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August 6, 2019

Norman E. Sharpless, M.D.
Acting Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Docket FDA-2019-D-1264

Dear Dr. Sharpless:

The American Cancer Society Cancer Action Network (ACS CAN) appreciates the opportunity to comment on the draft guidance "Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs, Guidance for Industry. ACS CAN, the nonprofit, nonpartisan advocacy affiliate of the American Cancer Society, supports evidence-based policy and legislative solutions designed to eliminate cancer as a major health problem. ACS CAN empowers advocates across the country to make their voices heard and influence evidence-based public policy change as well as legislative and regulatory solutions that will reduce the cancer burden.

Clinical trials are the key step in advancing potential new cancer treatments from the research setting to the cancer care clinic, and patient participation in trials is crucial to this success. Most cancer patients express a willingness to participate in clinical research, yet only a small fraction ultimately end up enrolling in a cancer clinical trial due to barriers that make participation difficult or even impossible[1]. While all patients face barriers to enrolling in cancer clinical trials, certain groups face even greater barriers than others, resulting in participation in clinical trials that does not represent the diversity of the population annually diagnosed with cancer in the U.S. Specifically, some racial and ethnic minorities are underrepresented, with the worst

[1] Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report, accessed at www.fightcancer.org/clinicaltrialbarriers

disparities experienced by elderly and low-income patients.[2,3,4] Our comments on the draft guidance are through the lens of cancer patients and cancer trials, which may entail considerations that differ slightly than for clinical trials in other disease areas.

Contrary to frequent explanations of low cancer clinical trial participation being the result of patient decision-making, the largest barriers preventing trial participation are generally outside of a patient's control. A recent meta-analysis of enrollment barriers to cancer clinical trials found that local trial availability prevented 55.6 percent of patients from taking part in trials and eligibility criteria on average keep 21.5 percent of patients from enrolling in clinical trials[5]. In other words, how a trial is designed and where it is conducted play the biggest roles in facilitating enrollment, and this draft guidance has the opportunity to address practices that may unintentionally result in disparate opportunities for trial participation.

Broad Support for Reducing Barriers

In 2018, a broad group of 17 stakeholders endorsed a set of recommendations aimed at reducing barriers to patient enrollment to clinical trials and included in those recommendations were many that are applicable to this guidance[6]. Where appropriate, these specific consensus recommendations are included in each of the relevant sections pertaining to the FDA draft guidance. The entire set of recommendations is included in an appendix to this letter.

Eligibility Criteria

The FDA recently issued draft guidance documents on specific oncology clinical trial inclusion criteria and we refer you to our comments on those guidance documents as many of the issues overlap[7].

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[2] Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: Race-, sex-, and age-based disparities. *J Am Med Assoc.* 2004;291(22):2720-2726. doi:10.1001/jama.291.22.2720

[3] Unger JM, Coltman CA, Crowley JJ, et al. Impact of the Year 2000 Medicare Policy Change on Older Patient Enrollment to Cancer Clinical Trials. *J Clin Oncol.* 2006;24(1):141-144. doi:10.1200/JCO.2005.02.8928.

[4] Unger JM, Hershman DL, Albain KS, et al. Patient Income Level and Cancer Clinical Trial Participation. *J Clin Oncol.* 2013;31(5):536-542. doi:10.1200/JCO.2012.45.4553

[5] Unger, J. M., Vaidya, R., Hershman, D. L., Minasian, L. M., & Fleury, M. E. (2019). Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. *JNCI: Journal of the National Cancer Institute*, *111*(3), 245–255. https://doi.org/10.1093/jnci/djy221

[6] Overcoming Barriers to Patient Enrolment in Therapeutic Clinical Trials for Cancer: Recommendations, accessed at: fightcancer.org/clinicaltrialbarriers

[7] Letter to FDA dated May 13, 2019 accessed at: https://www.fightcancer.org/policy-resources/comments-supporting-fda-guidance-modernize-clinical-trial-eligibility-criteria

We support the recommendations in the draft guidance to closely examine each eligibility criterion independently for scientific and ethical applicability and to reevaluate those criteria at each stage. Too often criteria are cut and pasted from trial to trial without consideration to whether they are appropriate or not.

