as well as benefits of cancer clinical trials compared with the general population.

The national geographic proportion of the population in an underrepresented group as a measurement approach is comparable across studies and is a feasible and equitable way to define recruitment success, especially for multicenter trials. However, a nationally based recruitment goal may be less appropriate if disease burden is high and there are biologic or cultural differences that need to be taken into account in an underrepresented group. In this situation, the disease-specific proportion of an underrepresented group may be a more appropriate measurement approach. In addition, a nationally based recruitment goal creates difficulties for local trials in areas that have relatively homogeneous populations. For some locally based trials it may only be feasible to define recruitment success in terms of a local geographic proportion of the population that is from the targeted underrepresented group, or an institution-specific proportion of the population from that underrepresented group.

The institution-specific proportion of underrepresented groups, whereas feasible, may lead to decreased generalizability of trial results, comparability across studies, and equity due to the variability in proportion of underrepresented groups served by different research institutions.

Framework for Choosing an A Priori Recruitment Goal for Underrepresented Groups

After discovering the varied measurement approaches for recruitment success of underrepresented groups that exist in the literature, as well as considering the challenges that arise when choosing an a priori recruitment goal, we are faced with the question: "What should the standard be for reporting on a trial's success in recruiting underrepresented populations?" In a recent article, Corbie-Smith et al.[46] provided practical guidelines for defining appropriate inclusion of minorities into clinical research trials. The article proposes three potential ways to achieve appropriate minority inclusion based on the goals of the investigator. If the goal of the investigator is to test hypotheses about possible differences in race or ethnicity, then the investigator should achieve this goal by using adequate statistical power to detect differences by race/

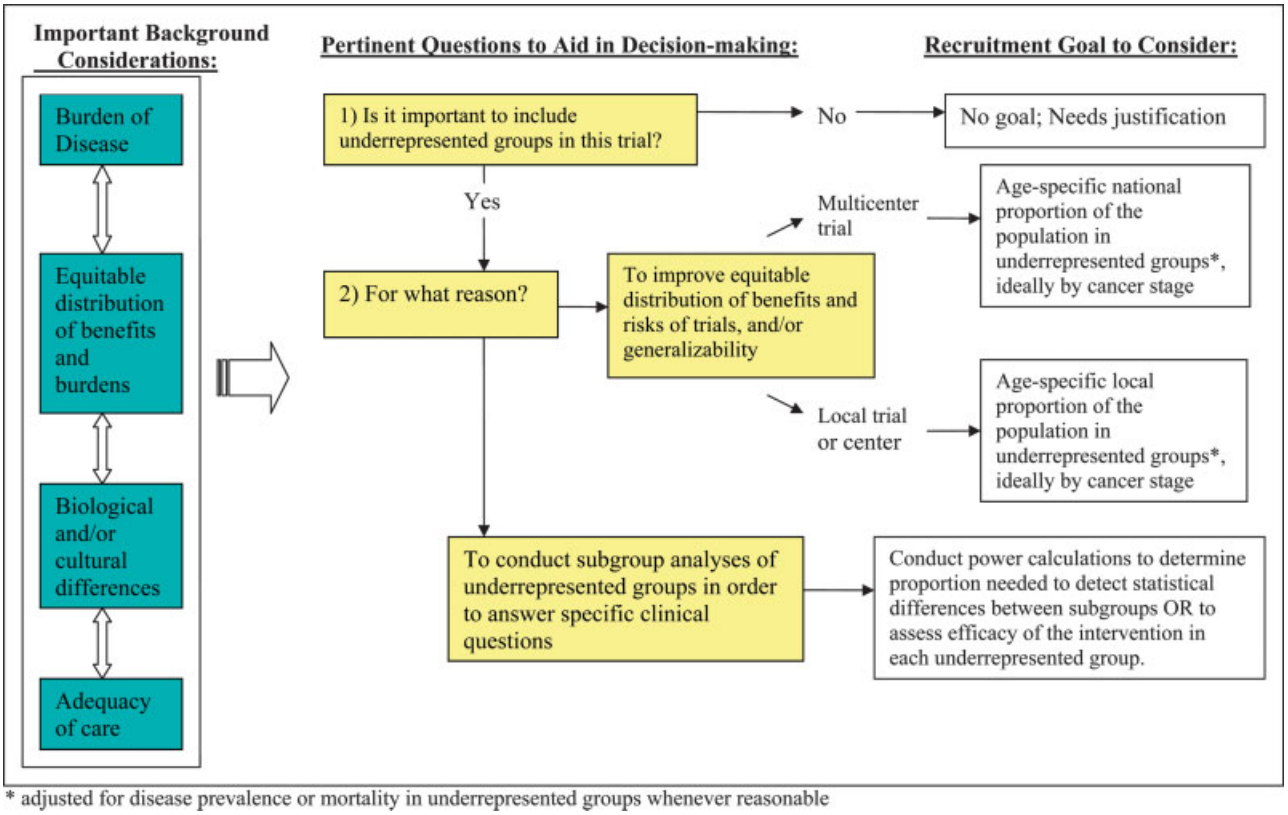

FIGURE 1. Framework for choosing an a priori recruitment goal for underrepresented groups in cancer-related trials.

