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When is a randomized controlled trial health equity-relevant? Development of a conceptual framework

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ABSTRACT

Objectives: Randomized controlled trials can provide evidence relevant to assessing the equity impact of an intervention, but such information is often poorly reported. We describe a conceptual framework to identify health equity-relevant randomized trials with the aim of improving the design and reporting of such trials.

Methods: An interdisciplinary and international research team engaged in an iterative consensus building process to develop and refine the conceptual framework via face-to-face meetings, teleconferences and email correspondence, including findings from a validation exercise whereby two independent reviewers used the emerging framework to classify a sample of randomized trials.

Results: A randomized trial can usefully be classified as "health equity-relevant" if it assesses the effects of an intervention on the health or its determinants of either individuals or a population who experience ill-health due to disadvantage defined across one or more social determinants of health. Health equity-relevant randomized trials can either exclusively focus on a single population or collect data potentially useful for assessing differential effects of the intervention across multiple populations experiencing different levels or types of social disadvantage. Trials that are not classified as "health equity-relevant" may nevertheless provide information that is indirectly relevant to assessing equity impact, including information about individual level variation unrelated to social disadvantage and potentially useful in secondary modelling studies.

Conclusion: The conceptual framework may be used to design and report randomized trials. The framework could also be used for other study designs to contribute to the evidence base for improved health equity.

[246]

Key words: health, equity, randomized controlled trials, framework

Strengths and limitations of this study

Randomized controlled trials can provide evidence on both the impact of interventions in general and differential impacts in different populations; improved reporting of the health equity implications of interventions is critical for informing decision making to address inequity.
A consensus building process was used to develop a conceptual framework to identify and classify health equity-relevant randomized trials.
A randomized trial is considered to provide health equity-relevant evidence if it assesses the effects of an intervention on the health or its determinants of either individuals or a population who experience ill-health due to disadvantage defined across socially structured characteristics (that is, one or more social determinants of health).
A limitation of this approach is that analyzing and publishing disaggregated data can be expensive and it is not desirable for all randomized trials to do subgroup analyses by PROGRESS-Plus characteristics.
The conceptual framework may be used to design health equity-relevant randomized trials (as well as other study types) and to identify equity-relevant studies that contribute to the evidence base for the twin concerns of improving overall health and health equity.

INTRODUCTION

Many countries have policy documents that reflect concern for social justice, with a goal to redressing disparities in health both within and between countries[1]. For example, within Canada, the difference in life expectancy between Indigenous and general populations is on average 10 years[2]. Differences in health between individuals or population groups within society, or health inequalities, are labelled “inequities” when considered unfair[3]. There are differing views on what counts as unfair and moral judgements about fairness may vary over time and between cultures[4]. For example, men have a shorter life expectancy (with less disability) than women, and there is controversy about whether this is inequitable[5]. Two common guiding principles, frequently advocated in public health policy documents, are that health inequalities can be considered unfair when they are potentially avoidable by organized social action and when the situation that causes poor health is out of the control of those affected[6]. This includes situations where choices are severely restricted by social, historic, economic, or built environments. For the purpose of this paper, we choose to define health equity in this way to reflect our collective interests in social justice, and the removal of social barriers posed by discrimination and stigmatization which affect participation by individuals or populations in opportunities for better health.

Healthcare decisions in most countries are commonly guided by different types of evidence, amongst which clinical evidence based on randomized controlled trials (“randomized trials”) usually holds particular prominence. Improved reporting of health equity in randomized trials is important as some interventions can aggravate rather than reduce inequities (“intervention generated inequities”)[7]. A review of public health media campaigns for health behaviour revealed that health information provision was more effective in motivating behaviour change among socio-economically advantaged groups and widened the observed gap in health behaviour between socio-economically disadvantaged groups[7]. Although improving average health is an important social goal, increased inequity is an undesirable side-effect. The improved reporting of health equity implications of interventions is critical, and the increased use of randomized trial designs are promoted in the areas of public health[8] and international development[9] to build evidence that informs equity-oriented decisions.

Randomized trials provide evidence on the impact of an intervention and, in principle, can also assess their impact on health equity; however, randomized trials often fail to report relevant socio-demographic factors[10]. In addition, subgroup analyses, even when appropriately powered are rarely conducted to assess whether the impact of the intervention differs across sub-groups in society (for example, differential impact by socioeconomic status, place of residence)[11]. To address the poor reporting and analysis of equity impacts in randomized trials, we are assessing the need for additional reporting guidelines for randomized trials that provide evidence about potential impact on health equity[12]. An extension of the internationally recognized Consolidated Standards for Reporting Trials (CONSORT) statement, an evidence-based guideline to encourage completeness and transparency of reporting in randomized trials[13] is underway. The purpose of this paper is to describe the development of a conceptual framework to identify when a randomized trial provides evidence about health equity. The conceptual framework may be helpful for the design and reporting of randomized trials by trialists, funders, journal editors, and other knowledge user groups.

METHODS

We convened a collaborative research team and advisory board including interdisciplinary and international knowledge users in a deliberative, consensus building process as part of a larger study described elsewhere[12]. We searched for and did not find any frameworks to define an equity-relevant randomized trial[12]. We then conducted a series of meetings that included representatives of potential knowledge user groups, including: bioethicists, clinicians, funders, journal editors, patient representatives, members of the public, policymakers, systematic review authors, and trialists. We engaged in a process to define features of randomized trials that provide evidence about health equity, which we define as “health equity-relevant” trials.

As a first step, we agreed on an operational definition of health equity for our work on health equity in randomized trials, drawing on social determinants of health theory that describes how socially structured health disadvantage is experienced and perpetuated[14]. We agreed, for this context, that the term ‘health equity’ implies that ideally everyone can attain their full health potential and that no one should be disadvantaged from doing so because of their social position or other socially determined circumstance[15]. Health equity addresses both access to health care as well as the broader concept of opportunities to achieve good health[6]. Moreover, we recognize that there are a range of characteristics of individuals or populations across which health inequities may exist, and that reasonable people hold different views about what counts as unfair[16].