Specifically, we recommend modernizing eligibility/inclusion/exclusion criteria to achieve the most relevant parameters that will ensure scientific integrity without unnecessarily excluding patients. Sponsors should ensure eligibility criteria do not preferentially exclude a racial or demographic group, e.g. upper age limits, or excluding comorbidities more highly associated with demographic or socioeconomic subgroups, unless specific scientific rationale for exclusion exists. (Consensus recommendation #18)

The FDA guidance did not suggest assessing how eligibility criteria impact the feasibility of the study, but this is one of the consensus recommendations endorsed by the wide variety of organizations and is important in assessing whether proposed criteria may generally or selectively restrict the potential pool of trial-eligible patients. Such an assessment requires access to large datasets of real patients and their clinical characteristics, a resource to which not all trial designers may have access.

We urge the development and sharing of resources that can be used for detailed assessment of accrual feasibility during the design phase of trials. These include patient and trial databases and modeling software. (Consensus recommendation #20)

We also support the recommendation to consider children and adolescents in trials initially designed to recruit only adults where possible and appropriate.

Trial Design and Methodology

Even if their participation does not pose safety concerns, certain patient populations, for example those with impaired organ function, advanced disease, brain metastases or lower performance status, are often excluded from trials due to concerns about “noise” in trial results. In such cases where safety is not a significant concern, such patients should be included in trials. Concerns about “noise” in results can be addressed through adaptive trial designs that include subgroups that are pre-specified expansion cohorts that are not included in primary data analyses as suggested by the draft guidance. We also support incorporating

pediatric development activities early in the clinical trial planning process. Importantly, however, considerations should be given to appropriate development of alternate formulations and dosing needed to include some pediatric populations.

Participant Burden

Clinical trial participation burden is an important factor that disproportionately deters low-income individuals from participating in cancer clinical trials. Research has shown a nearly 30 percent lower participation rate in cancer clinical trials for individuals with household incomes under $50,000[8] . For this reason, it is important to reduce financial burden and increase transparency of trial costs.

Consensus recommendations from our group related to participation follow, with the understanding that not all are within the control of FDA, sites, or sponsors.

- *Provide cost transparency by providing full coverage analyses on all trials to clearly articulate responsibility for all anticipated trial costs.*
  - Trial sponsors should collaborate with institutions to clearly define sponsor obligations with respect to covering supplies and services related to trials
  - Sites should provide patients considering enrolling in trials with information that enables the patients to consider how their direct and indirect costs would differ if they enrolled in the trial or received care outside the trial. (Consensus recommendation #13)

- *Ensure coverage of routine patient care costs incurred in cancer clinical trials by all payers.*
  - Further the implementation of existing federal requirements for private insurers to cover cancer clinical trial routine patient care costs in order to provide timely enrollment and avoid administrative burdens to enrolling patients on clinical trials.
  - Bolster state requirements to cover routine patient care costs in cancer trials.
  - Require state and federal insurance authorities to enforce routine patient care requirements.

[8] Patient Income Level and Cancer Clinical Trial Participation: A Prospective Survey Study JAMA Oncology January 2016 Volume 2, Number 1, Joseph M. Unger, PhD, Julie R. Gralow,MD, Kathy S. Albain, MD, Scott D. Ramsey,MD, Dawn L. Hershman, MD

- Ensure Medicaid coverage in all states and territories of routine patient care costs in cancer clinical trials. (Consensus recommendation #14)

- *Shield patients from out-of-pocket ancillary costs of trial participation such as travel, parking, and housing.*
  - Clarify policies to ensure reimbursement of ancillary costs is not seen as undue influence and ensure awareness of allowable reimbursements.
  - Fully utilize existing support resources (e.g. an American Cancer Society (ACS) Hope Lodge, ACS Road to Recovery transportation program, Lazarex Foundation, non-emergency medical transport), and develop new resources that shield or offset ancillary costs associated with trial participation. (Consensus recommendation #15)

- *Trial sponsors and research programs should explore the use of technology or other tools to reduce patient time and travel burdens associated with clinical trial participation.* (Consensus recommendation #17)

Enrollment and retention practices

Several of the recommendations made in the draft guidance related to enrollment and retention practices are aligned with our consensus recommendations. Specifically, we have recommended working with patients at the trial design phase to make them appealing to patients. (Consensus recommendation #16)

