Advancing Health Technology Assessment Methods that Support Health Equity

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Executive Summary

The primary objective of this paper is to establish methods for health technology assessment (HTA) in the United States (US) that will ensure that HTA advances society's goal to improve health equity for racial, ethnic, and other socially disadvantaged groups. HTA evaluates the evidence on health care technologies such as new drugs or surgical devices to provide information used by health insurers and other policymakers in decisions about insurance coverage, pricing, and payment.

The paper presents a list of recommendations to improve consideration of health equity within every step of an HTA review. Several key recommendations include:

1. HTA bodies should engage directly with patients and patient groups during the scoping of reviews to learn about the experiences of diverse groups of patients and understand their views of the potential impact of the intervention under review on health equity.

2. Establish a minimum threshold for adequate representation of racial and ethnic populations in clinical trials to provide incentives for improvement.

3. Even if clinical evidence suggests differences in the magnitude of net benefit by race, ethnicity, or socioeconomic status, do not calculate cost-effectiveness estimates for subpopulations defined solely by these characteristics.

4. Avoid using quantitative equity-informative economic evaluation as a substitute for a deliberative process that should integrate multiple important social values in policy decisions.

5. Use deliberative processes to highlight structural aspects of the health care system that should be changed in order to ensure that disparities are not worsened with the introduction of new interventions.

We have framed the findings of this paper as action statements, and ICER will immediately take each of these action statements as guides to our methods and procedures going forward. We will also disseminate this document among other HTA groups internationally, some of which have launched their own initiatives to examine equity more deeply. We will share this work with leaders in government who are responsible for the management of groups involved in HTA, including the Agency for Healthcare Research and Quality, the United States Preventive Services Task Force, and the Medicare Evidence Development and Coverage Advisory Committee. And we will ensure that life science organizations and payers with which we interact are aware of these recommendations and understand that we will hold them accountable for partnership in taking action to improve health equity in the US.

Introduction

The primary objective of this paper is to establish methods for health technology assessment (HTA) in the United States (US) that will ensure that HTA advances society's goal to improve health equity for racial, ethnic, and other socially disadvantaged groups. HTA evaluates the evidence on health care technologies to provide information used by health insurers and other policymakers in decisions about coverage, pricing, and payment that affect all Americans. The audience for this effort is broad and includes the following major groups: 1) HTA bodies, including those in the US and international HTA agencies also engaged in re-examining issues related to health equity; 2) life science companies and clinical researchers who design and conduct clinical trials that produce evidence to be assessed within HTA; 3) patient advocates and patient groups that engage with industry, HTA bodies, and payers to seek improved health equity; 4) academic researchers and organizations working as partners of HTA activities; and 5) payer and life science organizations that apply the results of internal and external HTA in making decisions about pricing and coverage.

Best practice in independent HTA conducted by groups like ICER requires that scientific methods to assess evidence be applied within a broader set of procedures for stakeholder engagement and public deliberation meant to align HTA with society's ethical goals.[1,2] One of these central goals is health equity, generally interpreted as meaning equal access to health care resources and the granting of extra priority to those services that would help reduce disparities in health outcomes for groups such as racial and ethnic communities that have been subject to historical patterns of racism.[3]

However, HTA is not intended to achieve only the single goal of improving health equity. It must also provide information that will help society achieve the most effective use of limited health system resources to maximize population health. Some have argued that pursuit of this other goal favors methods that potentially undermine health equity.[4-7] The underlying paradigm of HTA has also been criticized as reflecting the unequal power structures of our current society, creating a dynamic that disenfranchises the voices needed to address the roots of health inequity.[8] Areas of particular concern include the methods used to interpret clinical trial evidence that is not adequately representative of racial and ethnic minority groups; the way that quality of life and health gains are measured within cost-effectiveness analysis; the question of whether special priority should be given to the health of certain groups in society in order to close health disparities; and the role provided for patients and families to contribute to the HTA process.

