Ad Hoc Working Group on Clinical Trials Enrollment and Retention

National Cancer Institute Council of Research Advocates

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Working Group Report

AD HOC WORKING GROUP ON CLINICAL TRIALS ENROLLMENT AND RETENTION

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CONTENTS

Executive Summary

The NCI Council of Research Advocates (NCRA) convened a Working Group to identify opportunities to promote research aimed at developing the most successful strategies for improving patient enrollment and retention in cancer clinical trials, centered around the financial costs of participation in cancer clinical trials. This focus arose from a perception of the need to reduce financial barriers to clinical trial participation, based on evidence suggesting that financial barriers, minimal resources, and related implicit biases are all barriers to clinical trial accrual (Nipp, Hong, et al., 2019). Secondary attention was given to the role of researchers, clinicians, sponsors, and health care organizations in addressing financial costs of clinical trial participation. How financial cost barriers influence trial participation from disparity populations was given special consideration.

The Ad Hoc Working Group on Clinical Trials Enrollment and Retention was formed in June 2020 and over the subsequent eight months brought its expertise to multiple discussions. After a review of the literature, the Working Group identified gaps in the evidence, made recommendations that will ideally lead to new knowledge and outcomes, and offered future research considerations. The intent of the recommendations was to establish research, programs, and resources that could inform and address cost of clinical trial participation, fostering higher participation among adult cancer patients and survivors in clinical trials, while minimizing disparities in access and participation. The Working Group was motivated by its shared belief that clinical trials are an integral part of high-quality cancer care and should be available to all eligible patients and survivors.

The Working Group developed six recommendations that are described in the full report.

1. Identify the types of financial costs, financial concerns, and the extent of cost barriers to clinical trial participation.

2. Develop methodology, including novel technology, to collect cost-related data for those participating in clinical trials.

3. Develop methodology to understand the role of social determinants of health in clinical trial participation in diverse populations.

4. Generate evidence to more fully understand the role of different types of payers and insurance plans as a barrier or facilitator to clinical trial participation for various populations.

5. Create and evaluate interventions aimed at reducing cost barriers to trial participation and completion, align decision-making stakeholders on operational details and specifications, and establish strong partnerships across stakeholder groups.

6. Examine whether COVID-19-related adjustments to clinical trial requirements may reduce perceived and/or actual cost barriers to patient and survivor enrollment in and completion of trials.

In brief, there is a lack of evidence regarding the extent to which perceived and/or actual costs present a barrier to adult cancer patients and survivors enrolling in and completing clinical trials, particularly specific costs that are distinct from usual care. What interventions may be useful and how successful they may be in removing financial barriers and addressing the related disparities is unclear. NCI has several opportunities to advance research in a topic area that appears to receive minimal funding.

Background

Membership

The Working Group included individuals with expertise in cancer clinical trials, population science, health disparities, and patient advocacy. The Group was co-chaired by a nurse scientist and patient advocate. NCI provided an executive secretary and access to NCI expertise via ex officio members.

Functional Statement

The NCI Council of Research Advocates (NCRA) convened a Working Group to identify opportunities to promote research aimed at identifying the most successful strategies for improving patient enrollment and retention in cancer clinical trials, particularly for patients from underrepresented and minority populations. The primary focus was on the financial costs of participation in cancer clinical trials. Secondary consideration was given to the role of researchers, clinicians, sponsors, and other health care organizations in addressing these financial burdens.

Charge

On July 22, 2020, NCI Director Dr. Norman E. Sharpless provided the charge for the first Working Group meeting. He shared that NCI supports clinical trial programs that require continual refinement and innovation to maximize accrual rates and the diversity of accrual. He shared that NCI has seen some improvement in minority accrual rates over the past two decades, but they are still unacceptably low, with overall minority participants comprising about 25% of enrolled participants, and Black/African American participants comprising about 10% of enrolled participants. Dr. Sharpless asked how trials can be designed and conducted to maximize accrual rates so that all patients can benefit. He stated that addressing this question is how the Group can facilitate progress for patients, ensure that therapies are generalizable to multiple populations, and provide a proxy for good patient care via clinical trials. Dr. Sharpless noted that the Group exists to identify barriers to trial accrual, including such financial barriers as taking days off from work, parking costs, and the financial toxicity of therapies.

