JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Addressing Financial Barriers to Patient Participation in Clinical Trials: ASCO Policy Statement

Karen M. Winkfield, Jonathan K. Phillips, Steven Joffe, Michael T. Halpern, Dana S. Wollins, and Beverly Moy

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on September 13, 2018.

Corresponding author: Karen M. Winkfield, MD, PhD, Wake Forest Baptist Health, 1 Medical Center Blvd, Winston-Salem, NC 27157; e-mail: kwinkfie@wakehealth.edu.

0732-183X/18/3699-1/$20.00

ABSTRACT

Research conducted through clinical trials is essential for evaluating new treatment modalities, establishing new standards of cancer care, and ultimately improving and prolonging the lives of patients with cancer. However, participation in trials has been low, and this is attributable to various factors including patient financial barriers. Such financial barriers include the rising cost of cancer care; a lack of transparency in coverage policy; and the perception of ethical, compliance, or institutional impediments to patient financial support. ASCO convened a roundtable discussion with a variety of stakeholders to define the scope of the problem, as well as to identify clinical practice and policy solutions applicable at the institutional and system-wide levels. This statement summarizes key discussions from the ASCO Roundtable, as well as findings from the literature, and provides ASCO's recommendations for overcoming financial barriers that may otherwise prevent participation in clinical trials. These recommendations broadly address the following key areas: (1) improving the policy environment for coverage of clinical trials; (2) facilitating transparency among providers, patients, and payers for trial-related out-of-pocket costs; (3) refuting the specter of inducement to enable targeted financial support for patients; and (4) improving the available data on costs of cancer clinical trials.

J Clin Oncol 36. © 2018 by American Society of Clinical Oncology

INTRODUCTION

Clinical trials are essential for evaluating new treatment modalities, establishing new standards of cancer care and, ultimately, improving and prolonging the lives of patients with cancer.[1] Nevertheless, cancer clinical trials consistently have low rates of participation, especially when regarding patients from particular ethnic or racial, geographic, age, and other underserved demographic subgroups.[2-6] Factors contributing to low participation rates include narrow eligibility criteria and burdensome trial-related visits and testing, as well as organizational, attitudinal, and educational barriers among clinicians and patients.[7-10] The participation of diverse groups of patients in clinical trials is further hindered by other demographic factors such as socioeconomic status.[11,12] Ongoing collaboration among stakeholders is necessary to address the financial barriers to clinical trial participation and to improve patient enrollment and retention throughout the cancer care continuum.[13]

Financial toxicity, defined as the negative patient-level impacts of the cost of cancer care, has been implicated as causing distress that can reduce the patient's ability to enroll or continue with participation in a clinical trial.[11,14-17] Addressing these financial barriers may not only improve enrollment in clinical trials, but also improve the generalizability of research findings through broader trial participation. Equally important, removing financial barriers to clinical trial participation will help ensure access for patients who desire to participate. However, strategies for addressing financial barriers to participation in clinical trials have not been sufficiently explored in the literature and have yet to be widely implemented across the clinical research enterprise.

For these reasons, in 2017, the ASCO Health Disparities Committee prioritized the development of a set of recommendations to address the financial barriers to clinical trials participation in the cancer setting. The committee convened an ASCO Roundtable to discuss and define the scope of the problem and to identify clinical practice and policy solutions applicable at the institutional and system levels. Key stakeholders, including patient advocates, oncology clinicians, clinical researchers, bioethicists, regulatory and reimbursement experts, and industry representatives, shared their perspectives on issues including

DOI: https://doi.org/10.1200/JCO.18.01132

insurance coverage, ancillary expenses (defined as out-of-pocket costs, including relevant nonmedical expenses), and ethical concerns. Using findings from the ASCO Roundtable and from the published literature, ASCO developed a set of recommendations, presented herein, for overcoming the financial barriers that may otherwise prevent participation in clinical trials.

BACKGROUND ON PATIENT FINANCIAL BARRIERS TO CLINICAL TRIAL PARTICIPATION

Medicare and most private payers generally provide coverage for the costs of routine care associated with clinical trials that are either (1) funded by the federal government, (2) submitted to the US Food and Drug Administration (FDA), or (3) exempt from FDA submission requirements.[18] However, these payers often do not cover all trial-related costs. In addition to investigational or routine medical costs, a patient may also encounter trial-related, nonmedical expenses. The types of financial costs associated with participation in a clinical trial are summarized in Table 1. For the purposes of this statement, any costs that are passed on to a trial participant are collectively referred to as clinical trial–related out-of-pocket costs. These costs can represent a financial barrier to clinical trial participation for patients with cancer.

More broadly, financial barriers to clinical trial participation can be grouped into three categories: (1) financial toxicities of cancer care; (2) lack of transparency and gaps in coverage policy; and (3) ethical, statutory, or institutional barriers to assisting clinical trials participants with trial-related out-of-pocket costs.

Financial Toxicities of Cancer Care

The cost of routine cancer care has been escalating, even for insured patients, and these costs are expected to continue to increase.[19-21] Moreover, the proportion of direct medical costs shouldered by patients is growing because of increased cost-sharing and insurance premiums, and they may increase further as a result of limited networks and tiered formularies.[22] Sixty percent of the population of the United States resides at or below 400% of the federal poverty level. As such, a significant proportion of patients with cancer may be vulnerable to financial toxicity related to the cost of their care.[23] Recent data reveal that financial toxicity has detrimental effects on patients throughout the cancer care continuum, including increased mortality, poorer quality of life, reduced medication adherence, and decreased ability to engage in health care decision making, including the willingness or ability to enroll in clinical trials.[11,14-16,24-29]

