HHS Public Access

Author manuscript

Clin Trials. Author manuscript; available in PMC 2019 October 01.

Published in final edited form as:

Clin Trials. 2018 October ; 15(5): 509–521. doi:10.1177/1740774518792277.

The ethics of uninsured participants accessing healthcare in biomedical research: A literature review

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Abstract

Background/Aims: Sparse literature exists on the challenges and ethical considerations of including people with limited access to healthcare such as the uninsured and low-income in clinical research in high-income countries. However, many ethical issues should be considered with respect to working with uninsured and low-income participants in clinical research, including enrollment and retention, ancillary care, and post-trial responsibilities. Attention to the uninsured and low-income is particularly salient in the U.S. due to the high rates of uninsurance and underinsurance. Thus, we conducted a scoping review on the ethical considerations of biomedical clinical research with uninsured and low-income participants in high-income countries in order to describe what is known and to pinpoint areas of needed research on this issue.

Methods: MEDLINE/PubMed, Embase, and Scopus databases were searched using terms that described main concepts of interest (e.g. uninsured, underinsured, access to healthcare, poverty, ethics, compensation, clinical research). Articles were included if they met four inclusion criteria: (1) English; (2) high-income countries context; (3) about research participants who are uninsured or low-income, which limits their access to healthcare, and in biomedical clinical research that either had a prospect of direct medical benefit or were offered to them on the basis of their ill health; (4) recognizes and/or addresses challenges or ethical considerations of uninsured or low-income participants in biomedical clinical research.

Results: The searches generated a total of 974 results. Ultimately, 23 papers were included in the scoping review. Of 23 articles, the majority (n=19) discussed enrollment and retention of uninsured or low-income participants. Several barriers to enrolling uninsured and low-income groups were identified, including limited access to primary or preventative care; lack of access to institutions conducting trials or physicians with enough time or knowledge about trials; overall lack of trust in the government, research, or medical system; and logistical issues. Considerably fewer articles discussed treatment of these participants during the course of research (n=5) or post-trial responsibilities owed to them (n=4). Thus, we propose a research agenda that builds upon the existing literature by addressing three broad questions: (1) What is the current status of uninsured research participants in biomedical clinical research in high-income countries? (2) How should uninsured research participants be treated during and after clinical research? (3) How, if at all, should additional protections for uninsured research participants affect their enrollment?

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Conclusions: This review reveals significant gaps in both data and thoughtful analysis on how to ethically involve uninsured research participants. To address these gaps, we propose a research agenda to gather needed data and theoretical analysis that addresses three broad research questions.

Keywords

Ethic; clinical research; insurance; income; socioeconomic status; enrollment; post-trial; ancillary care

Introduction

Participation in clinical research can offer individuals with limited access to healthcare an opportunity to receive interventions for conditions that otherwise go untreated; however, these interventions are unproven. Discussions about the ethics of research with participants who lack access to healthcare center almost exclusively on trials in low and middle income countries (LMIC).[1–3] Moreover, existing literature that addresses people who are uninsured or otherwise lack healthcare access in high-income countries (HIC) focuses on community-based and non- therapeutic trials (i.e. educational interventions, natural history studies, survey/questionnaires, etc.).[4–13]

However, research participants in HIC who are uninsured or otherwise lack access to healthcare encounter limitations similar to those faced by participants in LMIC. Thus, their inclusion in research raises often overlooked but parallel ethical considerations.

Attention to including the uninsured in clinical research is particularly salient in the U.S. A significant proportion of the U.S. population (an estimated 8.8% or 28.2 million in 2016) lacks any insurance coverage,[14,15] many more are underinsured,[16] and for the first time since the Affordable Care Act passed in 2010, the uninsurance rate for adults in the U.S. is on the rise.[17] Moreover, a growing amount of data suggests that the uninsured encounter significant barriers in accessing healthcare, perceive discrimination when receiving treatment, and experience poorer health outcomes for both acute and chronic conditions.[18–26]

We conducted a scoping review on the ethical considerations of biomedical clinical research with uninsured and low-income participants in HIC in order to describe what is known and to pinpoint areas of needed research on this issue. Our review revealed that little attention has been paid to ethical issues regarding research participation of uninsured and low-income participants in HIC. Analyses that do address disadvantaged research participants often mention that minority groups are more likely to be uninsured and have low-income, but do not distinguish the effects of socioeconomic status from those of race, ethnicity, linguistic and cultural barriers, historical context, etc.[27–30]

Even when studies explore the challenges and ethical considerations of working with the uninsured, most only discuss issues regarding enrollment and retention, leaving other ethically challenging issues like ancillary and post-trial care relatively neglected. Building

on these results, we propose a research agenda to gather needed data and theoretical analysis, as well as raise attention to uninsured participants in biomedical clinical research.

Methods

Search strategy

A combination of controlled vocabulary terms (i.e., Medical Subject Headings, Emtree) and keywords were searched in the MEDLINE/PubMed, Embase, and Scopus databases on February 2018. Used terms described the main concepts of interest: uninsured, underinsured, access to healthcare, poverty, ethics, compensation, and clinical research (See Appendix A in the online supplementary material for MEDLINE search strategies). The references of eligible papers were also reviewed to identify additional relevant articles.