We also concur with the recommendation in the draft to ensure placement of trials at sites that would ensure diversity of trial participants. This recommendation was also among the consensus recommendations – specifically, ensuring that research sites selected for multi-site trials have diverse patient populations that reflect the broader population with cancer. (Consensus recommendation #21)

The draft guidance suggests working closely with community partners, a strategy that we support as reflected by our consensus recommendations. We believe that sponsors and trial sites should seek engagement and partnerships with community leaders and community-based organizations–especially those serving racial and ethnic minority groups as well as medically

underserved communities–to effectively disseminate information about the importance of clinical research participation as a social justice issue. (Consensus recommendation #23)

The draft guidance also suggests public outreach and education related to clinical trials, but caution should be exercised in expending time and money for large-scale public campaigns if evidence has not shown such activities to impact enrollment. It is possible that public awareness and education may be more effective in other disease areas, but in oncology public clinical trial awareness campaigns have not proven to be effective at altering trial enrollment[9,10]. More targeted campaigns directed only at newly diagnosed patients, rather than the public at large, or in conjunction with other activities have shown greater efficacy[11,12,13]. For this reason, the consensus recommendation is to focus awareness activities on newly diagnosed patients and their families. In particular, to promote general awareness among cancer patients and their families of clinical trial participation as a viable treatment option early during the course of patient care. (Consensus recommendation #9)

Not included in the FDA draft guidance is any mention of site trial screening protocols. Ad hoc or discretionary screening of patients for trial eligibility opens up the possibility of conscious or unconscious selection bias of patients considered for clinical trials. Our stakeholder group has recommended systematic screening of all patients to avoid selection bias, and we encourage FDA to include a recommendation in the guidance for systematic, rather than discretionary, trial screening. In order to achieve robust accrual, we believe sites should employ protocols or technology to make pre-screening incoming patients for trial eligibility more scalable and systematic. More specifically, sites should ensure that matching tools are easily available to providers in their workflow, standardize eligibility criteria so that it is machine-searchable, and standardize clinical trial protocols into formats easily incorporated into EMRs. (Consensus recommendation #6)

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[9] Moffitt K, Brogan F, Brown C, et al. Statewide cancer clinical trial navigation service. *J Oncol Pract.* 2010;6(3):127-132. doi:10.1200/JOP.200006

[10] Umutyan A, Chiechi C, Beckett LA, et al. Overcoming barriers to cancer clinical trial accrual. *Cancer*. 2008;112(1):212-219. doi:10.1002/cncr.23170

[11] Du W, Mood D, Gadgeel S, Simon MS. An Educational Video to Increase Clinical Trials Enrollment among Lung Cancer Patients. *J Thorac Oncol.* 2008;3(1):23-29. doi:10.1097/ JTO.0B013E31815E8BB2

[12] Du W, Mood D, Gadgeel S, Simon MS. An educational video to increase clinical trials enrollment among breast cancer patients. *Breast Cancer Res Treat.* 2009;117(2):339-347. doi:10.1007/ s10549-009-0311-7

[13] Stiles C, Johnson L, Whyte D, Nergaard TH, Gardner J, Wu J. Does Increased Patient Awareness Improve Accrual Into Cancer-Related Clinical Trials? *Cancer Nursing2.* 2011;34(5):E13-E19. doi:10.1097/NCC.0b013e31820254db

In oncology, recruitment and retention of underserved minorities has been demonstrably improved through the use of clinical trial navigators[14,15]. Among the consensus recommendations we offered as a way to address disparities in trial participation is to employ trial navigators, specifically, to provide clinical trial navigation services for patients from medically underserved groups to connect with publicly available support resources and culturally sensitive education materials. (Consensus recommendation #22) We encourage FDA to include this recommendation in the guidance as well.

Rare diseases

The draft guidance encourages early engagement with patient advocacy groups when the disease being studied is rare. While we agree with this suggestion, early and robust engagement with patients and patient advocacy groups is a fruitful strategy for successful clinical trial design regardless of the size of the population with a disease and should be practiced for all diseases.

Thank you again for the opportunity to provide comments, and we look forward to working with you to make sure cancer clinical trials are open and accessible to all patients who can safely participate. If you have any questions, please do not hesitate to contact Mark Fleury, PhD (mark.fleury@cancer.org), Principal, Policy Development - Emerging Science.

