January 27, 2025

SUBMITTED THROUGH FEDERAL E-RULEMAKING PORTAL

Christi A. Grimm
Inspector General
Office of Inspector General
U.S. Department of Health & Human Services
330 Independence Avenue, SW
Washington, DC 20201

Re: Solicitation of Proposals for New and Modified Safe Harbors and Special Fraud Alerts OIG-1124-N, 89 Fed. Reg. 93545 (Nov. 27, 2024) ("Annual Solicitation")

Dear Inspector General Grimm:

The American Cancer Society Cancer Action Network ("ACS CAN") appreciates the opportunity presented by the Annual Solicitation of the U.S. Department of Health and Human Services ("HHS"), Office of Inspector General ("OIG") to propose a new regulatory safe harbor to the federal health care program anti-kickback statute, 42 U.S.C. § 1320a-7b(b) ("AKS"). ACS CAN is the American Cancer Society's nonprofit, nonpartisan advocacy affiliate. Our mission is to make cancer a top priority for public officials at the federal, state, and local levels. We do this, in part, by advocating for evidence-based public policy change, including legislative and regulatory solutions that will reduce the cancer burden.

As discussed further in this letter, individuals who participate in cancer-related and other clinical trials incur two types of costs: direct medical costs ("direct costs") and indirect ancillary costs ("indirect costs"). Direct costs are the costs of care incurred by the participant in obtaining hospital, physician, laboratory, radiology and other health care items and services. Indirect costs are non-medical costs that, but for participation in the clinical trial at issue, the participant would not incur. These costs might include costs associated with travel, parking, lodging, childcare, and lost wages that, but for enrolling in the clinical trial, the participant would not have incurred.

For the reasons set forth in this letter, ACS CAN proposes the creation of a new safe harbor that, subject to a host of safeguards and limitations, would permit sponsors of clinical trials targeting cancer or other life-threatening diseases or conditions to cover certain indirect costs incurred by clinical trial participants without violating the AKS or Beneficiary Inducement CMP. The proposed safe harbor would not permit sponsors to cover any direct costs incurred by clinical trial participants.

ACS CAN first proposed this safe harbor in 2023, in response to the OIG's 2022 annual solicitation. Two other organizations, PhRMA and McKesson, proposed similar but not identical safe harbors. In its December 1, 2023 Semiannual Report to Congress, the OIG declined to adopt any of these three safe harbor proposals, stating: "Although OIG appreciates the goal of

improving diversity among clinical trial subjects, we have longstanding concerns regarding the routine waiver or subsidy of cost sharing obligations and the provision of other incentives to Federal health care program enrollees. We may consider this topic in future rulemaking." (As noted above, ASC CAN's proposed safe harbor does not cover "routine waiver or subsidy of cost sharing obligations.")

ACS CAN proposed this safe harbor again in 2024, in response to the OIG's 2023 annual solicitation. Once again, PhRMA and McKesson proposed similar but not identical safe harbors; and, once again, the OIG declined to adopt any of these proposals, repeating the reasoning from its 2023 Semiannual Report.

ASC CAN is proposing this safe harbor again in 2025 and asks the OIG to take a fresh look at our submission. Ensuring that clinical trials are representative of the population at large is critical to trial success, and—as reflected in recent work done by ACS CAN in collaboration with the Office of the Assistant Secretary for Planning and Evaluation ("ASPE")—the cost of participating in clinical trials remains a significant challenge and barrier for many individuals and families.

ACS CAN believes that adoption of its proposed safe harbor will remove the economic barriers that prevent many working class and low-income individuals from participating in clinical trials, and it will do so without causing overutilization, improper patient steering, or unfair competition, or otherwise implicating any of the AKS's policy objectives.

ASC CAN is joined in this letter by the American Association for Cancer Research (AACR), American Gastroenterological Association (AGA), American Society for Radiation Oncology (ASTRO), Association of American Cancer Institutes (AACI), Association for Clinical Oncology (ASCO), The Coalition for Clinical Trial Equity, Fight Colorectal Cancer, Head for the Cure Foundation, International Myeloma Foundation, LUNGevity Foundation, Melanoma Research Foundation, National Brain Tumor Society (NBTS), National Cancer Registrars Association (NCRA), National Comprehensive Cancer Network (NCCN), The National Pancreas Foundation, Oncology Nursing Society (ONS), Ovarian Cancer Research Alliance (OCRA), Pennsylvania Prostate Cancer Coalition (PPCC), Susan G. Komen, Triage Cancer, and ZERO Prostate Cancer.