Direct medical costs (eg, treatment, imaging), direct nonmedical or ancillary costs (eg, transportation and lodging, child care), and indirect costs (including patient time and the costs related to toxicities and lost wages) all contribute to financial toxicity. However, data on these costs among clinical trial participants that would enable targeted intervention to eliminate related financial barriers are lacking. Moreover, differences and disparities in the overall economic burden of cancer care exist among patients. Between 20% and 40% of adult patients with cancer report some combination of financial hardship, although patients at risk of such hardship are not always identified.[30,31] Patients with cancer are more likely than people without a cancer history to modify their behaviors as a result of these hardships and are more likely to report delayed prescription filling, use of less medication, or skipped medication doses.[32] Financial hardship associated with cancer care also varies by insurance status for patients younger than 65 years of age. For example, publicly insured or uninsured patients are almost twice as likely to report financial hardship, compared with privately insured patients.[30,32]

Patients with cancer seeking to enroll in a clinical trial may have been living for months or years with their diagnoses, already

Table 1. Financial Costs Associated with Clinical Trial Participation

Cost Type	Explanation and Example	Current Practice for Those Who Cover These Costs
Investigational care costs	Includes the specific therapeutic agent under investigation and additional services that would not have been required if the patient was receiving standard therapy (eg, extra blood draws for safety data, radiologic studies other than routine restaging examinations).	Research sponsor (although not all trial sponsors provide reimbursement for the additional or more frequent services).
Routine-care costs	Services that would have been provided to beneficiaries absent a clinical trial (ie, following standard care) and can include services for therapy, for prevention of complications, or for supportive care.	For insured patients, health insurance plans that cover clinical trials provide reimbursement for provider costs and beneficiaries or patients pay any cost sharing. If a health plan denies coverage for the entire trial or individual services within the trial that the trial sponsor or researcher consider routine OR in the case of uninsured patients, several options exist: 1. Research program might cover through philanthropy or connect patient with other nonprofit 2. Research program might ask trial sponsor (if industry) for funding to cover costs 3. Patient pays out of pocket
Nonmedical costs	Includes nonmedical costs for lodging, meals, dependent care, and transportation required for clinical trial participation.	There are three potential sources of coverage and few data about the frequency with which any of them are used: 1. Patients and families 2. Philanthropic support from the research program or other nonprofit 3. Some examples where trial sponsors are willing to cover costs, but ethical and compliance concerns compromise ability for sponsor support

having strained or exhausted their finances, and experienced the full range of negative consequences of financial toxicity. In this budget-sensitive context, patients are overwhelmingly likely to be concerned about their insurer's coverage policies for trial participation, as well as their own ability to pay for the noncovered costs associated with trial participation.[14,15] Early phase trials, with relatively more frequent clinical follow-up and higher risks of toxicity and associated clinical interventions, may present even greater financial risk to these patients.[14,33]

Lack of Transparency and Gaps in Coverage Policy

The Affordable Care Act (ACA) in 2010 mandated that most private insurers cover routine costs of care for individuals enrolled in approved clinical trials, closing a gap that frequently resulted in denial of insurance coverage for care associated with enrollment in a clinical trial.[34] To date, 39 states (including the District of Columbia) have also legislated some form of clinical trial coverage laws or cooperative agreements addressing the coverage of routine patient medical care costs associated with clinical trials, but the components of these laws vary significantly by state.[15] Nevertheless, certain limitations of these mandates can affect patients negatively, including the following:

- Insurers are not obligated to cover a clinical trial conducted at an institution outside of the plan's provider network, unless the plan otherwise covers out-of-network care. If an insurer opts to provide coverage in such a case, it can require higher out-of-network cost sharing.
- Regular cost-sharing provisions of plans still apply. For example, if a patient's plan carries a coinsurance rate of 20% for hospital services, they remain responsible for 20% of all routine-care costs associated with the clinical trial.
- Plans established before March 23, 2010, the ACA enactment date (so-called grandfathered plans), are not required to change their benefit structures to include coverage for costs associated with clinical trials. Plans lose their grandfathered status, however, with a reduction in benefits or increase in enrollee costs.
- Insurers are not required to cover drugs, devices, or procedures that are under investigation in the trial (and ambiguity exists when determining the services that are truly investigational). These investigational care costs are usually covered by the sponsor of a trial. ACA mandates related to the coverage of items and services needed to treat complications from investigational therapy are not strictly defined (a key difference compared with Medicare).
- Because insurers are not required to cover nonmedical or ancillary costs such as lodgings, meals, child or companion care, and transportation, these are generally paid out of pocket by patients and contribute to financial burden.

Related to coverage determinations, prior authorization policies (and other use management policies) can delay necessary cancer treatment, including initiation of a clinical trial. Studies have shown that despite these delays and staff burden, prior authorization requests are overwhelmingly approved, which calls into question their usefulness when balanced against the time-sensitive needs of patients with cancer.[35,36]

Public payer policy, such as that under Medicare and Medicaid, is distinct from the ACA mandate. For Medicare beneficiaries, the coverage of clinical trials dates back to a National Coverage Determination (NCD) promulgated in September 2000.[18] Under the NCD, Medicare covers routine costs for qualifying clinical trials and, similar to the ACA mandate, does not cover investigational, research-related, or other ancillary costs. However, an important barrier exists for patients enrolled in Medicare Advantage (MA) plans, who in 2017 composed one third of the Medicare population.[37] The Centers for Medicare & Medicaid Services (CMS) requires that MA patients enrolling in a clinical trial revert to coverage under the traditional Medicare fee-for-service (FFS) delivery system for trial-related services, although the MA plan is supposed to provide cost-sharing assistance.[38] This policy can confuse patients and providers, decrease transparency about responsibility for trial-related expenses, and ultimately create delays and disincentives for enrollment.[39]

For Medicaid patients, there are no federal mandates for clinical trial coverage. This results in a variation in state coverage policies under Medicaid for clinical trials. Currently, only 12 states and the District of Columbia have publicly available policies requiring such coverage in their Medicaid programs.[15] The degree to which other state Medicaid programs provide coverage of clinical trials is not always clear, creating a potential mechanism through which existing disparities in cancer care under Medicaid could be exacerbated.[40-42]