Sincerely,

/Filed electronically/

Lisa A. Lacasse, MBA
President
American Cancer Society Cancer Action Network

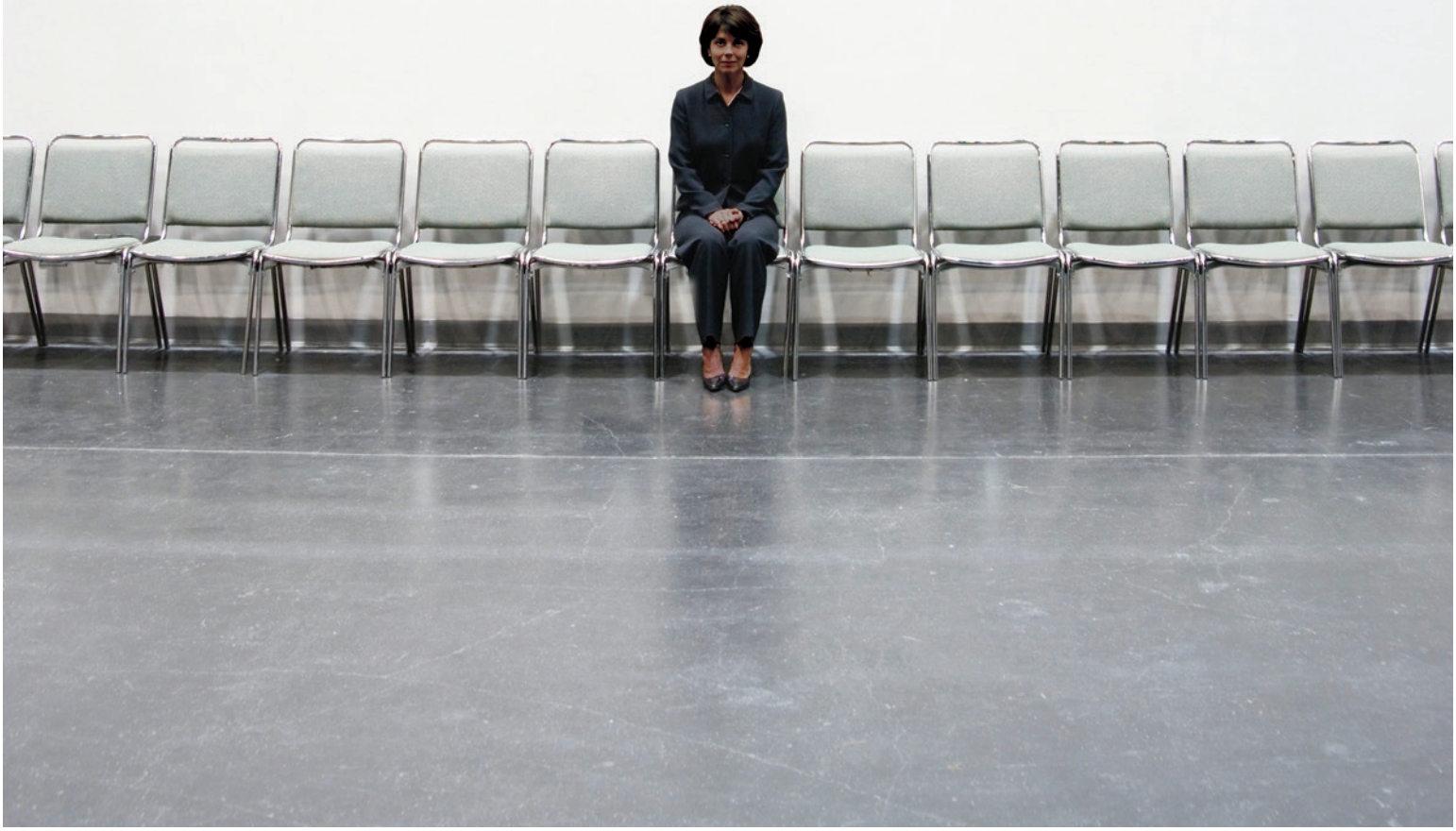
[14] Fouad MN, Acemgil A, Bae S, et al. Patient Navigation As a Model to Increase Participation of African Americans in Cancer Clinical Trials. *J Oncol Pract.* 2016;12(6):556-563. doi:10.1200/ JOP.2015.008946