I. Background

Clinical trials are used to help determine the safety and effectiveness of drugs and other medical products that are intended for use in the prevention, diagnosis, and treatment of disease, including cancer and other life-threatening conditions. Over the past 25 years, there has been growing concern that clinical trial participants do not accurately reflect the population at large, with working class, low income, and certain racial and ethnic groups significantly underrepresented in trial populations. As the Food and Drug Administration ("FDA") recently noted, this is true notwithstanding the fact that these populations often "bear a disproportionate burden for certain conditions or diseases relative to their proportional representation in the general population."[i]

Ensuring representative participation in clinical trials is critical for a host of medical, scientific, and ethical reasons. As the FDA has noted, representative participation (i) "can support more equitable and timely access to medical discoveries and innovations," (ii) "improve the generalizability of results across the intended patient populations," (iii) improve our understanding of the disease and/or medical product under study," and (iv) "inform the safe and effective use of the medical product for all patients.[ii]

Although there are myriad reasons for the lack of representative participation in clinical trials, one is straightforward: many individuals simply cannot afford to participate in clinical trials. As noted above, a clinical trial participant incurs two types of costs: direct costs and indirect costs.

- Direct costs, which again are not the subject of this proposal, are the costs of care incurred by the participant in obtaining hospital, physician, laboratory, radiology and other health care items and services. An example of a direct cost of care that a clinical trial participant might incur would be the payment of any cost-sharing obligations, such as copayment and coinsurance amounts, attendant to receiving health care items and services from a provider, supplier, or practitioner that may be covered by commercial or government payers, such as Medicare.[iii]

- Indirect costs, which are the subject of this proposal, are non-medical costs that, but for participation in the clinical trial at issue, the participant would not incur. For example, depending on the particular clinical trial and participant, indirect costs might include costs associated with travel, parking, lodging, childcare, and lost wages that, but for enrolling in the clinical trial at issue, the participant would not have incurred.

In many cases, these indirect costs are not *de minimis*. According to one study, for example, participants in cancer clinical trials incurred an average of $600 per month—or $7,200 per year—in indirect costs.[iv] Not surprisingly, indirect costs pose a far greater barrier to clinical trial participation by those with lower socioeconomic status (or "SES") than those with higher SES.[v] Two studies, for example, found that persons with annual household incomes below $50,000 were 30 percent less likely to participate in clinical trials than those with annual household incomes above $50,000.[vi] Another study found that almost 80 percent of cancer patients indicated they would be more likely to enroll in a clinical trial if sponsors supported them financially to offset non-medical costs.[vii] For its part, the OIG has flagged this particular issue on multiple occasions over the past 25 years.[viii]

In 2024, ACS CAN completed a collaboration with the office of the HHS Assistant Secretary for Planning and Evaluation ("ASPE") and Mathematica in which ACS CAN surveyed 112 current and recent cancer clinical trial participants about the cost and financial impact of trial participation.[ix] Almost two-thirds of participants reported financial stress associated with their clinical trial participation. This stress was tied to (i) traveling to trial sites, (ii) challenges paying for food or rent, and (iii) using savings and incurring credit card debt to compensate for added costs. We are grateful for HHS's collaboration on this research and are hopeful that concrete actions, such

as the adoption of our proposed safe harbor, will be taken to reduce the financial burden that trial participation can cause.

Given the importance of representative clinical trials and the direct correlation between SES and clinical trial participation, both the FDA and the larger stakeholder community support arrangements pursuant to which clinical trial sponsors cover the indirect costs of clinical trial participants. In 2024, for example, the FDA published draft guidance to promote representative clinical trials. The guidance notes that the FDA has issued several sets of recommendations over the years aimed at improving the representativeness of clinical trials, including but not limited to (i) "providing transportation assistance," (ii) "providing dependent care," and (iii) providing "reimbursement for costs incurred" by clinical trial participants.[x]

