Impact of COVID-19 on Clinical Trials Costs to Patients

Environmental Scan

June 25, 2024

Submitted to:
Trinidad Beleche
Office of the Assistant Secretary for Planning and Evaluation (ASPE)
U.S. Department of Health and Human Services
200 Independence Ave. S.W.
Washington, DC 20201

Work performed under:
Contract No. HHSP233201500035I, Task Order No. 75P00122F37070

Disclaimer
This research was performed by Mathematica. The findings and conclusions of this research are those of the authors and do not necessarily represent the views of ASPE or the U.S. Department of Health and Human Services (HHS). Links and references to information from non-governmental organizations is provided for informational purposes and is not an HHS endorsement, recommendation, or preference for the non-governmental organizations

Authors
Keri Calkins, PhD, Emily Crabtree, MPH, Emily Harrison, MPH, Nyna Williams, PhD (QA Reviewer), Kirsten Barrett, PhD (QA Reviewer)

Acknowledgments
The authors wish to thank Sue Felt-Lisk, Chris Palo, Donovan Griffin, and Barbara Collette at Mathematica for their contributions to this work. We would also like to acknowledge the following individuals:

Allison Kolbe, PhD, ASPE
Trinidad Beleche, PhD, ASPE
Deborah Porterfield, MD, MPH, ASPE
Jessica White, MPP, ASPE
Kathleen Miller, PhD MS, ASPE
Contract Officer's Representative, Marsha Clarke, PhD, ASPE
Hope King, PhD, MSPH, Centers for Disease Control and Prevention
Christine Lee, Pharm. D, PhD, Food and Drug Administration
Winifred (Ann) Meeker-O'Connell, Food and Drug Administration
Richard P. Moser, National Cancer Institute, National Institutes of Health
Kelly Blake, SCD, National Cancer Institute, National Institutes of Health
Courtney P. Williams, DrPH, University of Alabama at Birmingham

Suggested Citation

Calkins, K., E. Crabtree, E. Harrison, N. Williams, K. Barrett. "Impacts of COVID-19 on Clinical Trials Costs to Patients: Environmental Scan." D.C.: Mathematica Policy Research, June 2024.

Contents

Exhibits

Executive Summary

Background

Under the *Lessons Learned from the COVID-19 Pandemic* contract funded by the Office of the Assistant Secretary for Planning and Evaluation, Mathematica is identifying the impact of COVID-19 on the costs to patients associated with clinical trial participation and particularly how the use of novel strategies such as remote technologies affected costs to patients. One important component of this work is to conduct an environmental scan meant to provide context for survey development and help us identify gaps in the literature related to costs to patients participating in clinical trials, both before and during the COVID-19 pandemic. In particular, the environmental scan addressed the following topics:

1. The types of direct and indirect costs to patients associated with clinical trial participation, including any estimates of such costs in the literature.
2. Recognizing that payers are required to cover "routine care costs," the types of costs that are not considered "routine care" or may not be covered by payers.
3. Financial and nonfinancial barriers on participation in clinical trials by sociodemographic groups, with an emphasis on historically underrepresented groups.
4. The effect of COVID-19 on costs to patients, including cost implications of clinical trial innovations widely implemented during COVID-19 (for example, remote monitoring and decentralized trials) and efforts to increase diversity of trial participants by reducing barriers to participation.

Methods

We searched three academic databases to identify peer-reviewed literature published from 2010 to 2023 using key search terms related to the topics above. We also searched for grey literature on clinical trial, cancer research, and patient advocacy group websites, Google, and GoogleScholar. After completing the initial article review, we conducted a backward and forward snowball search using the articles we identified in the first round of the formal literature search to supplement our findings.

We identified 3,192 articles across the four search topics. After a title review for relevance, we removed 3,076 articles that did not focus on the topics of clinical trials costs to patients or barriers to clinical trial participation. We added an additional 88 relevant articles or sources from the grey literature to the abstract review for a total of 204 articles. Based on an abstract review of the 204 articles, we removed 161 articles that did not have a direct discussion of costs to patients or barriers to clinical trial participation, leaving 44 articles remaining from the initial review. We then conducted forward and backward snowball searches to add another 40 full text articles, yielding a total of 84 full text articles or resources included in the final environmental scan.

Key Takeaways

In Exhibit ES.1, we list the key findings by topic area, as well as the gaps we identified in the literature.

Exhibit ES.1. Key findings and gaps from the literature search

Topic	Summary of literature and key findings	Gaps in literature
Types and estimates of direct and indirect costs to patients in clinical trials	**Summary:** *A limited number of studies quantified direct or indirect costs to patients in clinical trials, with most studies focusing on estimates of travel costs and reimbursement.* • Direct costs included copays, coinsurance, deductibles, medication costs, and general out-of-pocket spending, with mixed evidence on whether patients enrolled in clinical trials have more out-of-pocket medical costs. • Travel costs were the most commonly reported indirect cost and ranged from $200 to $1,000 per month before the COVID-19 pandemic. • Other indirect costs included in the literature were dependent care, meals, and missed work or lost wages. • Researchers recommend collecting information about patient-reported financial toxicity during trials, but uptake of the recommendation is slow.	• Few studies directly compared the out-of-pocket direct costs for patients enrolled and not enrolled in clinical trials • Most studies focused on direct and indirect costs to patients were among patients with cancer. • Some studies reported financial toxicity as a composite measure rather than direct or indirect costs, but this metric is captured infrequently in clinical trials. • No papers quantified the impact of COVID-19-related modifications (remote monitoring, decentralized trials, and so on) on direct or indirect costs. • Lost wages might represent a significant cost to patients, but few studies quantified them.
Impact of policies requiring that payers cover "routine care costs" during clinical trials and costs covered by payers as "routine care"	**Summary:** *Information on what is covered under routine care is varied and limited. Variation in the implementation of these policies contributes to gaps in policy coverage.* • Coverage for routine care varied by payer and state over the last 20 years with Medicaid being the last to adopt coverage in all states. • Payers can still deny coverage for trials at out-of-network sites. • There was some evidence that newly adopted state-level policies requiring insurers to cover "patient care costs" in clinical trials had no statistical impact on clinical trial participation rates. • Patients still experience the financial burden of direct costs such as coinsurance, which routine care policies do not address.	• There is limited information in the literature on what costs payers consider routine care. • There are few studies on the impact of routine care policies and those that do exist show mixed effects on trial participation.

Topic	Summary of literature and key findings	Gaps in literature
Impact of financial and nonfinancial barriers on clinical trial participation among historically underrepresented groups	**Summary:** *Financial and nonfinancial barriers for some underrepresented groups have been addressed in the literature, with lower socioeconomic status identified as the one of the largest overarching barriers to trial participation.* • Socioeconomic factors (including education level, employment status, income level, and insurance status) contribute to observed disparities and present a significant barrier to trial participation, especially for Black and Hispanic patients, patients older than age 65, and rural patients. • Reimbursement for costs associated with clinical trials such as travel could address disparities in participation. • Nonfinancial barriers include patient awareness, encouragement from providers to participate, regional availability, distrust of the health system, logistical barriers, and ineligibility, including because of age and health status.	• There was limited information on the impact of COVID-19 on barriers to clinical trial enrollment. • There was also limited information on the difference in costs of participation by underrepresented group. • The literature generally focused on barriers for racial and ethnic minorities, rural populations and elderly populations but there was comparatively little evidence on barriers for other underrepresented populations such as pregnant and lactating people, LGBTQIA+ populations, children, or people with disabilities.
Effects of COVID-19 and clinical trial innovations like remote monitoring on costs to patients, diversity of trial participants, and barriers to trial participation	**Summary:** *No studies focused on the effects of COVID-19 on costs to patients, but some studies suggested there were benefits of clinical trial innovations on reducing barriers to trial participation.* • Some patients reported benefits from remote study visits such as reduced time commitment and travel costs (qualitative findings only). • Remote study visits presented some technological challenges for patients and could disadvantage older or low-income patients without reliable internet access.	• There were no cost estimates on the impact of remote study visits or other decentralized elements in trials on indirect costs such as travel. • There was limited information on the effects of the following innovations on costs, diversity, and barriers to participation: cost reimbursement, home visits and relaxed follow-up timeframes.

Based on these findings, we identified areas for future work to address some key gaps in the literature, including the following:

- Estimates of direct and indirect costs to patients, including out-of-pocket medical spending, travel costs, and lost work productivity, in by trial phase and type.
- Patient's experience with insurance coverage during the clinical trial, including instances of denied coverage for clinical trial monitoring tests or clinical trial sites that were out-of-network or types of care that were not considered 'routine care costs' during the trial.
- The impact of eligibility barriers on clinical trial participation and approaches to adapt trial inclusion and exclusion criteria to reduce eligibility barriers for underrepresented groups.

Patient's experience and comfort-level with remote monitoring, telehealth, or other remote technology.

I. Introduction

Under the Lessons Learned from the COVID-19 Pandemic contract funded by the Office of the Assistant Secretary for Planning and Evaluation (ASPE), Mathematica is working to better understand how the COVID-19 pandemic might have influenced the costs to patients enrolled in oncology clinical trials. This work includes an environmental scan and the development of a patient survey to inform the following research questions:

1. How did clinical trial innovations and strategies implemented during the COVID-19 pandemic, such as use of remote technologies, impact costs for participating patients?
2. What are the types of costs (direct and indirect) associated with participating in clinical trials? Were the types of costs different during the COVID-19 pandemic?
3. What are the patient costs associated with participating in oncology clinical trials? Did patient costs change over the course of the COVID-19 pandemic?
4. How do costs associated with clinical trial participation differ between sociodemographic groups? Did these costs change over the course of the COVID-19 pandemic?
5. What types of costs are typically not covered by payers? How are these costs different by payer type? Did the types of costs covered by payers change over the course of the COVID-19 pandemic?
6. What types of costs are typically covered by other non-payer organizations such as research centers, sponsors, patient advocacy groups or research institutions, which are not covered by payers? How did the types of costs change over the course of the COVID-19 pandemic?
7. Are there any lessons learned from pandemic-era clinical trial strategies and innovations to reduce costs for patients? What types of financial recruitment incentives might increase diversity in oncology clinical trials?

This environmental scan focuses on the literature that explores the financial and nonfinancial barriers to clinical trial participation, including direct and indirect costs to patients and differences for underrepresented groups. We also reviewed any available literature on the impact of COVID-19 or clinical trial innovations on these barriers. This environmental scan included information on costs and barriers associated with all types of clinical trials. The findings in this environmental scan focus on the following search topics, which touch on all of the research questions above.

- **Topic 1:** The types of direct and indirect costs to patients associated with clinical trial participation, including any estimates of such costs in the literature.
- **Topic 2:** Recognizing that payers are required to cover "routine care costs," the types of costs that are not considered "routine care" or may not be covered by payers, and any impact of COVID-19 or clinical trial innovations on routine care coverage.
- **Topic 3:** Financial and nonfinancial barriers on participation in clinical trials by sociodemographic groups, with an emphasis on historically underrepresented groups, and the impact of COVID-19 or clinical trial innovations on barriers to participation.
- **Topic 4:** Any changes in Topics 1 to 3, such as, costs to patients, routine care coverage, or barriers to clinical trial participation, during COVID-19 or because of clinical trial innovations (for example, remote monitoring or decentralized trials).

II. Methods

This chapter describes the methods we used for the environmental scan, including our search strategy and our process for reviewing articles.

A. Search strategy

We searched three databases to identify formal literature published from 2010 to 2023 related to the search topics: EBSCO Academic Search Premier, EBSCO Cumulative Index of Nursing and Allied Health Literature (CINAHL), and PubMed. We list some of the key search terms for each research topic in Exhibit II.1. Informed by background literature and feedback provided by ASPE, we chose our search terms to address the four search topics. We included all literature starting in 2010 to capture literature surrounding the Affordable Care Act's requirement that private insurers cover routine care costs in clinical trials.