Rationale for the Formation of the Working Group

Clinical trial participation represents a minority of the total cancer population and an even smaller proportion of disparity populations[1] (Chino & Zafar, 2019). Financial costs are thought to be a barrier to participation that may particularly negatively impact disparity populations. The Working Group was formed to explore the evidence that supports this hypothesis.

[1] In addition to the NIH-designated health disparity populations (Blacks/African Americans, Hispanics/Latinos, American Indians/Alaska Natives, Native Hawaiians and other Pacific Islanders, socioeconomically disadvantaged populations, underserved rural populations, and sexual and gender minorities), the Working Group deemed adolescents and young adults, and seniors as experiencing notable disparities in the cancer context.

Scope and Framing Questions

The Functional Statement and Charge presented a wide scope of potential topics that would have been challenging to adequately address within the available time frame. Thus, the Working Group decided to focus on adult cancer patients[2] and survivors[3] enrolling in and completing treatment, symptom management, and cancer control trials funded in part or total by NCI. Several types of clinical trials were excluded: (1) adult primary prevention trials were deemed out of scope because they involve healthy participants—who could potentially have different motivations and barriers to participating in clinical trials; (2) pediatric cancer trials were not considered because financial barriers for children and their families are distinct from those of adults—in addition, philanthropic support for pediatric cancer may reduce financial costs to trial participants; and (3) cancer care delivery trials were not included because they are a recent development for which there is inadequate information to evaluate patient costs.

The Working Group developed seven framing questions to guide its work.

1. To what extent are perceived and/or actual[4] costs[5] a barrier to adult cancer patients and survivors enrolling in and completing clinical trials?

2. What specific perceived and/or actual costs contribute most to patients not enrolling in or completing clinical trials?

3. Does the impact of perceived and/or actual costs on clinical trial enrollment in and completion of trials vary across different underserved populations for which data are available?

4. How are the specific perceived and/or actual costs most likely to contribute to patient decisions distinct from the costs of cancer care outside the trial setting?

5. What has research shown to be effective approaches to helping adult cancer patients and survivors overcome perceived and/or actual cost barriers to participation in clinical trials?

6. Are there particular trial participation requirements that increase perceived and/or actual costs to patients and survivors?

[2] Patients were defined as people receiving or registered to receive medical treatment. Decisions to participate in clinical trials may also involve caregivers and family members who may or may not bear financial responsibility for patients' care.

[3] Survivors were defined as individuals who have been diagnosed with cancer, from the time of diagnosis until the end of life. Survivors may be free from or living with cancer. As with patients, decisions to participate in clinical trials may also involve caregivers and family members who may or may not bear financial responsibility for patients' care.

[4] The Working Group distinguished between actual costs that can be estimated when trial participation is under consideration and the perception that costs will be problematic absent specific estimates. The literature suggests that perceived costs play an often-unspoken role in patient and survivor trial participation decisions, as well as clinician decisions to offer trials.

[5] For the purposes of this report, costs are considered to come in three categories: (1) out-of-pocket direct costs are the amount of money a patient or survivor pays for medical expenses that are not covered by a health insurance plan, including deductibles, coinsurance, copayments, and costs for non-covered health care services; (2) out-of-pocket indirect costs are incurred by patients or providers in connection with health care, such as transportation (e.g., public, mileage, tolls, and parking); lodging and meals; and child- or elder-care needs; and (3) productivity losses of patients, survivors, and caregivers arise from lost work due to absenteeism or early retirement, or impaired productivity at work.

7. What steps can researchers, clinicians,[6] health care organizations, regulators, and policymakers take to reduce excess costs in clinical trials?

Literature Review

The Working Group began its deliberations by reviewing several recent publications that place patient and survivor cost in the context of the complex process that must occur for a patient or survivor to enroll in a trial (American Cancer Society Cancer Action Network, 2018; Siembida et al., 2020; Unger et al., 2020; Unger et al., 2019). This work shows that the most common reasons patients and survivors do not enroll in trials are beyond their individual control, including not being eligible for an existing trial, not being offered the opportunity to participate, and not having access to trials at their local medical practice or through referral. A recently published systematic review found that just over half of patients and survivors invited to participate in trials will do so. The role of perceived and/or actual costs in preventing the other half from enrolling is the focus of this report.