For all these areas, there remains no consensus on best practices across academics, international HTA agencies, or private payers.[9] Perhaps in the past it has been too easy to claim that the scientific methods of HTA are objective and "neutral," but this status quo is no longer acceptable. As the US wrestles more openly with its legacy of racism and broader forms of discrimination, the

need to re-examine the relationship between HTA methods and ethical values has become urgent. Progress must be made to ensure that the methods of HTA fully incorporate considerations of health equity, and that the products of HTA provide policymakers with the tools they need to integrate considerations of health equity into all decisions in a robust, transparent manner.

Health Equity and the Scope of this Paper

There are numerous definitions and perspectives on the idea of health equity. One well-known definition has been proposed by the Centers for Medicare and Medicaid Services (CMS):

Health equity means the attainment of the highest level of health for all people, where everyone has a fair and just opportunity to attain their optimal health regardless of race, ethnicity, disability, sexual orientation, gender identity, socioeconomic status, geography, preferred language, or other factors that affect access to care and health outcomes.[10]

Another commonly cited definition is that promulgated by the World Health Organization (WHO):

Health equity is the absence of unfair, avoidable or remediable differences in health among population groups, defined by social, economic, demographic or geographic characteristics.[11]

Central to both definitions is the idea that all people should have an equal opportunity to achieve their optimal health, free of any barriers related to any personal characteristic – their race, ethnicity, gender identity, preferred language, where they live, etc. Given the practical challenges of covering the entire spectrum of health equity issues in this paper, and the recent heightened appreciation of the impact on health and wellbeing of ongoing racism embedded in US society, we have chosen to focus this paper on health inequity related to racial, ethnic, and socioeconomic status. We have included socioeconomic status because it is often correlated with race and ethnicity and because emerging methods in HTA using socioeconomic data offer new ways to understand health inequity.[1] Data on race, ethnicity, and socioeconomic status are often incomplete in the evidence generated by life science companies and not available to HTA bodies, so in this paper we also consider examining people's location or place of residence as a tool for assessing health inequities ultimately tied back to race, ethnicity, and/or socioeconomic status.

This is not to suggest that discrimination and other forms of inequity against people for other reasons related to their identity is not an ongoing, important problem for the US. For example, there are many layers of equity issues faced by people living with disabilities.[12] Separately, we have worked with members of the disability community to explore concerns regarding the potential for discrimination when the quality-adjusted life year (QALY) is used as the measure of health gain in cost-effectiveness analysis. Those discussions led to the development of a new measure, the equal value of life years gained (evLYG) that values extended life equally for all people, no matter their age or functional status.[13] There are many other people and communities that face inequity in the US health care system, and in no way should this paper be interpreted as suggesting that equity concerns for the US and for HTA are limited to racial, ethnic, or socioeconomic status. The focus of this paper does not imply that the needs and the goals of health equity are narrow.

Approach and Major Areas of Focus

This paper is one major product of an overall initiative to evaluate the health equity implications of HTA. We will focus on all of the major functions of HTA, including both procedures and methods, to explore the potential advantages and disadvantages of ways to improve their concordance with the goal of health equity. The project has been informed by the views of an Advisory Group of diverse health care participants. The ICER project team also performed interviews of six key opinion leaders and methods experts identified through a literature search and recommendations from the Advisory Group. These interviewees are noted in the Acknowledgments. Their interviews supplemented ICER's knowledge of this field and were used to generate ideas for new methods as well as to gather opinions on the potential advantages and limitations of existing methods that have been proposed to address health equity concerns.

There are several important limitations to our approach that should be noted. We did not perform a formal systematic review of methods in the literature or of practices of all international HTA bodies, although we did benchmark directly against the methods in use at the National Institute for Health and Care Excellence (NICE) in the United Kingdom, and the Canadian Agency for Drugs and Technology in Health (CADTH). We did not coordinate our efforts with other groups in the US embarked on similar efforts, including those organized by the Robert Wood Johnson Foundation, CMS, the Academy of Managed Care Pharmacy, and others. Additionally, although we worked closely with our Advisory Group, we did not publish a draft of this paper for public comment. These choices were made in light of the goals of this paper and limitations in the scale of what was feasible for us to accomplish within a reasonable time frame.