Exhibit II.1. Search terms for the database search

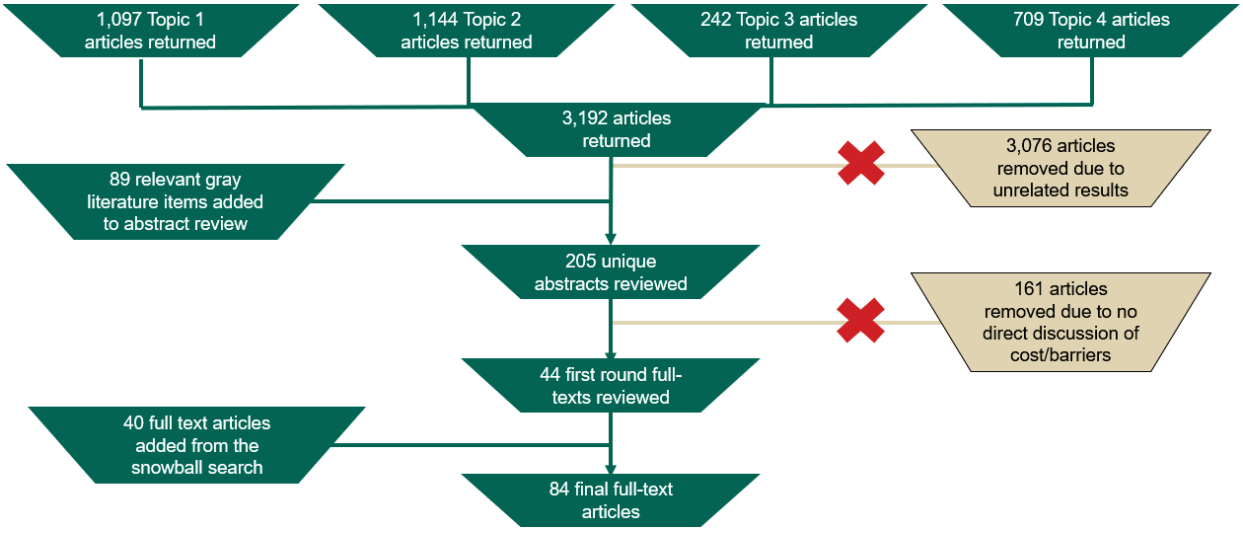
Topic Number	Research topic	Search query
1	Direct and indirect costs to patients in clinical trials	("financial toxicity" OR "financial burden" OR "cost to patients" OR "direct costs" OR "indirect costs" OR "patient costs" OR "cost to patient" OR "direct cost" OR "indirect cost" OR "patient cost" OR "reduce cost" OR "reduce costs" OR "out-of-pocket" OR "out-of-pocket")) AND ("clinical trial" OR "clinical trials")
2	Routine care cost policies	Search 1: (payer) OR payor OR Medicaid) OR Medicare or insurance) AND ("clinical trial" OR "clinical trials") AND (cost*) Search 2: "routine care cost" OR "routine care costs""
3	Barriers to clinical trial participation for historically underrepresented groups	((diversity) OR (representation) OR (underrepresented) OR (minority) OR (marginalized) OR (vulnerable) OR (barrier) OR (Hispanic) OR (Black) OR (Latino) OR (Asian) OR (female) OR (women) OR (child) OR (pediatric) OR (race) OR (ethnicity) OR (disability) OR ("older adults") OR (aging) OR (pregnant) OR (lactating) AND ("financial toxicity" OR "financial burden" OR "cost to patients" OR "direct costs" OR "indirect costs" OR "patient costs" OR "cost to patient" OR "direct cost" OR "indirect cost" OR "patient cost" OR "reduce cost" OR "reduce costs" OR "out-of-pocket" OR "out-of-pocket")) AND ("clinical trial" OR "clinical trials")
4	Effect of COVID-19 on clinical trial costs to patients	(COVID) OR (coronavirus) OR (pandemic) OR (innovation) OR (remote monitoring) OR (decentralized) OR (reform)) AND (clinical trial) AND ("financial toxicity" OR "financial burden" OR "cost to patients" OR "direct costs" OR "indirect costs" OR "patient costs" OR "cost to patient" OR "direct cost" OR "indirect cost" OR "patient cost" OR "reduce cost" OR "reduce costs" OR "out-of-pocket" OR "out-of-pocket" OR (cost))

We also searched the gray literature for resources mentioning key terms using the websites of organizations related to clinical trials or cancer research and advocacy groups, Google, and GoogleScholar. After completing the initial article review, we conducted a backward and forward snowball search using the articles we identified in the first round of the formal literature search to find additional references (see Figure II.1 for a schematic of the article review process). The full search strategy including the search syntax, is available in Appendix A.

B. Article review

Figure II.1 shows the number of articles identified in our search, excluded at each stage, and included in the final analysis. Using the four separate sets of search terms listed in Exhibit II.2, we identified 3,192 articles across the four topics. After a title review (or brief abstract review if unclear from the title) for relevance, we removed 3,076 articles that did not focus on the topics of clinical trials costs to patients or barriers to clinical trial participation.[1] After an initial screen of the gray literature results, we added 89 relevant articles or sources to the abstract review for a total of 205 articles. Because we found that the literature on clinical trials' costs to patients is limited, our scan does not focus on a specific subset of clinical trials. However, much of the literature on costs to patients focuses on oncology trials.

Exhibit II.2. Article review flowchart



We then reviewed the abstracts for the 205 articles and removed 161 that did not directly discuss costs to patients or barriers to clinical trial participation.[2] At this point, there were 44 remaining articles from the initial review. We then conducted forward and backward snowball searches to add another 40 full text articles, yielding a total of 84 full text articles or resources included in the final environmental scan.

[1] Some examples of articles removed based on title review were cost-effectiveness studies. A few articles had ambiguous titles, such as "The Current State of Clinical Trials Studying Hydrocephalus: An Analysis of ClinicalTrials.gov" (Abraham et al. 2020) but, after a brief review of the abstract, we found that the abstract's mention of "financial burden" refers to the cost of care to the health system overall, which is not within the scope of the environmental scan.

[2] For example, some articles provided commentary on the need for diversifying clinical trials or incorporating patient centered outcomes, such as out-of-pocket costs into trials, but they did not highlight estimates of costs or they cited other articles already included in the full text review, such as the commentary in "Incorporating Patient and Caregiver Experiences into Cardiovascular and Clinical Trial Design" (Collins et al. 2017).

III. Findings

In this section, we review the findings from the environmental scan by search topic, as defined in Section I. Some articles may touch on more than one topic; therefore, an article might appear more than once throughout the topic sections.

Topic 1: What are the types of direct and indirect costs to patients associated with clinical trial participation?

Key Topic 1 findings

- Few studies quantified direct or indirect costs to patients during clinical trials and no papers quantified the impact of COVID-19 or remote monitoring on direct or indirect costs.
- Indirect costs in the literature focused mainly on travel costs, which range between $200 to $1,000 per month before the COVID-19 pandemic.
- Lost wages might represent a significant cost to patients, but few studies quantified them.
- Measures of patient-reported financial toxicity are becoming more common, but clinical trials infrequently collect them.

Participation in clinical trials can result in direct and indirect costs to patients. Some of the direct costs for clinical trial participants described in the literature were copays, coinsurance, and deductibles (Caston et al. 2022), as well as medication costs and general out-of-pocket spending on medical care (Kilgore & Goldman 2008; Pisu et al. 2011). We define key cost terms in Exhibit III.1. Although researchers have found that direct costs are rising for non-pediatric National Cancer Institute trial participants (Bangs et al. 2019), **we identified few articles that quantify the direct costs that clinical trial participants face. Slightly more research exists on calculating the indirect costs of clinical trial participation, but none quantified the impact of the COVID-19 pandemic on indirect cost estimates.** Indirect costs included expenses for travel (for example, transportation, fuel, taxis or rideshares, tolls, parking, air travel, hotels), meals, dependent care (either for children or older adults), missed work, and companion costs (Reoma and Karp 2022). Here, we describe the literature on direct and indirect costs to patients participating in clinical trials. We summarize the number of studies that cover each cost type or topic in Exhibit III.2.

Exhibit III.1. Defining Key Cost Terms[1]

- Direct costs to patients during clinical trials are medical costs such as copays, co-insurance, or deductibles, as well as out-of-pocket costs for care such as medication, laboratory, or imaging costs.
- Indirect costs to patients during clinical trials are other costs associated with trial participation like travel, food, child or eldercare, and lost wages.
- Financial toxicity is the negative monetary effect of medical treatment and financial burden on quality of life.

[1]Chino and Zafar 2019

Direct costs

Exhibit III.2. Number of studies by cost type

Cost type	Study count
Caregiver support	3
Dependent care	6
Earnings loss	8
Financial toxicity	6
Insurance costs	1
Out-of-pocket medical expenses	13
Travel costs	24
Quality of life	7

Direct out-of-pocket costs for cancer patients in clinical trials or receiving standard of care can reach up to a few hundred dollars per month. Exhibit III.3 provides a list of the articles that include estimates of costs to patients, including direct and indirect costs. In total, five articles provide cost estimates for direct, out-of-pocket medical expenses associated with cancer care or trial participation. Both patients enrolled in clinical trials and those receiving standard care may face significant direct costs. One longitudinal survey found standard care cancer patients pay an average of nearly $400 per month for out-of-pocket expenses related to their care (Chino et al. 2018). In a separate cross-sectional study, researchers found cancer patients reporting financial distress may pay over $700 per month out-of-pocket average for standard of care (Chino et al. 2017). A 2011 study of stage I and II breast cancer survivors found that patients mean total monthly direct out-of-pocket costs associated with standard of care were $316 per month (Pisu et al. 2011). For cancer patients participating in clinical trials, one survey found that the average monthly out-of-pocket expenses were $742 (Borno et al, 2022a). We did not identify any articles that provide cost estimates for non-cancer care.

Exhibit III.3. Type of trial-related cost estimates to patients, by article

Article	Earnings loss	Out-of-pocket medical expenses	Travel costs
Borno et al. 2018			✓
Borno et al. 2022a		✓	✓
Borno et al. 2022b			✓
Chino et al. 2017		✓	
Chino et al. 2018		✓	✓
Gafford et al. 2017	✓		✓
Huey et al. 2021			✓
Kilgore & Goldman 2008		✓	
Lee et al. 2020			✓
Nipp et al. 2015			✓
Nipp et al. 2016			✓
Nipp et al. 2019a			✓

Academic sources disagree on whether clinical trial participants face more direct costs than patients receiving standard care. Some studies that seek to determine the cost burden to patients participating in clinical trials found little to no difference compared with the costs that patients receiving standard cancer treatment face (Kilgore & Goldman 2008, Sidana et al. 2022). Kilgore and Goldman (2008) calculated prescription drug costs and out-of-pocket costs (not defined by the study team) for patients participating in phase III oncology clinical trials and compared them with the costs of patients receiving standard cancer care. Using multivariate regression, the study team estimated that clinical trial

participants paid, on average, $131 more for prescription drugs than standard care patients within a six-month period but did not spend significantly more on out-of-pocket expenses . In a survey of patients presenting to a medical oncology clinic from 2018 to 2020, researchers found that a significantly higher proportion of clinical trial patients reported out-of-pocket expenses exceeding $1,000 in the prior month than patients receiving standard care (Borno et al. 2022a). Borno et al. (2022a) found that clinical trial participants may, in fact, pay nearly $500 more per month on average for out-of-pocket costs associated with care compared with standard care cancer patients. We did not identify any articles that attempted to quantify patients' costs for non-cancer clinical trials.

Indirect costs

Studies on indirect costs to patients in clinical trials focus largely on travel (that is, transportation and lodging). Travel costs in the literature ranged from $200 to $1,000 per month depending on proximity to trial site, phase of clinical trial, and in-state versus out-of-state patients. Nipp et al. (2019a) found that, on average, patients enrolled in cancer trials from 2015 to 2017 spent at least $600 per month on travel (such as gasoline, tolls, parking, flights, and hotels) related to their care. Among those who participated in clinical trials, the study team calculated that patients who lived in-state spent $212 per month on travel, those who lived in the New England region spent $330 per month, and those who lived outside the region spent $795 per month. The study included patients from phase I, II, and III oncology trials, but most were phase I trial participants. Nipp et al. (2019a) also explored the impact of monthly reimbursements for patients' indirect costs. Participants receiving reimbursement reported greater improvement in their travel-related financial concerns than those who did not receive reimbursement. Although such findings may seem obvious, the study team notes that reducing travel-related expenses for trial participants may have wider impacts on trial participation and outcomes (for example, improving quality of life, symptom burden, or treatment adherence). Prior studies found similar results, although out-of-region patients spent slightly more on average ($900) in 2013–2014 as compared to 2015–2017 (Nipp et al. 2015). Nipp et al. (2016) also reported that offering reimbursement for indirect costs significantly increased the rate of recruitment.

A survey conducted by Huey et al. (2021) found similar travel costs, as a cohort of patients participating in phase I oncology clinical trials from October 2018 and January 2020 reported spending $600 per month on average for travel, hotels, food, and other non-medical costs; nearly half (48 percent) of survey respondents reported spending at least $1,000 per month on costs related to participating in a clinical trial. We also identified literature on a financial reimbursement program that covered travel-related expenses for oncology clinical trial participants and their caregivers. Borno et al. (2022b) found that 22 percent of patients paid $300 to $1,000 and 11 percent paid more than $1,000 per month for travel. Considering cost based on travel distance, Borno et al. (2018) found that low-income patients spent more on travel than middle- or high-income oncology clinical trial participants ($15.82 versus $3.14 and $3.91, respectively, per trip based on $0.10 cost per mile); the authors theorized that the travel cost discrepancy could be attributable to low-income patients having to commute from rural homes to urban trial settings. The same study found that White clinical trial participants spent more on travel than Black or Asian participants ($5.32, $2.36, and $2.77, respectively), though the study noted that these disparities might be based on the demographics of rural California, where the study population was based (Borno et al., 2018).