Finally, ambiguity in the term routine costs, which has never been fully defined by CMS but is nevertheless the foundation of the ACA mandate and Medicare NCD, can expose patients to financial risks. Often, the number or type of tests and treatments that could be considered routine may depend on perspective. Examples of this ambiguity include the long-term radiographic follow-up of asymptomatic trial participants or the provision of costly supportive care therapy mandated in a trial to reduce potential adverse effects of the investigational agent. This lack of clarity contributes to an environment in which patients may enroll in a trial with little information about their financial responsibility. Indeed, the local investigators and clinicians often do not have a clear idea of routine-care costs. Overall, the results of studies of the effects of insurance mandates on clinical trial enrollment have been mixed.[34,43]

Ethical, Compliance, and Institutional Impediments to Patient Financial Support

Monetary reimbursement from an institution, charitable foundation, or a research sponsor for a patient's ancillary, out-of-pocket, or other direct costs could help mitigate financial barriers to trial enrollment. However, ethical concerns about patient coercion or undue inducement and legal concerns about kickbacks and false claims compliance (eg, billing fraud) have hampered the uptake of such financial assistance programs. Strictly speaking, coercion in the context of clinical research must involve a threat by an individual or institution that reduces a patient's freedom to decline participation in a trial. It is important to note, then, that financial incentives or reimbursement are offers and not threats, and therefore cannot be coercive.[44-46]

A more germane ethical concern is the concept of undue inducement, wherein something perceived as beneficial distorts an individual's judgment such that unreasonable risks are taken, or deeply held values are forsaken.[47] The broader bioethics literature

surrounding undue inducement is primarily concerned with ensuring appropriate informed consent. Where payment for participation exists, concerns focus on the possibility that patients may engage in deception to enroll or that such payments may disproportionally influence the decisions of socioeconomically disadvantaged individuals.[45] It is important to point out that these concerns may be less relevant to cancer clinical trials. It would be difficult to feign late-stage lung cancer to secure payment for trial enrollment, and any near-term increase in enrollment rates for patients of lower socioeconomic status would serve to improve the representativeness of cancer clinical trial populations that currently face unjust access barriers caused by financial toxicity.[14]

The issues surrounding the appropriateness of compensation are nuanced and may revolve on a protocol-specific basis around the particular risks to patients and the methods and amounts of payment, emphasizing the need for judicious institutional review board (IRB) oversight. However, the lack of clarity regarding appropriate compensation in the current clinical research environment is problematic. Misplaced concern about undue inducement among research sponsors, IRBs, and other stakeholders may discourage the provision of financial support for participation in clinical trials. The result is an interrelated ethical issue: limiting the ability of financially strained or impoverished patients to enroll in a clinical trial for which they would otherwise qualify.

Building on these ethical concerns, federal regulations governing human participants research require investigators to minimize the possibility of coercion or undue inducement when enrolling clinical trial participants.[48-51] However, these regulations do not prohibit financial support for study participants or necessarily equate such support with undue inducement. For example, when the FDA reviews protocol documents and approves applications for an Investigational New Drug it does not typically consider payment incentives for research participants to be undue inducement, and instead defers to local IRBs to ensure the appropriateness of remuneration.[52]

The statutory obligations related to public payers are more challenging. The Social Security Act prohibits offering remuneration to Medicare or Medicaid beneficiaries if compensation is likely to influence selection of providers and/or services. Medicare and Medicaid regulations impose stiff penalties for any entity doing so. Specifically, sponsor offers to pay cost-sharing amounts owed by Medicare beneficiaries have long been regarded by CMS as a potential fraud and abuse problem, complicating targeted financial support for participants covered under Medicare.[53] This perception can negatively affect the availability of third-party needs-based copay support. Whether and how these concerns would apply to reimbursement for a specific participant's nonmedical ancillary costs also remain unclear.

The Department of Health and Human Services' Office of Inspector General (OIG) has proposed exemptions related to these prohibitions for clinical studies, but has never finalized implementation[54]; to date, limited case-by-case exceptions to these provisions exist. For example, in 2015, the OIG allowed a manufacturer to cover beneficiary copays related to a device under a coverage with evidence development agreement with CMS.[55] OIG's rationale was threefold: (1) charging copays to the beneficiaries risked unblinding the study; (2) the manufacturer agreed to pay for the intervention in the control group after the study was completed, which was viewed as necessary to ensure adequate enrollment to support coverage with evidence development; and (3) the decision minimized the risks of increased costs to federal health care programs. Whether institutions can safely extrapolate this and other examples to other similar cases in the future remains unclear.

ASCO RECOMMENDATIONS

To address the financial barriers to clinical trial participation, ASCO recommends that efforts be focused on three primary objectives:

- Facilitate transparency of information about clinical trial costs among providers, patients, and payers to ease patient financial burdens, and to prevent financial surprises, associated with clinical trials.
- Reduce concerns about inducement by defining appropriate mechanisms to provide targeted financial support for clinical trial participants at risk of financial hardship.
- Improve available data on the costs of clinical trial participation, including ancillary costs, and the share of those costs borne by patients.

To achieve these objectives, ASCO offers several recommendations, which are summarized in Table 2.

Recommendation 1: Improve Payer Clinical Trial Coverage Policies

Clinical trial cost payment policies, including explicit definitions of routine costs and prior authorization policies, should be revised so that they are made consistent, streamlined, and transparent to all stakeholders. Current payment policies to be addressed include those under the Medicare Clinical Trials NCD, related ACA provisions, and statutes governing state Medicaid programs.