The Working Group then examined the results of a literature search designed to identify peer-reviewed publications published from January 1, 2010, to July 1, 2020, that were relevant to the framing questions and reported the results of original research in US populations. Of the 44 identified publications, the methodological approaches included existing data analyses (33%), quantitative surveys (33%), qualitative interviews (15%), and single arm interventions (15%). There were no randomized controlled trials. The sample sizes varied from very small (9) to extremely large (729,844), with a median of 159 participants. The median decreased to 97 participants when existing data analyses were excluded. Most studies were conducted at academic medical centers alone or in combination with community settings.

Most of the published studies were related to framing questions 1, 2, and 3; five or fewer were related to framing questions 4 to 7. Insurance and travel (transportation and/or lodging) were addressed in about half the studies, while other studies used more loosely defined categories. No study enumerated specific costs or distinguished trial-related costs from costs of usual care. A limited number of studies focused on or were powered to examine specific disparity populations.

NCI Funding

Several efforts were made to identify NCI funding of extramural research into the cost barriers to participant enrollment in and completion of clinical trials, including potentially related disparities. For example, three separate searches of NIH funding data using the Query, View, and Report System identified about 75 funded grants that might relate to the interests of the Working Group. Only a handful had titles suggesting they addressed questions of interest to the Working Group. Of those, none included relevant specific aims. Similarly, a search of the clinicaltrials.gov website identified about 70 registered trials that were potentially funded by NCI and addressed patient and survivor cost barriers to trial enrollment and completion. Only one included a relevant objective and endpoint. The conclusion from these searches is that the results showed low sensitivity because terms like “trial participation” and “financial” are widely used in grant applications that do not propose studies relevant to the framing questions. NCI funding in this area would be difficult to accurately assess without substantial manual review of grant applications.

[6] Clinicians were defined as health professionals who take care of patients, including physicians, physician assistants, advanced practices nurses, and nurses.

The funding source searches did suggest that some research into cost barriers to patient and survivor enrollment in and completion of clinical trials was being conducted within several large funding initiatives. This was confirmed by an examination of the funding sources for the 44 published studies in the literature review. About half of those publications listed NCI support. This included 29 different sources, most of which were large initiatives in which tracking the specific aims of every study conducted is difficult [e.g., Cancer Center Support Grants, NCI's National Clinical Trials Network (NCTN), and NCI Community Oncology Research Program (NCORP)]. Investigator-initiated funding grants were noted five times; none of these awards included a specific aim relevant to the framing questions. Overall, the Working Group concluded that NCI funding of extramural research into the cost barriers to patient and survivor enrollment in and completion of clinical trials appears limited.

Conclusion

Overall, the Working Group found that the existing pool of published and ongoing studies was inadequate to definitively address any of the framing questions. Further investigation is necessary to meet the goals of reducing cost barriers to trial participation and completion, to increase accrual overall and within disparity populations, and to promote equitable access to trials.

Recommendations

Recommendation 1:

Identify the types of financial costs, financial concerns, and the extent of cost barriers to clinical trial participation.

This recommendation primarily addresses framing question 1: To what extent are perceived and/or actual costs a barrier to adult cancer patients and survivors enrolling in and completing clinical trials? It also addresses framing questions 2, 3, and 7.

Rationale

Although 35 of the 44 peer-reviewed publications selected for review sought to describe and understand trial participation costs, there were methodological limitations and inconsistencies that made it difficult to draw conclusions. No study attempted to tabulate actual costs and most studies looked at just one or two sources of potential cost (e.g., insurance and transportation but not lost wages). Some studies referenced a specific trial protocol under consideration, whereas others used hypothetical examples. How cost barriers were captured varied from specific questions about types of costs to questions about barriers in general. Studies were almost exclusively focused on trial enrollment, leaving issues related to ongoing participation unexamined. Few studies had the ability to assess disparities. Whereas some studies suggested that patients and survivors who faced potential insurance and transportation barriers were less likely to participate in a trial, other studies reported no association of those factors with participation. Several studies documented that patients and clinicians have different perspectives on potential cost barriers. Overall, the Working Group concluded there is a need for systematic, prospective examination of costs as a barrier to clinical trial enrollment and completion.