Lost wages may comprise a significant amount of indirect costs to patients. Gafford et al. (2017) estimated the cost implications of opening the Midwest Cancer Alliance clinical trial sites affiliated with the University of Kansas Medical Center, which provided patients with in-state access to oncology clinical trials. Based on assumptions related to travel costs, the authors estimated that patients enrolled in in-state clinical trials would incur about $3,240 per year in indirect costs on average (~$280 in milage and ~$2,960 in lost wages), which represented a significant savings compared with the estimated $9,200 in indirect costs to patients that had to previously travel out-of-state for clinical trial access (~$1,900 in milage, ~$1,400 in lodging, and ~$5,900 in lost wages). This was the only study we identified that directly estimated lost wages.

Parking costs at appointments vary by site but could be burdensome, depending on the number of appointments required. Finally, although not specific to patients enrolled in clinical trials, Lee et al. (2020) quantified the parking fees from the 63 National Cancer Institute-designated cancer centers and found that only 32 percent of centers offered free parking for all patients and that parking costs varied considerably across sites (median hourly costs = $2, IQR= $0, $5; median daily costs = $5, IQR = $0, $10). The authors estimated based on average number of expected visits that costs for parking during a standard course of outpatient treatment could reach up to $800 for breast cancer and $665 for head and neck cancer.

Financial toxicity

Rather than recording direct or indirect costs, some studies examine composite measures of patient-reported financial toxicity, which is broadly defined as the financial consequences or burden related to medical treatment. Two commentary articles reiterated the importance of addressing the financial toxicity related to clinical trial participation (Gharzai & Jagsi 2023, Winkfield et al. 2018). Many studies measured financial toxicity among clinical trial participants using a survey or overall toxicity score rather than providing estimates of costs to patients. Although authors have used various measures of financial toxicity in the literature, several studies we identified leveraged the Comprehensive Score for financial Toxicity (COST) measure, which was validated by de Souza et al. (2017). The COST measure is an 11-item patient reported outcome measure in which patients report how much they agree with statements about their financial distress on a Likert scale from "Not at all" (0 points) to "Very much" (4 points). Example statements include: "I feel financially stressed," "My out-of-pocket medical expenses are more than I thought they would be," and "My cancer or treatment has reduced my satisfaction with my present financial situation." Other approaches to measuring financial toxicity included multi-item questionnaires with Likert scale responses focused on financial concerns specific to clinical trial enrollment (Wong et al. 2016). Gharzai and Jagsi (2023) argue for incorporating collection of financial toxicity measures, such as COST and information on direct and indirect costs to patients, during the conduct of clinical trials. They also indicate that further development of culturally sensitive measures of financial toxicity is necessary, because the COST measure was developed using a patient population that was overly-representative of non-Hispanic White participants (74 percent) compared to the general population (58 percent). **Systematic reviews indicate that financial toxicity is infrequently assessed during the conduct of clinical trials.** Olivier et al. 2023 completed a systematic review to assess how financial toxicity was characterized in cancer clinical trials, among trials that reported any quality-of-life

outcomes.[3] Only 73 cancer trials measured quality-of-life outcomes, of which about half (53 percent) assessed financial burden and only three percent provided any financial compensation or payments to patients. The systematic review identified the following measures of financial toxicity in the literature: the 'COST' measure, the Patient-Reported Outcome for Fighting FInancial Toxicity measure, and a single item question in the QLQ-C30 instrument ("Has your physical condition or medical treatment caused you financial difficulties?). The authors also noted that the drug was provided by the sponsor in about 70 percent of the 73 cancer trials that reported quality-of-life outcomes, which helps to limit the potential out-of-pocket costs to patients. Another literature review focused on the extent to which financial toxicity was incorporated as an end point into studies involving radiation (Prasad et al. 2022). The review included both observational studies and clinical trials involving radiation from 2001 to 2020 and found that less than 1 percent of studies included financial toxicity as an end point, increasing from 0.1 percent in 2001 to 1.5 percent in 2020. The authors found that financial toxicity was often measured using the single item question from the QLQ-C30 questionnaire, as identified by Olivier et al. (2023) and suggested incorporating more financial toxicity measures into research. Kunos and Abdallah (2020) reviewed early and late-stage trials for those with ovarian cancer to assess the extent to which trials measure financial toxicity. Among the articles, 27 percent discussed the financial burden of ovarian cancer on patients, but none were in the context of the trials or specific to novel radiopharmaceutical therapies. We also identified two additional studies in which quality-of-life questionnaires and financial toxicity monitoring were introduced into ongoing trials. Among gynecologic malignancy patients, increased financial toxicity was associated with worse quality-of-life among trial patients (Andring et al. 2023). In a trial that incorporated financial toxicity screening among patients undergoing treatment for metastatic cancer, about one third of patients experienced financial toxicity (Blinder et al. 2023).

The few studies examining differences in financial toxicity by clinical trial participation had mixed findings. One study compared patient reported financial toxicity using a set of 10 questions adapted from the Medical Expenditure Panel Survey from the Agency for Healthcare Research and Quality. The authors found no differences in financial toxicity between those enrolled in clinical trials and those receiving standard of care for patients with multiple myeloma or lymphoma (cancer of the plasma cells or lymphatic system) (Sidana et al. 2022). However, Keilson et al. (2022) examined differences in the COST measure of financial toxicity by clinical trial enrollment for patients with cholangiocarcinoma (cancer of the bile ducts) and found that patients in clinical trials reported higher financial toxicity than patients who were not enrolled in a clinical trial, despite having higher reported quality-of-life.

[3] The systematic review included all studies and trials that assessed patient-reported outcomes that focused on quality of life. Quality-of-life was assessed via a variety of questionnaires in these studies. One example quality-of-life questionnaire was the European Organisation for Research and Treatment of Cancer's Quality of Life Questionnaire-30 (QLQ-C30), which measures patients physical, psychological, and social function (Kaasa et al. 1994).

Topic 2: Coverage for "routine care costs" during clinical trials

Key Topic 2 findings

- Coverage for routine care varied by payer and state over the last 20 years, but as of 2022, Medicare, Medicaid, and private insurance must cover routine care costs.
- There is limited information on what costs are considered routine care by payer, and no articles discussed the impact of COVID-19 on payments for or the definition of routine care.
- Despite routine cost coverage, payers can still deny coverage for trials at out-of-network sites, and direct costs such as coinsurance or copays during trials might not be covered.

Over the past two decades, various legislation has been introduced that requires payers to cover "routine care costs" for patients enrolled in clinical trials. In 2000, Medicare required coverage for routine costs of a clinical trials (Social Security Act §1862(a)(1)(E)). The Affordable Care Act (Public Health Service Act §2709) expanded the requirement to cover routine care costs to private payers, and the requirement expanded to all Medicaid beneficiaries in 2022 (Social Security Act §1905(a)(30)). But, as of 2019, only 10 states and the District of Columbia required Medicaid to cover routine care costs in clinical trials, and the types of costs that are considered routine can vary significantly, potentially subjecting patients to financial toxicity because of clinical trial participation in the years prior before 2022 (Obeng-Gyasi et al. 2019). **We found few articles that discuss how particular payers define "routine care" during trials. Some articles estimated the impact of newly adopted state-level policies requiring insurers to cover "patient care costs" in clinical trials on clinical trial enrollment rates, but none discussed the costs to patients associated with routine care coverage or changes because of COVID-19.** There was evidence that newly adopted state-level policies requiring insurers to cover "patient care costs" in clinical trials had no statistical impact on clinical trial participation rates. Exhibit III.4 lists the articles that discuss insurance coverage for routine care, other non-medical costs, or both during clinical trials and includes which types of insurance the articles mention.

Exhibit III.4. Articles discussing insurance coverage for routine and non-medical care during clinical trials

Article	Payer type				Costs covered by payer	
	Private	Medicaid	Medicare	Veterans Affairs or Military	Non-medical	Routine care
Bierer et al. 2021	✓	✓	✓		✓	✓
Bodurtha Smith et al. 2022	✓	✓	✓			✓
Caston et al. 2022		✓			✓	✓
Ellis et al. 2012	✓		✓			✓
Mackay et al. 2016	✓	✓	✓	✓		✓
Martin et al. 2014	✓		✓			✓
Mupfudze et al. 2021		✓			✓	✓
Unger et al. 2023	✓	✓				✓
Winkfield et al. 2018	✓	✓	✓		✓	✓

Definitions of routine care

Several commentary articles identified the challenge in defining routine care during trials. Researchers suggest that there is considerable patient confusion about the costs that they might incur while participating in a clinical trial, which could contribute to concern over costs—some patients might not know that routine care costs associated with clinical trials are covered by insurance as a provision of the ACA, and others might not know that they could face out-of-pocket expenses while participating in a clinical trial (Manne et al. 2015). A commentary article by Bierer et al. (2021) highlighted the complexity of defining "routine care coverage," which could include "ancillary medical care, physician and hospital visits, and treatment of research-related injury." The authors also highlight that trials that qualify for routine care coverage among Medicaid beneficiaries only represent a small proportion of all trials and that those without insurance have no access to trials. The authors of a different commentary article highlighted some key limitations of the ACA legislation on routine care cost coverage, including unclear coverage provisions for experimental or phase I trials, the absence of a clear definition of routine care costs, and unclear coverage of routine surveillance tests during clinical trial follow-up (Martin et al. 2014).

Access barriers despite routine care cost coverage

Despite requirements to cover routine care costs, gaps in policy coverage can limit access to trials for those with insurance. A commentary article assessed what proportion of women with gynecologic malignancies had access to in-network cancer centers accredited by the National Cancer Institute. The authors found that 40 percent of Medicare Advantage plans and 33 percent of private insurance plans did not have in-network cancer centers, which limited their patients' access to clinical trials because of out-of-network costs despite requirements for routine care coverage (Bodurtha Smith et al. 2022). Martin et al. (2014) also mentioned that a key limitation of the ACA legislation is that plans are only required to cover out-of-network clinical trial costs if the plan already provides coverage for out-of-network services. The American Society of Clinical Oncology issued a policy statement focused on barriers to clinical trial participation that described the limitations for out-of-network care and the financial burden associated with cost-sharing such as coinsurance during clinical trials (Winkfield et al. 2018). The American Society of Clinical Oncology also recommended that payers have clear definitions of routine costs and streamline the prior authorization process.

Other results relevant to routine care costs

Studies found ACA's routine care coverage legislation had limited impact on trial participation before COVID-19. Mackay et al. (2016) estimated the change in the number of people in Kansas ages 19 to 64 with health insurance coverage for clinical trial participation after the ACA through 2014. The authors found the ACA had limited impact on coverage rates for clinical trial participation because self-funded and Medicaid plans were not subject to the ACA requirements and because most people who were uninsured before the ACA remained uninsured after. Prior to the implementation of the ACA, Ellis et al. (2012) examined the impact of state-level policies requiring insurers to cover patient care costs in clinical trials on the rates of clinical trial enrollment in these states. The authors found no difference in clinical trial participation rates among National Cancer Institute Community Clinical Oncology Program practices in states with and without coverage mandates. The authors suggested that the varying strength of states' policies may have attenuated the impact, though one study of trial enrollment at a single large

cancer center found an increase in insurance clearance for oncology clinical trials for privately insured patients after the implementation of the ACA (Kehl et al. 2017).

Before 2022, state Medicaid policies were complex and restricted access to clinical trials for beneficiaries. Mupfudze et al. (2021) conducted a qualitative analysis with pediatric bone marrow transplant financial coordinators across 10 states in 2019 and found that only 2 states required Medicaid to cover routine medical costs for patients in clinical trials (Florida and Texas). One state (Michigan) provided coverage for transportation and lodging through Medicaid but did not have legislation requiring routine care coverage during clinical trials. Although state coverage of routine care was not prevalent prior to 2022, there was evidence of a growing proportion of clinical trial patients enrolled in Medicaid. Unger et al. (2023) examined the impact of Medicaid expansion on the number and proportion of clinical trial patients covered by Medicaid across the Southwest Oncology Group Cancer Research Network from 1992 to 2020 and observed a 19 percent increase in the odds of patients using Medicaid insurance in clinical trials after expansion. Female Medicaid beneficiaries had a greater increase in clinical trial participation than male beneficiaries during this period, but there were no significantly different trends by race, ethnicity, or age. Starting in 2022, all state Medicaid plans must cover routine care costs during clinical trials, but we did not identify any articles that evaluated the impact of this new policy (Social Security Act §1905(a)(30)).

Topic 3: Financial and nonfinancial barriers to clinical trial participation for underrepresented groups

Key Topic 3 findings

- We found disparities in trial participation in the literature for Black and Hispanic patients, patients older than age 65, and rural patients.
- There was mixed evidence that racial and ethnic minorities experienced greater out-of-pocket costs or reported more financial barriers to clinical trial participation. However, the literature often cited differences in socioeconomic factors, such as education level, income, and insurance type, as an underlying cause of disparities and presented them as a large barrier to trial participation.
- Nonfinancial barriers include patient awareness, regional availability, and ineligibility, including because of age and health status.