[15] Ghebre RG, Jones LA, Wenzel JA, Martin MY, Durant RW, Ford JG. State-of-the-science of patient navigation as a strategy for enhancing minority clinical trial accrual. *Cancer*. 2014;120(S7):1122-1130. doi:10.1002/cncr.28570

Appendix A: Consensus Recommendations for Addressing Clinical Trial Enrollment Barriers

Overcoming Barriers *to Patient Enrollment in Therapeutic Clinical Trials for Cancer*

Recommendations



Recommendations

Introduction

The objective of cancer research is to generate new knowledge that can be used to improve survival and quality of life for patients with cancer. Clinical trials are the key step in advancing potential new treatments for patients with cancer from the research setting to the cancer care clinic, and patient participation in trials is crucial to their success. Most patients express a willingness to participate in clinical research, yet only a small fraction ultimately end up enrolling in a cancer clinical trial. In fact, analyses show that around 20% of cancer clinical trials fail due to insufficient patient enrollment.

The disconnect between patient interest and actual participation in cancer clinical trials is due to numerous barriers that discourage or prevent patients from enrolling. These barriers are discussed in greater detail in the accompanying document "Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report." In the report, the barriers are divided into provider and institutional barriers, patient barriers, and trial-design barriers.

While the barriers facing patients are numerous, the magnitude of each category of barriers varies significantly. For instance, studies indicate that more than 55% of patients seeking cancer care will not have a clinical trial available for their condition at the location where they are seeking treatment, and another 17% will not meet eligibility requirements. As a result, the population of patients who could possibly enroll in a local trial is just over a quarter of all patients. In other words, the barrier for nearly 75% of patients is the fact that their local institution does not have a clinical trial for which they are eligible.

Successfully overcoming barriers to patient enrollment requires not only understanding the barriers, but developing specific steps to address these barriers. The following consensus recommendations have been developed and endorsed by the array of stakeholders listed at the end of this document. These recommendations address a broad spectrum of barriers that are further detailed in the companion report. The recommendations are grouped by category, and require both programmatic activities and policy changes to be realized.

Note: ***All recommendations are directed at cancer therapeutic trials and cancer patients.***

Provider and Institutional Barriers

Context: Providers and institutions have a significant impact on cancer clinical trial enrollment through decisions regarding which and how many trials to open at a site, the quantity and type of research personnel employed, whether and how they identify and attempt to enroll patients in open trials, as well as investment in other research infrastructure. Together, these factors account for the largest influence on whether patients are able to enroll in a clinical trial.

1) Build and maintain a pool of diverse, research-trained staff which includes dedicated research positions as well as providers with multiple roles, with special attention to developing workforce reflective of underrepresented populations.

2) Maintain or increase funding from all trial sponsors, including NCI, for dedicated site research staff who can open trials and recruit patients, so that trial conduct is scalable and sustainable.

3) Provide dual-role staff—clinical staff providing patient care along with fulfilling research roles—with appropriate incentives to promote their participation in clinical research activities.
   a) Institutions should create protected time, a range of incentives, additional resources, and recognition for dual-role staff to conduct clinical research.
   b) Fully utilize nonmonetary incentives like quality or accreditation metrics to drive clinical research activity.

4) Sites should manage trial portfolios so that they match patient characteristics in the community that is served by a practice's catchment area.

5) Stakeholders should collaborate to develop free or affordable technology, tools and processes targeted toward non-research sites/providers that make matching patients to trial opportunities and referral of patients interested in trial participation easier.

6) In order to achieve robust accrual, sites should employ protocols or technology to make prescreening incoming patients for trial eligibility more scalable and systematic.
   a) Ensure that matching tools are easily available to providers in their workflow
   b) Standardize eligibility criteria so that it is machine-searchable
   c) Standardize clinical trial protocols into formats easily incorporated into EMRs

7) Create and implement ways to streamline the process and reduce effort needed to open clinical trials
   a) Expand use of standardized contracting for clinical trial conduct (e.g. Accelerated Clinical Trial Agreement, TransCelerate, Society for Clinical Research Sites, etc.)
   b) Continue to develop operational and contracting models for research enabled sites to participate in clinical trials just-in-time, where clinical trials are opened where applicable patients are identified.
   c) Expand and encourage use of Central IRBs for multi-site trials.
   d) Smaller practice sites should consider participation in research networks as a way to gain access to shared research infrastructure and clinical trials.