Considerations

Research conducted in response to this recommendation should endeavor to

- Capture information on all categories of actual or perceived cost (out-of-pocket direct costs, out-of-pocket indirect costs, and productivity loss);
- Assess the association of costs with protocol phase, type (e.g., treatment, cancer control, or symptom management), and requirements (e.g., cost per visit and costs of uncovered tests or procedures);
- Include objectives pertaining to potential disparities and attain the sample sizes necessary for meaningful analyses of those objectives;
- Incorporate both prospective data collection and secondary analysis of existing data (e.g., registries, electronic health records, Flatiron Health, and CancerLinQ®), as well as trial screening logs;
- Include practice settings where trial participation is rarely or never offered;
- Understand how clinician perceptions of cost influence decisions about offering trials to patients and survivors, including willingness to refer to trials not available in the local practice.

Desired Outcome

Identification of cost barriers to clinical trial enrollment and completion that could be addressed with programs and resources.

Recommendation 2:

> **Develop methodology, including novel technology, to collect cost-related data for those participating in clinical trials.**

This recommendation primarily addresses framing question 2: What specific perceived and/or actual costs contribute most to patients not enrolling in or completing clinical trials? It also addresses framing questions 1, 3, and 4.

Rationale

About half of the 44 peer-reviewed publications selected for review attempted to capture information about specific costs. As noted for recommendation 1, none of these studies attempted to tabulate total costs and most looked at just one or two sources of potential cost. The specific costs and how they were assessed were so variable as to make comparisons across studies impossible. For example, some studies attempted to capture one aspect of out-of-pocket indirect costs by using travel distance, whereas others looked at travel time and/or specific transportation needs, sometimes including lodging, sometimes not. The potential productivity losses due to travel time or trial participation were rarely captured. A second example is insurance, where studies universally asked about "coverage" rather than specific out-of-pocket direct costs that would be borne by patients and survivors. The Working Group concluded that developing standard and feasible approaches for capturing cost information is essential to identifying and addressing costs as a barrier to clinical trial enrollment and completion.

Considerations

Methods developed in response to this recommendation should seek to

- Simultaneously capture three types of costs incurred by patients and survivors participating in trials: out-of-pocket direct costs, out-of-pocket indirect costs, and productivity losses (defined under footnote 5).

- Define each type of cost broadly. For example, out-of-pocket direct costs should include non-covered items like over-the-counter medications. Out-of-pocket indirect costs should include public and private transportation, including mileage, tolls, and parking for the latter. Food and lodging, as well as the costs of having others take on child and elder care, should also be considered. Finally, a full accounting of cost would include income loss due to the ways in which trial participation may impact employment and wages.

- Make use of technology to ease the burden of data collection. For example, information about out-of-pocket direct costs from billing databases could be linked to study data. The use of mobile devices to gather information merits exploration.

- Include comparisons to the cost of equivalent treatments delivered as usual care.

- Assess whether collected data are comparable across disparity populations or if there is variability that must be considered in analyzing and interpreting results.

Desired Outcome

Tools to facilitate ongoing monitoring of and research into perceived and/or actual cost barriers to clinical trial enrollment and completion, which would also support the evaluation of interventions aimed at reducing barriers.

Recommendation 3:

Develop methodology to understand the role of social determinants of health in clinical trial participation in diverse populations.

This recommendation primarily addresses framing question 3: Does the impact of perceived and/or actual costs on clinical trial enrollment in and completion of trials vary across different underserved populations for which data are available? It also addresses framing questions 1 and 2.

Rationale

The Working Group noted that the formal definition of costs used in the research community and adapted for this report does not account for competing financial demands—such as housing and food costs for patients' and survivors' families—that may create barriers to trial participation and completion. Anecdotal experiences suggest patients and survivors may not consider these as cost barriers to trial participation or may be unwilling to admit to facing such demands. The concept of social determinants of health[7] provides a useful model for thinking about competing financial demands and how they can contribute to disparities in patient and survivor enrollment in and completion of clinical trials.