With an estimated 5 percent of eligible populations participating in clinical trials, there are numerous barriers to participation (Gerber et al. 2015). A report from the American Cancer Society Cancer Action Network highlighted several key patient-level barriers to enrollment, including awareness and education regarding trial availability, travel burden and transportation costs, and direct medical costs (Allen et al. 2018). Historically underrepresented groups may also face additional barriers because of overlapping systemic challenges (for example, those who are uninsured may not believe they are eligible to participate in clinical trials, while those who live in rural areas may not reliably be able to travel to clinical trial sites). The literature highlighted a number of groups that are underrepresented in clinical trial participation including racial and ethnic minorities, especially Black, Hispanic, and American Indian and Alaska Native populations, rural populations, populations with low socioeconomic status, and older adults (Allen et al. 2018; Borno et al. 2018; Caston et al. 2022; Cook et al. 2010; Perni et al. 2021; Riaz et al. 2023). Although there may be additional underrepresented groups in clinical trial participation, such as people with

disabilities, pregnant/lactating people, and LGBTQIA+ populations, the literature lacked information on their underrepresentation. Below we describe several articles that discuss the financial and nonfinancial barriers to clinical trial participation, particularly by historically underrepresented groups.

Financial barriers

The main financial barriers to clinical trial participation cited in the literature were cost concerns (in particular out-of-pocket costs for direct medical costs and indirect costs such as travel, as well as insufficient insurance coverage). Chino and Zafar (2019) reviewed the literature on the impact of financial toxicity on clinical trial participation and found that worries about out-of-pocket expenses and concerns about insurance coverage result in lower-income patients being less likely to participate in clinical trials. In a study of 1,256 cancer patients, worries about health insurance coverage of clinical care costs represented one of the strongest barriers to clinical trial participation (Nipp et al. 2016). Information on actual costs of additional out-of-pocket expenses was limited, with one study reporting a substantial proportion of patients in cancer clinical trial taking on credit card debt and spending more than 10 percent of income on medical expenses, which equated to an estimated $600 a month per participant (Nipp et al. 2019a). For participants receiving Medicaid benefits, there were historically no federal mandates for clinical trial coverage, making it prohibitively expensive for many Medicaid beneficiaries to participate in clinical trials (Winkfield et al. 2018). In addition, lack of transparency of potential trial-related out-of-pocket costs and payers' clinical trial coverage policies were barriers to participation (Winkfield et al. 2018). Here, we summarize the findings on financial barriers in the literature and review any literature in which financial barriers might differ for underrepresented groups.

Lower socioeconomic status, including lower income, underinsurance, and lower educational attainment, might confound the association between being in an underrepresented group and lower rates of clinical trial participation. We found several articles that suggest that underrepresented groups, such as racial minority patients and younger adult patients, have lower socioeconomic status, which could explain their lower rates of participation. In a survey of clinical trial sites, MacLennan et al. (2023) found that survey respondents at clinical trial sites reported that lack of reimbursement and lack of payment for participation, in addition to lack of translator services, were the biggest barriers to improving diversity and inclusion in clinical trials. Socioeconomic factors, such as underinsurance and having less than a high school education, were found to be the biggest barrier to minority recruitment in multiple papers and were found to be stronger barriers than race (Duma, 2017; Williams et al. 2021; Manne et al. 2016). One study highlighted that populations with historically lower financial resources including uninsured patients and minority patients were found to have lower clinical trial enrollment overall (Nipp et al. 2019b). Perni et al. (2022) found that patients who reported financial burden were younger and more likely to have incomes less than $60,000 USD. In another study Black patients and patients in areas of higher disadvantage had lower odds of enrollment, highlighting the confounding effects of systemic issues and socioeconomic status (Caston et al. 2022).

Two studies, however, found that racial minorities either were no more likely to report financial burden or were less likely to report financial burden than non-Hispanic White patients. Using the Health Information National Trends Survey of U.S. adults, 55 percent of respondents reported at least one cost-related factor that would influence their willingness to participate in a clinical trial (C. Williams et al.

2023). Patients who were "not living comfortably on their current income" were more likely to report a cost-related factor that would influence trial participation, but there was no association with reported annual household income. In this survey, younger age, non-Hispanic White race, and higher education levels were associated with increased reporting of cost-related factors influencing trial enrollment. Among patients with cancer who were enrolled in clinical trials and referred for financial assistance, 57 percent reported financial burden and 41 percent reported cost concerns (Perni et al. 2022). Patients with lower income were more likely to report both financial burden and cost concerns, and there were no significant differences by other sociodemographic or clinical factors (such as sex, race, type of insurance, trial type, or trial phase).

Patients in rural areas or those living farther from the clinic commonly reported financial barriers. In a survey of rural patients with cancer in West Virginia, 53 percent listed monetary burden and 36 percent listed commute as strongly influential factors in their decision to participate in a clinical trial (Virani et al. 2011). Among the approximately 5,500 survey respondents in a survey about factors associated with clinical trial participation, lower income and longer distance to the clinic were both statistically significantly associated with lower rates of clinical trial participation, and lower income patients reported more concerns about how to pay for clinical trials (Unger et al. 2013). In a separate survey of about 1,300 breast, colon, and lung cancer patients at eight Southwest Oncology Group clinical sites, annual household income less than $50,000 was associated with a 32 percent lower odds of clinical trial participation (Unger et al. 2016). The association between income and trial participation was magnified among two subgroups in this study: those living more than 13 miles from the clinic and women, who had significantly lower odds of trial participation (43 percent lower and 36 percent lower, respectively).

Non-financial barriers

Non-financial barriers identified in the literature included lack of patient or provider knowledge about clinical trials, mistrust, complexity of protocol requirements and exclusions, lack of invitation or encouragement from providers to participate, logistical barriers (including the ability to take time off of work, travel, and caregiving coverage), and individual patient factors (Chino & Zafar 2019; Nipp et al. 2019b; Paidipati et al. 2022). These individual level barriers to clinical trial participation include fear of adverse effects, mistrust in science, cultural or religious beliefs, and poor health literacy (Duma et al. 2017, Rocque et al. 2022). These findings were consistent with findings from a survey of 1,256 patients assessing demographic factors and attitudinal barriers that found that the most significant barriers were fear of side-effects, worry about health insurance, and efficacy concerns (Manne et al. 2015). Below we summarize the findings on non-financial barriers in the literature and review any instances in which non-financial barriers might differ for underrepresented groups.

Two studies suggested that lack of information on available clinical trials were barriers for rural patients and racial and ethnic minorities. In a study focusing on barriers to rural patients' access to clinical trials only 19.6 percent of rural patients surveyed reported that their health care teams discussed clinical trials with them. Among those who did discuss clinical trials with their care team, 59.8 percent said their decision not to participate in a clinical trial was strongly influenced by discouragement from their oncologist, and 49.4 percent cited discouragement from a family physician. Monetary burden, the commute, and lack of information were also cited as highly influential factors in deciding to participate in

a clinical trial (Virani et al. 2011). Hamel et al. (2016) also cited medical staff's awareness of trial availability as a barrier to participation for racial and ethnic minorities with cancer.

Although there was some mixed evidence, studies generally found that racial minorities and rural patients are no less likely to be willing to participate in clinical trials. Using a linkage of patient-reported outcomes, electronic health records, and clinical trial data, Caston et al. (2022) evaluated the association between underrepresented patient populations and clinical trial eligibility, interest, and enrollment for patients with breast or ovarian cancer. After adjusting for age, cancer type, insurance type, living in a rural area, and their zip code's Area Deprivation Index, Black patients had similar odds of trial eligibility but lower odds of interest (odds ratio [OR]=0.40; 95 percent confidence interval [CI]: 0.18, 0.90) and enrollment (OR=0.56; 95 percent CI: 0.32, 0.98) in clinical trials as compared to White patients. Clinical trial eligibility, interest, and enrollment did not differ for rural versus urban patients. Patients living in areas of high neighborhood disadvantage, as measured by the area deprivation index (ADI) had lower odds of enrolling in clinical trials than those in areas of lower ADI (OR=0.46; 95 percent CI=0.24, 0.89). Similar results were found using data from the Health Information National Trends Survey in 2020, where Williams et al. (2021) detailed the association between history of clinical trial participation and age, race/ethnicity, rural versus urban residence, insurance coverage, and health status. In a multivariate regression, Non-Hispanic Black patients were more likely to be invited to join a trial (OR=1.85; 95 percent CI=1.13, 3.02), but less likely to participate in the trial than non-Hispanic White patients (OR=0.28; 95 percent CI=0.09, 0.87). Rural residents were less likely to be invited to join a trial compared to urban residents (OR=0.33; 95 percent CI=0.17, 0.65). However, one study cited by Hamel et al. (2016) suggested that overall, individuals from minority populations are as likely as White individuals to consent to participate if they are offered a clinical trial. Further, in the National Academies of Sciences, Engineering, and Medicine's 2022 report on "Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups", the literature on willingness to participate generally indicated that racial minorities and those in rural areas were no less likely to be willing to participate if asked (NASEM 2022). Some key papers in this report include Langford et al.'s (2014) review of National Cancer Centers Program data, which found that there were no differences in willingness to participate in trials for Asian, Black, and Hispanic Americans as compared with White Americans. Those living in rural areas were also no less likely to be willing to participate in a large study in Arkansas of more than 5,000 individuals (McElfish et al. 2018) and in a small study across several southern states and Puerto Rico (Thetford et al. 2021). In general, most studies did not find differences in willingness to participate in trials for underrepresented groups. One of the two studies with differing results was fielded in one southern state (Caston et al. 2022), and the other was fielded at the beginning of the COVID-19 pandemic (Williams et al 2021), limiting their generalizability.

Availability and proximity of clinical trials were noted as barriers to enrollment that particularly affected under-resourced and rural communities. In a qualitative study of low-income, multiethnic patients with cancer, despite financial reimbursement from the Lazarex Cancer Foundation for expenses associated with trial participation, patients reported significant barriers related to the time commitment required for trial participation, as well as indirect costs such as lodging and travel (Medina et al. 2023). There were a number of studies focusing on barriers to clinical trial participation for rural individuals. In a study of patients enrolled in clinic trials between 1993 and 2014 at the University of California San Francisco the researchers found that patients from lower-income areas (n=5,799) traveled longer

distances than patients from higher-income areas (n=5,773; 58.3 vs. 17.8 miles, respectively; $p < .001$) (Borno et al. 2018). The same study also found that White patients (83 percent) traveled longer distances than Black patients (4.4 percent), with median distances of 29.9 and 13.9 miles, respectively ($p < .001$); however, the study cited California's demographic mix in rural areas as the likely main factor in travel distance disparity, as rural areas of the state have a greater number of White residents. In tandem with individual proximity to clinical trials, availability of clinical trials was also cited as a barrier to participation. In addition, Hamel et al. (2016) created a multilevel model to analyze disparities in clinical trials at the system, individual, and interpersonal level. Using their model, the team reported a limited number of trials available both nationally and regionally, as well as inadequate hospital infrastructures and resources to participate in clinical research. These factors were found to disproportionately affect enrollment for minority populations who are more likely to receive their care at under-resourced hospital systems.

Complexity of clinical trial protocols present particular barriers for older adults. Duma et al. (2017) found that because of the aggressive therapies involved in most clinical trials, elderly patients may be unwilling to accept the additional treatment toxicity which may not be aligned with their care goals. Duma and colleagues also mentioned that older adults are more likely to have comorbidities that may make them ineligible for trial participation. In a study conducted by BrintzenhofeSzoc et al. (2022) using focus group interviews of older adults who were patient representatives for the National Cancer Institute's Community Oncology Research Program, other barriers to enrollment included complex consent forms, not being referred to trials, patient costs, cultural insensitivity, limited accessibility in community setting and transportation issues.

There is some evidence that Black and Hispanic patients are more likely to report logistical barriers to clinical trial participation, such as difficulty being able to secure time off work or obtaining childcare. Qualitative research among Black and Hispanic patients found that in addition to barriers such as trust, logistical barriers such as time conflicts and childcare responsibilities were important factors that precluded participation in research (Calderon et al. 2006).

Several studies found that underrepresented racial and ethnic minorities and rural patients were less likely to meet trial eligibility criteria because of more advanced disease, worse health status, or potentially implicit bias. In an asthma trial, patients from underrepresented racial and ethnic groups were less likely to meet the inclusion criteria of adequate response to the methacholine challenge (Hardie et al. 2010). The authors indicated that the cutoff for adequate response did not account for known differences in methacholine responsiveness for racial and ethnic minorities, indicating a need to account for disparities in exclusion criteria in trial design. Several other studies indicated that racial minorities may not meet eligibility criteria because of more advanced disease or delayed diagnoses, which may be driven by lower rates of cancer screening and confounded by socioeconomic differences (Giuliano et al. 1998; Ward et al. 2004; King et al. 2011). Later stage at diagnosis, which may preclude eligibility, was more common among rural patients (Virani et al. 2011). A pair of companion papers looking at enrollment of pediatric patients in a bronchiolitis trial found that Hispanic patients were less likely to be deemed 'appropriate' with vague justifications for their ineligibility (Coon et al. 2022; Popkin et al. 2022).