Recommendation 1a: Payers should have clear definitions of routine costs. Currently, the patchwork of regulatory and statutory provisions does not guarantee meaningful access to clinical trials in a way that limits patient costs. The ACA provisions mandating coverage of the routine-care costs associated with clinical trials, although important, perpetuate the ambiguity surrounding the definition of routine costs. This has created a gray area in which not all private plans are held to the same standard (eg, in the case of coverage for supportive care for toxicities). In addition, certain private insurance plans are not covered by the ACA clinical trial provisions. If necessary, to resolve these issues, ASCO is committed to engaging stakeholders such as study sponsors, payers, clinical investigators, and leaders and regulators in human participants protection to gain consensus and explicitly define that which constitutes the routine costs related to cancer clinical trials. These standardized definitions are critical for subsequent recommendations, which will require sponsors and research sites to be transparent about expected costs, to properly design study protocols and budgets, and to communicate financial information to patients.

Recommendation 1b: Payers should streamline prior authorization processes and facilitate trial enrollment through provider

Table 2. Identified Problem Areas and ASCO Recommendations

Problem Area	Recommendation
Multiple problems exist in current coverage mandates for costs associated with clinical trial participation.	**Recommendation 1: Improve payer clinical trial coverage policies.** **Recommendation 1a**: Payers should have clear definitions of routine costs. **Recommendation 1b**: Payers should streamline prior authorization processes and facilitate trial enrollment through provider reimbursement of clinical trial–related services. **Recommendation 1c**: State Medicaid programs should universally guarantee coverage of routine-care costs of clinical trials for their beneficiaries. **Recommendation 1d**: CMS should revise current policy that requires Medicare Advantage beneficiaries to revert to fee-for-service coverage during clinical trials. **Recommendation 1e**: CMS's Innovation Center should explore the effectiveness of alternative payment models in support of clinical trial accrual.
Cost transparency is limited, contributing to patient financial uncertainty and providing a disincentive for clinical trial participation.	**Recommendation 2: During the clinical trials development and enrollment process, provide patients with clear, transparent information about potential trial-related patient out-of-pocket costs and include mechanisms to support patient financial and health literacy.** **Recommendation 2a**: Clinical trial sponsors should perform, and make available to enrolling institutions, comprehensive, prospective coverage analyses. **Recommendation 2b:** Research sites should consider offering in-house financial navigation and counseling to patients or consider partnering with organizations that provide such services. **Recommendation 2c**: Clinical trials should be designed to minimize incremental costs, consistent with scientific objectives and participant safety.
Perceptions of inducement limit patient financial support and reimbursement strategies.	**Recommendation 3: Remove impediments to ethically appropriate financial compensation for trial-related out-of-pocket costs; provision of such financial support should not be considered undue inducement.** **Recommendation 3a**: Office for Human Research Protections should develop guidance on targeted financial support.
Costs for participating in cancer clinical trials can contribute to barriers to patient access. Data on these costs (and their consequences) are limited.	**Recommendation 4: Incentivize research that will better characterize patient costs incurred for participating in cancer clinical trials, and support the longer-term development of tools to identify and mitigate the risk of trial-associated financial hardship.**

Abbreviation: CMS, Centers for Medicare & Medicaid Services.

reimbursement of clinical trial–related services. Variability in prior authorization introduces delays and staff burden without otherwise improving the treatment received, outcomes, or the experience of care among patients with cancer. Worse, patients can be held responsible for unexpected costs associated with their trial participation because of unclear prior authorization requirements surrounding time-sensitive treatment. Establishment of preauthorization and precertification processes at the clinical trial sites is recommended, but when this is not available or feasible, prior authorization specifically related to clinical trials should be streamlined to minimize the administrative burden and to reduce delays in initiation of therapy. ASCO has previously developed recommendations for payers regarding streamlining prior authorization for cancer drug therapies, which should be adapted for treatment in clinical trials whenever applicable.[56]

Ensuring that patients are aware of the option to enroll in a clinical trial, and are adequately informed of the benefits and risks of such options, requires a commitment on the part of oncology care teams. However, such screening and enrollment activities consume valuable time and resources and therefore may detract from many other competing clinical priorities. This is particularly true when such activities are largely unrecognized by current reimbursement mechanisms, and this gap may contribute to low participation rates. ASCO has previously recommended the creation of specific current procedural terminology codes for such services to increase the recruitment of trial participants.[57] Moreover, CMS recently finalized the addition of a proposed Improvement Activity in the Quality Payment Program, focused on achieving health equity through clinical trial enrollment. Participating providers can earn points, and potentially incentive payments, for Leadership in Clinical Trials or Community-Based Participatory Research (CBPR) programs. This activity includes leadership in clinical trials, research alliances or CBPR programs that identify tools, research, or processes that can focus on minimizing disparities in health care access, care quality, affordability, or outcomes.[58] Given the acknowledgment of the value of such services, there should be a concerted effort by all payers to reimburse providers for such trial-related services.

Recommendation 1c: State Medicaid programs should universally guarantee coverage of routine-care costs of clinical trials for their beneficiaries. ASCO has repeatedly called for reforms to cancer care under state Medicaid programs, including an explicit guarantee of coverage for the routine-care costs of clinical trials.[40,41] Although some states have established such coverage documents, a broader lack of clear policy and responsibility for payment may discourage enrollment, limit access, and increase disparities in cancer outcomes. State Medicaid programs should universally guarantee coverage of clinical trials for all beneficiaries, including coverage of routine costs in line with provisions governing Medicare and those introduced by the ACA.

Recommendation 1d: CMS should revise current policy that requires MA beneficiaries to revert to FFS coverage during clinical trials. In line with previous ASCO recommendations, because of potential provider and patient confusion about coverage during trial participation, current CMS policy requiring MA patients to revert to FFS coverage upon enrollment in a clinical trial should be revised.