The major areas of focus for the paper are the following elements of HTA:

1. Selecting health care interventions for assessment
2. Engaging patients and patient groups in the HTA process
3. Evaluating the diversity of participants in clinical trials
4. Analyzing results by subpopulations
5. Measuring the opportunity to reduce health disparities
6. Promoting health equity through quantitative methods of cost-effectiveness analysis
7. Promoting health equity through deliberative methods of appraisal

For each of these areas of HTA practice, the white paper will describe current practice, including the range of approaches used by academics and at HTA organizations internationally.

The potential impact of current methods on health equity concerns will be evaluated, following which we will present a list of potential new methods that may help improve the ability of HTA to advance health equity. Each potential new method will be analyzed for advantages and limitations.

Selecting Interventions for Assessment

The scope of health care interventions to be reviewed, and the timing of those reviews, are often mandated by law for international HTA agencies. In many countries, funding/reimbursement of an intervention requires approval of the national HTA agency, and in this situation "sponsors" of drugs or other interventions determine when to submit information to commence an HTA review. However, for HTA organizations that do not have the resources or the mandate to review all new drugs or other interventions, the selection of topics reflects the confluence of multiple considerations. The Agency for Healthcare Research and Quality's Effective Health Care Program makes available a list of selection criteria for its evidence reviews, but none addresses health equity or health care disparities.[14] As shown below, the second to last of ICER's current criteria for prioritizing topics for review focuses on health disparities:

- Represent important new treatments or other interventions that offer significant potential for improved patient outcomes, such as drugs with new mechanisms of action or delivery system innovations that could change the paradigm of care for many patients
- Are likely to raise new questions about the comparative clinical effectiveness of similar treatments
- Have the potential for significant financial impact on patients and the health system, either by the costs of the intervention itself or by setting a pricing precedent that may affect many other treatments
- That present new opportunities to improve health outcomes and/or health system value through specific clinical or policy actions by payers, physicians, patients and policymakers
- Are particularly relevant to the public due to prevalence, severity, disparities, and cost
- Are likely to receive FDA approval within 1 year [emerging drug or device therapies only]
- Examine potentially overused or underused treatments or tests
- Address wide variation in approaches to delivery system design and/or financing
- Involve underserved communities with the potential to reduce health disparities
- May leverage current health reform initiatives

One of the challenges of considering health equity as a consideration in topic selection is determining how to define it and whether a more algorithmic approach to topic selection is needed in order for health equity to play a consequential role among the many other considerations. A second issue is whether HTA is viewed in general as a function that is required or accelerates funding for services or one that is more likely to reduce access. This context will shift depending on the evidence supporting the intervention, its perceived cost-effectiveness, and the specific insurance and delivery system of greatest relevance. Nonetheless, it is important to recognize that

in some situations the patient community will welcome HTA of a new intervention that may be of specific help for them, whereas in other situations the selection of an intervention for HTA review will be viewed as a negative, and patients would prefer that an HTA organization avoid evaluation of a particular intervention, even if the intervention itself is one with the promise to reduce disparities in health outcomes.

Recommendations:

1. **Establish clear mechanisms such as formal checklists for integrating health equity considerations into topic selection.**

2. **HTA bodies should engage directly with patients and patient groups during the scoping of reviews to learn about the experience of diverse patients and understand their views of the potential impact of the intervention under review on health equity.**

Discussion: Health equity is one of many different criteria that HTA programs should use to prioritize topics for assessment. To help formalize consideration of health equity, measures of the impact of health inequity should be considered for formal inclusion in deliberations on topic selection. One of these measures is health disparities across racial, ethnic, or socioeconomic groups. Evidence on whether these groups experience systematically worse outcomes in a particular treatment area should be included in information discussed during topic selection.

Although health equity considerations should be weighed explicitly alongside other selection criteria, it is unlikely that an algorithmic approach similar to multi-criteria decision analysis (MCDA) can be made consistent enough to be employed to guide topic selection. Moreover, the data to support full MCDA including equity considerations does not exist. Nonetheless, to avoid the risk of relegating health equity to a minor role, it seems reasonable to have a formal checklist of all criteria that must be consistently used to guide internal HTA discussions on topic selection.