These recommendations are consistent with the FDA's guidance document for Institutional Review Boards ("IRBs") and clinical investigators, "Payment and Reimbursement to Research Subjects."[xi] In that document, the FDA makes two important points. First, the agency again emphasizes that it "does not consider reimbursement for travel expenses to and from the clinical trial site and associated costs"—including but not limited to airfare, parking, and lodging—"to raise issues regarding undue influence." Second, the guidance provides that with respect to all other remuneration, the IRB should review the amount, method and timing of such payments or reimbursement "to assure that neither are coercive or present undue influence."[xii]

To summarize, then, all public and private stakeholders, including the FDA, view promoting representative clinical trials as a high priority; and these same stakeholders (i) have concluded that indirect costs create significant barriers to achieving representative clinical trials and (ii) support the removal of these barriers.

II. Proposed Safe Harbor

Notwithstanding the above consensus, many clinical trial sponsors are reluctant to cover indirect costs incurred by clinical trial participants. A principal reason for this reluctance is that offering such coverage to Medicare, Medicaid, and other federal health care program beneficiaries may implicate the AKS and/or the federal beneficiary inducement civil monetary law, 42 U.S.C. § 1320a-7a(a)(5) ("Beneficiary Inducement CMP"). To address this barrier to promoting representative clinical trials, ACS CAN proposes the creation of a new regulatory safe harbor that, subject to a host of safeguards and limitations, would permit sponsors of clinical trials targeting cancer or other life-threatening diseases or conditions to cover certain indirect costs incurred by clinical trial participants without violating the AKS or Beneficiary Inducement CMP and without offering routine waiver or subsidy of cost sharing obligations, which OIG has objected to in the past.

A. Text

Under the proposed safe harbor, 42 C.F.R. § 1001.952 would be amended to add a new section 1001.952(ll), which would provide as follows:

(ll) **Coverage of Indirect Clinical Trial Costs**.

(1) As used in section 1128B of the Act, "remuneration" does not include indirect cost payments or indirect cost stipends offered by the sponsor of an approved clinical trial to a human subject participating in that approved clinical trial if the conditions in paragraphs ll(1)(i) through (iv) of this section are met.

(i) The indirect cost payment or indirect cost stipend is provided pursuant to a written protocol that has been reviewed and approved in advance by the Institutional Review Board responsible for the approved clinical trial;

(ii) In the case of remuneration in the form of indirect cost payments:

(a) the written protocol specifies:

(i) each category of indirect costs for which payment will be made (e.g., travel, lodging, parking, etc.),

(ii) with respect to each category, whether the payment will be made to the human subject (in the form of reimbursement) or directly to the vendor providing the item or service to the human subject, and

(iii) any monetary caps or other limitations that will apply to such payments; and

(b) the purpose, amount, date, and method of payments made to or on behalf of each human subject is contemporaneously documented by the sponsor;

(iii) In the case of remuneration in the form of an indirect cost stipend:

(a) the written protocol specifies:

(a) the amount of the stipend,

(b) the period (e.g., one month) or activity (e.g., one visit) the stipend covers,

(c) the indirect cost categories the stipend covers (e.g., travel and lodging), and

(d) the methodology used to calculate the stipend; and

(b) the payment amount and date of each stipend provided to each human subject is contemporaneously documented by the sponsor;

(iv) The documentation required by paragraph ll(1) is made available to the Secretary upon request.

(2) For purposes of paragraph (ll) of this section:

(i) *Approved clinical trial* has the meaning set forth in section 2709(d) of the Public Health Service Act.[xiii]

(ii) *Human subject* has the meaning set forth in 21 C.F.R. § 56.102(e).[xiv]

(iii) *Indirect cost payment* means a payment that is made directly to a human subject, or to a vendor on behalf of a human subject, that covers the actual, additional, non-medical costs incurred by a human subject relating exclusively to their participation in an approved clinical trial.

(iv) *Indirect cost stipend* means a flat, pre-determined dollar amount that is in intended to cover, for a designated period of time (e.g., one month) or in connection with a specified activity (e.g., one visit), the actual, additional, non-medical costs incurred by a human subject relating exclusively to their participation in an approved clinical trial.