Evidence shows that across the social determinants of health for individuals and population groups, people may experience disparities in health status, access to services, and the quality of care received[14]. Social determinants may be multifactorial and interact with one another. They can also be dependent on the context and setting, such as the local political or social climate and the form of health systems in which individuals and populations are situated[17]. One organizing framework is "PROGRESS-Plus" that depicts social determinants of health and enables the examination of the relationships within and between the multiple and socially-structured characteristics that may influence the opportunities for health of individuals and populations: **P**lace of residence, **R**ace[1]/ethnicity/culture/language, **O**ccupation, **G**ender/Sex, **R**eligion, **E**ducation, **S**ocioeconomic status, and **S**ocial capital[18-20]. Due to advances in thinking about causal associations/linkages between degree of control in the living environment and socio-economic inequities in health related outcomes, "Control" was included with "Social Capital"[21]. PROGRESS-"Plus" represents additional context-specific personal or setting characteristics that may be associated with health inequities and that are relevant to our study: 1) individual characteristics e.g. disability, age, sexual orientation; 2) features of relationships with effects on power differentials that impact personal autonomy e.g. children who suffer passive smoking because their parents smoke in the home; and 3) time-dependent transitions e.g. migration and/or refugee status[22, 23]. The degree to which PROGRESS-Plus characteristics are associated with health inequity depends on time, place, and interaction between the different dimensions.

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[1] We adopt the American Anthropological society (1998) statement on race: "Present-day inequalities between so-called "racial" groups are not consequences of their biological inheritance but products of historical and contemporary social, economic, educational, and political circumstances."

A conceptual framework was developed and feedback on the concepts and format of the conceptual framework was invited from over 40 clinicians and methodologists in face-to-face meetings, teleconferences and email. Furthermore, we gathered opinions from many others in local seminars and at international conferences. This feedback was incorporated through iterative adjustments to the conceptual framework.

The conceptual framework was tested with the research team and advisory board[12]. A search for randomized trials was designed with a librarian scientist (JM) in MEDLINE, using text words and subject headings for the concepts of PROGRESS-Plus and a validated filter for randomized trials[24](Appendix A). We developed this search by testing whether it identified a reference set of 10 articles classified as health equity-relevant according to our framework[12]. The search was run from 2013-2015 and generated 4316 hits. Of these, 1,025 were judged to be equity-relevant based on title and abstract screening. These 1,025 articles were arranged in random order, then screened in full-text by two independent reviewers for eligibility using the definition of a health equity-relevant trial. We screened for eligibility until we identified 200 health equity-relevant trials, selected as the sample size for a concurrent methods study (in progress). Disagreements were discussed and resolved by consensus, and the definition revised based on discussion. The research team and advisory board confirmed the final adjustments to the conceptual framework.

RESULTS

A randomized trial is considered to provide health equity-relevant evidence if it actually or potentially assesses the effects of an intervention on the health or its determinants of either individuals or a population who experience ill-health due to social disadvantage (Figure 1). These randomized trials can either exclusively focus on individuals or populations experiencing socially structured disadvantage, or consist of a mixed group and collect data potentially useful for assessing differential effects of the intervention across PROGRESS-Plus characteristics (Table 1). The evidence from these randomized trials may be used to mitigate socially structured health disadvantage, that is, contribute to understanding of the extent to which the intervention in question is effective in population groups who experience disadvantage. To identify 200 health equity-relevant randomized trials, 643 articles were screened. Screening confirmed that the criteria for health equity-relevance could be applied to randomized trials consistently.

We considered five aspects of randomized trials and their relevance to define a randomized trial as health equity-relevant: 1) type of interventions, 2) stated objective about equity, 3) estimation of differential impacts, 4) levels of health equity-relevant data, and 5) setting and context.

Table 1. Examples of health equity-relevant studies

Includes individuals or a population that experiences ill-health due to social disadvantage (defined across PROGRESS-Plus) Assesses the effects of the intervention on the health or its determinants of either individuals or a population who experience ill-health due to disadvantage defined across one or more social determinants of health Either exclusively focus on individuals or a population, or includes a mixed group			
"PROGRESS" criteria examples		"Plus" criteria examples	
Assesses effectiveness of the intervention solely for groups who are considered to be at a social disadvantage	Assesses effectiveness of the intervention for groups considered to be at a social disadvantage compared with other groups considered to be at less of a disadvantage	Assesses effectiveness of the intervention solely for groups who are considered to be at a social disadvantage	Assesses effectiveness of the intervention for groups considered to be at a social disadvantage compared with other groups considered to be at less of a disadvantage
A trial of an intervention to prevent domestic violence in Aboriginal communities[25].	A trial of an informed choice invitation on uptake of screening for diabetes in primary care assessed differences in effectiveness by socio-economic status[26].	A trial that tests a vocational intervention aimed at improving employment for people diagnosed with severe mental illness[27].	A trial of a schooling conditional cash transfer program on the behavior of young women assessed effectiveness separately based on enrollment status at the start of the study: those who have dropped out versus stayed in school[28].

1. Type of intervention

We agreed that the type of intervention (e.g. pharmacologic, non-pharmacologic, health systems) was not relevant to identifying a randomized trial as health equity-relevant. Although health equity is sometimes considered relevant only to public health or upstream interventions, we found many examples of clinical or pharmacologic interventions that met our health equity-relevant definition. For example, we considered a randomized trial that evaluated a clinical intervention to promote asthma education for individual inner-city child asthma patients that improved health outcomes[29] to be health equity-relevant.

2. Stated objective about equity

We found that a randomized trial did not need to have an explicit objective about improving health equity to be classified as health equity-relevant. For example, a study that implemented a weight loss intervention for native Hawaiians and other Pacific Islanders did a secondary analysis of sociodemographic variables[30] but did not identify health equity, inequalities or disparities as part of its objectives. However, the analysis of effects across income groups provides evidence about effectiveness of treatment for a population that is potentially disadvantaged in relation to opportunities for health.

3. Estimate of differential impacts

For the sake of transparency and to assess whether observed interactions are likely to result from multiple comparisons, it is critically important that an *a priori* plan of analysis is described that all examined interactions are reported upon. Any post-hoc subgroup analyses of randomized trial data (e.g. across equity characteristics) are at risk of identifying spurious interactions, and need to be interpreted with caution. There is, however, increasing recognition that data disaggregation is particularly important, such as analyses across sex/gender[31]. For health equity, it is important to also consider gradients of effect across social stratifying factors such as income quintiles or with indices that reflect distribution such as the concentration index[32].

Many randomized trials include a broad range of population groups, with limited details on socio-demographic characteristics and do not provide disaggregated data that could be used to assess whether effects of interventions differ between groups within the population. Furthermore, some randomized trials use detailed socio-demographic data to adjust analyses for baseline imbalances rather than deliberately exploring whether socio-demographic characteristics modify the effect of the interventions under study, thus losing the ability to assess similarities or differences in effects across these characteristics[33]. This represents a missed opportunity for providing evidence about equity.