Lastly, topic selection begins a phase of "scoping" of an HTA review. During scoping the HTA program should engage with patients and patient groups directly to seek their guidance on many aspects of the upcoming review. Learning about the experience of diverse patients and their views of the potential impact of the intervention on health equity should be listed as a key goal of the HTA program before they begin to analyze evidence or pursue other facets of the assessment.

3. **When a topic under consideration for HTA review involves a condition of high priority for particular racial, ethnic, or other disadvantaged communities, engage in discussion with the relevant communities to understand their perspectives on the potential impact of the assessment.**

Discussion: As noted above, HTA programs should be aware that the relevant patient community for a given health care intervention may prefer to avoid HTA review if possible. Although this consideration should not govern whether topics are selected, it will be important for the HTA program to address this issue at the very outset of topic consideration so that patient community concerns can be addressed as quickly as possible.

4. **Ensure that health equity is viewed as a factor in the scoping of all reviews, not just those in which the preponderance of individuals are from a racial or ethnic community.**

Discussion: Even when a topic has been selected that is equally prevalent across racial and ethnic communities, there may be access inequities that lead to important disparities in outcomes. And even if there are no known notable disparities in health outcomes, HTA programs should still seek input on the role that health inequity plays in the current treatment/access landscape, and the potential impact of the intervention in addressing those inequities.

Engaging Patients and Patient Groups in the HTA Process

The central importance of patient engagement across the functions of HTA has gained greater attention in recent years.[15] A review of international examples of patient and public involvement in HTA shows how the incorporation of patient perspectives can add important dimensions often overlooked in the evaluation of health technologies.[16] Involvement of patients and patient groups during the HTA process can be a valuable collaboration for both the patient community as well as the HTA body; early engagement provides an opportunity for the patient community to influence the scope and context of the assessment, and ground the health economic modeling and meeting deliberations on what matters most to the patient.[17] When done well, patient engagement in HTA can create assessments that best represent those directly affected by the health intervention under review.[17]

However, in order for patient groups to meaningfully participate in an HTA process, significant commitment may be required in terms of staff resources and the time needed to become familiar with HTA methodology and to engage the larger patient community.[17] Taking steps to ensure inclusion of diverse elements across the community can prove challenging in light of the speed and intensity of an HTA assessment. There are many barriers to getting input from patients from diverse backgrounds, including health literacy, lack of trust in health care authorities, and geographic and socio-economic factors.[18] But to address health equity, and to build a truly patient-centric process for understanding the preferences and experiences of all patients, it is imperative that HTA programs and organized patient groups work together to bring diverse views into HTA and the review process.

Recommendations:

1. **Broaden connections with patient and public networks to gain more diverse input into HTA evaluations.**

Discussion: HTA programs need to broaden the methods they use to connect with patient communities. There are multiple avenues for achieving this goal. First, in addition to partnering with disease-specific organizations for an assessment, HTA programs should expand their outreach to include advocacy groups that represent a greater diversity of the patient community. Examples of such advocacy groups include the Black Women's Health Imperative, the National Hispanic Health Alliance, Asian Women for Health, the Association of Asian American Community Health Organizations, the Patient Advocate Foundation's Patient Insight Institute, and the National Coalition for LGBTQ Health.

HTA programs can also expand their networks by working with local community and faith-based institutions and individual leaders. Community-based organizations are culturally and linguistically effective in responding to the priorities of their community, and can be helpful intermediaries to communicate patient needs and preferences to improve health equity.[19] These organizations and individuals can help advise on appropriate language/terms, engagement methods, and how to elicit patient input effectively for HTA research purposes.

Second, HTA programs should encourage and expect patient groups to conduct substantial outreach and engagement with patients from diverse racial, ethnic, and socioeconomic communities when submitting input into an assessment. And third, HTA programs themselves can seek connection with individual patients beyond those connected to patient groups. Clinical experts and life science companies can be asked for referrals of patients who may wish to participate. In addition, social media can also be used to recruit individuals with diverse backgrounds and experiences to participate in HTA activities. Once identified, there is likely to be further education needed to help ensure full inclusion of those patients throughout the HTA process.