(iv) *Institutional Review Board (IRB)* has the meaning set forth in 21 C.F.R. § 56.102(g).[xv]

(v) *Life-threatening disease or condition* has the meaning set forth in section 2709(e) of the Public Health Service Act.[xvi]

(vi) *Sponsor* has the meaning set forth in 21 C.F.R. § 56.102(j).[xvii]

B. Explanation

Before turning to how the proposed safe harbor fares with respect to the various factors enumerated in the Annual Solicitation, we would like to highlight the safeguards built into the proposed safe harbor.

- First, the proposed safe harbor would not apply to all clinical trials. The safe harbor would apply only to "approved clinical trials" as defined in section 2709(d) of the Public Health Service Act ("PHSA"). Among other limitations, that definition only includes clinical trials that are conducted in relation "to the prevention, detection, or treatment of cancer or other life-threatening disease or condition" and, pursuant to section 2709(e) of the PHSA, a disease or condition only qualifies as "life-threatening" if "the likelihood of death is probable unless the course of the disease or condition is interrupted." Simply put, the universe of clinical trials to which the proposed safe harbor would apply would be limited.

- Second, the proposed safe harbor would protect only a narrow category of remuneration. Specifically, the safe harbor is designed to protect only the reimbursement of those actual, additional, non-medical costs incurred by a human subject that relate exclusively to their participation in an approved clinical trial.

    - Thus, the proposed safe harbor would not protect any remuneration that might incentivize a patient to purchase or order any health care item or service. For example, the proposed safe harbor would not protect remuneration in the form of a waiver of a patient's cost-sharing obligations.

    - Further, the proposed safe harbor would not protect the coverage of all non-medical costs. For example, costs associated with traveling to a clinical trial site that is far from the participant's residence (such as lodging, fuel, and parking) might be covered by the safe harbor. However, many other costs (such as toiletries, clothing, and entertainment) would not be covered.

- Third, every approved clinical trial (as defined in the proposed safe harbor) is subject to the oversight of an IRB, and every IRB has a preexisting legal obligation to ensure that the study in question has the safeguards necessary to protect participants from either "coercion or undue influence."[xviii] As an added safeguard, in order to receive protection under the proposed safe harbor, indirect cost payments and indirect cost

stipends must be provided pursuant to a detailed written protocol that has been reviewed and approved in advance by the relevant IRB.

- Fourth, in addition to the written protocol approved by the IRB, the safe harbor requires documentation relating to both indirect cost payments and indirect cost stipends. These documentation requirements ensure that the government is able to confirm that all payments meet the definition of "indirect cost payments" or "indirect cost stipends," as applicable, and that the arrangement otherwise meets the conditions of the safe harbor.

C. Discussion

As set forth in the Annual Solicitation, the OIG considers a number of factors in reviewing proposals for additional safe harbors, including the extent to which the proposals may result in an increase or decrease in (i) overutilization of health care services, (ii) costs to Federal health care programs resulting from such overutilization, (iii) patient freedom of choice among health care providers, (iv) competition among health care providers, (v) access to health care services, (vi) the quality of health care services, and (vii) the ability of health care facilities to provide services in medically underserved areas or to medically underserved populations. OIG also considers "the existence (or nonexistence) of any potential financial benefit to health care professionals or providers that may influence their decision whether to" (i) "order a health care item or service" or (ii) "arrange for a referral of health care items or services to a particular practitioner or provider."

1. Overutilization; Program Costs

The proposed safe harbor will not result in overutilization—that is, the ordering of items or services that are not medically necessary. As a threshold matter, whether participating in a clinical trial or not, patients who have cancer or another life-threatening condition typically will receive routine care, and both Medicare and Medicaid cover the costs associated with such routine care whether they are incurred in or outside a clinical trial. Further, the proposed safe harbor does not protect any remuneration that is provided to any physician or other provider, supplier, or practitioner who is able to order health care items or services. To the contrary, the only person who will receive remuneration under the proposed safe harbor is the human subject participating in the clinical trial at issue, and that individual is not able to order health care items or services. Simply put, and like the proposed arrangement in OIG Advisory Opinion 98-6, the purpose of the proposed safe harbor here is "to induce participation in a scientific study, not to induce utilization of Medicare covered services."[xix]

Because the proposed safe harbor will not result in overutilization, it cannot (by definition) result in any inappropriate increase in federal health care program costs. It is true, of course, that a drug or device that is the subject of a clinical trial may, depending on a host of factors, ultimately be approved by the FDA and covered and reimbursed by Medicare, Medicaid and/or other government health care programs. But any increase in program costs as a result of these approval, coverage, and reimbursement decisions would neither be the result of overutilization

(again, the ordering of medically unnecessary items or services) nor attributable to the remuneration permitted by the proposed safe harbor (i.e., the coverage of indirect costs incurred by clinical trial participants suffering from life-threatening conditions).