Recommendation 1e: CMS's Innovation Center should explore the effectiveness of alternative payment models in support of clinical trial accrual. Alternative payment models hold the promise of controlling costs and improving clinical care, although this is typically accomplished through financial incentives for providers. Their potential role in reducing patient financial burdens incurred through participating in clinical trials is therefore not clear. CMS's Innovation Center should explore the effectiveness of alternative payment models (eg, CMS's Oncology Care Model, ASCO's Patient-Centered Oncology Payment model, and others) in encouraging clinical trial accrual, particularly through the lowering of patient out-of-pocket or other nonmedical ancillary costs. Exploring processes to recognize the time and effort providers devote to enrolling patients in clinical trials within alternative payment models will also be necessary.

Recommendation 2: During the Clinical Trials Development and Enrollment Process, Provide Patients With Clear, Transparent Information About Potential Trial-Related Patient Out-of-Pocket Costs and Include Mechanisms to Support Patient Financial and Health Literacy

Coverage of nonmedical out-of-pocket costs, such as lodging and transportation, through sponsor contracts can substantially reduce a patient's financial burden. However, full coverage of nonmedical ancillary expenses associated with participation in clinical trials is rarely provided by the sponsor because of uncertain expectations of what such coverage entails and because of concerns about unduly inducing patient enrollment.

Recommendation 2a: Clinical trial sponsors should perform, and make available to enrolling institutions, comprehensive, prospective coverage analyses; whenever possible, these coverage analyses should include estimated trial-related out-of-pocket costs. As a first critical step in establishing a study budget, a comprehensive coverage analysis and estimation of out-of-pocket costs for clinical trial participants is imperative to ensure transparency at a level that will adequately inform all parties of the anticipated costs and financial obligations ahead of time. Adequate information to substantiate patient informed consent includes access to cost information derived from a comprehensive coverage analysis. The goal is to ensure that there is a reasonable expectation of out-of-pocket costs before enrollment and participation. To that end, the National Cancer Institute's National Clinical Trials Network and other sponsors of clinical trials should require that clinical trial development always include comprehensive, prospective coverage analysis that contains estimated patient out-of-pocket costs.

This coverage analysis should always include estimated out-of-pocket costs in study budgets, to ensure that these costs can be covered and do not become the responsibility of the participant. These estimates could then be further refined through communication with the various clinical sites and customized on the basis of practice and community resources and potential patient circumstance. Tools to help practices develop such estimates could be developed and distributed through collaborations such as ASCO's Research Community Forum.

In the coverage analysis, trial sponsors should specifically provide financial support for all items and services that are not part of routine patient care (as defined in Recommendation 1a) to prevent financial hardships for the patient or research program for the cost of these services. It is important that these sponsor determinations of coverage for nonroutine costs be accurate, consistent, and communicated transparently for all sites participating in a study. Trial sponsors should also identify routine patient care services and tests (including the typical frequency of services and tests) to help ensure that all routine-care items can be billed to an insurance company and to help avoid coverage declines. This will also likely have the indirect benefits of reducing risk to patients and helping integrate research into routine clinical workflow. Explicit coverage analysis along these lines will allow subsequent recommendations for financial navigation and targeted financial support.

Recommendation 2b: Research sites should consider offering in-house financial navigation and counseling to patients or consider partnering with organizations that provide such services. Navigating the financial complexities of cancer care, which are often exacerbated in the context of trials, is a challenge for most patients. Programs aimed at helping patients understand their coverage as well as providing payment assistance are necessary. To close the gap, as well as to provide optimal information and reduce unexpected or incorrect billing of expenses, well-trained research and billing staff, together with completion of per-patient preauthorization and precertification processes, and financial navigation services for clinical trial participants are essential.

Recommendation 2c: Clinical trials should be designed to minimize incremental costs, consistent with scientific objectives and participant safety. Best practices for investigator-initiated studies (eg, number of follow-up visits or additional laboratory draws for protocol-associated correlative work, budget guidance, estimates of out-of-pocket costs) that may ameliorate the potential for patient financial toxicity related to clinical trial participation are needed. Sponsors (eg, the federal government, industry) should seek to minimize those incremental costs in their study designs. This means avoiding low-value trial-specific visits, scans, and other procedures that are not critical to the science or to ensuring participant safety. If necessary, a consensus-based process with participation from investigators, the National Cancer Institute, and cooperative groups could help develop such standards. The FDA and the National Institutes of Health have recently released standardized protocol templates[59] that could serve as a starting point for this effort, pending modification and dissemination.

Recommendation 3: Remove Impediments to Ethically Appropriate Financial Compensation for Trial-Related Out-of-Pocket Costs; Provision of Such Financial Support Should Not be Considered Undue Inducement

Concern over patient inducement from targeted financial support for participating in clinical trials is misplaced. Assuming an otherwise acceptable clinical trial protocol approved by an IRB, targeted financial support for clinical trial participants should not be considered undue inducement. Rather, targeted financial support ensures that clinical trial participants are made whole in the economic sense throughout their participation. Indeed, patients who contribute to science and therapeutic advancement by participating in trials should be protected from incremental financial costs as a matter of justice. A recently proposed framework

for the ethical compensation of research participants comes to the same conclusion: so long as reimbursed costs are accurate, such payments cannot be unduly influential because they do not result in a net benefit to a research participant.[45]

Although a more responsive and robust coverage policy environment for clinical trials will help address financial barriers for well-insured patients, the reality is that many Americans will continue to be under- and uninsured in the foreseeable future and could benefit greatly from targeted financial assistance to ameliorate the costs incurred during trial participation. Often, these patients are precisely the sociodemographic groups already underrepresented in clinical research. Pilot financial assistance programs have demonstrated promise in improving clinical trial accrual and even clinical outcomes.[60] One study reported that this type of financial support is typically modest, at approximately $500 per month per patient.[14] Going forward, the complexity and variability of patient experiences may necessitate additional individualized and flexible (ie, prospective as opposed to reimbursement-based) solutions to overcome financial barriers to obtaining care, particularly in the context of clinical trials. Practical considerations for IRBs and investigators pursuing such reimbursement for participants, to both improve patient engagement and to facilitate clinical research, continue to be explored.[45,61]