Considerations

Methods developed in response to this recommendation should

- Focus initially on the social determinants of health that affect economic stability, particularly food insecurity, housing instability, and poverty;
- Measure patient- and survivor-specific social determinants using screening questions developed for clinical use;
- Assess whether and to what extent social determinants vary across disparity populations;
- Explore linkages of trial participant residential information, such as ZIP code, to neighborhood-level data to gain insight into community-level barriers to clinical trial participation.

[7] Social determinants of health are conditions in the environments in which people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks.

Desired Outcome

Uncover previously unrecognized barriers to trial participation and identify opportunities to address trial participation barriers through community-based interventions.

Recommendation 4:

> **Generate evidence to more fully understand the role of different types of payers and insurance plans as a barrier or facilitator to clinical trial participation for various populations.**

This recommendation primarily addresses framing question 4: How are the specific perceived and/or actual costs most likely to contribute to patient decisions distinct from the costs of cancer care outside the trial setting? It also addresses framing questions 3 and 7.

Rationale

The Working Group identified a handful of publications suggesting that variations in insurance coverage for routine care costs incurred while participating in clinical trials continue to create participation barriers, despite Affordable Care Act regulations enacted in 2014 ensuring that non-grandfathered private insurance plans include such coverage. It seems likely that the same challenges will occur as states implement a recent mandate for Medicaid to cover routine services provided in connection with cancer clinical trials. Medical practices report that national coverage analyses conducted through an NCI–American Society of Clinical Oncology (ASCO) partnership have been instrumental in addressing some of these challenges, but how this effort has impacted the out-of-pocket direct costs for patients and survivors participating in trials is unclear.

Considerations

Research conducted in response to this recommendation should attempt to

- Capture the minimum information needed to characterize whether a plan/payer is subject to or exempt from regulations requiring reimbursement for routine patient care services delivered in connection with a clinical trial;
- Parse patient and survivor out-of-pocket direct costs into the specific categories of deductibles, coinsurance, and copayments, as well as costs for non-covered health care services;
- Determine if insurance processes create barriers to accessing existing coverage, such as complex rules, extensive paperwork, or multiple levels of pre-utilization review;
- Explore whether variations in coverage contribute to disparities.

Desired Outcome

Inform regulatory efforts and insurance plan design; support the development of resources to help patients, survivors, and clinicians understand whether a specific plan/payer covers routine patient care costs; and estimate any out-of-pocket direct costs arising from cost-sharing requirements or lack of coverage for routine patient care costs in connection with clinical trial participation.

Recommendation 5:

Create and evaluate interventions aimed at reducing cost barriers to trial participation and completion, align decision-making stakeholders on operational details and specifications, and establish strong partnerships across stakeholder groups.

This recommendation primarily addresses framing question 5: What has research shown to be effective approaches to helping adult cancer patients and survivors overcome perceived and/or actual cost barriers to participation in clinical trials? It also addresses framing question 7.

Rationale

The literature review identified four publications that reported on non-randomized, single arm interventions that sought at least partially to help patients and survivors overcome cost barriers to trial participation (Fouad et al., 2016; Holmes et al., 2012; Nipp, Lee, et al., 2016; Nipp, Lee, et al., 2019). All four interventions included some form of financial navigation[8] and three provided direct financial assistance. Most patients and survivors receiving interventions had some evidence of unmet need at the time they were recruited to the study. The results suggest that the interventions increased the proportion of eligible patients and survivors who enrolled in and completed trials. Overall, the Working Group identified a need to better understand what strategies are being used, whether they increase trial participation and completion, and how effective strategies can be sustained.

Considerations

Research and other activities conducted in response to this recommendation should seek to

- Build on knowledge generated by research conducted in response to recommendations 1 to 4.
- Assess the inclusion of clinical trial considerations in financial navigation programs provided at academic and community practice settings. Questions of interest include when and how patients and survivors are screened for financial risk, who makes patients and survivors aware of financial navigation services, whether financial navigation services address trial participation directly, the availability of direct financial support such as transportation reimbursement to facilitate trial participation, how such programs are staffed and budgetarily supported, and the incorporation of community resources into programs.
- Examine whether the availability of financial navigation programs is associated with the volume of patients from disparity populations cared for in a practice setting.
- Inventory and share information from NCI-designated Cancer Centers, NCTN Groups, and NCORP Research Bases to identify financial navigation intervention efforts or studies for which results have not been published, then convene interested parties to share experiences and consider potential research collaborations.