ethnicity. If the goal of the investigator is to generate hypotheses about possible differences by race or ethnicity, then the investigator should do exploratory analyses. Lastly, if the goal of the investigator is to ensure equity, then the investigator should select subjects so that results can be generalized to affected populations. The article then gives examples of different measurement approaches that could be used for each of these goals. By using the empiric evidence from our review along with NIH guidelines, we propose a framework to choosing an a priori recruitment goal based on the research question and study location (Fig. 1). As opposed to prior work, our framework stresses the importance of using consistent measurement approaches as the basis of recruitment goals for underrepresented groups.

To decide on a recruitment goal for underrepresented groups, the investigator must consider the burden of disease, the adequacy of care, equity in distribution of benefits and burdens of cancer trials, and whether there are known or potential biologic or cultural differences within specific underrepresented groups.[8,46] By using these background considerations, we recommend that the investigator answer two questions when setting recruitment goals for underrepresented groups: 1) How important is it to include underrepresented groups in the trial? If it is not important, then there needs to be clear justification why not. For example, if an investigator plans to conduct a Phase I trial on a rare cancer with a known low burden of disease in underrepresented groups, then the investigator may be able to justify that there is no need for a recruitment goal for specific underrepresented groups. If an investigator does want to recruit underrepresented groups into the trial, then the investigator needs to ask: 2) For what reason do you want to include underrepresented groups?

If the investigator wants to improve equitable distribution of the benefits and burdens of clinical trials, potentially improve generalizability, and/or improve comparability of recruitment strategies for underrepresented groups across studies, then a geographic proportion of underrepresented groups is the appropriate measurement approach to consider. More specifically, the investigator would want to decide whether the trial is a multicenter or local trial. For *multicenter* trials, investigators should consider setting recruitment goals for underrepresented groups as equal to the age-specific national proportion of the population in the underrepresented groups, adjusting for disease

prevalence or mortality in underrepresented groups whenever reasonable. This would enhance equity, comparability, and potentially generalizability, while decreasing the risk of unnecessary oversampling of underrepresented groups. *Local trials* could set appropriate recruitment goals using the age-specific local geographic proportion of the population in the underrepresented groups, adjusted for disease prevalence or mortality in underrepresented groups whenever reasonable.

We encourage investigators to adjust for disease prevalence or mortality when using geographic proportions of underrepresented groups as recruitment goals especially if the disease burden is high in a particular underrepresented group. However, this could potentially lead to oversampling of underrepresented groups, and must be weighed carefully for each trial. Therefore, an investigator must justify whether or not to adjust for disease burden in specific underrepresented groups when setting recruitment goals. Prevalence and mortality were chosen as possible ways to account for disease burden because they are feasible and useful in chronic diseases such as cancer. Prevalence data may be more easily obtained at the state and national level using registries such as the Surveillance Epidemiology and End Results (SEER) registries, whereas mortality data may be easier to find on a local level for counties using the Centers for Disease Control and Prevention (CDC) Wonder website and ICD-10 codes.

Recruitment based on cancer stage is another important way to account for disease burden. Many times cancers present in more advanced stages in underrepresented groups because of a multitude of reasons such as limited access to care. For example, breast carcinoma has a relatively low incidence in African American women compared with Caucasian women, yet it is associated with higher mortality because African American women present with more advanced stages of disease.[2,47] We therefore encourage investigators to recruit underrepresented groups proportionally by cancer stage.

Besides improving equity, comparability, and generalizability, investigators may want to conduct subgroup analyses based on a hypothesis regarding a specific underrepresented group. In this case, the recruitment goal would be based on a priori power calculations to determine the number of people needed to detect differences between subgroups. This would allow investigators to have sufficient power to effectively compare results for underrepresented groups, as opposed to relying on post-hoc analyses that may be inadequate.

Implications

Cancer-related clinical trials should have clear measurement approaches for recruiting underrepresented populations, and investigators should specify their recruitment goals a priori. Moreover, recruitment success should be evaluated and reported for underrepresented groups more frequently, not just by reviews of multiple trials but as part of the routine reporting of individual cancer trials. However, mandatory recruitment targets could foreseeably have negative ethical consequences for voluntary enrollment of underrepresented groups. By routinely setting recruitment goals based on specific measurement approaches for recruitment of underrepresented groups, and by routinely reporting on whether these recruitment goals were met, investigators will be able to better adhere to NIH guidelines. This consistent approach will improve equity in cancer trials, and advance our knowledge of the effectiveness of different recruitment strategies for underrepresented groups.

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