Topic 4: Impact of COVID-19 and clinical trial innovations on costs to patients and barriers

Key Topic 4 findings

- More information is needed on the impact of COVID-19 on costs to patients, routine care coverage, and barriers to clinical trial enrollment.
- The impact of clinical trial innovations such as remote monitoring and decentralized trials on barriers to trial enrollment was mixed. Patients reported reduced travel costs and time commitment, but remote monitoring presented some technological challenges for patients, particularly older or low-income patients without reliable internet access.

We did not identify any studies that estimated the impact of COVID-19 on costs to patients directly. Instead, we identified several studies highlighting the lessons learned from the COVID-19 pandemic more broadly and summarized the resulting clinical trial innovations necessary to continue trials during the pandemic**.** These articles also briefly touched on the impact of COVID-19 or clinical trial innovations on barriers to clinical trial participation. Exhibit III.5 lists the articles that mention either the impact of COVID-19 on barriers to clinical trial participation or detail the clinical trial innovations that occurred during the COVID-19 pandemic. After Exhibit III.5 we highlight some of the findings from these articles.

Exhibit III.5. Summary of articles discussing the impact of COVID-19 on barriers to clinical trials or clinical trial innovations

Authors	Clinical trial innovations discussed in article				
	Decentralized trials	Digital data collection	Home visits	Relaxing follow-up time frame	Remote recruitment or visits
Brody et al. 2022					Remote survey data collection
Ejem et al. 2023					Social media recruitment, telephone visits
MacLennan et al. 2023	Cell phone applications, Telehealth	Digital consent, Electronic/digital data collection devices	Home study visits		Telemedicine study visits
Masoli et al. 2021	Trials@Home Initiative[a]	Digital consent			Telephone follow-up
Murphy et al. 2023					Social media recruitment
Raciborski et al. 2023					Telemedicine study visits
Sehrawat et al. 2023	Remote visits/monitoring and digital health technology	Digital consent; Digital health technology-motion and gait sensors, smartwatches; Digital data collection			Remote interviews

Authors	Clinical trial innovations discussed in article				
	Decentralized trials	Digital data collection	Home visits	Relaxing follow-up time frame	Remote recruitment or visits
Tan et al. 2020	Virtual or remote study locations	Digital health technology- wearable technology, digital biomarkers			Telemedicine study visits
M. Williams et al. 2023				Relaxed protocol for timing of study visits	

[a] Trials@Home- Centre of Excellence Remote and Decentralised Clinical Trials. Available from: https://trialsathome.com/

Transition to remote clinical trial recruitment and care delivery generally benefited patients but presented technology challenges. Sehrawat et al. (2023) provided an overview of opportunities for clinical trial innovations and decentralization in light of the COVID-19 pandemic. Some of these innovations include data advances in electronic health record and digital health technology systems, as well as real-time querying of patient data. Other approaches that might reduce nonfinancial barriers such as travel and time off work for clinical trial participants include conducting electronic informed consent and remote monitoring. The authors suggest, however, that technology requirements, such as internet access and familiarity with software for virtual visits, and privacy concerns might pose challenges. Tan et al. (2020) also detailed the benefits and challenges associated with some necessary adaptations to oncology clinical trials in light of COVID-19. These adaptations include decentralization efforts such as using remote study visits, remote treatment delivery, and the leveraging patient's local laboratory and imaging facilities. These adaptations could improve patient's financial and travel burdens. We found one study, a survey of clinical trial sites, which indicates that uptake of clinical trial innovations and decentralized trials was widespread during the COVID-19 pandemic with around 80 percent of sites were offering remote study visits (MacLennan et al. 2023).

In a survey with patients and caregivers in the United Kingdom on remote delivery of clinical trials in the beginning of the COVID-19 pandemic, researchers found that patients reported fewer financial and nonfinancial barriers related to "the required time commitment, need for childcare, and travel and parking expenses" (Masoli et al. 2021). Yet, patients also reported concerns about using remote technology and feeling less supported. In a behavioral health trial that occurred during the COVID-19 pandemic, telehealth delivery of behavioral interventions was more cost-effective for trial sponsors in terms of reduced costs to recruit participants, and the authors observed no differences in participation rates for those in receiving telehealth versus in-person behavioral sessions (Murphy et al. 2023). A behavioral health trial for veterans during COVID-19 also found that telehealth delivery was more cost-effective than in-person delivery, and there was also some evidence that telehealth delivery increased participation in the behavioral health intervention (Raciborski et al. 2023). The literature did suggest some challenges associated with transition to remote trial delivery. Brody et al. (2022) detailed the impact of transitioning to remote processes on a palliative care trial focused on enrolling Hispanic patients and found that remote delivery presented challenges for patients without internet access or who were uncomfortable with new technology.

Other studies highlighted the success of using remote recruitment tools such as social media to enroll patients during the COVID-19 pandemic. A randomized control trial focused on enrolling older adults in Canada during the COVID-19 pandemic compared recruitment rates across a mail campaign, newspaper advertising, and Facebook outreach and found that Facebook outreach had the best efficacy (Murphy et al. 2023). A study recruiting breast cancer survivors at two US clinic sites found similar success with social media-based recruitment during the COVID-19 pandemic (Ejem et al. 2023). The authors found that participants recruited via Facebook were generally similar in terms of sociodemographic characteristics to those recruited in the clinic sites, but those recruited via Facebook were slightly more likely to have an annual income over $40,000 (83 versus 71 percent; p-value=0.02).

VI. Discussion and Conclusions

To inform our understanding of the costs and barriers that patients might face when participating in a clinical trial, as well as the impact of COVID-19 on those costs and barriers, we gathered related literature for this environmental scan. Our findings are listed in Exhibit VI.I. One key finding was that Black and Hispanic patients, patients over age 65, and rural patients have lower clinical trial participation, which might be driven in part by lower socioeconomic status. Below we summarize the literature that suggests strategies to address barriers to clinical trial enrollment.

Some strategies in the literature that may help address some key barriers to clinical trial enrollment include nurse navigators and decentralized approaches to trials. The use of decentralized or remote trials may help to reduce barriers to enrollment like travel and time commitment (Raciborski et al. 2023, Sehrawat et al. 2023). A study at the University of Southern California found that nurse navigators increased the recruitment rate of Black patients with breast cancer into clinical trials and enrolled 86 percent of eligible patients into clinical trials (Holmes et al. 2012). Guerra et al. (2022) wrote a commentary article on approaches to advance equity in cancer clinical trials. Some of these approaches include the use of patient or nurse navigators to increase understanding of trial benefits and provide decision-making support. The authors also stressed the need for financial and social needs assistance to cover out-of-pocket trial expenses like transportation. Duke Cancer Institute's Health Disparities & Equity Program implemented a patient navigator program to help patients through both routine cancer care and a Community Health Ambassador Program to promote awareness about clinical trial opportunities (Barrett et al. 2016).

Several studies argued that financial support or reimbursement during trials may help to overcome financial barriers and improve representation (Unger and Fleury 2019, Largent and Lynch 2018, Winkfield 2020). In a nationally representative survey of US adults, Hispanic respondents requested higher amounts of compensation to participate in clinical research than non-Hispanic White or Black respondents (Walter et al. 2013). The authors found that a payment of approximately $350 would yield proportional representation, or willingness to participate, in clinical research. A cancer prevention trial increased the proportion of Black participants from 27.2 percent to 31.5 percent, and the number of total recruits for the trial at sites that received Minority Recruitment Enhancement Grants (MREGs) (Cook et al. 2010). The MREGs were $50,000 grants to trial sites that funded salary support for a minority outreach coordinator, reimbursement for parking and gas for participants, and other recruitment materials. A financial reimbursement program focused on increasing the number and diversity of participants at a cancer clinical trial site in Dallas, Texas (Gerber et al. 2022). The reimbursement program, funded by Lazarex Cancer Foundation, provided funding to patients for non-clinical costs associated with trial participant, including travel and lodging, for patients with household incomes up to 700 percent of the Federal poverty rate. Financial support will be up to $1,500 per month for patients at 400 percent of the Federal poverty rate, up to $1,125 per month for patients between 401 and 550 percent of the Federal poverty rate, and up to $750 per month for patients between 551 and 700 percent of the Federal poverty rate. Another financial reimbursement program funded by the Lazarex Cancer Foundation at two cancer centers in California found that implementing the reimbursement program was feasible at a comprehensive cancer center; however, there was no evidence of improved clinical trial enrollment rates for those receiving reimbursement. The biggest barrier to clinical trial enrollment reported in the study

was ineligibility due to screening procedures (Borno et al. 2022b). Finally, an open-label, phase IV trial among Black and Hispanic patients with multiple sclerosis was specifically designed to promote retention and decrease burden by providing reimbursement for childcare, transportation, earnings loss, and travel and by providing more flexibility in visit windows (Williams et al. 2023).

In Exhibit IV.1, we summarize the topic areas for the environmental scan and the key findings for each topic. We also detail the areas where there are gaps in the literature. Based on these findings, topics for future work could include the following (additional detail offered in the right column of Exhibit IV.1):

- Estimates of direct and indirect costs to patients, including out-of-pocket medical spending, travel costs, and lost work productivity, in by trial phase and type.
- Patient's experience with insurance coverage during the clinical trial, including instances of denied coverage for clinical trial monitoring tests or clinical trial sites that were out-of-network or types of care that were not considered 'routine care costs' during the trial.
- The impact of eligibility barriers on clinical trial participation and approaches to adapt trial inclusion and exclusion criteria to reduce eligibility barriers for underrepresented groups.
- Patient's experience and comfort-level with remote monitoring, telehealth, or other remote technology.

Exhibit IV.1. Environmental scan findings by topic area

Topic	Key Findings	Gaps in Literature	Questions for Further Exploration
Types and estimates of direct and indirect costs to patients in clinical trials	• Direct costs include coinsurance, copays, deductibles, medication costs, and general out-of-pocket spending, with mixed evidence on whether patients enrolled in clinical trials have more out-of-pocket medical costs. • Travel costs ranged from $200 to $1,000 per month prior to the COVID-19 pandemic. • Other indirect costs include travel meals, dependent care, missed work or lost wages, and companion costs. • Research supports collecting patient-reported financial toxicity, but uptake in clinical trials is slow.	• Few studies quantified differences in direct costs for patients enrolled and not enrolled in clinical trials. • Most studies on direct and indirect costs focused on patients with cancer. • Indirect costs in the literature focused mainly on travel costs.[4] • No papers quantified the impact of COVID-19-related modifications (remote monitoring, decentralized trials, and so on) on direct or indirect costs. • Lost wages may represent a significant cost to patients, but few studies quantified them.	• What are the out-of-pocket medical costs related to clinical trial participation (coinsurance, copays, deductibles, etc.…)? • What are the out-of-pocket non-medical costs related to clinical trial participation (transportation, lodging, childcare, etc.…)? • How does clinical trial participation impact lost work productivity?

[4] See Exhibit III.2 for a breakdown of the different types of costs covered in the literature and the number of articles that discuss each type of cost.

Topic	Key Findings	Gaps in Literature	Questions for Further Exploration
Impact of policies requiring that payers cover "routine care costs" during clinical trials and costs covered by payers as "routine care"	• Coverage for routine care varied by payer and state over the last 20 years with Medicaid being the last to adopt coverage in all states. • Payers can still deny coverage for trials at out-of-network sites. • The financial burden of direct costs like coinsurance is not addressed by routine care policies.	• There is limited information on what costs are considered routine care by payer. • There are few studies on the impact of routine care policies and those that do show mixed effects on trial participation. • No articles discussed the impact of COVID-19 or clinical trial innovations on routine care costs	• What medical costs related to clinical trial participation are not covered by insurance or the trial? • To what extent do insurers deny coverage of certain medical procedures or test during clinical trials? • To what extent do insurers consider any of the trial providers or clinical sites to be out-of-network?
Impact of financial and nonfinancial barriers on clinical trial participation among historically underrepresented groups	• Socioeconomic factors (including education level, age, employment status, income level, and insurance status) contribute to observed disparities and present a significant barrier to trial participation, especially for Black and Hispanic patients, patients older than age 65, and rural patients. Nonfinancial barriers include patient awareness, encouragement from providers to participate, regional availability, and ineligibility, including due to age and health status.	• More information on the impact of COVID-19 on barriers to clinical trial enrollment is needed. • No findings for barriers for pregnant and lactating people, LGBTQIA+ populations, or people with disabilities.	• What are eligibility barriers for patients interested in participating in trials and to what extent they differ for underrepresented groups? • What are the barriers to trial participation for other underrepresented groups, such as pregnant and lactating people, LGBTQIA+ populations, or people with disabilities? • How does availability of clinical trials impact patients in rural areas? • Are there differences in direct and indirect costs for underrepresented groups?
Effect of the COVID-19 and clinical trial innovations like remote monitoring on costs to patients, diversity of trial participants, and barriers to trial participation	• Some patients reported benefits from remote study visits like reduced time commitment and travel costs (qualitative findings only). • Remote study visits presented some technological challenges for patients and could disadvantage older or low-income patients without reliable internet access.	• There were no cost estimates on the impact of remote study visits or other decentralized trial elements on indirect costs like travel. • There was limited information on the effects of the following innovations on costs, diversity, and barriers to participation: cost reimbursement, home visits and relaxed follow-up timeframes.	• What is the uptake of remote study visits or use of offsite facilities, like local laboratory or medical office for tests or visits, in clinical trials? • What is the impact of remote study visits or other clinical trial innovations have on travel costs and financial burden associated with participating in the trial? • Are there challenges for patients associated with telehealth technology during trials?