When trialists do not have a pre-specified primary research objective of estimating differential impacts but nevertheless collect data on social determinants of health characteristics, then an opportunity exists to assess subgroup effects. The scope for a randomized trial to contribute health equity data may not be immediately apparent to the randomized trial designer. For example, even if each trial's statistical power to identify differential effects may be low, combining data from several trials, (e.g. in meta-analyses), may substantially enhance statistical precision to identify and estimate the strength of such interactions. Data from randomized trials can also be combined with data from observational studies, or analyzed with methods that incorporate explicit Bayesian priors and/or theories about differential impacts based on well-established bodies of evidence and theory. Thus, collecting data about outcomes across social determinants of health may provide useful information for future and additional analyses, now greatly facilitated by global initiatives to allow data-sharing[34].

It is equally important to report analyses where no differences in effects are found since these may identify hypotheses for testing in future studies and any failure to identify effects due to low statistical power. If a health program is equally effective in relative terms, if disadvantaged populations have a higher baseline risk, there will be a greater reduction in absolute events for disadvantaged populations[35]. Such information is valuable for understanding the impact and potential for interventions to improve or exacerbate health inequities.

4. Levels of health equity-relevant data

According to our conceptual framework, an equity-relevant randomized trial may both focus on individuals or a population experiencing socially structured disadvantage and collect data on differential impacts of the intervention in the form of subgroup effects, thus providing more than one level of health equity-relevant data. For example, a randomized trial of a video module that aimed to increase the use of a United States poison center by low-income parents is focused on a population experiencing social disadvantage, but it also provides evidence across language proficiency strata by conducting a subgroup analysis[36]. The use of different intervention approaches is complementary and aims to address the multifactorial and intersecting characteristics of populations and individuals that affect health outcomes.

5. Setting and context

The population characteristics that influence socially structured disadvantage depend on the broader features of setting and context such as social, historical and political systems and require careful consideration. For example, a study with Japanese citizens conducted in Japan would not be classified as an equity-relevant trial unless the participants were also considered to be disadvantaged across another dimension such as sex/gender or income.

We recognize that health equity concerns arise from an array of characteristics; judgments about particular individual or population health determinants are concerns for inequity and may be more difficult because of the need to carefully consider the context of the randomized trial and characteristics, such as age or disability. Studies that report interventions related to overcoming health disadvantage need to consider the relationship between the intervention and how it might relate to equity/inequity, such as an intervention to promote school enrolment and health outcomes between participants who have dropped out versus stayed in school[37].

DISCUSSION

Operationalizing a definition of a health equity-relevant trial required consideration of broader issues and meanings of social justice informed by values, context and the impact of different social arrangements. Our conceptual framework engages users to consider and identify the many instances of health equity-relevant evidence and the potential contributions to broader societal dialogues. The evidence from these randomized trials may be used to mitigate socially structured health disadvantage, that is, contribute to understanding of the extent to which the intervention in question is effective in population groups who experience disadvantage

The conceptual framework is proposed as a way to identify and operationalize understandings about how randomized trials can provide evidence about health equity and in particular complements two previous intervention frameworks related to improving health equity. Margaret Whitehead's typology is based on the underlying theory of change and guides consideration of appropriate application of interventions to address health inequity; interventions fall into one of four main categories: strengthening individuals; strengthening communities; improving living and working conditions; promoting healthy macro-policies[15]. Hilary Graham's typology identifies three main approaches: addressing health inequity gaps, gradients or targeted approaches[38]. Our conceptual framework builds on these classification systems and suggests ways randomized trials can provide health equity-relevant evidence for an intervention, even when providing evidence about equity is not the central aim. Our conceptual framework has potential applications to inform other study designs, and is not limited to that of randomized trials.

It is our view that opportunities to provide health equity-relevant evidence should be considered up front in randomized trial conception and design and reported transparently. While different users will hold different definitions and priorities in regards to disadvantage and opportunities for health, we argue that consideration of individual or population characteristics and societal context is of paramount importance. Moreover, consideration of equity aligns with and supports an approach to decision-making that enables consideration of distributional goals, and outcomes aimed at addressing health inequity[38]. Knowledge about differential effects (or lack thereof) using social determinants of health theory, operationalized across PROGRESS-Plus characteristics can contribute to build knowledge aimed at improved application of effective interventions.

The approach to health equity supported by the conceptual framework promotes thinking about randomized trials as more than just a means of developing evidence about average efficacy or effectiveness. It highlights opportunities for all randomized trials to contribute to a broader social agenda about reducing health inequity. In doing so, it upholds international policy on "research for health" that advocates for the development of research methods to promote better knowledge and standardization of reporting mechanisms[39, 40].

Limitations and strengths

A limitation of this approach is that analyzing and publishing disaggregated data can be expensive and it is not desirable for all randomized trials to do subgroup analyses by

PROGRESS-Plus characteristics. We propose that when possible data on equity-relevant characteristics be collected, even when the study may not have sufficient power to perform sub-group analyses. In this way, data about characteristics linked to health equity may be made available for other researchers to use in pooled analyses, modeling or systematic reviews. Additionally, other knowledge sources/systems are essential to understand health inequities and not all social determinants of health are a source of "disadvantage". The proposed conceptual framework, therefore, is designed to engage users in deliberation about designing and reporting studies that can provide evidence useful to understand distribution of effects, rather than only average effects. Strengths of the conceptual framework are the use of a collaborative approach to development, and the iterative testing of the framework with examples of randomized trials.

CONCLUSION

The conceptual framework defines features of health equity-relevant trials that can be used to design and report both randomized trials and other study designs to improve the evidence base about how to improve health equity. Opportunities to provide health equity-relevant evidence should be considered upfront in trial concept and design. The conceptual framework can provide a stimulus to build knowledge about effects of interventions on health equity and is a first step to improve application of effective interventions and to build evidence that is of greatest relevance and use to individuals and populations.

Authors' contributions

JJ and VW conceived of and led the design of the work described in the manuscript. JJ, MW, MP, EK, DG, JP, JV, CW, MT, SE, LM, RC, JM, AL, YB, LGC, RA, HW, MY, TP, BS, KP, ON, SB, BR, HS, YA, GW, PT, VW participated in and provided substantial contributions to the analysis and interpretation during development of the work described in the manuscript. JJ, MW, MP, EK, DG, JP, JV, CW, MT, SE, LM, RC, JM, AL, YB, LGC, RA, HW, MY, TP, BS, KP, ON, SB, BR, HS, YA, GW, PT, VW made contributions to drafts of this manuscript and have reviewed and revised it for important intellectual content and approved the final version. JJ and VW are responsible for the first and final drafts of this manuscript.