It is important not to fall into the trap of assuming the amount of such payments should determine the degree of influence over lower-income patients. When costs associated with participation are reimbursed, no net change in patient finances occurs; rather, an otherwise eligible patient is able to participate in a medically appropriate clinical trial, enhancing patient autonomy while improving the speed and generalizability of research. Indeed, restricting trial participation on the basis of ability to pay has been characterized as unethical and damaging to the clinical research enterprise.[62]

Nevertheless, the ambiguity of current statutory, regulatory, and institutional requirements surrounding financial support is sufficient to discourage widespread use of these types of assistance programs. In light of the position of the FDA and the Office for Human Research Protections that payment for clinical trial participation does not necessarily constitute undue inducement, state and federal policymakers and regulators should explicitly exempt cancer clinical trials from policies that could be interpreted as precluding appropriate financial reimbursement for the out-of-pocket costs associated with participation. This is necessary because of existing statutes that would preclude any form of ethical reimbursement, as determined by an IRB, to accrue to Medicare beneficiaries. Some states, such as California, have already passed legislation related to reimbursement for ancillary costs[63]; such legislation could serve as a model for similar legislative action at the state or federal level.[64]

Recommendation 3a: Office for Human Research Protections should develop guidance on targeted financial support. Oversight authority for the day-to-day conduct of human participants research rests with IRBs. However, IRBs may not feel comfortable independently defining the scope of allowable financial support related to clinical trial participation. Therefore, a role exists for the Office for Human Research Protections to develop and disseminate guidance to enable interested parties (eg, institutions, charitable foundations, industry) to provide financial support to patients who may otherwise forego clinical trial participation, for inclusion in protocol documents.

Recommendation 4: Incentivize Research that Will Better Characterize Patient Costs Incurred for Participating in Cancer Clinical Trials and Support the Longer-Term Development of Tools to Identify and Mitigate the Risk of Trial-Associated Financial Hardship

Increasing attention is being given to the high costs of cancer care, but the current economic burden associated with cancer clinical trial participation remains largely unknown. Research in the late 1990s found direct medical costs to be approximately 7% to 10% higher for cancer clinical trial participants than for nonparticipants.[65,66] However, it is unclear whether other cost domains such as nonmedical costs are proportionately higher among clinical trial participants. Quantifying the additional costs, beyond those of routine care, is an unmet research need that could enable more targeted interventions to lower financial barriers to clinical trial participation.

Organizations funding clinical trials should support grants for research related to the costs of participation in cancer clinical trials. Health services research funders should also incentivize research into disparities in patient financial hardship while participating in clinical trials, as well as into the development and clinical use of tools to gauge the risk and degree of such hardship. Looking to the future, collaborations will be necessary to continue the dialogue around development of a long-term clinical and health services research agenda for exploring ideal mechanisms for lowering the financial hardship associated with clinical trial participation.

Improvements in cancer care depend on improving the quality of clinical research. With a small fraction of eligible patients with cancer participating in clinical trials, and disparities in access associated with sociodemographic characteristics, there is a clear need to take concerted steps to remove the existing barriers to clinical trial enrollment. ASCO's recommendations, aimed at closing these gaps and addressing the financial costs for patients participating in clinical trials, will serve to improve the nation's cancer research enterprise, to ensure that no patient is denied access to clinical trials for financial reasons, and to be certain that patients are not harmed financially because of their contributions to advancing the treatment of those who are yet to come.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Karen M. Winkfield, Jonathan K. Phillips, Steven Joffe, Dana S. Wollins, Beverly Moy
Collection and assembly of data: Michael T. Halpern
Data analysis and interpretation: Steven Joffe, Michael T. Halpern, Beverly Moy
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