Selection criteria

We followed PRISMA guidelines for our scoping review (Figure 1). One author (HC) screened the titles and abstracts of results to assess their relevance to the research question. A second author (CG) verified eligibility of the references, including when eligibility was unclear. Articles passed the title/abstract screening if they did not meet any of the exclusion criteria and clearly met at least three of the inclusion criteria. When the eligibility of an article was unclear on only one inclusion criteria, we included the article in the second screening. Two authors (HC and CG) then reviewed the full-text of articles that passed the first screening to confirm that all inclusion criteria were met.

One author (HC) applied the same selection criteria for both the title/abstract and full-text screening for articles in the references of eligible papers from the original MEDLINE/PubMed, Embase, and Scopus databases.

All included articles met four inclusion criteria: (1) English; (2) HIC context (determined by World Bank high-income economies, including the U.S., Canada, Australia, and certain countries in Europe and Asia); (3) about research participants who are uninsured or low-income, which limits their access to healthcare, and in biomedical clinical research that either had the prospect of direct medical benefit or was offered to them on the basis of their ill health; (4) recognizes and/or addresses challenges and/or ethical considerations of uninsured or low-income participants in biomedical clinical research.

We excluded articles if they met any of three exclusion criteria: (1) letters, books, and book reviews; (2) studies about or involving research participants who are in marginalized or minority groups that are more likely to be uninsured or low-income, but focus on challenges and barriers due to characteristics such as minority status and not insurance or income; (3) studies about or involving research participants in non-biomedical or healthy volunteer trials without prospect of benefit. Although the uninsured are often discussed in the context of non-biomedical or healthy volunteer trials, we excluded these trials because the ethically salient issues for participants receiving medical care or benefit differ from issues raised by trials in which participants cannot reasonably expect such care or are not seeking medical benefit. For example, bioethicists worry about payment and possible undue inducement of healthy volunteer research participants, who are usually motivated by money.[31,32] Payment

may be less of a factor for participants who join research in order to access healthcare, and other factors (e.g. desire for healthcare, provision of ancillary care or post-trial care) may be more likely to affect ethical analyses on how to recruit, enroll, and treat this particular group of uninsured participants. Moreover, the moral imperative to include uninsured participants who are ill in therapeutic trials - or to not unjustly exclude for their "protection" - differs from that of participants in non-therapeutic or non-biomedical trials.

Data extraction

One author (HC) independently extracted data from the studies that met our inclusion criteria into standardized tables (Tables 2, 3, 4). All authors reviewed and agreed upon the analysis of the data.

Included articles fell into two broad categories: 1) conceptual papers that discuss ethical treatment of uninsured or low-income participants at various stages of biomedical clinical research in HIC, or 2) empirical papers on the perspectives of the uninsured or low-income on clinical trials or on the barriers of enrolling and/or retaining uninsured or low-income participants. We further categorized the conceptual and empirical articles by the stage of research they discussed: enrollment and retention (Table 2), treatment during the course of research (Table 3), or post-trial responsibilities (Table 4).

We further extracted themes from each of the articles included in our review. Themes regarding "enrollment and retention" included barriers for enrollment and retention, informed consent, financial incentives, exploitation, and undue inducement among others. Although retention refers to treatment during the course of research, we grouped it with enrollment because the papers that addressed one often addressed the other. Themes regarding "treatment during the course of research" included considerations such as ancillary care and compensation for research-related harms for purposes other than retention. Themes regarding "post-trial responsibilities" included post-trial care and access.

Results

The searches generated a total of 974 results from PubMed/MEDLINE (551), Embase (117), and Scopus (366). After removing duplicates, 797 unique publications remained. Of the 797 results, 27 passed an initial title/abstract screening and were read in full. Twelve articles were excluded because they either met one of the three exclusion criteria or because they did not meet the all four inclusion criteria, leaving 15 eligible articles (Figure 1).

Nineteen articles were extracted from the references of the 15 articles via a title/abstract screening. Eight of the 19 ultimately passed the full-text screening and were included in our review for a total of 23 articles (Figure 1).

Characteristics of reviewed articles

Of the 23 results, there were 13 empirical articles and 10 conceptual articles. Ten of the 13 empirical articles involved uninsured or low-income participants, and the remaining three empirical articles were literature reviews of barriers to enrollment and/or retention in clinical research of disadvantaged or underrepresented groups (including uninsured and low-

income)[33–35] (Table 1). The reviews did not focus solely on the uninsured or low-income, and/or looked at a different subset of clinical trials.

Eight of the 10 conceptual articles reviewed challenges or ethical considerations of involving uninsured or low-income research participants in biomedical clinical research. Two were newspaper or magazine articles, published in *The New York Times* [36] and *The Scientist* [37] respectively (Table 1). The majority (n=19) of the articles in our review discussed enrollment and retention of uninsured or low-income participants.[33–36,38–52] Considerably fewer articles discussed treatment of these participants during the course of research (n=5)[1,2,40,51,53] or post-trial responsibilities owed to uninsured or low-income participants (n=4) [1,36,37,40] (Table 3). Three papers [1,36,40] discussed more than one of these issues.