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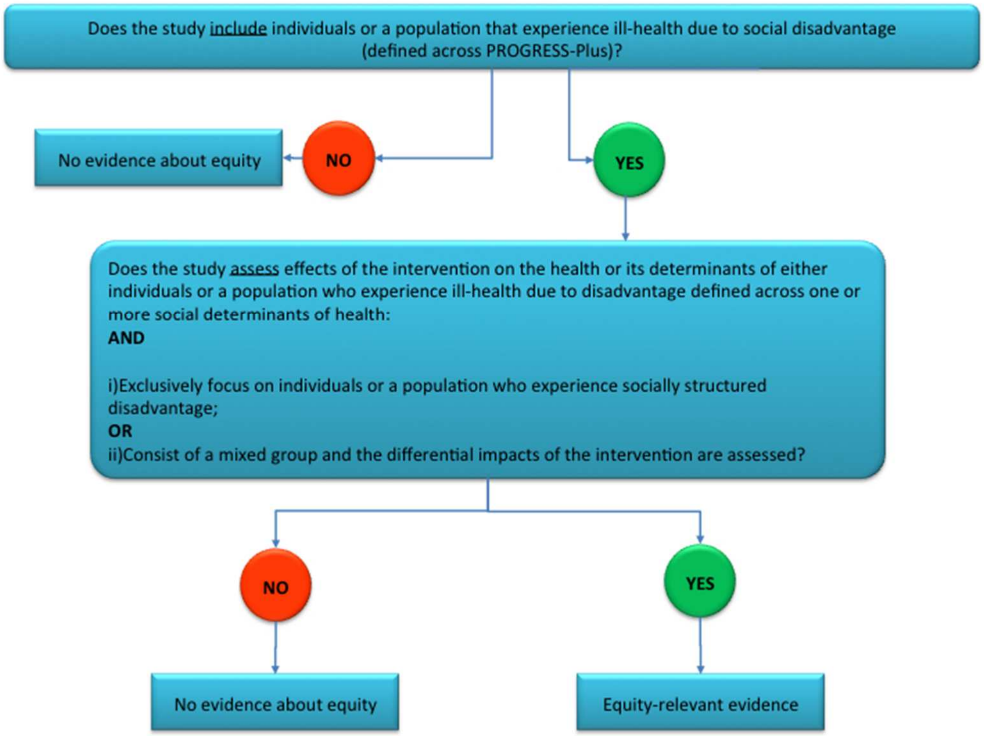

Does the study include individuals or a population that experience ill-health due to social disadvantage (defined across PROGRESS-Plus)?

Does the study assess effects of the intervention on the health or its determinants of either individuals or a population who experience ill-health due to disadvantage defined across one or more social determinants of health:
AND

i)Exclusively focus on individuals or a population who experience socially structured disadvantage;
OR
ii)Consist of a mixed group and the differential impacts of the intervention are assessed?

254x190mm (72 x 72 DPI)

Appendix A

1. exp Gender Identity/

2. (gender-based or gender-related or gender factors).tw.

3. ((sex or gender) adj2 (analysis or factor$ or inequit$ or disparit$ or inequalit$)).tw.

4. exp sex factors/

5. exp geriatrics/

6. ((ethnic$ or race or racial or religio$ or cultur$ or minorit$ or refugee or indigenous or aboriginal) adj3 (analysis or disparit$ or inequalit$ or inequit$)).tw.

7. exp homosexuality/

8. exp disabled persons/

9. ((poverty or low-income or socioeconomic$ or socio-economic$ or social) adj2 (analysis or disadvantage$ or factor$ or inequalit$ or depriv$ or inequit$ or disparit$)).tw.

10. exp Educational Status/

11. exp Socioeconomic Factors/

12. ((discriminat$ or social exclu$ or social inclu$) adj3 (religion or culture or race or racial or aboriginal or indigenous or ethnic$)).tw.

13. ((urban or rural or inner-city or slum) adj2 (analysis or inequit$ or disparit$ or inequalit$)).tw.

14. ((resource-poor or (low-income adj countr$) or (middle income adj countr$) or africa or developing countr$ or south america or china or asia or latin america) adj2 (relevance or analysis or applicab$ or inequit$ or disparit$ or inequalit$)).tw.

15. (inequalit$ or in-equalit$ or equit$ or inequit$ or in-equit$ or disparit$).tw.

16. exp indigenous populations/

17. ((native* or Indian or aborigin*) adj2 (American* or Canadian* or Alaska*)).tw.

18. (first adj2 nation*).tw.

19. (aborigin$ or metis or inuit$ or eskimo$ or esquimaux or aleut or yuit or inughuit or unanga* or alutiiq or inup#ia* or kalaallit or Inuktitut or Nunavut or nunavik or cree or

dene or haida or salish or Mohawk or ojibway or yupik or tribal or arctic).tw.

20. exp american native continental ancestry group/ or oceanic ancestry group/

21. or/1-20

22. randomized controlled trial.pt.

23. Clinical trial.mp,pt.

24. (random$ or placebo).mp.

25. (field experiment or field experiments).tw.

26. (cluster$ adj2 randomi$).tw.

27. or/22-26

28. 21 and 27

29. limit 28 to english

30. limit 29 to yr="2013"

31. limit 29 to yr="2014"

32. limit 29 to yr="2015"

When is a randomized controlled trial health equity-relevant? Development and validation of a conceptual framework.

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When is a randomized controlled trial health equity-relevant? Development and validation of a conceptual framework

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ABSTRACT

Background: Randomized controlled trials can provide evidence relevant to assessing the equity impact of an intervention, but such information is often poorly reported. We describe a conceptual framework to identify health equity-relevant randomized trials with the aim of improving the design and reporting of such trials.

Methods: An interdisciplinary and international research team engaged in an iterative consensus building process to develop and refine the conceptual framework via face-to-face meetings, teleconferences and email correspondence, including findings from a validation exercise whereby two independent reviewers used the emerging framework to classify a sample of randomized trials.