2. Patient Freedom of Choice

With respect to patient freedom of choice, the government's principal concern is the steering of patients to particular providers not because the providers are the most convenient for the patient or offer the highest quality items or services, but because the provider is paying the referring individual or entity a kickback. For example, where Lab A offers a physician $25 for each referral of a Medicare or Medicaid beneficiary, the physician may steer patients to Lab A, even though Lab B and Lab C are more convenient for the patient and offer higher quality services than Lab A. The proposed safe harbor will not result in improper patient steering for several reasons.

- As a threshold matter, the proposed safe harbor will not protect incentives offered to patients by providers, suppliers or practitioners to obtain medical care. For example, were a hospital or physician to offer to waive the cost-sharing obligations of a Medicare beneficiary participating in an approved clinical trial, this remuneration would be not protected under the proposed safe harbor.

- Further, by defining the terms "indirect cost payments" and "indirect cost stipends" to cover only "actual, additional, non-medical costs incurred by a human subject relating exclusively to their participation in an approved clinical trial," the safe harbor effectively ensures that the remuneration provided to a given patient will do nothing more than put that patient in precisely the same economic position they would have been in had they decided not to participate in the clinical trial. Put somewhat differently, while the safe harbor might incentivize a patient to participate in an approved clinical trial by removing any economic disincentive to do so, the safe harbor will not incentivize a patient to seek care that is not medically necessary or to seek medically necessary care from any particular provider, supplier, or practitioner.

- Finally, as an added safeguard, all indirect cost payments and indirect cost stipends must be documented and provided consistent with the terms and conditions of a written protocol that has been reviewed and approved in advance by the relevant IRB, which (as noted above) has a preexisting legal obligation to ensure that the study in question has the safeguards necessary to protect participants from either "coercion or undue influence."

3. Provider Competition

With respect to unfair competition, the government's principal concern is that where referrals are controlled by those (e.g., physicians) receiving remuneration from a provider (e.g., Lab A), the medical marketplace suffers because new competitors (e.g., Labs B and C) may no longer be

able to win business with superior quality, service, or price. For precisely the same reasons the proposed safe harbor will not result in any improper patient steering, it also will not result in any unfair competition. Simply put, the safe harbor does not provide any economic incentive to any patient to obtain health care items or services from any particular provider, supplier, or practitioner. As such, the proposed safe harbor will have no impact on the ability of providers, suppliers or practitioners to compete against one another based on quality, service, or price (much less an impact that could be characterized as unfair).

4. Health Care Access and Quality; Underserved Areas and Populations

For all the reasons set forth in Section I above, promulgation of the proposed safe harbor should (i) increase access to health care services, (ii) increase the quality of health care services, and (iii) increase the ability of health care facilities to provide services in medically underserved areas or to medically underserved populations. Again, the objective of the proposed safe harbor is to remove a significant economic barrier to achieving representative clinical trials, which, as the FDA has emphasized, supports early access to medical discoveries, improves the generalizability of results across patient populations, improves our understanding of the diseases and medical products being studied, and informs the safe and effective use of medical products for all patients. Indeed, with respect to cancer patients living in rural areas specifically, studies have shown that while such patients traditionally have had poorer treatment outcomes when compared to their urban counterparts, this disparity is erased when rural patients are enrolled in clinical trials.[xx]

The OIG itself made this point in a December 2023 advisory opinion:

> …the Proposed Arrangement [involving the subsidization of certain Medicare cost-sharing obligations in the context of a clinical trial] appears to be a reasonable means of promoting enrollment in the Study… According to Requestor, the out-of-pocket cost-sharing expenses to participate in the Study would be cost prohibitive for many Medicare beneficiaries who otherwise would participate in the Study, and Requestor's cost-sharing subsidy may be essential to enrolling a sufficient number of participants to complete the Study. In addition, the cost-sharing subsidies that would be offered under the Proposed Arrangement appear to be a reasonable means to facilitate enrollment of a socioeconomically diverse set of participants by removing a potential financial barrier to participation in the Study. The subsidy also may reduce the likelihood that participants would fail to complete the entire course of the Study, which involves a number of clinical visits over an 18-month period plus potential follow-up visits every 6 months thereafter.[xxi]