Enrollment and retention

Most of the papers (19/23) in our review described challenges and ethical considerations of enrollment and retention. Eleven [33–35,38–45] of the 19 papers were empirical studies, and eight [36,46–52] were conceptual studies (Table 2).

The empirical papers on enrollment and retention identified several barriers to enrolling uninsured and low-income groups, both independent of and associated with other demographic factors (Table 2). Eight papers [33–35,38,39,41,43,45] explicitly mentioned that uninsured or low-income participants should be enrolled. Of the eight, six [33,35,38,39,41,45] gave reasons of scientific validity, five [33,34,38,39,43] gave reasons of benefiting or addressing disparate health outcomes for groups with greatest burden of disease, and two [33,34] gave reasons of fair access to trial benefits. Barriers to enrollment included limited access to primary or preventative care due to uninsurance or low-income, which lead to later diagnoses and development of co-morbid conditions that met exclusion criteria, lack of access to institutions conducting trials or to physicians with enough time or knowledge about trials, and overall lack of trust in the government, research, or medical system.[33–35,38,39,41,45] Logistical issues such as lack of time, transportation, or daycare services for children constituted barriers for both enrollment and retention of uninsured or low-income participants in clinical research.[33,34,38,39,44,45] One paper [42] cited informed consent bias as a potential barrier

Two papers, Grady et al.[40] and Slomka et al.[44] discussed ways to promote uninsured or low-income participation in clinical research. Grady et al.[40] focused on respect for participants, while Slomka et al.[42] focused on financial incentives.

Interestingly, the focus group and patient interview studies [38,40,43,44] found that uninsured or low-income communities were willing to participate in biomedical clinical research despite logistical, structural, and personal barriers to enrollment. Given the difficulty of enrolling and retaining low-income groups despite willingness to participate, Webb et al.[45] and Humphreys and Weisner [41] suggest study design (i.e. exclusion criteria) may be disproportionally excluding uninsured, low-income, or minority patients.

To address barriers to both enrollment and retention, seven studies propose strategies such as financial assistance for transportation or time spent in research (n=4), [33,35,39,45]

collaboration with the community or community leaders to improve trust (n=7), [33,35,37,39,40,44,45] reminder calls (n=2),[33,45] financial incentives (n=5),[33,35,43–45] and monitoring of medical welfare throughout the trial (n=2).[33,40]

The eight conceptual papers on enrollment and retention discussed concerns about whether or not to enroll (n=6), [36,46,48–50,52] informed consent (n=6), [36,46,47,49,50,51] exploitation and undue inducement (n=4). [36,46,47,49] Stone [50] raised concerns about informed consent and explicitly recommended limiting the type of trials open to uninsured and low-income participants to minimal risk research or research with direct benefits. Kolata and Eichenwald [36] remained ambivalent about whether or not uninsured participants should be enrolled or excluded. El-Sadr and Capps,[46] Merrill,[48] and Pace et al.[49] explicitly argued for the inclusion of uninsured and low-income participants in cancer, AIDS, and general clinical trials respectively. Welsh et al.[52] argued for inclusion of minority groups that are more likely to face economic barriers. Guerrero and Heller [47] and Vasgird et al.[51] raised issues about informed consent due to power dynamics between patients and physicians, exploitation, undue inducement, and lack of compensation for research related harms.

Treatment during the course of research

Five of 23 papers mentioned ethical considerations regarding the treatment of uninsured and low-income participants during the course of research, specifically ancillary care (n=4)[1,2,40,53] and compensation for research-related harms (n=1)[51] (Table 3). Three [2,40,53] of five were empirical, and two [1,51] were conceptual.

The three empirical papers stated or hypothesized that uninsured or low-income people expected ancillary care during research participation. Jacobson et al.[2] found that low-income participants would not participate in research without ancillary care provision, and Grady et al.[40] reported that representatives from low-income, urban communities in the U.S. saw ancillary care throughout the course of research as necessary to respect participants.

None of the empirical papers proposed when or how much ancillary care to provide. In fact, Jacobson et al.[2] raised a concern that providing ancillary care could exacerbate participants' misunderstanding of the purpose of research as treatment or potentially be a form of coercion of low-income participants. Koblin et al.[53] suggested that unrealistic expectations of ancillary care may be a problem for uninsured participants that must be adequately addressed before enrolling them. However, one conceptual paper, Dal-Ré et al.,[1] proposed ancillary care as a method to ensure a fair level of benefits to participants who lack access to healthcare.

The other conceptual paper about treatment of uninsured and low-income participants during the course of research, Vasgird et al.,[51] focused on compensation for research-related harms, arguing that without compensation for research-related harms, uninsured participants remain vulnerable during the course of research participation.

Post-trial care and access

Four papers mention post-trial access (n=3)[1,36,40] or post-trial care (n=2)[37,40] for uninsured or low-income research participants (Table 4). Three of the four papers were conceptual, two of which were newspaper or magazine articles.

Clemmitt [37] suggested that research community members believed that ongoing medical care post-trial was required to ethically enroll low-income participants. Grady et al.[40] described how representatives of low-income communities raised concerns about post-trial access to medications and healthcare in general for uninsured research participants. These representatives stated that trials should have post-trial plans to adequately provide care to uninsured participants, even if that means the research team has to continue to provide that care.