Results: A randomized trial can usefully be classified as "health equity-relevant" if it assesses the effects of an intervention on the health or its determinants of either individuals or a population who experience ill-health due to disadvantage defined across one or more social determinants of health. Health equity-relevant randomized trials can either exclusively focus on a single population or collect data potentially useful for assessing differential effects of the intervention across multiple populations experiencing different levels or types of social disadvantage. Trials that are not classified as "health equity-relevant" may nevertheless provide information that is indirectly relevant to assessing equity impact, including information about individual level variation unrelated to social disadvantage and potentially useful in secondary modelling studies.

Conclusion: The conceptual framework may be used to design and report randomized trials. The framework could also be used for other study designs to contribute to the evidence base for improved health equity.

Key words: health, equity, randomized controlled trials, framework

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Randomized controlled trials can provide evidence on both the impact of interventions in general and differential impacts in different populations. This is critical for decision making to address inequity.
- A consensus building process was used to develop and validate a conceptual framework to identify and classify health equity-relevant randomized trials.
- The proposed conceptual framework engages users in a deliberative process to design and report studies to provide evidence that is useful to understand the distribution of effects rather than only average effects.
- A limitation is that the analysis and publishing of disaggregated data can be expensive and may not be desirable for all randomized controlled trials.
- The conceptual framework may be used to design health equity-relevant randomized trials (as well as other study types) and to identify health equity-relevant studies that contribute to an evidence base that improves overall health and health equity.

INTRODUCTION

Many countries have policy documents that reflect concern for social justice, with a goal to redressing disparities in health both within and between countries[1]. For example, within Canada, the difference in life expectancy between Indigenous and general populations is on average 10 years[2]. Differences in health between individuals or population groups within society, or health inequalities, are labelled “inequities” when considered unfair[3]. There are differing views on what counts as unfair and moral judgements about fairness may vary over time and between cultures[4]. For example, men have a shorter life expectancy (with less disability) than women, and there is controversy about whether this is inequitable[5]. Two common guiding principles, frequently advocated in public health policy documents, are that health inequalities can be considered unfair when they are potentially avoidable by organized social action and when the situation that causes poor health is out of the control of those affected[6]. This includes situations where choices are severely restricted by social, historic, economic, or built environments. The causes of health inequity are multidimensional and include factors described as social determinants of health and health sector factors. For the purposes of this paper, we choose to define health equity in this way to reflect our collective interests in social justice, and the removal of social barriers posed by discrimination and stigmatization which affect participation by individuals or populations in opportunities for better health.

Healthcare decisions in most countries are commonly guided by different types of evidence, amongst which clinical evidence based on randomized controlled trials (“randomized trials”) usually holds particular prominence. To be useful for health equity policy, considerations for differences within and between groups and gradients of effects across socially stratifying factors are critical. Considering health equity is important to direct approaches that are either universal and intended to address health inequity for a whole population, or that are focused and directed at a specific subgroup that experiences health inequity. Improved reporting of health equity in randomized trials is important as some interventions can aggravate rather than reduce inequities (“intervention generated inequities”)[7]. A review of public health media campaigns for health behaviour revealed that health information provision was more effective in motivating behaviour change among socio-economically advantaged groups and widened the observed gap in health behaviour between socio-economically disadvantaged groups[7]. Although improving average health is an important social goal, increased inequity is an undesirable side-effect. The improved reporting of health equity implications of interventions is critical, and the increased use of randomized trial designs are promoted in the areas of public health[8] and international development[9] to build evidence that informs equity-oriented decisions.

Randomized trials provide evidence on the impact of an intervention and, in principle, can also assess their impact on health equity; however, randomized trials often fail to report relevant socio-demographic factors[10]. In addition, subgroup analyses, even when appropriately powered are rarely conducted to assess whether the impact of the intervention differs across sub-groups in society (for example, differential impact by socioeconomic status, place of residence)[11]. To address the poor reporting and analysis of equity impacts in randomized trials, we are assessing the need for additional reporting guidelines for randomized trials that provide evidence about potential impact on health equity[12]. An extension of the internationally recognized Consolidated Standards for Reporting Trials (CONSORT) statement, an evidence-based guideline to encourage completeness and transparency of reporting in randomized trials[13] is underway. The purpose of this paper is to describe the development and validation of a conceptual framework to identify when a randomized trial provides evidence about health equity. The conceptual framework may be helpful for the design and reporting of randomized trials by trialists, funders, journal editors, and other knowledge user groups.

METHODS

We convened a collaborative research team and advisory board including interdisciplinary and international knowledge users in a deliberative, consensus building process as part of a larger study described elsewhere[12]. We searched for and did not find any frameworks to define an equity-relevant randomized trial[12]. We then conducted a series of meetings that included representatives of potential knowledge user groups, including: bioethicists, clinicians, funders, journal editors, patient representatives, members of the public, policymakers, systematic review authors, and trialists. We engaged in a process to define features of randomized trials that provide evidence about health equity, which we define as “health equity-relevant” trials.

As a first step, we agreed on an operational definition of health equity for our work on health equity in randomized trials, drawing on social determinants of health theory that describes how socially structured health disadvantage is experienced and perpetuated[14]. We agreed, for this context, that the term ‘health equity’ implies that ideally everyone can attain their full health potential and that no one should be disadvantaged from doing so because of their social position or other socially determined circumstance[15]. Health equity addresses both access to health care as well as the broader concept of opportunities to achieve good health[6]. Moreover, we recognize that there are a range of characteristics of individuals or populations across which health inequities may exist, and that reasonable people hold different views about what counts as unfair[16].

Evidence shows that across the social determinants of health for individuals and population groups, people may experience disparities in health status, access to services, and the quality of care received[14]. Social determinants may be multifactorial and interact with one another. They can also be dependent on the context and setting, such as the local political or social climate and the form of health systems in which individuals and populations are situated[17]. One organizing framework is “PROGRESS-Plus” that depicts social determinants of health and enables the examination of the relationships within and between the multiple, interacting and socially-structured characteristics that may influence the opportunities for health of individuals and populations: **P**lace of residence, **R**ace[1]/ethnicity/culture/language, **O**ccupation, **G**ender/Sex, **R**eligion, **E**ducation, **S**ocioeconomic status, and **S**ocial capital[18-20]. Due to advances in thinking about causal associations/linkages between degree of control in the living environment and socio-economic inequities in health related outcomes, “Control” was included with “Social Capital”[21]. PROGRESS-“Plus” represents additional context-specific personal or setting characteristics that may be associated with health inequities and that are relevant to our study: 1) individual characteristics e.g. disability, age, sexual orientation; 2) features of relationships with effects on power differentials that impact personal autonomy e.g. children who suffer passive

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[1] We adopt the American Anthropological society (1998) statement on race: “Present-day inequalities between so-called "racial" groups are not consequences of their biological inheritance but products of historical and contemporary social, economic, educational, and political circumstances.”

smoking because their parents smoke in the home; and 3) time-dependent transitions e.g. migration and/or refugee status[22, 23]. The degree to which PROGRESS-Plus characteristics are associated with health inequity depends on time, place, and interaction between the different dimensions.