[8] Financial navigation is support given to patients, survivors, and their families to help them reduce hardship related to the cost of treatment for cancer. Activities can include understanding insurance plan coverage and out-of-pocket direct and indirect health care costs, and identifying strategies to reduce costs by things such as accessing patient assistance programs. Financial navigation may be offered as part of patient navigation or may be provided separately by designated financial counselors, social workers, or clinicians.

Desired Outcome

Creation and implementation of evidence-based and sustainable financial navigation services aimed at helping patients and survivors overcome cost barriers to clinical trial enrollment and completion.

Recommendation 6:

> **Examine whether COVID-19-related adjustments to clinical trial requirements may reduce perceived and/or actual cost barriers to patient and survivor enrollment in and completion of trials.**

This recommendation primarily addresses framing question 7: What steps can researchers, clinicians, health care organizations, regulators, and policymakers take to reduce excess costs in clinical trials? It also addresses framing questions 5 and 6.

Rationale

A unique opportunity exists to determine if changes to cancer clinical trials during the COVID-19 pandemic addressed some of the financial barriers to trial participation. Capturing information from this experience will accelerate the identification and implementation of strategies to help patients and survivors overcome cost barriers to clinical trial participation.

Considerations

Research conducted in response to this recommendation should

- Identify COVID-19-related adjustments[9] with the potential to reduce perceived and/or actual cost barriers to enrollment in and completion of clinical trials;
- Estimate the impact of identified adjustments on trial participation long term;
- Assess whether patients and survivors, including those from disparity populations, find the identified adjustments acceptable relative to previous approaches.

Desired Outcome

Approaches to the conduct of clinical trials that simultaneously meet regulatory requirements and minimize perceived and/or actual cost barriers to clinical trial enrollment and completion.

[9] ASCO and others have enumerated specific changes with potential trial participant benefits, including remote consent, reducing the collection of research-only biospecimens, and decreasing travel to research sites by allowing for local administration of treatment, imaging, laboratory tests, and patient assessments (Park et al., 2021; Pennell et al., 2021).

Suggestions Outside the Working Group Scope

Although the Working Group was tasked with developing recommendations for trials funded in part or total by NCI, members hope other organizations that fund clinical trials will leverage these recommendations and adopt any resulting strategies that prove efficacious. NCI should consider how to engage other funders in activities related to these recommendations.

The Working Group encourages NCI to convene similar groups to look at financial barriers to clinical trial participation and completion in the pediatric setting and in the primary prevention context, and to monitor these concerns in cancer care delivery trials.

During its deliberations, the Working Group identified many non-patient-level barriers to clinical trial participation for eligible patients and survivors. These included challenges faced by community practices seeking to provide access to clinical trials, difficulty matching eligible individuals to open trials, and clinician hesitancy in offering trials to specific patients and survivors. NCI support for efforts to understand and address these issues is a necessary complement to activities resulting from the recommendations in this report.

Some Working Group members expressed concern about the variable attitudes of institutional review boards toward reimbursement of actual participant expenses. Although permissible under current regulations and Food and Drug Administration guidance, some boards reportedly consider reimbursement in the same category as the provision of participant incentives, which results in reimbursement being deemed potentially coercive and thus either limited or not allowed. NCI should ensure that its institutional review boards and grantees understand the distinction between potentially coercive incentives and justifiable reimbursement. The overall goal is to help reduce the financial costs that patients incur as part of a clinical trial, as opposed to paying patients for participating in research, as done by some trials involving healthy participants.

The Working Group supports recommendations made by the Strategic Planning Working Group of the NCI Clinical Trials and Translational Research Advisory Committee that would decrease trial complexity and cost and decentralize trial activities. These recommendations are highly likely to reduce perceived and/or actual costs to adult cancer patients and survivors enrolling in and completing clinical trials.

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