Kolata and Eichewald [36] raised concerns about lack of post-trial access for uninsured research participants due to potential health consequences of terminating treatment, while Dal-Ré et al.[1] proposed post-trial access to experimental medications as another strategy to provide a fair level of benefits to participants who are uninsured or otherwise lack access to healthcare.

Discussion

Limitations

The review has several limitations. First, the “uninsured” consists of a diverse group of people who lack access to healthcare to various extents and for various reasons, have different needs, and require different ethical considerations in clinical research. Second, many studies in our review focus on minority or marginalized groups (e.g. African Americans, Latino women, homeless, drug addicts) who are more likely to be uninsured or broadly study low-income, socioeconomically disadvantaged groups. Thus, many of the ethical considerations discussed apply not just to uninsured participants but also underinsured or other marginalized participants. Third, some existing studies that do discuss exploitation, ancillary care, and post-trial access were excluded because they focus on LMIC or on paying healthy volunteers, and do not recognize the particular circumstances of the uninsured seeking healthcare through research in HIC.[3,31,32,54] Fourth, the majority (20/23)[2,35–53] of our studies address U.S. participants only, leaving out other HIC some of which have different healthcare systems. Finally, our review focuses on biomedical clinical research, and not on the ethical treatment of uninsured research participants in trials such as non-vaccine healthy volunteer studies, non-treatment community-based research such as survey studies, public health research, or natural history studies. These types of research raise different ethical issues that should be analyzed separately, and may be areas for future research.

Implications & future research

This scoping review reveals the lack of attention to the ethics of clinical research in HIC with uninsured and low-income people who are seeking healthcare. The articles in this review, although limited in number, seem to agree that uninsured persons should be included

in research, and that special consideration might be needed in informed consent, financial compensation, ancillary care, compensation for research-related injury, and post-trial responsibilities. However, there are significant gaps in both data and thoughtful analysis on how to ethically involve uninsured research participants in biomedical clinical research offered to them on the basis of their ill health or with a prospect of direct medical benefit.

Building on the literature and gaps identified by this systematic review, we propose future research to begin to address three broad questions (Table 5).

(1) What is the current status of the uninsured research participant in biomedical clinical research?—The articles in this review do not make clear how often uninsured participants are enrolled in treatment or vaccine trials or how they are treated during research participation. Inconsistencies exist between included articles, with some suggesting low rates of research participation of the low-income and uninsured and others suggesting an increasing rate of participation, and several noting that no clear picture exists. However, it is not unreasonable to think that the uninsured face barriers in accessing clinical trials. Some authors from the 1990s cancer literature noted that even patients with insurance were prevented from enrolling in cancer clinical trials because of costs and insurance reimbursement policies.[55]

Future research should try to elucidate the enrollment rate of uninsured and low-income participants in treatment or vaccine trials, and whether there are particular types of trials uninsured participants are more likely to be enrolled in or excluded from. The latter is especially important since data suggest that certain minority groups are more likely to be enrolled in phase I healthy volunteer trials than in later phase treatment trials.[56] Similarly, given the increasing private sponsorship of clinical trials in the U.S.[57] looking at uninsured participants in publicly funded versus privately funded trials could address interesting ethical questions such as 1) Are uninsured participants more likely to enroll in trials sponsored by pharmaceutical companies or by public sponsors? 2) Are they treated differently (e.g. insurance coverage, ancillary care or post-trial care provision) in these trials? And, 3) Are there ethical differences in what uninsured participants are owed based on the funding source of a trial?

There are also no available data about what happens when those who are uninsured are injured in research or suffer an adverse event, nor the extent to which researchers pay attention to issues of uninsurance and income in transitioning participants to needed healthcare at the end of a study.

Moreover, we do not know whether or to what extent research institutions and investigators take healthcare access into account when deciding about enrollment, ancillary care, or post trial care. Similarly, do certain institutional policies or protocols exclude participants based on health insurance status? Do any provide medical care or coverage of medical costs (and which ones) for their research participants? Do the composition and attitudes of the institution’s staff affect enrollment of uninsured patients in clinical trials?[58]

Given the possibility that socioeconomic status could independently affect willingness and ability to participate in trials,[36] future research should also look at the effects of insurance and income on research participation independently of other demographic factors such as race or gender or the interaction of these factors.[58]

Gathering data about the current status of the uninsured in research may also begin to answer other research questions about how uninsured participants are and should be treated during and after research.

(2) How should uninsured research participants be treated during and after clinical research?—The broader literature on relevant ethical issues like ancillary care and post-trial access does not focus on the uninsured or on HIC.[3,54] Little has been written about similarities or differences between research participants or lack of healthcare access in LMIC and HIC. These comparisons could inform how we treat or should treat research participants who lack access to healthcare in HIC. For example, Jacobsen et al.[2] proposed collecting data on ancillary care practices in HIC using the descriptive methodologies used in LMIC and comparing the findings.

Moreover, attention to post-trial responsibilities, a relatively recent idea introduced by the Declaration of Helsinki (2000), is still sparse in any context. Conceptual papers could address any particular considerations in determining post-trial responsibilities to research participants who are uninsured or otherwise lack access to healthcare access in HIC.