Our environmental scan concludes that there is limited research that quantifies direct or indirect costs to patients during clinical trials and no studies on the impact of the COVID-19 pandemic or clinical trial innovations on these costs. Among the available literature, travel costs and patient-reported financial toxicity are most often studied, and much of the literature focused on cancer clinical trials. There were also limited findings on what type of care is considered routine care by insurers during the course of a clinical trial and limited findings on the impacts of COVID-19 on this coverage or associated costs. However, we did find evidence that routine care coverage policies did not address other insurance-related barriers to clinical trial participation like clinical trial sites being considered out-of-network. Finally, we found literature that indicates that Black and Hispanic patients, patients over age 65, and rural patients are less likely to participate in clinical trials. Because differences in socioeconomic factors, like education level, income, and insurance type, may be an underlying cause of these disparities, addressing the cost of participating in clinical trials might have a downstream effect of improving clinical trial participation among these groups. Further information on estimates of direct and indirect costs to patients by clinical trial type (phase and disease) and on differences for underrepresented groups is needed, including among people with disabilities and older adults. Research to estimate the impact of certain clinical trial innovations like the shift to remote monitoring prompted by the COVID-19 pandemic on these costs could inform whether increased uptake of a decentralized trial approach could address financial and nonfinancial barriers to clinical trial participation.

References

Allen, J., Bergman, K., Bruinooge, S., Davis, A., Downs, C. G., Ferris, A., Fleury, M., Fredette, P., Hirsch, B., Hofacker, J., Lichtenfeld, L., Lubejko, B., Massett, H., McKee, A., Michaels, M., Minasian, L., Patrick-Lake, B., Purvis, J., & Puckrein, G. A. (2018). *Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report*. https://www.fightcancer.org/sites/default/files/Nationalpercent20Documents/Clinical-Trials-Landscape-Report.pdf

Andring, L. M., Corrigan, K. L., Rooney, M., Bailard, N., Domingo, M., Fellman, B., Varkey, J., Foster-Mills, T., Kazantsev, T., Lin, L., Jhingran, A., Colbert, L., Eifel, P., Klopp, A. H., & Joyner, M. (2023). Patient Reported Outcomes for Women Undergoing Definitive Chemoradiation for Gynecologic Cancer: A Prospective Clinical Trial. *Practical Radiation Oncology*, S1879-8500(23)00224-2. https://doi.org/10.1016/j.prro.2023.07.004

Bangs, R., & Crispino, T. (2019). From the other side: The patient perspective on cancer clinical trials. *Urologic Oncology*, *37*(5), 331–335. https://doi.org/10.1016/j.urolonc.2018.01.003

Barrett, N. J., Hawkins, T. V., Wilder, J., Ingraham, K. L., Worthy, V., Boyce, X., Reyes, R., Chirinos, M., Wigfall, P., Robinson, W., & Patierno, S. R. (2016). Implementation of a Health Disparities & Equity Program at the Duke Cancer Institute. *Oncology Issues*, *31*(5), 48–57. https://doi.org/10.1080/10463356.2016.11884124

Bierer, B. E., White, S. A., Gelinas, L., & Strauss, D. H. (2021). Fair payment and just benefits to enhance diversity in clinical research. *Journal of Clinical and Translational Science*, *5*(1), e159. https://doi.org/10.1017/cts.2021.816

Blinder, V. S., Deal, A. M., Ginos, B., Jansen, J., Dueck, A. C., Mazza, G. L., Henson, S., Carr, P., Rogak, L. J., Weiss, A., Rapperport, A., Jonsson, M., Spears, P. A., Cella, D., Gany, F., Schrag, D., & Basch, E. (2023). Financial Toxicity Monitoring in a Randomized Controlled Trial of Patient-Reported Outcomes During Cancer Treatment (Alliance AFT-39). *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *41*(29), 4652–4663. https://doi.org/10.1200/JCO.22.02834

Bodurtha Smith, A. J., Pena, D., & Ko, E. (2022). Insurance-Mediated Disparities in Gynecologic Oncology Care. *Obstetrics and Gynecology*, *139*(2), 305–312. https://doi.org/10.1097/AOG.0000000000004643

Borno, H. T., Zhang, L., Siegel, A., Chang, E., & Ryan, C. J. (2018). At What Cost to Clinical Trial Enrollment? A Retrospective Study of Patient Travel Burden in Cancer Clinical Trials. *The Oncologist*, *23*(10), 1242–1249. https://doi.org/10.1634/theoncologist.2017-0628

Borno, H. T., Zhang, L., Zhang, S., Lin, T. K., Skafel, A., Nieves, E., Dornsife, D., Johnson, R., Rhoads, K., Small, E., & Spicer, D. (2022). Implementation of a Multisite Financial Reimbursement Program in Cancer Clinical Trials Integrated With Patient Navigation: A Pilot Randomized Clinical Trial. *JCO Oncology Practice*, *18*(6), e915–e924. https://doi.org/10.1200/OP.21.00328

Borno, H. T., Zhang, S., Lin, T. K., Zhang, L., Palmer, N. R., Nguyen, C., Kaplan, C., & Ryan, C. J. (2022). Evaluating the impact of financial toxicity among cancer clinical trial participants. *International Journal of Cancer Care and Delivery*, *2*(1). https://doi.org/10.53876/001c.30796

BrintzenhofeSzoc, K., Canin, B., Casas-Silva, E., Denicoff, A., Braun-Inglis, C., Okado, I., & Bakos, A. (2022). Through the Lens of Patient Partners: Challenges in Accrual of Older Adults to NCI Clinical Trials. *Journal of the National Cancer Institute. Monographs*, *2022*(60), 125–134. https://doi.org/10.1093/jncimonographs/lgac022

Brody, A. A., Convery, K. A., Kline, D. M., Fink, R. M., & Fischer, S. M. (2022). Transitioning to Remote Recruitment and Intervention: A Tale of Two Palliative Care Research Studies Enrolling Underserved Populations During COVID-19. *Journal of Pain and Symptom Management*, *63*(1), 151–159. https://doi.org/10.1016/j.jpainsymman.2021.06.017

Calderón, J. L., Baker, R. S., Fabrega, H., Conde, J. G., Hays, R. D., Fleming, E., & Norris, K. (2006). An Ethno-medical Perspective on Research Participation: A Qualitative Pilot Study. Medscape General Medicine, 8(2), 23.

Caston, N. E., Lalor, F., Wall, J., Sussell, J., Patel, S., Williams, C. P., Azuero, A., Arend, R., Liang, M. I., & Rocque, G. B. (2022). Ineligible, Unaware, or Uninterested? Associations Between Underrepresented Patient Populations and Retention in the Pathway to Cancer Clinical Trial Enrollment. *JCO Oncology Practice*, *18*(11), e1854–e1865. https://doi.org/10.1200/OP.22.00359

Chino, F., Peppercorn, J. M., Rushing, C., Kamal, A. H., Altomare, I., Samsa, G., & Zafar, S. Y. (2017). Out-of-Pocket Costs, Financial Distress, and Underinsurance in Cancer Care. *JAMA Oncology*, *3*(11), 1582–1584. https://doi.org/10.1001/jamaoncol.2017.2148

Chino, F., Peppercorn, J. M., Rushing, C., Nicolla, J., Kamal, A. H., Altomare, I., Samsa, G., & Zafar, S. Y. (2018). Going for Broke: A Longitudinal Study of Patient-Reported Financial Sacrifice in Cancer Care. *Journal of Oncology Practice*. https://doi.org/10.1200/JOP.18.00112

Chino, F., & Zafar, S. Y. (2019). Financial Toxicity and Equitable Access to Clinical Trials. *American Society of Clinical Oncology Educational Book*, *39*, 11–18. https://doi.org/10.1200/EDBK_100019

Cook, E. D., Arnold, K. B., Hermos, J. A., McCaskill-Stevens, W., Moody-Thomas, S., Probstfield, J. L., Hamilton, S. J., Campbell, R. D., Anderson, K. B., & Minasian, L. M. (2010). Impact of supplemental site grants to increase African American accrual for the Selenium and Vitamin E Cancer Prevention Trial. *Clinical Trials (London, England)*, *7*(1), 90–99. https://doi.org/10.1177/1740774509357227

Coon, E. R., Schroeder, A. R., Lion, K. C., & Ray, K. N. (2022). Disparities by Ethnicity in Enrollment of a Clinical Trial. Pediatrics, 149(2), e2021052595. https://doi.org/10.1542/peds.2021-052595

de Souza, J. A., Yap, B. J., Wroblewski, K., Blinder, V., Araújo, F. S., Hlubocky, F. J., Nicholas, L. H., O'Connor, J. M., Brockstein, B., Ratain, M. J., Daugherty, C. K., & Cella, D. (2017). Measuring financial toxicity as a clinically relevant patient-reported outcome: The validation of the COmprehensive Score for financial Toxicity (COST). *Cancer*, *123*(3), 476–484. https://doi.org/10.1002/cncr.30369

Duma, N., Aguilera, J. V., Paludo, J., Haddox, C. L., Velez, M. G., Wang, Y., Leventakos, K., Hubbard, J. M., Mansfield, A. S., Go, R. S., & Adjei, A. A. (2017). Representation of Minorities and Women in Oncology Clinical Trials: Review of the Past 14 Years. *Journal of Oncology Practice*. https://doi.org/10.1200/JOP.2017.025288

Ejem, D. B., Wechsler, S., Gallups, S., Khalidi, S., Coffee-Dunning, J., Montgomery, A. P., Stevens, C. J., Keene, K., Rocque, G. B., Chamberlin, M., Hegel, M. T., Azuero, A., Pisu, M., Ellis, D., Ingram, S. A., Lawhon, V. M., Gilbert, T., Morrissette, K., Morency, J., … Lyons, K. D. (2023). Enhancing Efficiency and Reach Using Facebook to Recruit Breast Cancer Survivors for a Telephone-Based Supportive Care Randomized Trial During the COVID-19 Pandemic. *JCO Oncology Practice*, *19*(11), 1020–1030. https://doi.org/10.1200/OP.23.00117

Ellis, S. D., Carpenter, W. R., Minasian, L. M., & Weiner, B. J. (2012). Effect of state-mandated insurance coverage on accrual to community cancer clinical trials. *Contemporary Clinical Trials*, *33*(5), 933–941. https://doi.org/10.1016/j.cct.2012.06.001

Gafford, J. A., Gurley-Calvez, T., Krebill, H., Lai, S. M., Christiadi, & Doolittle, G. C. (2017). Expanding Local Cancer Clinical Trial Options: Analysis of the Economic Impact of the Midwest Cancer Alliance in Kansas. *Academic Medicine*, *92*(9), 1274–1279. https://doi.org/10.1097/ACM.0000000000001612

Gerber, D. E., Lakoduk, A. M., Priddy, L. L., Yan, J., & Xie, X.-J. (2015). Temporal Trends and Predictors for Cancer Clinical Trial Availability for Medically Underserved Populations. *The Oncologist*, *20*(6), 674–682. https://doi.org/10.1634/theoncologist.2015-0083

Gerber, D. E., Tiro, J. A., McNeill, L. H., Williams, E. L., Zhu, H., Lee, S. J. C., Leavey, P. J., Sadeghi, N., Kapinos, K. A., Dornsife, D. L., Nguyen, V., Wileyto, E. P., & Guerra, C. E. (2022). Enhancing access to and diversity in cancer clinical trials through a financial reimbursement program: Protocol to evaluate a novel program. *Contemporary Clinical Trials*, *121*, 106922. https://doi.org/10.1016/j.cct.2022.106922

Gharzai, L. A., & Jagsi, R. (2023). Incorporating financial toxicity considerations into clinical trial design to facilitate patient-centered decision-making in oncology. *Cancer*, *129*(8), 1143–1148. https://doi.org/10.1002/cncr.34677

Giuliano, A. R., Mokuau, N., Hughes, C., Tortolero-Luna, G., Risendal, B., Ho, R. C. S., Prewitt, T. E., & Mccaskill-Stevens, W. J. (2000). Participation of Minorities in Cancer Research: The Influence of Structural, Cultural, and Linguistic Factors. Annals of Epidemiology, 10(8, Supplement 1), S22–S34. https://doi.org/10.1016/s1047-2797(00)00195-2

Guerra, C. E., Fleury, M. E., Byatt, L. P., Lian, T., & Pierce, L. (2022). Strategies to Advance Equity in Cancer Clinical Trials. *American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Annual Meeting*, *42*, 1–11. https://doi.org/10.1200/EDBK_350565

Hamel, L. M., Penner, L. A., Albrecht, T. L., Heath, E., Gwede, C. K., & Eggly, S. (2016). Barriers to Clinical Trial Enrollment in Racial and Ethnic Minority Patients With Cancer. *Cancer Control: Journal of the Moffitt Cancer Center*, *23*(4), 327–337. https://doi.org/10.1177/107327481602300404