5. Provider Influence

Finally, as to "the existence (or nonexistence) of any potential financial benefit to health care professionals or providers that may influence their decision whether to" (i) "order a health care item or service" or (ii) "arrange for a referral of health care items or services to a particular practitioner or provider," the proposed safe harbor would not protect any financial benefit that is provided to any health care provider, supplier, or practitioner. Again, the safe harbor would only protect a narrow category of remuneration ("indirect cost payments" and "indirect cost stipends") provided to a narrow category of individuals ("human subjects") under a narrow set of circumstances ("approved clinical trials").

III. Conclusion

As the OIG notes in the Annual Solicitation, the agency "seeks to identify and develop safe harbors that protect beneficial and innocuous arrangements and safeguard Federal health care programs and their beneficiaries from the harms caused by fraud and abuse." ACS CAN believes that the narrowly tailored safe harbor it proposes squarely meets this test:

- for all the reasons set forth in Section I, by effectively eliminating a significant economic barrier to the participation of patients in clinical trials, the safe harbor will help achieve a priority of the federal government—ensuring that the makeup of participants in clinical trials is representative of the makeup of the U.S. population as a whole; and

- for all the reasons set forth in Section II, this objective can be achieved without causing overutilization, a concomitant increase in program costs, improper patient steering, unfair competition, or any of the other types of fraud or abuse that the AKS is intended to prevent.

* * *

In closing, the undersigned organizations would like to thank the OIG again for this opportunity to propose a new AKS safe harbor. Please feel free to contact Mark.Fleury@cancer.org if we can answer any questions the agency might have or provide any additional information the agency might need relating to our proposed safe harbor. Finally, if you would be kind enough to confirm the agency's receipt of this request and identify the individual who will serve as the OIG's point-of-contact with respect thereto, it would be greatly appreciated.

Sincerely,

American Cancer Society Cancer Action Network (ACS CAN)
American Association for Cancer Research (AACR)
American Gastroenterological Association (AGA)
American Society for Radiation Oncology (ASTRO)
Association of American Cancer Institutes (AACI)
Association for Clinical Oncology (ASCO)
The Coalition for Clinical Trial Equity

Fight Colorectal Cancer
Head for the Cure Foundation
International Myeloma Foundation
LUNGevity Foundation
Melanoma Research Foundation
National Brain Tumor Society (NBTS)
National Cancer Registrars Association (NCRA)
National Comprehensive Cancer Network (NCCN)
The National Pancreas Foundation
Oncology Nursing Society (ONS)
Ovarian Cancer Research Alliance (OCRA)
Pennsylvania Prostate Cancer Coalition (PPCC)
Susan G. Komen
Triage Cancer
ZERO Prostate Cancer

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[i] "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies Guidance for Industry – Draft Guidance" (June 2024) ("2024 FDA Guidance"), at 3. *See also*, "Clinical Trial Diversity," FDA Fact Sheet, at 1 ("Participants in clinical trials should represent the patients that will use the medical products.").

[ii] 2024 FDA Guidance at 3. *See also* FDA Drug Trials Snapshots Summary Report 2023, at 19 ("FDA is committed to working with sponsors to identify barriers to overcome and to leverage best practices that contribute towards improving" the representativeness of clinical trials.).

[iii] Medicare National Coverage Decisions Manual, Ch. 1, Part 4, §310.1.

[iv] Nipp RD, Powell E, Chabner B, Moy B. Recognizing the Financial Burden of Cancer Patients in Clinical Trials. Oncologist. 2015;20(6):572-575. doi:10.1634/theoncologist.2015-0068.