A better understanding of the ethics of enrolling uninsured participants and how they should be treated during and after biomedical clinical research may also help to influence guidance and policies on compensation for research-related harms, ancillary care, and post-trial care.

(3) How, if at all, should additional protections for uninsured research participants affect their enrollment?—Many existing ethical discussions about the uninsured and low-income in research took place in late 1990s and early 2000s, as evidenced by the dates of the papers in our review. However, both healthcare and clinical research have changed significantly in the last decade. Uninsurance rates in the U.S., which reached their peak in 2013 prior to Medicaid expansion and other Affordable Care Act changes, have started to rise again.[14,17] One challenge is balancing fair participant selection and concerns about scientific validity with concerns about undue inducement when offering participants access to healthcare services that they otherwise cannot access. How should possible exploitation be considered when determining who to enroll in a study? Should financial compensation or ancillary care for uninsured or low-income participants be different from other enrollees, how would such differences be justified, and how can we prevent both exploitation and undue inducement? Addressing these questions would expand the existing literature on undue inducement and exploitation, which preferentially focuses on payment rather than other benefits, or on healthy volunteers rather than low-income participants primarily seeking healthcare access.[31,32,59–61]

Findings from our scoping review have potential implications beyond setting a research agenda. Research teams conducting biomedical clinical research in HIC should pay more

attention to the existence (or lack thereof) of uninsured or low-income participants in their trials. The themes identified and discussed by the reviewed articles may help teams assess their treatment of participants who are uninsured or otherwise lack access to healthcare and make changes to ensure that their studies remain ethical. Paying more attention on both a broad and individual level to the plight of the uninsured and underinsured may help improve the treatment of vulnerable and forgotten participants caught in the throes of a healthcare crisis.

Conclusion

Overall, our review reveals a lack of attention to uninsured and low-income individuals in the research context, and even less attention on the salient ethical issues of including uninsured and low-income participants in biomedical clinical research. Despite this, there are many important ethical questions and challenges that should be addressed especially in the current climate of healthcare access in the U.S. We hope that by elucidating the dearth of empirical and theoretical research, we will prompt additional studies guided by our proposed research agenda that may lead to future practices and protections regarding uninsured and low-income research participants.

Acknowledgments

We thank Alicia A. Livinski, NIH Library, for literatures searching and manuscript preparation assistance.

Appendix A: MEDLINE/PubMed search strategies, searching studies published in English:

Underinsured + clinical study + ethics/compensation

(uninsured OR underinsured) AND (“clinical trial”[tw] OR “clinical trials”[tw] OR “clinical study”[tiab] OR “clinical studies”[tiab] OR “clinical research”[tiab] OR “Clinical Studies as Topic”[Mesh] OR subject[tiab] OR subjects[tiab] OR participant*[tiab] OR volunteer*[tiab] OR “patient participation”[tiab] OR “research subject”[tiab] OR “research subjects”[tiab] OR “patient selection”[tiab] OR “human experimentation”[tiab] OR “Volunteers”[Mesh] OR “Patient Participation”[Mesh] OR “Research Subjects”[Mesh] OR “Human Experimentation”[Mesh] OR “Patient Selection”[mesh]) AND (ethic* OR exploit* OR “Ethics, Research”[Mesh] OR “undue inducement”[tiab] OR compensation[tiab] OR compensate*[tiab] OR incentive*[tiab]OR incentive*[tiab] OR “Compensation and Redress” [Mesh])

Clinical study + ethics + poverty

(“clinical trial”[tw] OR “clinical trials”[tw] OR “clinical study”[tiab] OR “clinical studies” [tiab] OR “clinical research”[tiab] OR “Clinical Studies as Topic”[Mesh] OR “human experimentation”[tiab] OR “Human Experimentation”[Mesh]) AND (subject[tiab] OR subjects[tiab] OR volunteer*[tiab] OR “patient participation”[tiab] OR “research subject” [tiab] OR “research subjects”[tiab] OR “patient selection”[tiab] OR “Volunteers”[Mesh] OR “Patient Participation”[Mesh] OR “Research Subjects”[Mesh] OR “Patient Selection”[mesh]

OR participant[ti]) AND (ethic* OR exploit* OR “Ethics, Research”[Mesh] OR “undue inducement”[tiab] OR compensation[tiab] OR compensate*[tiab] OR incentive*[tiab] OR incentive*[tiab] OR “Compensation and Redress”[Mesh]) AND (“Poverty”[Mesh] OR poor[tiab] OR “low income”[tiab] OR disadvantaged[tiab] OR indigent[tiab] OR indigence[tiab] OR poverty[tiab] OR “socioeconomic disadvantage”[tiab] OR “socioeconomic disadvantaged”[tiab] OR underinsured OR uninsured)