2. **Address barriers that hinder the inclusion of diverse patient perspectives within the current patient engagement framework.**

Discussion: There are several important steps that HTA programs can take to reduce the risk of patients facing specific barriers to engagement that will undermine the broader goal of inclusiveness in the service of health equity. First, all materials created to inform and guide patients in engagement with the HTA program must be accessible to patients from diverse backgrounds. This includes attention to levels of technical jargon, and ideally should include formal translations or mechanisms through which individuals can access guidance from someone who speaks their preferred language. Tools to guide the development of accessible health materials are available from sources such as the Agency for Healthcare Research and Quality.[20] With 45 million Americans unable to read above a 5th-grade level,[21] low literacy should be a primary consideration when developing HTA data collection tools and methods.

Second, logistical and financial barriers to broader inclusion must be addressed. For in-person meetings, some mechanism must exist for consideration of the transportation needs of patients living in different communities. In addition, not all people are able to take time off during the workday to attend a call with an HTA program or participate in public testimony at a meeting. HTA programs therefore need to have a formal plan for accommodations to minimize these barriers, such as scheduling calls outside of regular hours or allowing remote or recorded testimony at a public meeting.

Third, HTA programs should have a clear framework for managing potential financial barriers to participation in HTA evaluations and other activities. Not every HTA program will have the resources to compensate patients and patient groups for submitting information or participating in a limited number of calls or meetings. However, patients who engage more extensively, including providing expert review of entire draft reports, and participating on policy roundtables within public HTA meetings, should be compensated at the same level as other experts or stakeholders. HTA programs may also explore options for non-financial support such as providing limited child or elder care support when needed.

3. **Adopt methods of patient insights research to reduce barriers for individual patient input.**

Discussion: In addition to gathering input from direct involvement of patient representatives, HTA also considers patient perspectives through reviews of patient-based evidence.[22] For example, Social Media Research (SMR) has been proposed as another solution to improve the representativeness and comprehensiveness of patient insights for HTA, as long as appropriate measures are taken to address the ethical, legal and social considerations in gathering and using such information for HTA purposes.

A framework for applying SMR to HTA is currently under development by the HTAi Patient and Citizen Involvement Group.[23] Although we are unaware of real-world case studies of the use of SMR data, this group argues that SMR could be used to identify themes and inspire new ideas, with the intention of follow-up with more robust methods to further explore those themes. The HTAi group also recommends that validation of SMR insights should be sought through other types of evidence (e.g., testimonials, surveys) to strengthen the credibility of SMR.

4. **Consider the creation of an Advisory Group to give one-time or ongoing input into the health equity implications of HTA methods and procedures.**

Discussion: HTA programs can benefit from concerted input from an external Advisory Group that includes representatives with diverse experience in working with communities across the range of racial, ethnic, and socioeconomic status. Advisory Groups of this type could help HTA staff prioritize areas for examination, explore implicit bias in the underlying assumptions about how HTA should function, and pressure-test potential changes to methods and procedures prior to implementation. Advisory Groups can also serve as excellent sources of connections with others who may have complementary expertise to help guide HTA efforts to address health equity.

Evaluating the Diversity of Participants in Clinical Trials

Since HTA commonly takes place near the time a new drug or other intervention enters practice, it relies primarily on evidence from clinical trials to inform the evaluation of the relative effectiveness and risks of health technologies. However, the lack of diversity in clinical trial populations, which has implications for generalizability, fairness, and public trust, continues to be a challenge. Efforts have been made by federal research and regulatory authorities over the last three decades to create policies and guidance for researchers and industries to enhance the diversity of clinical trial populations. One such effort is the National Institutes of Health (NIH) Revitalization Act of 1993, which mandated the inclusion of women and racial and ethnic minority groups in clinical trials.[24] This policy has been updated in more recent years to help improve compliance and reporting.[25] Likewise, the US Food and Drug Administration (FDA) has issued successive guidance documents that have called for greater diversity in clinical trials. The FDA guidance documents have addressed various topics, ranging from requiring the use of standardized terminologies for demographic information[26] to modifications of eligibility criteria, enrollment practices, and trial designs.[27] Notably, in 2022, the FDA provided a draft set of recommendations for clinical trial developers on the approach to developing a race and ethnicity diversity plan that will lead to greater representation of underrepresented racial and ethnic populations.[28] The Food and Drug Omnibus Reform Act (FDORA) enacted in December 2022 now requires clinical trial sponsors to submit "diversity action plans" to FDA for most drug and device studies based on the draft FDA guidance unless otherwise waived or excepted.[27]