REFERENCES

1. Unger JM, LeBlanc M, Blanke CD: The impact of positive SWOG treatment trials on population survival. Presented at the ASCO Annual Meeting, Chicago, IL, June 2-6, 2017 (abstr 6513)
2. Murthy VH, Krumholz HM, Gross CP: Participation in cancer clinical trials: Race-, sex-, and age-based disparities. JAMA 291:2720-2726, 2004
3. Lara PN Jr, Higdon R, Lim N, et al: Prospective evaluation of cancer clinical trial accrual patterns: Identifying potential barriers to enrollment. J Clin Oncol 19:1728-1733, 2001
4. Galsky MD, Stensland KD, McBride RB, et al: Geographic accessibility to clinical trials for advanced cancer in the United States. JAMA Intern Med 175: 293-295, 2015
5. Fouad MN, Lee JY, Catalano PJ, et al: Enrollment of patients with lung and colorectal cancers onto clinical trials. J Oncol Pract 9:e40-e47, 2013
6. Duma N, Vera Aguilera J, Paludo J, et al: Representation of minorities and women in oncology clinical trials: Review of the past 14 years. J Oncol Pract 14:e1-e10, 2018
7. Beaver JA, Ison G, Pazdur R: Reevaluating eligibility criteria - Balancing patient protection and participation in oncology trials. N Engl J Med 376: 1504-1505, 2017
8. Somkin CP, Altschuler A, Ackerson L, et al: Organizational barriers to physician participation in cancer clinical trials. Am J Manag Care 11:413-421, 2005
9. Fu S, McQuinn L, Naing A, et al: Barriers to study enrollment in patients with advanced cancer referred to a phase I clinical trials unit. Oncologist 18: 1315-1320, 2013
10. Meropol NJ, Wong YN, Albrecht T, et al: Randomized trial of a Web-based intervention to address barriers to clinical trials. J Clin Oncol 34: 469-478, 2016
11. Unger JM, Gralow JR, Albain KS, et al: Patient income level and cancer clinical trial participation: A prospective survey study. JAMA Oncol 2:137-139, 2016
12. Arnold KB, Hermos JA, Anderson KB, et al: Retention of black and white participants in the selenium and vitamin E cancer prevention trial (SWOG-coordinated intergroup study S0000). Cancer Epidemiol Biomarkers Prev 23:2895-2905, 2014
13. Polite BN, Adams-Campbell LL, Brawley OW, et al: Charting the future of cancer health disparities research: A position statement from the American Association for Cancer Research, the American Cancer Society, the American Society of Clinical Oncology, and the National Cancer Institute. J Clin Oncol 35:3075-3082, 2017
14. Nipp RD, Powell E, Chabner B, et al: Recognizing the financial burden of cancer patients in clinical trials. Oncologist 20:572-575, 2015
15. Wong YN, Schluchter MD, Albrecht TL, et al: Financial concerns about participation in clinical trials among patients with cancer. J Clin Oncol 34:479-487, 2016
16. Zafar SY, Peppercorn JM, Schrag D, et al: The financial toxicity of cancer treatment: A pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. Oncologist 18:381-390, 2013
17. Zafar SY, Abernethy AP: Financial toxicity, Part I: A new name for a growing problem. Oncology (Williston Park) 27:80-81, 149, 2013
18. Centers for Medicare & Medicaid Services: National coverage determination (NCD) for routine costs in clinical trials (310.1). https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=1
19. Mariotto AB, Yabroff KR, Shao Y, et al: Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst 103:117-128, 2011
20. Kantarjian H, Steensma D, Rius Sanjuan J, et al: High cancer drug prices in the United States: Reasons and proposed solutions. J Oncol Pract 10: e208-e211, 2014
21. Dieguez G, Ferro C, Pysenson BS: Milliman research report: A multi-year look at the cost burden of cancer care. http://www.milliman.com/uploadedFiles/insight/2017/cost-burden-cancer-care.pdf
22. The Kaiser Family Foundation and Health Research & Educational Trust: Employer health benefits. 2016 annual survey. http://files.kff.org/attachment/Report-Employer-Health-Benefits-2016-Annual-Survey
23. Henry J. Kaiser Family Foundation: Distribution of the total population by federal poverty level (above and below 400% FPL). http://www.kff.org/other/state-indicator/population-up-to-400-fpl/
24. Chino F, Peppercorn JM, Rushing C, et al: Out-of-pocket costs, financial distress, and underinsurance in cancer care. JAMA Oncol 3:1582-1584, 2017
25. Ramsey S, Blough D, Kirchhoff A, et al: Washington State cancer patients found to be at greater risk for bankruptcy than people without a cancer diagnosis. Health Aff (Millwood) 32: 1143-1152, 2013
26. Ramsey SD, Bansal A, Fedorenko CR, et al: Financial insolvency as a risk factor for early mortality among patients with cancer. J Clin Oncol 34:980-986, 2016
27. Kaisaeng N, Harpe SE, Carroll NV: Out-of-pocket costs and oral cancer medication discontinuation in the elderly. J Manag Care Spec Pharm 20: 669-675, 2014
28. Dusetzina SB, Winn AN, Abel GA, et al: Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol 32:306-311, 2014
29. Doshi JA, Li P, Huo H, et al: Association of patient out-of-pocket costs with prescription abandonment and delay in fills of novel oral anticancer agents. J Clin Oncol 36:476-482, 2018
30. Yabroff KR, Dowling EC, Guy GP Jr, et al: Financial hardship associated with cancer in the United States: Findings from a population-based sample of adult cancer survivors. J Clin Oncol 34:259-267, 2016
31. Altice CK, Banegas MP, Tucker-Seeley RD, et al: Financial hardships experienced by cancer survivors: A systematic review. J Natl Cancer Inst 109:djw205, 2016
32. Zheng Z, Han X, Guy GP Jr, et al: Do cancer survivors change their prescription drug use for financial reasons? Findings from a nationally representative sample in the United States. Cancer 123: 1453-1463, 2017
33. Nipp RD, Lee H, Powell E, et al: Financial burden of cancer clinical trial participation and the impact of a cancer care equity program. Oncologist 21:467-474, 2016
34. Klamerus JF, Bruinooge SS, Ye X, et al: The impact of insurance on access to cancer clinical trials at a comprehensive cancer center. Clin Cancer Res 16:5997-6003, 2010
35. Agarwal A, Freedman RA, Goicuria F, et al: Prior authorization for medications in a breast oncology practice: Navigation of a complex process. J Oncol Pract 13:e273-e282, 2017
36. Anders B, Shillingburg A, Newton M: Oral antineoplastic agents: Assessing the selay in care. Chemother Res Practi 2015: 512016, 2015
37. Jacobson G, Damico A, Neuman T, et al: Medicare advantage 2017 spotlight: Enrollment market update. https://www.kff.org/medicare/issue-brief/medicare-advantage-2017-spotlight-enrollment-market-update/
38. Centers for Medicare & Medicaid Services: Mandatory reporting of National Clinical Trial (NCT) identifier numbers on Medicare claims – Qs & As. https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/Downloads/Mandatory-Clinical-Trial-Identifier-Number-QsAs.pdf
39. ASCO: Insurance coverage of clinical trials https://www.asco.org/research-progress/clinical-trials/insurance-coverage-clinical-trials
40. Polite BN, Griggs JJ, Moy B, et al: American Society of Clinical Oncology policy statement on Medicaid reform. J Clin Oncol 32:4162-4167, 2014
41. ASCO: Guarantee coverage of clinical trials participation for Medicaid patients. http://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/2016-ASCO-Policy%20Brief%20on%20Medicaid%20Coverage%20of%20Trials.pdf
42. Weber JS, Levit LA, Adamson PC, et al: American Society of Clinical Oncology policy statement update: The critical role of phase I trials in cancer research and treatment. J Clin Oncol 33: 278-284, 2015
43. Ellis SD, Carpenter WR, Minasian LM, et al: Effect of state-mandated insurance coverage on accrual to community cancer clinical trials. Contemp Clin Trials 33:933-941, 2012
44. Hawkins JS, Emanuel EJ: Clarifying confusions about coercion. Hastings Cent Rep 35:16-19, 2005
45. Gelinas L, Largent EA, Cohen IG, et al: A framework for ethical payment to research participants. N Engl J Med 378:766-771, 2018
46. US Department of Health & Human Services: National commission for the protection of human subjects of biomedical and behavioral research: The Belmont Report, part C. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html
47. Emanuel EJ: Undue inducement: Nonsense on stilts? Am J Bioeth 5:9-13, discussion W8-11, W17, 2005
48. US Food & Drug Administration: Code of Federal Regulations, 21CFR 50.20. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.20
49. US Food & Drug Administration: Code of Federal Regulations, 45CFR 46.116. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html
50. US Food & Drug Administration: Code of Federal Regulations, 21CFR 56.111(b).
51. US Food & Drug Administration: Code of Federal Regulations, 45CFR 46.111(b).https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html
52. US Food and Drug Administration: Payment to and reimbursement research subjects - information sheet. https://www.fda.gov/RegulatoryInformation/Guidances/ucm126429.htm
53. Centers for Medicare & Medicaid Services: Clarification of Medicare payment for routine costs in a clinical trial. https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/se0822.pdf