Clinical study + ethics/compensation + poverty/uninsured + access to care

(“clinical trial”[tw] OR “clinical trials”[tw] OR “clinical study”[tiab] OR “clinical studies”[tiab] OR “clinical research”[tiab] OR “Clinical Studies as Topic”[Mesh] OR subject[tiab] OR subjects[tiab] OR volunteer*[tiab] OR “patient participation”[tiab] OR “research subject”[tiab] OR “research subjects”[tiab] OR “patient selection”[tiab] OR “human experimentation”[tiab] OR “Volunteers”[Mesh] OR “Patient Participation”[Mesh] OR “Research Subjects”[Mesh] OR “Human Experimentation”[Mesh] OR “Patient Selection”[mesh]) AND (ethic* OR exploit* OR “Ethics, Research”[Mesh] OR “undue inducement”[tiab] OR compensation[tiab] OR compensate*[tiab] OR incentive*[tiab] OR incentive*[tiab] OR “Compensation and Redress”[Mesh]) AND (“Poverty”[Mesh] OR poor[tiab] OR “low income”[tiab] OR disadvantaged[tiab] OR indigent[tiab] OR indigence[tiab] OR poverty[tiab] OR “socioeconomic disadvantage”[tiab] OR “socioeconomic disadvantaged”[tiab] OR underinsured OR uninsured) AND (“access to healthcare”[tiab] OR “access to care”[tiab] OR “fair benefits”[tw] OR “Delivery of Health Care”[mesh] OR “Health Services Accessibility”[mesh] OR “healthcare delivery”[tiab] OR “health services accessibility”[tiab] OR “post-trial access”[tiab])

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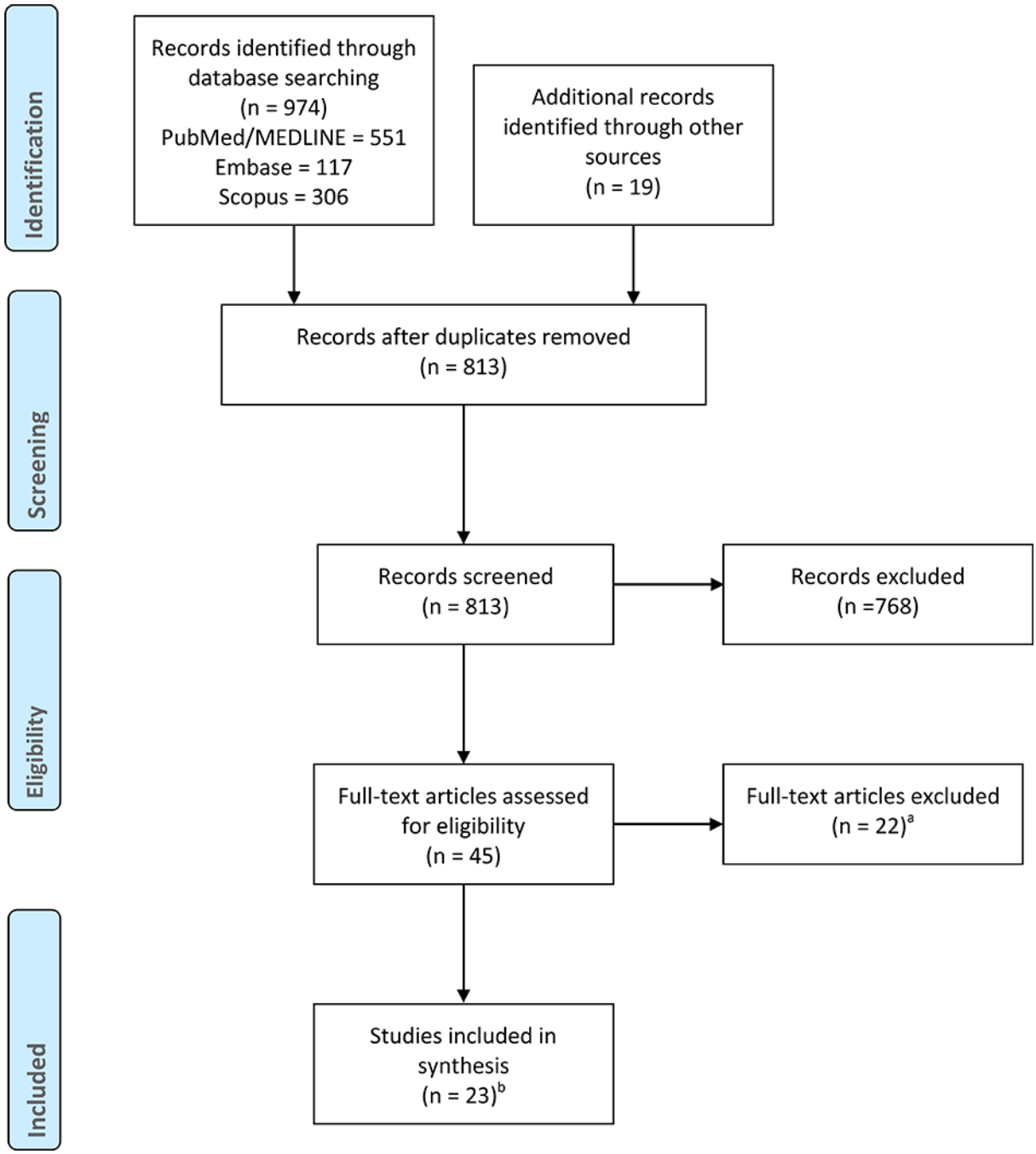

Figure 1.

Flow chart of included studies.