Hardie, G., Liu, R., Darden, J., & Gold, W. M. (2010). Ethnic differences in methacholine responsiveness and word descriptors in African Americans, Hispanic-Mexican Americans, Asian-Pacific Islanders, and Whites with mild asthma. The Journal of Asthma: Official Journal of the Association for the Care of Asthma, 47(4), 388–396. https://doi.org/10.3109/02770903.2010.481341

Holmes, D. R., Major, J., Lyonga, D. E., Alleyne, R. S., & Clayton, S. M. (2012). Increasing minority patient participation in cancer clinical trials using oncology nurse navigation. *American Journal of Surgery*, *203*(4), 415–422. https://doi.org/10.1016/j.amjsurg.2011.02.005

Huey, R. W., George, G. C., Phillips, P., White, R., Fu, S., Janku, F., Karp, D. D., Naing, A., Piha-Paul, S., Subbiah, V., Tsimberidou, A. M., Pant, S., Yap, T. A., Rodon, J., Meric-Bernstam, F., Shih, Y.-C. T., & Hong, D. S. (2021). Patient-Reported Out-of-Pocket Costs and Financial Toxicity During Early-Phase Oncology Clinical Trials. *The Oncologist*, *26*(7), 588–596. https://doi.org/10.1002/onco.13767

Kaasa, S., Bjordal, K., Aaronson, N., Moum, T., Wist, E., Hagen, S., & Kvikstad, A. (1995). The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. *European journal of cancer (Oxford, England : 1990)*, *31A*(13-14), 2260–2263. https://doi.org/10.1016/0959-8049(95)00296-0

Kehl, K. L., Fullmer, C. P., Fu, S., George, G. C., Hess, K. R., Janku, F., Karp, D. D., Kato, S., Kizer, C. K., Kurzrock, R., Naing, A., Pant, S., Piha-Paul, S. A., Subbiah, V., Tsimberidou, A. M., & Hong, D. S. (2017). Insurance Clearance for Early-Phase Oncology Clinical Trials Following the Affordable Care Act. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, *23*(15), 4155–4162. https://doi.org/10.1158/1078-0432.CCR-16-3027

Keilson, J. M., Lindsey, S., Bachini, M., Medin, C. R., Berk, A., Cornew, S., & Maithel, S. K. (2022). Patient reported outcomes: Financial toxicity is a barrier to clinical trials and personalized therapy in cholangiocarcinoma. *Journal of Surgical Oncology*, *126*(6), 1003–1010. https://doi.org/10.1002/jso.27012

Kilgore, M. L., & Goldman, D. P. (2008). Drug costs and out-of-pocket spending in cancer clinical trials. Contemporary Clinical Trials, 29(1), 1–8. https://doi.org/10.1016/j.cct.2007.04.004

King, A. C., Cao, D., Southard, C. C., & Matthews, A. (2011). Racial differences in eligibility and enrollment in a smoking cessation clinical trial. Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association, 30(1), 40–48. https://doi.org/10.1037/a0021649

Kunos, C. A., & Abdallah, R. (2020). Financial Toxicity Encountered in Therapeutic Radiopharmaceutical Clinical Development for Ovarian Cancer. *Pharmaceuticals (Basel, Switzerland)*, *13*(8), 181. https://doi.org/10.3390/ph13080181

Langford, A. T., Resnicow, K., Dimond, E. P., Denicoff, A. M., Germain, D. St., McCaskill-Stevens, W., Enos, R. A., Carrigan, A., Wilkinson, K., & Go, R. S. (2014). Racial/ethnic differences in clinical trial enrollment, refusal rates, ineligibility, and reasons for decline among patients at sites in the National Cancer Institute's Community Cancer Centers Program. Cancer, 120(6), 877–884. https://doi.org/10.1002/cncr.28483

Largent, E. A., Heffernan, K. G., Joffe, S., & Lynch, H. F. (2020). Paying Clinical Trial Participants: Legal Risks and Mitigation Strategies. *Journal of Clinical Oncology*, *38*(6), 532–537. https://doi.org/10.1200/JCO.19.00250

Largent, E. A., & Lynch, H. F. (2018). Addressing Financial Barriers to Enrollment in Clinical Trials. *JAMA Oncology*, *4*(7), 913–914. https://doi.org/10.1001/jamaoncol.2018.0492

Lee, A., Shah, K., & Chino, F. (2020). Assessment of Parking Fees at National Cancer Institute–Designated Cancer Treatment Centers. *JAMA Oncology*, *6*(8), 1295. https://doi.org/10.1001/jamaoncol.2020.1475

Mackay, C. B., Gurley-Calvez, T., Erickson, K. D., & Jensen, R. A. (2016). Clinical trial insurance coverage for cancer patients under the Affordable Care Act. *Contemporary Clinical Trials Communications*, *2*, 69–74. https://doi.org/10.1016/j.conctc.2015.12.002

MacLennan, D. L., Plahovinsak, J. L., MacLennan, R. J., & Jones, C. T. (2023). Clinical Trial Site Perspectives and Practices on Study Participant Diversity and Inclusion. *Clinical Pharmacology & Therapeutics*, *113*(3), 670–679. https://doi.org/10.1002/cpt.2817

Manne, S., Kashy, D., Albrecht, T., Wong, Y.-N., Lederman Flamm, A., Benson, A. B., Miller, S. M., Fleisher, L., Buzaglo, J., Roach, N., Katz, M., Ross, E., Collins, M., Poole, D., Raivitch, S., Miller, D. M., Kinzy, T. G., Liu, T., & Meropol, N. J. (2015). Attitudinal barriers to participation in oncology clinical trials: Factor analysis and correlates of barriers. *European Journal of Cancer Care*, *24*(1), 28–38. https://doi.org/10.1111/ecc.12180

Martin, P. J., Davenport-Ennis, N., Petrelli, N. J., Stewart, F. M., Appelbaum, F. R., & Benson, A. (2014). Responsibility for Costs Associated With Clinical Trials. *Journal of Clinical Oncology*, *32*(30), 3357–3359. https://doi.org/10.1200/JCO.2014.57.1422

Masoli, J. A. H., Down, K., Nestor, G., Hudson, S., O'Brien, J. T., Williamson, J. D., Young, C. A., Carroll, C., & NIHR Remote Trial Delivery Working Group. (2021). A report from the NIHR UK working group on remote trial delivery for the COVID-19 pandemic and beyond. *Trials*, *22*(1), 911. https://doi.org/10.1186/s13063-021-05880-8

McElfish, P. A., Long, C. R., Selig, J. P., Rowland, B., Purvis, R. S., James, L., Holland, A., Felix, H. C., & Narcisse, M. (2018). Health Research Participation, Opportunity, and Willingness Among Minority and Rural Communities of Arkansas. Clinical and Translational Science, 11(5), 487–497. https://doi.org/10.1111/cts.12561

Medina, S. P., Zhang, S., Nieves, E., Dornsife, D. L., Johnson, R., Spicer, D., & Borno, H. T. (2023). Experiences of a Multiethnic Cohort of Patients Enrolled in a Financial Reimbursement Program for Cancer Clinical Trials. *JCO Oncology Practice*, *19*(5), e801–e810. https://doi.org/10.1200/OP.22.00429

Mupfudze, T. G., Preussler, J. M., Sees, J. A., SanCartier, M., Arnold, S. D., & Devine, S. (2021). A Qualitative Analysis of State Medicaid Coverage Benefits for Allogeneic Hematopoietic Cell Transplantation (alloHCT) for Patients with Sickle Cell Disease (SCD). *Transplantation and Cellular Therapy*, *27*(4), 345–351. https://doi.org/10.1016/j.jtct.2021.01.022

Murphy, A. L., Turner, J. P., Rajda, M., Allen, K. G., Pinter, K., & Gardner, D. M. (2023). Effectiveness and cost analysis of methods used to recruit older adult sedative users to a deprescribing randomized controlled trial during the COVID-19 pandemic. *Exploratory Research in Clinical and Social Pharmacy*, *9*, 100214. https://doi.org/10.1016/j.rcsop.2022.100214

National Academies of Sciences, Engineering, and Medicine. 2022. Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups. Washington, DC: The National Academies Press. https://doi.org/10.17226/26479.

Nipp, R. D., Hong, K., & Paskett, E. D. (2019). Overcoming Barriers to Clinical Trial Enrollment. *American Society of Clinical Oncology Educational Book*, *39*, 105–114. https://doi.org/10.1200/EDBK_243729

Nipp, R. D., Lee, H., Gorton, E., Lichtenstein, M., Kuchukhidze, S., Park, E., Chabner, B. A., & Moy, B. (2019). Addressing the Financial Burden of Cancer Clinical Trial Participation: Longitudinal Effects of an Equity Intervention. *The Oncologist*, *24*(8), 1048–1055. https://doi.org/10.1634/theoncologist.2019-0146

Nipp, R. D., Lee, H., Powell, E., Birrer, N. E., Poles, E., Finkelstein, D., Winkfield, K., Percac-Lima, S., Chabner, B., & Moy, B. (2016). Financial Burden of Cancer Clinical Trial Participation and the Impact of a Cancer Care Equity Program. *The Oncologist*, *21*(4), 467–474. https://doi.org/10.1634/theoncologist.2015-0481

Nipp, R. D., Powell, E., Chabner, B., & Moy, B. (2015). Recognizing the Financial Burden of Cancer Patients in Clinical Trials. *The Oncologist*, *20*(6), 572–575. https://doi.org/10.1634/theoncologist.2015-0068

Olivier, T., Haslam, A., & Prasad, V. (2023). Is financial toxicity captured in quality of life assessments in oncology randomized clinical trials? *Journal of Cancer Policy*, *36*, 100423. https://doi.org/10.1016/j.jcpo.2023.100423

Paidipati, C. P., Foxwell, A. M., Mooney-Doyle, K., Tiller, D., Pinto-Martin, J., & Ulrich, C. M. (2023). Caregiver Perspectives on the Benefits, Burdens, and Moral Distress of Participation in Cancer Clinical Trials. *Journal of Family Nursing*, *29*(1), 89–98. https://doi.org/10.1177/10748407221098187

Perni, S., Azoba, C., Gorton, E., Park, E. R., Chabner, B. A., Moy, B., & Nipp, R. D. (2022). Financial Toxicity, Symptom Burden, Illness Perceptions, and Communication Confidence in Cancer Clinical Trial Participants. *JCO Oncology Practice*, *18*(9), e1427–e1437. https://doi.org/10.1200/OP.21.00697

Perni, S., Moy, B., & Nipp, R. D. (2021). Disparities in phase 1 cancer clinical trial enrollment. *Cancer*, *127*(23), 4464–4469. https://doi.org/10.1002/cncr.33853

Pisu, M., Azuero, A., Meneses, K., Burkhardt, J., & McNees, P. (2011). Out of pocket cost comparison between Caucasian and minority breast cancer survivors in the Breast Cancer Education Intervention (BCEI). *Breast Cancer Research and Treatment*, *127*(2), 521–529. https://doi.org/10.1007/s10549-010-1225-0

Popkin, R., Taylor-Zapata, P., & Bianchi, D. W. (2022). Physician Bias and Clinical Trial Participation in Underrepresented Populations. *Pediatrics*, *149*(2), e2021054150. https://doi.org/10.1542/peds.2021-054150

Prasad, R. N., Royce, T. J., Chino, F., Jagsi, R., & Palmer, J. D. (2022). Financial Toxicity as an End Point in Prospective Clinical Trials Involving Radiation Therapy. *Advances in Radiation Oncology*, *7*(6), 100970. https://doi.org/10.1016/j.adro.2022.100970

Raciborski, R. A., Hamerling-Potts, K. K., Mitchell, E. L., Sullivan, S. R., Kapil-Pair, N., Landes, S. J., Jager-Hyman, S., & Goodman, M. (2023). Cost comparison of in-person and telehealth modalities for a suicide safety planning group intervention: Interim results from the "Project Life Force" randomized clinical trial. *Frontiers in Psychiatry*, *14*, 1215247. https://doi.org/10.3389/fpsyt.2023.1215247

Reoma, L. B., & Karp, B. I. (2022). The Human Cost: Patient Contribution to Clinical Trials in Neurology. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics*, *19*(5), 1503–1506. https://doi.org/10.1007/s13311-022-01292-x

Riaz, I. B., Islam, M., Ikram, W., Naqvi, S. A. A., Maqsood, H., Saleem, Y., Riaz, A., Ravi, P., Wang, Z., Hussain, S. A., Warner, J. L., Odedina, F. T., Duma, N., Singh, P., Kehl, K. L., Kamran, S. C., Murad, M. H., Landman, A., Van Allen, E., & Bryce, A. H. (2023). Disparities in the Inclusion of Racial and Ethnic Minority Groups and Older Adults in Prostate Cancer Clinical Trials: A Meta-analysis. *JAMA Oncology*, *9*(2), 180–187. https://doi.org/10.1001/jamaoncol.2022.5511