A conceptual framework was developed and feedback on the concepts and format of the conceptual framework was invited from over 40 clinicians and methodologists in face-to-face meetings, teleconferences and email. These communications used randomized trial examples to structure conversation and debate about the meaning of "health equity-relevant". Furthermore, we gathered opinions from many others in local seminars and at international conferences. This feedback was incorporated through iterative adjustments to the conceptual framework.

The conceptual framework was tested with the research team and advisory board[12]. A search for randomized trials was designed with a librarian scientist (JM) in MEDLINE, using text words and subject headings for the concepts of PROGRESS-Plus and a validated filter for randomized trials[24](Appendix A). We developed this search by testing whether it identified a reference set of 10 articles classified as health equity-relevant according to our framework[12]. The search was run from 2013-2015 and generated 4316 hits. Of these, 1,025 were judged to be equity-relevant based on title and abstract screening. These 1,025 articles were arranged in random order, then screened in full-text by two independent reviewers for eligibility using the criteria developed to define a health equity-relevant trial. We screened for eligibility until we identified 200 health equity-relevant trials, selected as the sample size for a concurrent methods study (in progress). The sample of trials was tested with the conceptual framework for consistency of concepts. Conversation and debate about concepts occurred and led to consensus around five aspects of randomized trials, and the definition was revised to reflect the consensus reached in these discussions. The research team and advisory board confirmed the final adjustments to the conceptual framework (Figure 1).

RESULTS

A randomized trial is considered to provide health equity-relevant evidence if it actually or potentially assesses the effects of an intervention on the health or its determinants of either individuals or a population who experience ill-health due to social disadvantage (Figure 2). These randomized trials can either exclusively focus on individuals or populations experiencing socially structured disadvantage, or consist of a mixed group and collect data potentially useful for assessing differential effects of the intervention across PROGRESS-Plus characteristics (Table 1). The evidence from these randomized trials may be used to mitigate socially structured health disadvantage, that is, contribute to understanding of the extent to which the intervention in question is effective in population groups who experience disadvantage. To identify 200 health equity-relevant randomized trials, 643 articles were screened. Screening confirmed that the criteria for health equity-relevance could be applied to randomized trials consistently.

Five aspects of randomized trials are reported as findings and reflect the debated points during the validation of the conceptual framework concepts. We considered five aspects of randomized trials and their relevance to define a randomized trial as health equity-relevant: 1) type of interventions, 2) stated objective about equity, 3) estimation of differential impacts, 4) levels of health equity-relevant data, and 5) setting and context.

Table 1. Examples of health equity-relevant studies

Includes individuals or a population that experiences ill-health due to social disadvantage (defined across PROGRESS-Plus) Assesses the effects of the intervention on the health or its determinants of either individuals or a population who experience ill-health due to disadvantage defined across one or more social determinants of health Either exclusively focus on individuals or a population, or includes a mixed group			
"PROGRESS" criteria examples		"Plus" criteria examples	
Assesses effectiveness of the intervention solely for groups who are considered to be at a social disadvantage	Assesses effectiveness of the intervention for groups considered to be at a social disadvantage compared with other groups considered to be at less of a disadvantage	Assesses effectiveness of the intervention solely for groups who are considered to be at a social disadvantage	Assesses effectiveness of the intervention for groups considered to be at a social disadvantage compared with other groups considered to be at less of a disadvantage
A trial of an intervention to prevent domestic violence in Aboriginal	A trial of an informed choice invitation on uptake of screening for	A trial that tests a vocational intervention aimed at improving employment for people	A trial of a schooling conditional cash transfer program on the behavior of young

communities[25].	diabetes in primary care assessed differences in effectiveness by socio-economic status[26].	diagnosed with severe mental illness[27].	women assessed effectiveness separately based on enrollment status at the start of the study: those who have dropped out versus stayed in school[28].

1. Type of intervention

We agreed that the type of intervention (e.g. pharmacologic, non-pharmacologic, health systems) was not relevant to identifying a randomized trial as health equity-relevant. Although health equity is sometimes considered relevant only to public health or upstream interventions, we found many examples of clinical or pharmacologic interventions that met our health equity-relevant definition. For example, we considered a randomized trial that evaluated a clinical intervention to promote asthma education for individual inner-city child asthma patients that improved health outcomes[29] to be health equity-relevant.

2. Stated objective about equity

We found that a randomized trial did not need to have an explicit objective about improving health equity to be classified as health equity-relevant. For example, a study that implemented a weight loss intervention for native Hawaiians and other Pacific Islanders did a secondary analysis of sociodemographic variables[30] but did not identify health equity, inequalities or disparities as part of its objectives. However, the analysis of effects across income groups provides evidence about effectiveness of treatment for a population that is potentially disadvantaged in relation to opportunities for health.

3. Estimate of differential impacts

For the sake of transparency and to assess whether observed interactions are likely to result from multiple comparisons, it is critically important that an *a priori* plan of analysis is described that all examined interactions are reported upon. Any post-hoc subgroup analyses of randomized trial data (e.g. across equity characteristics) are at risk of identifying spurious interactions, and need to be interpreted with caution. There is, however, increasing recognition that data disaggregation is particularly important, such as analyses across sex/gender[31]. The exploration of interactions should be situated within a theoretical perspective [32] and/or empirical evidence as a base from which effect measure interactions may be assessed. For health equity, it is important to also consider gradients of effect across social stratifying factors such as income quintiles or with indices that reflect distribution such as the concentration index[33].

Many randomized trials include a broad range of population groups, with limited details on socio-demographic characteristics and do not provide disaggregated data that could be used to assess whether effects of interventions differ between groups within the population. Furthermore, some randomized trials use detailed socio-demographic data to adjust analyses for baseline imbalances rather than deliberately exploring whether socio-demographic characteristics modify the effect of the interventions under study, thus losing the ability to assess similarities or differences in effects across these characteristics[34]. This represents a missed opportunity for providing evidence about equity.