54. Office of the Inspector General: Special Advisory Bulletin – Offering Gifts and Other Inducements to Beneficiaries. https://oig.hhs.gov/fraud/docs/alertsandbulletins/sabgiftsandinducements.pdf

55. Office of the Inspector General: Advisory Opinion No. 15-07. https://oig.hhs.gov/fraud/docs/advisoryopinions/2015/AdvOpn15-07.pdf

56. ASCO: American Society of Clinical Oncology policy statement on the impact of utilization management policies for cancer drug therapies. https://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/2017-ASCO-Utilization-Management-Statement.pdf

57. Hurria A, Levit LA, Dale W, et al: Improving the evidence base for treating older adults with cancer: American Society of Clinical Oncology statement. J Clin Oncol 33:3826-3833, 2015

58. Centers for Medicare & Medicaid Services: Medicare Program: CY 2018 updates to the Quality Payment Program; and Quality Payment Program: Extreme and uncontrollable circumstance policy for the transition year. https://www.gpo.gov/fdsys/pkg/FR-2017-11-16/pdf/2017-24067.pdf

59. NIH Office of Science Policy: NIH releases e-Protocol writing tool and final NIH-FDA clinical trial template for phase 2 and 3 IND/IDE studies. https://osp.od.nih.gov/2017/05/02/nih-releases-e-protocol-writing-tool-and-final-nih-fda-clinical-trial-template-for-phase-2-and-3-indide-studies/

60. Nipp RD, Powell E, Finkelstein D, et al: 2014. Alleviating financial burden for cancer patients in clinical trials. J Clin Oncol 32, 2014 (suppl; abstr 10).

61. Dominguez D, Jawara M, Martino N, et al: Commonly performed procedures in clinical research: A benchmark for payment. Contemp Clin Trials 33: 860-868, 2012

62. Emanuel EJ, Joffe S, Grady C, et al: Clinical research: Should patients pay to play? Sci Transl Med 7:298ps16, 2015

63. California Cancer Clinical Trials Program, AB-1823 § 101990 (September 26, 2016). https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201520160AB1823

64. Largent EA, Lynch HF: Addressing financial barriers to enrollment in clinical trials. JAMA Oncol 4:913-914, 2018

65. Fireman BH, Fehrenbacher L, Gruskin EP, et al: Cost of care for patients in cancer clinical trials. J Natl Cancer Inst 92:136-142, 2000

66. Goldman DP, Berry SH, McCabe MS, et al: Incremental treatment costs in National Cancer Institute-sponsored clinical trials. JAMA 289:2970-2977, 2003

Affiliations

Karen M. Winkfield, Wake Forest Baptist Medical Center, Winston-Salem, NC; **Jonathan K. Phillips** and **Dana S. Wollins**, American Society of Clinical Oncology, Alexandria, VA; **Steven Joffe**, University of Pennsylvania Perelman School of Medicine; **Michael T. Halpern**, Temple University, Philadelphia, PA; and **Beverly Moy**, Massachusetts General Hospital, Boston, MA.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Addressing Financial Barriers to Patient Participation in Clinical Trials: ASCO Policy Statement

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Karen M. Winkfield
Consulting or Advisory Role: Novartis

Jonathan K. Phillips
No relationship to disclose

Steven Joffe
No relationship to disclose

Michael T. Halpern
Consulting or Advisory Role: Solstice Health Communications
Research Funding: AbbVie

Dana S. Wollins
Honoraria: Abbott Laboratories (I), AbbVie (I), Amgen (I), Johnson & Johnson (I), Pfizer (I), Procter & Gamble (I)

Beverly Moy
Consulting or Advisory Role: MOTUS (I)

Acknowledgment

We thank the Lazarex Cancer Foundation for funding the ASCO Roundtable on Addressing Financial Barriers to Clinical Trials Participation. We also thank and acknowledge the efforts of the Steering Group and invited speakers and participants of the Roundtable: Dana Dornsife, R. Donald Harvey, Robert Johnson, Teresa L. Stewart, Danielle Carnival, Kenneth W. Culver, Andrea Denicoff, Lola A. Fashoyin-Aje, Mark Fleury, Patrick Gavin, Sybil Green, Kimberly Head, Jennifer Malin, Ryan Nipp, Deborah Pearson, Blase Polite, Joanne Regnault, Eric Rubin, Veena Shankaran, Olivia Sloan, Kelly Willenberg, Robin Yabroff, and Yousuf Zafar.