Rocque, G. B., Andrews, C., Lawhon, V. M., Frazier, R., Ingram, S. A., Smith, M. L., Wagner, L. I., Zubkoff, L., Tung, N., Wallner, L. P., & Wolff, A. C. (2023). Oncologist-Reported Barriers and Facilitators to Enrolling Patients in Optimization Trials That Test Less Intense Cancer Treatment. *JCO Oncology Practice*, *19*(2), e263–e273. https://doi.org/10.1200/OP.22.00472

Sehrawat, O., Noseworthy, P. A., Siontis, K. C., Haddad, T. C., Halamka, J. D., & Liu, H. (2023). Data-Driven and Technology-Enabled Trial Innovations Toward Decentralization of Clinical Trials: Opportunities and Considerations. *Mayo Clinic Proceedings*, *98*(9), 1404–1421. https://doi.org/10.1016/j.mayocp.2023.02.003

Sidana, S., Allmer, C., Larson, M. C., Dueck, A., Yost, K., Warsame, R., Thanarajasingam, G., Cerhan, J. R., Paludo, J., Rajkumar, S. V., Habermann, T. M., Nowakowski, G. S., Lin, Y., Gertz, M. A., Witzig, T., Dispenzieri, A., Gonsalves, W. I., Ansell, S. M., Thompson, C. A., & Kumar, S. K. (2022). Patient Experience in Clinical Trials: Quality of Life, Financial Burden, and Perception of Care in Patients With Multiple Myeloma or Lymphoma Enrolled on Clinical Trials Compared With Standard Care. *JCO Oncology Practice*, *18*(8), e1320–e1333. https://doi.org/10.1200/OP.21.00789

Tan, A. C., Ashley, D. M., & Khasraw, M. (2020). Adapting to a Pandemic—Conducting Oncology Trials during the SARS-CoV-2 Pandemic. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, *26*(13), 3100–3103. https://doi.org/10.1158/1078-0432.CCR-20-1364

Thetford, K., Gillespie, T. W., Kim, Y., Hansen, B., & Scarinci, I. C. (n.d.). Willingness of Latinx and African Americans to Participate in Nontherapeutic Trials: It Depends on Who Runs the Research. Ethnicity & Disease, 31(2), 263–272. https://pubmed.ncbi.nlm.nih.gov/33883867/

Unger, J. M., & Fleury, M. E. (2019). Reimbursing Patients for Participation in Cancer Clinical Trials. *JAMA Oncology*, *5*(7), 932–934. https://doi.org/10.1001/jamaoncol.2019.0141

Unger, J. M., Gralow, J. R., Albain, K. S., Ramsey, S. D., & Hershman, D. L. (2016). Patient Income Level and Cancer Clinical Trial Participation in a Prospective Survey Study. *JAMA Oncology*, *2*(1), 137–139. https://doi.org/10.1001/jamaoncol.2015.3924

Unger, J. M., Hershman, D. L., Albain, K. S., Moinpour, C. M., Petersen, J. A., Burg, K., & Crowley, J. J. (2013). Patient Income Level and Cancer Clinical Trial Participation. *Journal of Clinical Oncology*, *31*(5), 536–542. https://doi.org/10.1200/JCO.2012.45.4553

Unger, J. M., Xiao, H., Vaidya, R., LeBlanc, M., & Hershman, D. L. (2023). Medicaid Expansion of the Patient Protection and Affordable Care Act and Participation of Patients With Medicaid in Cancer Clinical Trials. *JAMA Oncology*, *9*(10), 1371–1379. https://doi.org/10.1001/jamaoncol.2023.2800

Virani, S., Burke, L., Remick, S. C., & Abraham, J. (2011). Barriers to Recruitment of Rural Patients in Cancer Clinical Trials. *Journal of Oncology Practice*, *7*(3), 172–177. https://doi.org/10.1200/JOP.2010.000158

Walter, J. K., Burke, J. F., & Davis, M. M. (2013). Research Participation by Low-Income and Racial/Ethnic Minority Groups: How Payment May Change the Balance. *Clinical and Translational Science*, *6*(5), 363–371. https://doi.org/10.1111/cts.12084

Ward, E., Jemal, A., Cokkinides, V., Singh, G. K., Cardinez, C., Ghafoor, A., & Thun, M. (2004). Cancer disparities by race/ethnicity and socioeconomic status. CA: A Cancer Journal for Clinicians, 54(2), 78–93. https://doi.org/10.3322/canjclin.54.2.78

Williams, C. P., Geiger, A. M., Norton, W. E., de Moor, J. S., & Everson, N. S. (2023). Influence of Cost-Related Considerations on Clinical Trial Participation: Results from the 2020 Health Information National Trends Survey (HINTS). *Journal of General Internal Medicine*, *38*(5), 1200–1206. https://doi.org/10.1007/s11606-022-07801-0

Williams, C. P., Senft Everson, N., Shelburne, N., & Norton, W. E. (2021). Demographic and Health Behavior Factors Associated With Clinical Trial Invitation and Participation in the United States. *JAMA Network Open*, *4*(9), e2127792. https://doi.org/10.1001/jamanetworkopen.2021.27792

Williams, M. J., Okai, A. F., Cross, A. H., Monson, N. L., Vartanian, T., Thrower, B. W., Reder, A. T., English, J. B., Wu, G. F., Bernitsas, E., Yap, S., Ndrio, J., Pei, J., Mowry, E. M., Magrini, F., Acosta, J., & Amezcua, L. (2023). Demographics and baseline disease characteristics of Black and Hispanic patients with multiple sclerosis in the open-label, single-arm, multicenter, phase IV CHIMES trial. *Multiple Sclerosis and Related Disorders*, *76*, 104794. https://doi.org/10.1016/j.msard.2023.104794

Winkfield, K. M. (2020). Improving access to cancer clinical trials by reducing the financial burden. *Cancer*, *126*(1), 14–16. https://doi.org/10.1002/cncr.32523

Winkfield, K. M., Phillips, J. K., Joffe, S., Halpern, M. T., Wollins, D. S., & Moy, B. (2018). Addressing Financial Barriers to Patient Participation in Clinical Trials: ASCO Policy Statement. *Journal of Clinical Oncology*, *36*(33), 3331–3339. https://doi.org/10.1200/JCO.18.01132

Wong, Y.-N., Schluchter, M. D., Albrecht, T. L., Benson, A. B., Buzaglo, J., Collins, M., Flamm, A. L., Fleisher, L., Katz, M., Kinzy, T. G., Liu, T. M., Manne, S., Margevicius, S., Miller, D. M., Miller, S. M., Poole, D., Raivitch, S., Roach, N., Ross, E., & Meropol, N. J. (2016). Financial Concerns About Participation in Clinical Trials Among Patients With Cancer. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *34*(5), 479–487. https://doi.org/10.1200/JCO.2015.63.2463

Appendix A:

Complete Search Strategy

We used the following approaches to identify relevant literature, which we organized in Zotero:

1. **Searched Elton B. Stephens Co. (EBSCO) Academic Search Premier, EBSCO Cumulative Index of Nursing and Allied Health Literature (CINAHL), and PubMed for peer-reviewed journal articles.** We list the search query for each research topic and the initial article count in PubMed as of October 24, 2023, for reference below in Exhibit A.1.

Exhibit A.1. Initial PubMed search result counts, by research topic

Topic Number	Search topic	Search query	Initial article count in PubMed
1	Direct and indirect costs to patients in clinical trials	("financial toxicity" OR "financial burden" OR "cost to patients" OR "direct costs" OR "indirect costs" OR "patient costs" OR "cost to patient" OR "direct cost" OR "indirect cost" OR "patient cost" OR "reduce cost" OR "reduce costs" OR "out-of-pocket" OR "out-of-pocket")) AND ("clinical trial" OR "clinical trials")	1,078
2	Routine care cost policies	Search 1: (payer) OR payor OR Medicaid) OR Medicare or insurance) AND ("clinical trial" OR "clinical trials") AND (cost*) Search 2: "routine care cost" OR "routine care costs""	1,139 17
3	Barriers to clinical trial participation for historically underrepresented groups	((divers*) OR (representation) OR (underrepresent*) OR (minorit*) OR (marginalized) OR (vulnerable) OR (barrier*) OR (Hispanic) OR (Black) OR (Latin*) OR (Asian) OR (female*) OR (womenTitle/Abstract]) OR (child*) OR (pediatric*) OR (race) OR (ethnicit*) OR (disabilit*) OR ("older adults") OR (aging) OR (pregnan*) OR (lactat*) OR ("Health Disparate, Minority and Vulnerable Populations"[Mesh]) OR "Sexual and Gender Minorities"[Mesh]) AND ("financial toxicity" OR "financial burden" OR "cost to patients" OR "direct costs" OR "indirect costs" OR "patient costs" OR "cost to patient" OR "direct cost" OR "indirect cost" OR "patient cost" OR "reduce cost" OR "reduce costs" OR "out-of-pocket" OR "out-of-pocket")) AND ("clinical trial" OR "clinical trials"OR ("Clinical Trials as Topic"[Mesh]))	428
4	Effect of COVID-19 on clinical trial costs to patients	(("COVID-19"[MeSH Terms]) OR ("SARS-CoV-2"[MeSH Terms]) OR (COVID) OR (coronavirus) OR (pandemic) OR (innovat*) OR (remote monitor*) OR (decentral*) OR (reform*)) AND (clinical trial*) AND ("financial toxicity" OR "financial burden" OR "cost to patients" OR "direct costs" OR "indirect costs" OR "patient costs" OR "cost to patient" OR "direct cost" OR "indirect cost" OR "patient cost" OR "reduce cost" OR "reduce costs" OR "out-of-pocket" OR "out-of-pocket" OR (cost))	698

We identified these search terms by reviewing a subset of relevant literature for common terminology. We restricted the search to articles published between 2010 and 2023 for Topics 1, 2, and 3 to focus on findings immediately before and during COVID-19 and between 2020 to 2023 for Topic 4, which focus on the time after the start of the COVID-19 pandemic in 2020. We leveraged Zotero's de-duplicating function to filter to unique articles across the three databases and then restricted further by reviewing abstracts and excluding articles that met the following criteria:

- Focus on countries other than the United States;
- Do not include results either related to costs to patients, "routine care" costs and coverage, barriers to participation for historically underrepresented groups, or clinical trial innovations during COVID-19.

We prioritized the initial screening of articles by relevance of the title and the final review of full text by relevance of the title and abstract. After applying the exclusion criteria, we expected this approach to yielded 29 peer-reviewed articles across the four topics.

1. **Snowball search**: We implemented a forward and backward snowball search using the peer-reviewed articles for all topics identified from the initial database search. This approach yielded an additional 20 peer-reviewed articles across the four topics.
2. **Search resource pages on websites of key organizations**: We conducted focused searches on the websites related to clinical trials and cancer research and advocacy groups for information related costs and barriers associated with clinical trial participation and diversity in clinical trials. Examples include (1) fda.gov with a search for "clinical trial diversity"[5]; (2) nih.gov with a search for "clinical trial diversity"; (3) American Cancer Society with a search for "clinical trial cost", "treatment cost", and "care cost"; (4) National Coalition for Cancer Survivorship with a search for "clinical trial"; (5) Alliance for Clinical Trials in Oncology with a search for "financial toxicity", "treatment cost", and "care cost"; (6) Center for Information and Study on Clinical Research Participation with a search for "clinical trial diversity" and "clinical trial cost", "clinical trial cost"; "treatment cost", and "care cost" (7) Association of Clinical Research Professionals with a search for "clinical trial cost", "treatment cost", and "care cost" ; and (8) National Health Council with a search for "clinical trial cost", "treatment cost", and "care cost." This approach yielded 24 relevant articles across the four topics.
3. **Google Scholar and Google searches to identify additional grey literature**: We conducted broad searches in Google Scholar and in Google to skim for relevant grey literature or data that was not uncovered in previous searches. We applied the same general exclusion criteria to results as in the database searches; however, we did not systematically apply these criteria to each search. Further, the Google searches returned many results and we prioritized those that appeared most relevant by their titles.

For searches in Google Scholar, we used the following search terms and filtered to results since 2010:

- financial toxicity allintitle: clinical trial
- "cost to patients" allintitle: clinical trial
- allintitle: clinical trial diversity
- allintitle: clinical trial underrepresented
- "routine care" policy financial toxicity clinical trials

[5] Note: using "cost" as a search term yields many extraneous results regarding the cost of conducting clinical trials rather than the cost to patients, while using the search term "cost to patients" often yields few results. To minimize the number of extraneous results on extensive websites like fda.gov or nih.gov, we focused on grey literature related to clinical trial participation among historically underrepresented groups and found that the search term "diversity" is commonly used.

- allintitle: cancer patient survey cost

For Google searches, we used the following search terms and filtered to results since 2010:

- clinical trial COVID-19 innovation
- "cost to patients" clinical trials
- routine care cost financial toxicity clinical trial
- cost barriers to clinical trial participation
- clinical trial patient survey cost

This approach yielded 37 relevant articles across the four topics.

Mathematica Inc.

Our employee-owners work nationwide and around the world.

Find us at **mathematica.org** and **edi-global.com**.

Mathematica®
Progress Together