[v] *See, e.g.*, Sateren WB, Trimble EL, Abrams J, et al. How sociodemographics, presence of oncology specialists, and hospital cancer programs affect accrual to cancer treatment trials. J Clin Oncol. 2002;20:2109–2117; and Baquet CR, Ellison GL, Mishra SI. Analysis of Maryland cancer patient participation in National Cancer Institute-supported cancer treatment clinical trials. J Clin Oncol. 2008;26:3380–3386. *See also*:

- Syed ST, Gerber BS, Sharp LK. Traveling towards disease: transportation barriers to health care access. J Community Health. 2013 Oct;38(5):976-93. doi: 10.1007/s10900-013-9681-1. PMID: 23543372; PMCID: PMC4265215;
- Etminani-Ghasrodashti, R., Kan, C., & Mozaffarian, L. (2021). Investigating the Role of Transportation Barriers in Cancer Patients' Decision Making Regarding the Treatment Process. Transportation Research Record, 2675(6), 175–187. https://doi.org/10.1177/0361198121991497; and
- Evan M Graboyes, MD, MPH, FACS, Krisda H Chaiyachati, MD, MPH, MSHP, Jennifer Sisto Gall, MPH, Wenora Johnson, BSBM, Jerry A Krishnan, MD, PhD, Sapna S McManus, MD, MHA, Letitia Thompson, MPA, Lawrence N Shulman, MD, K Robin Yabroff, PhD, Addressing Transportation Insecurity Among Patients With Cancer, JNCI: Journal of the National Cancer Institute, Volume 114, Issue 12, December 2022, Pages 1593–1600, https://doi.org/10.1093/jnci/djac134.

- King CJ, Chen J, Dagher RK, Holt CL, Thomas SB. Decomposing differences in medical care access among cancer survivors by race and ethnicity. Am J Med Qual. 2015 Sep-Oct;30(5):459-69. doi: 10.1177/1062860614537676. Epub 2014 Jun 5. PMID: 24904178; PMCID: PMC4257897.

[vi] 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; Unger JM, Cook E, Tai E, Bleyer A. The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies. Am Soc Clin Oncol Educ B. 2016;36:185-198.

[vii] Adams DV, Long S, Fleury ME. Association of Remote Technology Use and Other Decentralization Tools With Patient Likelihood to Enroll in Cancer Clinical Trials. JAMA Netw Open. 2022;5(7):e2220053. doi:10.1001/jamanetworkopen.2022.20053. *See also* Takvorian SU, Cuerra CE, Schepero W. A Hidden Opportunity – Medicaid's Role in Supporting Equitable Access to Clinical Trials, N Engl J Med 2021; 384:1975-1978, doi: 10.1056/NEJMp2101627, (noting than "racial and ethnic minority groups may be especially likely to be affected by financial barriers to study participation, which include the costs associated with more frequent clinic visits, time away from work, and travel-related expenses.") https://www.nejm.org/doi/10.1056/NEJMp2101627?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed.

[viii] *See, e.g.*, OIG Advisory Opinion 98-6 (May 1, 1998) (permitting the remuneration at issue will "ensure that economically disadvantaged patients are not precluded from the study"); OIG Advisory Opinion 00-05 (Jun. 30, 2000), at 5 (same); OIG Advisory Opinion 06-05 (Apr. 26, 2006), at 3 (clinical trials "can impose substantial financial, logistical, and other burdens on patients and their families"); OIG Advisory Opinion 08-11 (Sep. 17, 2008), at 8 (permitting the remuneration at issue will "ensure that economically disadvantaged patients are not precluded from the study"); OIG Advisory Opinion 21-13 (Sep. 29, 2021), at 7 (the "Study is specifically designed to collect and analyze data on underrepresented minorities" and the remuneration at issue "appear[s] to be a reasonable means to facilitate enrollment of a diverse set of subjects by removing a potential financial barrier to participation in the Study"); OIG Advisory Opinion 22-05 (Mar. 11, 2022), at 7 ("[a]ccording to Requestor, the out-of-pocket costs to participate in the Study would be cost prohibitive for many Medicare beneficiaries who otherwise would participate in the Study, and Requestor's cost-sharing subsidy" would be "a reasonable means to facilitate enrollment of a socioeconomically diverse set of subjects by removing a potential financial barrier to participation in the Study"); OIG Advisory Opinion 23-11 (Dec. 21, 2023), at 7 ("the cost-sharing subsidies that would be offered under the Proposed Arrangement appear to be a reasonable means to facilitate enrollment of a socioeconomically diverse set of participants by removing a potential financial barrier to participation in the Study").