Patient Barriers

Context: On average, only a quarter of patients have local trials available for which they are eligible to enroll. Not all eligible patients are asked to enroll, but typically over half of those asked consent. The four most-cited reasons for declining participation are: fear of side effects, loss of control, logistics involved in participation, and cost concerns.

Recommendations:

8) Present cancer patients with specifically identified trial options as part of the physician-patient treatment decision discussion using evidence based methods.

9) Promote general awareness among cancer patients and their families of clinical trial participation as a viable treatment option early during the course of patient care.

10) Non-site specific trial matching and navigation services should be available for patients not provided trial options by their provider or institution. These services should clearly communicate roles and objectives.

11) Research stakeholders should develop evidence-based methods, materials and resources for:
    a) Just-in-time clinical trial education
    b) Patient-facing decision support

    These methods, materials, and resources should be collected, evaluated and made available to the community. Research programs should provide these resources and services to patients, families and caregivers.

12) Improve informed consent documents and processes to ensure education and comprehension by patients of the research in which they are contemplating participation.

13) Provide cost transparency by providing full coverage analyses on all trials to clearly articulate responsibility for all anticipated trial costs.
    a) Trial sponsors should collaborate with institutions to clearly define sponsor obligations with respect to covering supplies and services related to trials.
    b) Sites should provide patients considering enrolling in trials with information that enables the patients to consider how their direct and indirect costs would differ if they enrolled in the trial or received care outside the trial.

14) Ensure coverage of routine patient care costs incurred in cancer clinical trials by all payers.
    a) Further the implementation of existing federal requirements for private insurers to cover cancer clinical trial routine patient care costs in order to provide timely enrollment and avoid administrative burdens to enrolling patients on clinical trials.
    b) Bolster state requirements to cover routine patient care costs in cancer trials.
    c) Require state and federal insurance authorities to enforce routine patient care requirements.
    d) Ensure Medicaid coverage in all states and territories of routine patient care costs in cancer clinical trials.

15) Shield patients from out-of-pocket ancillary costs of trial participation such as travel, parking, and housing.
    a) Clarify policies to ensure reimbursement of ancillary costs is not seen as undue influence and ensure awareness of allowable reimbursements.
    b) Fully utilize existing support resources (e.g. ACS Hope Lodge, Road to Recovery, Lazarex Foundation, non-emergency medical transport), and develop new resources that shield or offset ancillary costs associated with trial participation.

16) Design trials to be more patient-centric by using patient input during the design and implementation phases.

17) Trial sponsors and research programs should explore the use of technology or other tools to reduce patient time and travel burdens associated with clinical trial participation.

Recommendations

Trial-Design Barriers

Context: Trial-design features like inclusion/exclusion criteria significantly affect the number of patients eligible to participate in a clinical trial.

18) Modernize eligibility/inclusion/exclusion criteria to achieve the most relevant parameters that will ensure scientific integrity without unnecessarily excluding patients.
    a) Ensure eligibility criteria do not preferentially exclude a racial or demographic group, e.g. upper age limits, or excluding comorbidities more highly associated with demographic or socioeconomic subgroup unless specific rationale for exclusion exists.

19) Encourage broad-panel biomarker testing programs to help promote simultaneous pre-screening for multiple targeted therapy trials.

20) Develop and share resources that can be used for detailed assessment of accrual feasibility during the design phase of trials. These include patient and trial databases and modeling software.