Despite the existing policies and guidelines from NIH and FDA, analysis of recent trials shows that racial and ethnic minority populations in the US continue to be largely underrepresented. For example, an evaluation of 290 FDA-approved drugs posted on FDA Drug Trials Snapshot between 2014 and 2021 showed that Black or African American participants were underrepresented in about 85% of clinical trials, with a median representation of about a third of the disease burden in this population.[25] Similarly, an analysis of over 200 pivotal clinical trials used to inform 31 ICER assessments showed that relative to the disease population, Black or African American people were underrepresented in over 70% of the trials, while Hispanic or Latino people were underrepresented in about 50% of the trials.[29] Another analysis showed that industry-funded trials were associated with less reporting of race and ethnicity and with a lower representation of racial and ethnic minority groups compared to trials funded by the US government.[30] The pivotal clinical trials of aducanumab, a high-profile new treatment for Alzheimer's disease, offer a notable example of the scope of the problem: even though Alzheimer's disease is more prevalent among people in communities of color in the US, Black or African American and Hispanic or Latino individuals made up only 0.6% and 3.2%, respectively, of the over 3000 patients enrolled in the two aducanumab pivotal trials.[31]

In recent years, there has been a broad call to action to improve diversity in clinical trial enrollees from many stakeholders. For example, many individual pharmaceutical companies have created initiatives including proactive solutions such as dedicated clinical trial diversity internal teams, training for clinical trial sites, modifying recruitment, trial eligibility, and specific elements of protocol design, and establishing baseline data on diversity from which to assess future progress.[32-36] Patient groups and advocacy organizations have continued to provide awareness about the lack of diversity in clinical trials and have taken on prominent roles in training and facilitating partnerships with communities to learn more about barriers to clinical trial participation. The Metastatic Breast Cancer Alliance BECOME (Black Experience of Clinical Trials and Opportunities for Meaningful Engagement) Research Project, which aimed to better represent Black people in cancer research by increasing access to clinical trials, is an example of such community partnership projects.[37] As for payers, although private insurers have less leverage over the clinical trial development programs for new drugs and devices, the Centers for Medicare and Medicaid Services (CMS) has recently leveraged its "Coverage with Evidence Development" policy as a payer to require that qualifying studies recruit and retain participants that are representative of the populations affected by the condition.[38,39]

A recent report from the National Academies of Sciences, Engineering, and Medicine, which highlighted the serious costs and consequences of the lack of clinical trial diversity, provided detailed system-level recommendations on ways to drive change on a broader level.[40] These recommendations focused on four major themes: 1) reporting and accountability; 2) federal incentives; 3) remuneration; 4) education, workforce, and partnership. Given the unique role HTA plays in providing a systematic analysis of clinical effectiveness, social and economic impact, and the ethical and contextual considerations associated with using a health technology, HTA bodies have a large role to play in support of the first theme (enhancing the transparency of reporting and accountability), by developing standardized approaches to evaluating clinical trial diversity that can hold evidence developers accountable.

Recommendations:

1. **Evaluate racial and ethnic diversity using established racial and ethnic categories.**

Discussion: Although there is no clear consensus on how to define race and ethnicity, in the US, the Office of Management and Budget (OMB) established definition of five racial categories (White, Black or African American, American Indian, and Alaskan Native, Asian, and Native Hawaiian and other Pacific Islander) and one ethnic category (Hispanic or Latino) is used for federal research and regulatory purposes. Specifically, the NIH Revitalization Act of 1993 was revised in 2001 to help improve consistent reporting of race and ethnicity by requiring the use of OMB's racial and ethnic categories in all NIH-defined Phase III clinical trials.[25] Similarly, the FDA released a guidance in 2016,

which provided instructions on using the OMB's standardized racial and ethnic categories for regulatory purposes.[26]