[a]Excluded articles included studies not about high-income countries (n=2), studies that did not acknowledge challenges or ethical considerations (n=5), studies that focused on minority populations without considering the impact of uninsurance or low income (n=6), and studies not about participants in biomedical trials that either had a prospect of direct medical benefit or was offered to them on the basis of their ill health (n=9). Some of the excluded articles fit

into more than one of these categories. Those articles were categorized by their primary reason for exclusion.

[b]Three primary articles were part of the systematic reviews included, and the Ford et al. 2008 systematic review was included in the Boneveski et al. 2014 systematic review. We included these articles because we wanted to capture the amount of attention paid to the challenges and ethical considerations of working with the uninsured and low-income in research, and because the primary papers and the systematic reviews framed themselves in unique ways.

Table 1.

Scoping review article type by frequency.

Article Type	Articles (n=23), No. (%)
Empirical article	13 (57%)
Survey	1[53]
Interview	2[2,44]
Focus group	3[38,40,43]
Systematic review	3[33–35]
Other descriptive study	4[39,41,42,45]
Conceptual article	10 (43%)
News article	2[36,37]
Review article	8[1,46–52]

Table 2.

Papers that discuss enrollment and retention of uninsured research participants.

Empirical				
Author/year	**Country**	**Study design**	**Ethical theme(s) discussed**	**Main findings**
Bonevski et al. 2014[33]	U.S., Canada Europe, Australia	Systematic review on socially disadvantaged groups	Enrollment, retention	Research should include socially disadvantaged populations and address the significant barriers to enrolling and retaining these groups.
Farmer et al. 2007[38]	U.S.	Focus groups with African American and low-income white women	Enrollment	Mistrust of research, lack of community structure, and logistical factors pose barriers of enrolling low socioeconomic status minorities and women.
Ford et al. 2008[34]	Developed countries (broad)	Systematic review on underrepresented populations in cancer trials	Enrollment	Lack of health insurance and low socioeconomic status is associated with reduced enrollment in cancer clinical trials. This problem must be addressed both on the level of individual studies and policy.
Gross et al. 2005[39]	U.S.	Case control study of older women with breast cancer	Enrollment	Low socioeconomic status, independent of race, was associated with lower trial enrollment in older women with breast cancer. This may be due to bad access to centers conducting trials, later-stage cancers, co- morbid conditions, logistical barriers, or biological impacts of poverty.
Grady et al. 2006[40]	U.S.	Focus group with urban community representatives	Enrollment	Mistrust and logistical issues, including post-trial worries, pose barriers of enrolling low socioeconomic status communities in research.
Humphreys & Weisner 2000[41]	U.S.	Retrospective study on alcohol treatment patients	Enrollment	Exclusion criteria in alcohol trials disproportionately exclude low socioeconomic status patients.
Mitchell & Kline 2008[42]	U.S.	Case control study of emergency department patients being offered a minimal-risk study	Enrollment	Uninsured patients were less likely to participate in a minimal-risk study in the emergency department. Studies should pay attention to informed consent biases.
Nyamathi et al. 2004[43]	U.S.	Focus group with homeless minority groups	Enrollment	Homeless minority groups are interested in participating in vaccine trials. Mistrust of government and research as well as lack of education pose barriers to participation.
Slomka et al. 2007[44]	U.S.	Interview study with low- income, African-American drug users	Enrollment	Impoverished drug users will participate in research only if financially compensated. They are not worried about risk of exploitation or undue inducement as long as compensation is proportional to risks and inconvenience.
Shavers- Hornaday et al. 1997[35]	U.S.	Literature review on possible reasons for low research participation of African Americans	Enrollment	Uninsurance and lack of access to healthcare can disproportionally exclude minorities from trials due to limited relationship with doctors who are knowledgeable about trials and increased likelihood of late-stage or co-morbid conditions that meet exclusion criteria.
Webb et al. 2010[45]	U.S.	Interventional study on minority, low-income women	Enrollment, retention	Minority women who have no insurance or low- income were more willing to participate in a prevention study that offered treatment. This suggests the difficulty enrolling and recruiting of uninsured or low-income may be due to study design.
Conceptual				
Author/year	**Country**	**Ethical theme(s) discussed**	**Main takeaway**	