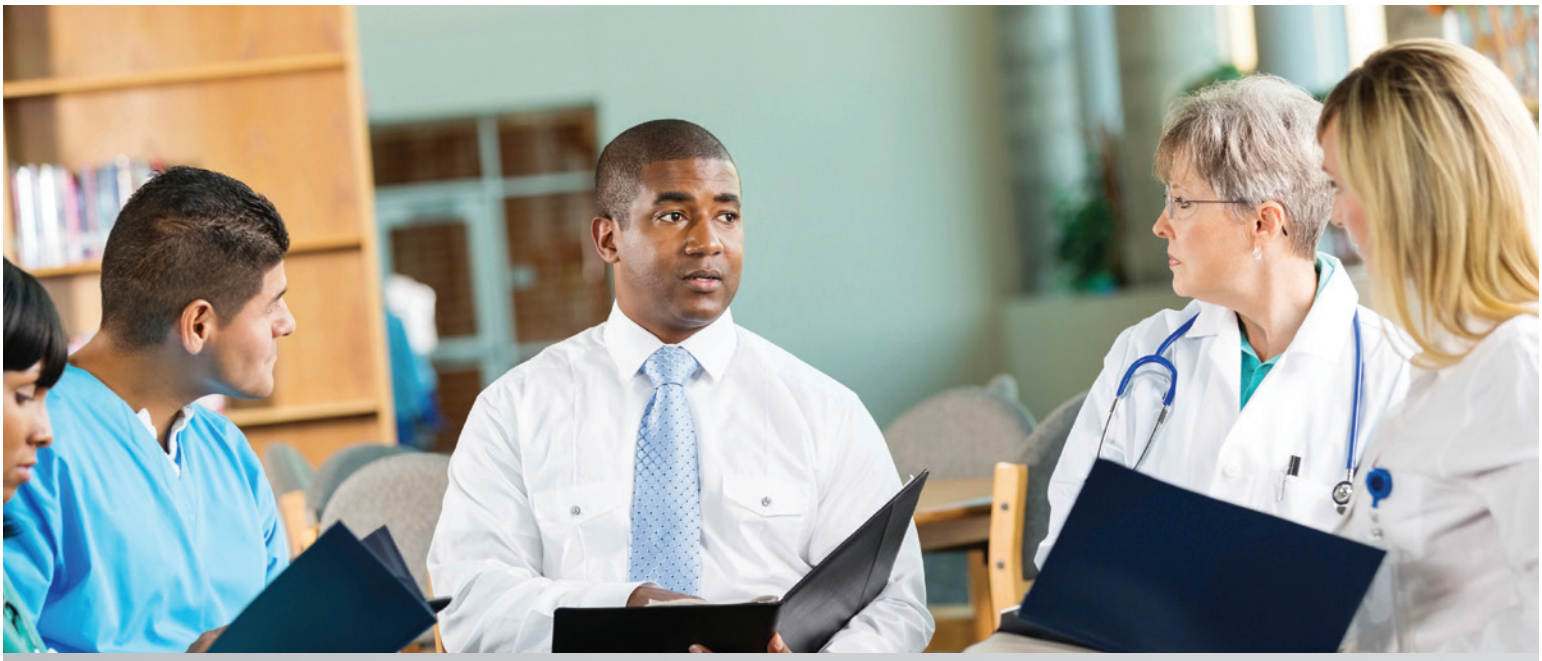
Disparities

Context: The demographics of participants in registrational trials for cancer drugs do not match the demographics of the U.S. cancer population, due in large part to many of these trials occurring outside of the U.S. Participants in NCI trials skew significantly younger than the U.S. cancer population and both minorities and the poor are also underrepresented in such trials.

21) Ensure that research sites selected for multi-site trials have diverse patient populations that reflect the broader population with cancer.

22) Provide clinical trial navigation services for patients from medically underserved groups to connect with publicly available support resources and culturally sensitive education materials.

23) Seek engagement and partnerships with community leaders and community-based organizations–especially those serving racial and ethnic minority groups as well as medically underserved communities–to effectively disseminate information about the importance of clinical research participation as a social justice issue.



These recommendations have been endorsed by the following organizations:

American Cancer Society

Cancer Action Network — American Cancer Society

AACI — Association of American Cancer Institutes

ACCC — Association of Community Cancer Centers

Cancer Support Community — A Global Network of Education and Hope

Fight Colorectal Cancer

Friends of Cancer Research

IMS Health & Quintiles are now IQVIA

Leukemia & Lymphoma Society

LIVESTRONG

LUNGevity — Find it. Treat it. Live.

National Minority Quality Forum

ONS — Oncology Nursing Society

Pancreatic Cancer Action Network

Research Advocacy Network — Advancing Patient-Focused Research

SIGNALPATH — RESEARCH • REWIRED

Sustainable Healthy Communities — Every Life. Every Day.

An accompanying report is available at: https://www.acscan.org/policy-resources/clinical-trial-barriers