When trialists do not have a pre-specified primary research objective of estimating differential impacts but nevertheless collect data on social determinants of health characteristics, then an opportunity exists to assess subgroup effects. The scope for a randomized trial to contribute health equity data may not be immediately apparent to the randomized trial designer. For example, even if each trial's statistical power to identify differential effects may be low, combining data from several trials, (e.g. in meta-analyses), may substantially enhance statistical precision to identify and estimate the strength of such interactions. Data from randomized trials can also be combined with data from observational studies, or analyzed with methods that incorporate explicit Bayesian priors and/or theories about differential impacts based on well-established bodies of evidence and theory. The problem of multiple tests and the effects on power can be addressed if all analyses of interaction are shown, as well as whether the interaction is defined as departure from "multiplicativity" or "additivity" or both. These interaction analyses should be described [35] in the randomized trial registration and in the protocol paper. It is our view that opportunities to provide health equity-relevant evidence should be considered up front in randomized trial conception and design and reported transparently. Thus, collecting data about outcomes across social determinants of health may provide useful information for future and additional analyses, now greatly facilitated by global initiatives to allow data-sharing[36].

It is equally important to report analyses where no differences in effects are found since these may identify hypotheses for testing in future studies and any failure to identify effects due to low statistical power. If a health program is equally effective in relative terms, if disadvantaged populations have a higher baseline risk, there will be a greater reduction in absolute events for disadvantaged populations[37]. Such information is valuable for understanding the impact and potential for interventions to improve or exacerbate health inequities.

4. Levels of health equity-relevant data

According to our conceptual framework, an equity-relevant randomized trial may both focus on individuals or a population experiencing socially structured disadvantage and collect data on differential impacts of the intervention in the form of subgroup effects, thus providing more than one level of health equity-relevant data. For example, a randomized trial of a video module that aimed to increase the use of a United States poison center by low-income parents is focused on a population experiencing social disadvantage, but it also provides evidence across language proficiency strata by conducting a subgroup analysis[38]. The use of different intervention approaches is complementary and aims to address the multifactorial and intersecting characteristics of populations and individuals that affect health outcomes.

5. Setting and context

The population characteristics that influence socially structured disadvantage depend on the broader features of setting and context such as social, historical and political systems and require careful consideration. For example, a study with Japanese citizens conducted in Japan would not be classified as an equity-relevant trial unless the participants were also considered to be disadvantaged across another dimension such as sex/gender or income.

We recognize that health equity concerns arise from an array of characteristics; judgments about particular individual or population health determinants are concerns for inequity and may be more difficult because of the need to carefully consider the context of the randomized trial and characteristics, such as age or disability. Studies that report interventions related to overcoming health disadvantage need to consider the relationship between the intervention and how it might relate to equity/inequity, such as an intervention to promote school enrolment and health outcomes between participants who have dropped out versus stayed in school[39].

DISCUSSION

Operationalizing a definition of a health equity-relevant trial required consideration of broader issues and meanings of social justice informed by values, context and the impact of different social arrangements. Our conceptual framework engages users to consider and identify the many instances of health equity-relevant evidence and the potential contributions to broader societal dialogues. The evidence from these randomized trials may be used to mitigate socially structured health disadvantage, that is, contribute to understanding of the extent to which the intervention in question is effective in population groups who experience disadvantage

The conceptual framework is proposed as a way to identify and operationalize understandings about how randomized trials can provide evidence about health equity and in particular complements two previous intervention frameworks related to improving health equity. Margaret Whitehead's typology is based on the underlying theory of change and guides consideration of appropriate application of interventions to address health inequity; interventions fall into one of four main categories: strengthening individuals; strengthening communities; improving living and working conditions; promoting healthy macro-policies[15]. Hilary Graham's typology identifies three main approaches: addressing health inequity gaps, gradients or targeted approaches[40]. Our conceptual framework builds on these classification systems and suggests ways randomized trials can provide health equity-relevant evidence for an intervention, even when providing evidence about equity is not the central aim. Our conceptual framework has potential applications to inform other study designs, and is not limited to that of randomized trials.

It is our view that opportunities to provide health equity-relevant evidence should be considered up front in randomized trial conception and design and reported transparently. While different users will hold different definitions and priorities in regards to disadvantage and opportunities for health, we argue that consideration of individual or population characteristics and societal context is of paramount importance. Moreover, consideration of equity aligns with and supports an approach to decision-making that enables consideration of distributional goals, and outcomes aimed at addressing health inequity[40]. Knowledge about differential effects (or lack thereof) using social determinants of health theory, operationalized across PROGRESS-Plus characteristics can contribute to build knowledge aimed at improved application of effective interventions.

The approach to health equity supported by the conceptual framework promotes thinking about randomized trials as more than just a means of developing evidence about average efficacy or effectiveness. It highlights opportunities for all randomized trials to contribute to a broader social agenda about reducing health inequity. In doing so, it upholds international policy on "research for health" that advocates for the development of research methods to promote better knowledge and standardization of reporting mechanisms[41, 42].

Limitations and strengths

A limitation of this approach is that analyzing and publishing disaggregated data can be expensive and it is not desirable for all randomized trials to do subgroup analyses by PROGRESS-Plus characteristics. We propose that, when possible, data on equity-relevant characteristics be collected, even when the study may not have sufficient power to perform sub-group analyses. In this way, data about characteristics linked to health equity may be made available for other researchers to use in pooled analyses, modeling or systematic reviews. Additionally, other knowledge sources/systems are essential to understand health inequities and not all social determinants of health are a source of "disadvantage". As well, relationships within and between social determinants of health mean that there may be a need to explicitly identify the factors that are relevant and therefore have been focused upon, as not every facet of inequity is relevant to every research question. The proposed conceptual framework, therefore, is designed to engage users in deliberation about designing and reporting studies that can provide evidence useful to understand distribution of effects, rather than only average effects. Strengths of the conceptual framework are the use of a collaborative approach to development, and the iterative testing of the framework with examples of randomized trials.

CONCLUSION

The conceptual framework defines features of health equity-relevant trials that can be used to design and report both randomized trials and other study designs to improve the evidence base about how to improve health equity. Opportunities to provide health equity-relevant evidence should be considered upfront in trial concept and design. The conceptual framework can provide a stimulus to build knowledge about effects of interventions on health equity and is a first step to improve application of effective interventions and to build evidence that is of greatest relevance and use to individuals and populations.