Empirical				
Author/year	**Country**	**Study design**	**Ethical theme(s) discussed**	**Main findings**
El-Sadr & Capps 1992[46]	U.S.	Enrollment, informed consent	AIDS clinical trials have disproportionally low enrollment of low socioeconomic status, minority participants due to lack of access to institutions conducting trials, disillusionment with the medical system, lack of relationships with primary care physicians, and logistical barriers. Social workers should provide support.	
Guerrero & Heller 2003[47]	U.S.	Exploitation, undue inducement, informed consent	Low socioeconomic status raises concerns of exploitation and undue inducement. The informed consent process currently is insufficient.	
Kolata & Eichenwald 1999[36]	U.S.	Enrollment, exploitation, undue inducement, informed consent	Uninsured participants use clinical research as a form of healthcare. This poses ethical problems for either enrollment or exclusion of uninsured participants. The lack of post-trial care also poses a problem for uninsured research participants.	
Merill 1999[48]	U.S.	Enrollment	Cancer research should be enrolling uninsured and underinsured participants who currently face barriers to participation. Insurance coverage should be provided for all National Cancer Institute sponsored, peer-reviewed cancer trials.	
Pace et al. 2003[49]	U.S.	Enrollment, exploitation, undue inducement, informed consent	Uninsured participants should be enrolled in clinical research. Exploitation and undue inducement do not pose enough of a problem to merit exclusion.	
Stone 2003[50]	U.S.	Enrollment, exploitation, undue inducement, informed consent	Informed consent as it stands does not fully protect economically or educationally disadvantaged research participants from exploitation and undue inducement. IRBs may need to limit the types of trials allowed to minimal risk or research with direct benefits.	
Vasgird et al. 2000[51]	U.S.	Enrollment, informed consent	Informed consent as it stands does not fully protect uninsured research participants. Uninsured participants may not have other options than research for healthcare.	
Welsh et al. 1994[52]	U.S.	Enrollment	Lack of insurance poses barriers to enrollment of minorities because of lack of relationship with primary care providers, lack of trust in medicine, and lack of access to evaluation, diagnoses, and trial referral. Financial incentives, ancillary care, and transportation may help enroll minorities.	

Table 3.

Papers that discuss treatment of uninsured participants during course of research

Empirical				
Author/year	**Country**	**Study design**	**Ethical theme(s) discussed**	**Main findings**
Jacobson et al. 2016[2]	U.S.	Interviews with low- income people	Ancillary Care	Low-income people expect ancillary care if they participate in clinical research. This may call into concern their informed consent.
Grady et al. 2006[40]	U.S.	Focus group with urban community representatives	Ancillary Care	Community engagement, fair payment, and provision of care may encourage participation.
Koblin et al. 1998[53]	U.S.	Survey study of populations with highrisk of HIV	Ancillary Care	Those without insurance in high-risk populations of HIV infection were more willing to enroll in vaccine trials. However, these groups may expect free ancillary care during the trial, so decisions about ancillary care have to be addressed.
Conceptual				
Author/year	**Country**	**Ethical theme(s) discussed**	**Main takeaway**	
Dal-Ré et al. 2016[1]	U.S., EU, Canada	Ancillary care	In order to provide a favorable risk-benefit ratio and prevent exploitation, researchers may provide ancillary care and other benefits to participants who lack access to healthcare.	
Vasgird et al. 2000[51]	U.S.	Compensation for research related harms	Without compensation for research-related harms, uninsured participants remain unethically vulnerable during the course of research participation.	

Table 4.

Papers that mention post-trial care and access for uninsured research participants.

Empirical				
Author/year	**Country**	**Study design**	**Ethical theme(s) discussed**	**Main findings**
Grady et al. 2006[40]	U.S.	Focus group with urban community representatives	Post-trial access, post-trial care	Uninsured people from low socioeconomic status communities worry about post-trial care and access, which may pose a barrier to their enrollment.
Conceptual				
Author/year	**Country**	**Ethical theme(s) discussed**	**Main takeaway**	
Clemmitt 1991[37]	U.S.	Post-trial care	Low-income participants must receive ongoing medical care after a trial concludes in order for their enrollment to be ethical.	
Dal-Ré et al. 2016[1]	U.S., EU, Canada	Post-trial access	In order to provide a favorable risk-benefit ratio and prevent exploitation, researchers may provide post-trial access to participants who lack access to healthcare.	
Kolata & Eichenwald 1999[36]	U.S.	Post-trial care	Uninsured research participants often do not receive post-trial care unless they can find another trial and feel abandoned.	

Table 5.

Proposed research agenda for biomedical research with uninsured research participants in high-income countries.

What is the current status of the uninsured research participant in biomedical clinical research?
1. How often are uninsured participants included in biomedical research? 2. Are there certain types of studies more likely to include or exclude uninsured research participants, for example by condition or phase? 3. Are uninsured research participants treated any differently with respect to ancillary care, treatment of adverse events, or post-trial transitions? 4. Are there differences in enrollment or treatment of uninsured participants based on the funding source of a trial? 5. How often do research institutions or investigators take healthcare access into account when deciding about enrollment, ancillary care, or post trial care? 6. How well are research participants informed about the costs to them of participation? 7. How does insurance and socioeconomic status affect research participants independently of other demographic factors such as race or gender?
How should uninsured research participants be treated during and after clinical research?
1. Is the treatment of uninsured participants in high-income countries different or similar to treatment of participants in low and middle income countries who lack access to health care? 2. Should uninsured research participants in high-income country research receive differential ancillary care, coverage for medical costs, or compensation for research related injury? 3. Do researchers have special responsibilities in transitioning uninsured research participants at the end of a trial? Or in providing post-trial access? 4. How should guidance or institutional policies address the challenges and ethical considerations of including uninsured or low-income participants?
How, if at all, should additional protections for uninsured research participants affect their enrollment?
1. Should issues of post-trial and ancillary care affect enrollment of participants who lack access to healthcare and require more resources? If so, how? 2. How should fair participant selection and concerns about scientific validity be balanced with concerns about undue inducement for participants who cannot access needed healthcare services outside of research? 3. Should recent changes in uninsurance rates or in clinical research influence how we think about enrollment of uninsured research participants? 4. How should risks of exploitation be minimized or avoided?