[ix] Financial stress associated with oncology clinical trial participation, ASPE, 2025, accessed at:https://aspe.hhs.gov/reports/financial-stress-clinical-trial

[x] 2024 FDA Guidance, at 14.

[xi] *See* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects (accessed January 1, 2025).

[xii] Indeed research suggests that even the provision of cash incentives to participate in clinical trials does not result in undue or unjust inducements. *See* S. Halpern, et al., Effectiveness and Ethics of Incentives for Research Participation 2 Randomized Clinical Trials AMA Intern Med. 2021;181(11):1479-1488. doi:10.1001/jamainternmed.2021.545. Published online September 20, 2021.

[xiii] Section 2709(d) of the Public Health Service Act provides as follows:

(d) Approved clinical trial defined

(1) In general

In this section, the term "approved clinical trial" means a phase I, phase II, phase III, or phase IV clinical trial that is conducted in relation to the prevention, detection, or treatment of cancer or other life-threatening disease or condition and is described in any of the following subparagraphs:

(A) Federally funded trials. The study or investigation is approved or funded (which may include funding through in-kind contributions) by one or more of the following:

(i) The National Institutes of Health.

(ii) The Centers for Disease Control and Prevention.

(iii) The Agency for Health Care Research and Quality.

(iv) The Centers for Medicare & Medicaid Services.

(v) cooperative group or center of any of the entities described in clauses (i) through (iv) or the Department of Defense or the Department of Veterans Affairs.

(vi) A qualified non-governmental research entity identified in the guidelines issued by the National Institutes of Health for center support grants.

(vii) Any of the following if the conditions described in paragraph (2) are met:

(I) The Department of Veterans Affairs.

(II) The Department of Defense.

(III) The Department of Energy.

(B) The study or investigation is conducted under an investigational new drug application reviewed by the Food and Drug Administration.

(C) The study or investigation is a drug trial that is exempt from having such an investigational new drug application.

(2) Conditions for departments

The conditions described in this paragraph, for a study or investigation conducted by a Department, are that the study or investigation has been reviewed and approved through a system of peer review that the Secretary determines-

(A) to be comparable to the system of peer review of studies and investigations used by the National Institutes of Health, and

(B) assures unbiased review of the highest scientific standards by qualified individuals who have no interest in the outcome of the review.

[xiv] 21 C.F.R. § 56.102(e) provides as follows: "*Human subject* means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient."

[xv] 21 C.F.R. § 56.102(g) provides as follows: "*Institutional Review Board (IRB)* means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to

assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act."

[xvi] Section 2709(e) of the Public Health Service Act provides as follows:

> *(e) Life-threatening condition defined*
>
> *In this section, the term "life-threatening condition" means any disease or condition from which the likelihood of death is probable unless the course of the disease or condition is interrupted.*

[xvii] 21 C.F.R. § 56.102(j) provides as follows: "*Sponsor* means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators."

[xviii] *See* 21 C.F.R. § 56.111(b) ("When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.").

[xix] OIG Advisory Opinion 98-6 (May 1, 1998), at 8. See also OIG Advisory Opinion 00-05 (Jun. 30, 2000), at 4 (the purpose of the remuneration at issue "is to induce participation in a HCFA-sponsored scientific study, not to induce utilization of Medicare covered services.") and OIG Advisory Opinion 23-11 (Dec. 21, 2023), at 7 ("the Proposed Arrangement would pose a low risk of overutilization or inappropriate utilization of items and services payable by a Federal health care program. Because the cost-sharing subsidies are specifically designed to facilitate enrollment of individuals in the Study and help prevent attrition during the course of the Study, it is possible that overall utilization of items and services may increase, but there is nothing to suggest that such an increase would be inappropriate").

[xx] Unger JM, Moseley A, Symington B, Chavez-MacGregor M, Ramsey SD, Hershman DL. Geographic Distribution and Survival Outcomes for Rural Patients With Cancer Treated in Clinical Trials. JAMA Netw Open. 2018;1(4):e181235. doi:10.1001/jamanetworkopen.2018.1235.

[xxi] OIG Advisory Opinion 23-11 (Dec. 21, 2023), at 7.