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Contributions: JJ and VW conceptualized the study design. JJ led the writing and coordination of the manuscript development. JJ, MW, MP, EK, DG, JP, JV, CW, MT, SE, LM, RC, JM, AL, YB, LCG, RA, HW, MY, TP, BS, KP, ON, SB, BR, HS, YA, GW, PT, VW provided substantial input on the direction of the study and the development of the conceptual framework. All authors participated in the critical revision of the manuscript for important intellectual content, and approved the final version of the manuscript.

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Figure 1. Description of the conceptual framework development process

Figure 2. The Conceptual Framework

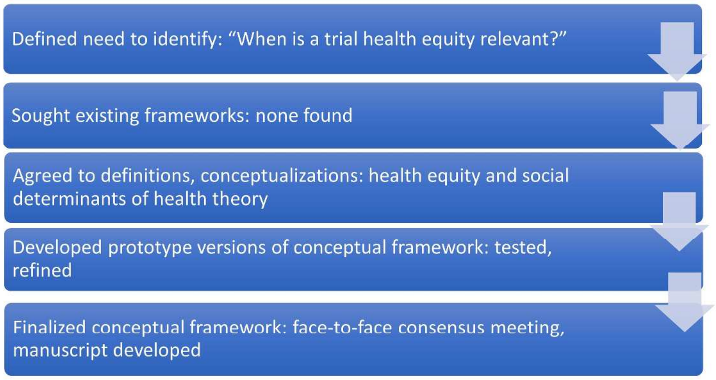

Figure 1. Description of framework development process

338x190mm (300 x 300 DPI)

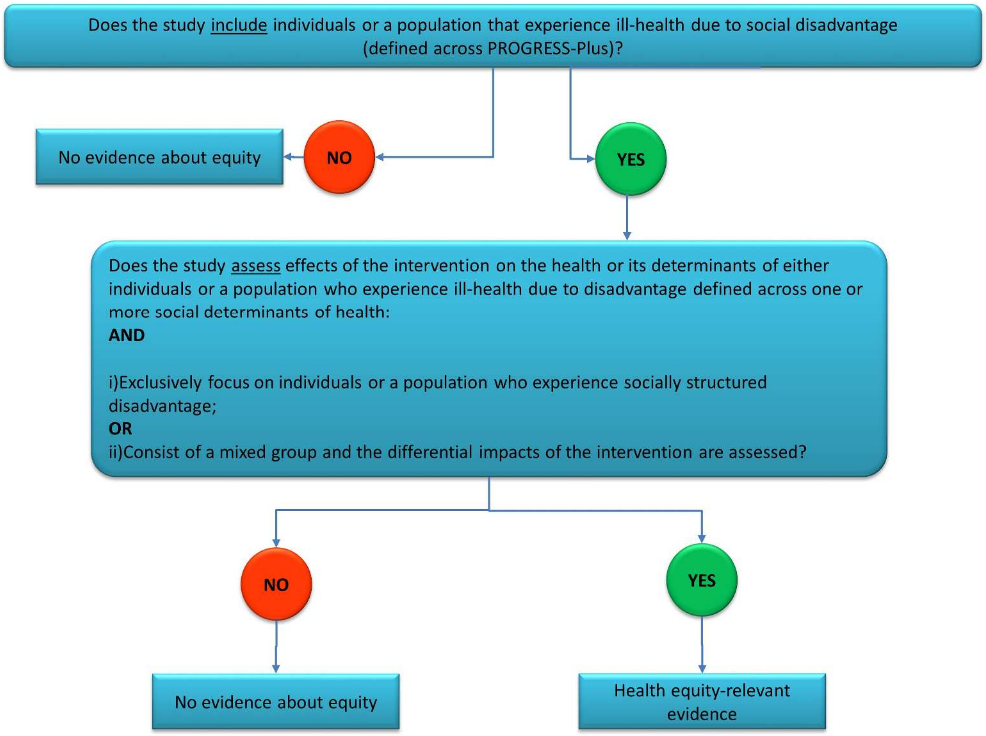

Figure 2. Conceptual framework

254x190mm (300 x 300 DPI)

Appendix A

1. exp Gender Identity/

2. (gender-based or gender-related or gender factors).tw.

3. ((sex or gender) adj2 (analysis or factor$ or inequit$ or disparit$ or inequalit$)).tw.

4. exp sex factors/

5. exp geriatrics/

6. ((ethnic$ or race or racial or religio$ or cultur$ or minorit$ or refugee or indigenous or aboriginal) adj3 (analysis or disparit$ or inequalit$ or inequit$)).tw.

7. exp homosexuality/

8. exp disabled persons/

9. ((poverty or low-income or socioeconomic$ or socio-economic$ or social) adj2 (analysis or disadvantage$ or factor$ or inequalit$ or depriv$ or inequit$ or disparit$)).tw.

10. exp Educational Status/

11. exp Socioeconomic Factors/

12. ((discriminat$ or social exclu$ or social inclu$) adj3 (religion or culture or race or racial or aboriginal or indigenous or ethnic$)).tw.

13. ((urban or rural or inner-city or slum) adj2 (analysis or inequit$ or disparit$ or inequalit$)).tw.

14. ((resource-poor or (low-income adj countr$) or (middle income adj countr$) or africa or developing countr$ or south america or china or asia or latin america) adj2 (relevance or analysis or applicab$ or inequit$ or disparit$ or inequalit$)).tw.

15. (inequalit$ or in-equalit$ or equit$ or inequit$ or in-equit$ or disparit$).tw.

16. exp indigenous populations/

17. ((native* or Indian or aborigin*) adj2 (American* or Canadian* or Alaska*)).tw.

18. (first adj2 nation*).tw.

19. (aborigin$ or metis or inuit$ or eskimo$ or esquimaux or aleut or yuit or inughuit or unanga* or alutiiq or inup#ia* or kalaallit or Inuktitut or Nunavut or nunavik or cree or dene or haida or

salish or Mohawk or ojibway or yupik or tribal or arctic).tw.

20. exp american native continental ancestry group/ or oceanic ancestry group/

21. or/1-20

22. randomized controlled trial.pt.

23. Clinical trial.mp,pt.

24. (random$ or placebo).mp.

25. (field experiment or field experiments).tw.

26. (cluster$ adj2 randomi$).tw.

27. or/22-26

28. 21 and 27

29. limit 28 to english

30. limit 29 to yr="2013"

31. limit 29 to yr="2014"

32. limit 29 to yr="2015