However, it is worth noting that the OMB race and ethnicity definitions were developed in 1997 and have not been revised since; therefore, these definitions may be missing the specificity of the changing US population. Relatedly, some of the categories are somewhat arbitrary and combine widely diverse groups (e.g., "Asians") in single buckets. Updates to how census race and ethnicity data is collected and classified have been proposed.[41] However, for now, using the OMB racial and ethnic categories in the US context is currently the best approach to move beyond the previous simplistic definitions of race (e.g., White versus non-White) into more representative categories. Furthermore, although the reporting of race and ethnicity is still generally poor, the majority of clinical trials that capture and report race and ethnicity typically adhere to the OMB-defined categories. Therefore, these established categories provide a baseline to evaluate racial and ethnic diversity in a consistent manner across trials.

2. **Evaluate clinical trial diversity quantitatively by comparing to disease-specific prevalence estimates.**

Discussion: Many published analyses on clinical trial diversity define 'adequate representation' based on population demographic breakdown (e.g., using the US Census estimates). While this represents an important way of evaluating if a clinical trial is representative of the population, using the epidemiology of the condition will more likely be reflective of the broad goal of clinical trial diversity – for a clinical trial to be representative of the intended patient population likely to use the health technology being evaluated.

A potential limitation of this approach is the lack of reliable disease-specific prevalence estimates for some racial and ethnic groups, particularly in the case of rare diseases. Furthermore, because there is no consensus on how to define race and ethnicity, groups and researchers that generate epidemiologic studies need not adopt the minimum race and ethnicity categories defined by OMB. Thus, the prevalence estimates from some of these sources for some conditions may have racial and ethnic categories that do not match the racial and ethnic categories reported in clinical trials, limiting the use of such data. When there are no reliable disease-specific prevalence estimates, considerations should be given to evaluate clinical trial diversity based on population estimates (e.g., US census demographic breakdown) and to interpret the finding accordingly.

3. **Establish a minimum threshold for adequate representation of racial and ethnic populations to provide incentives for improvement.**

Discussion: There is currently no minimum threshold for adequate representation of racial and ethnic groups in clinical trials. However, a "participation-to-prevalence ratio" between 0.8 and 1.2 was previously used by investigators to indicate adequate representation of women in clinical trials

and <0.8 or >1.2 to represent under or overrepresentation.[42,43] We explored a modified version of this criteria in evaluating the diversity of the clinical trials informing ICER assessments, using a criterion of <0.8 to represent underrepresentation for any demographic characteristics being examined (race, ethnicity, sex, age) and ≥0.8 to indicate adequate representation.[29] This approach has the advantage that it is very easy to apply and interpret. For example, if Black or African American individuals represent about 10% of a particular disease population, a clinical trial with at least 8% Black or African American participants will be considered to adequately represent Black or African American individuals (8/10 = 0.8).

A minimum participation-to-prevalence ratio of 0.8 for each racial and ethnic group helps to achieve the goal of inclusiveness, with the benefit of improving our understanding of the relative effectiveness and safety of the intervention in different populations. However, it is important to note that in many cases and for some of the racial and ethnic groups, even if the clinical trial population matches the intended patient population 1:1, the trial may still not be adequately powered to examine subgroup differences. Therefore, in situations where prior data indicates that an intervention may perform differently for a subpopulation defined by race or ethnicity, it would be important for investigators to consider the appropriate study design and power requirement that would allow for further subgroup analyses. In other situations, when no prior data indicates race or ethnicity will impact safety or effectiveness, using the proposed criteria of a participation-to-prevalence ratio of at least 0.8 helps to achieve the goal of inclusiveness and may still allow for testing hypotheses that can be followed up with an adequately powered study.

4. **Provide an overall diversity rating for each trial that communicates the racial and ethnic diversity of the clinical trial population.**

Discussion: Providing an overall rating that captures the demographic diversity of clinical trials included in HTA will elevate the conversation on clinical trial diversity and enhance transparency and accountability, consequently promoting equity in clinical trials of new drugs. Furthermore, it encourages and recognizes the efforts of drug developers that have appropriately included diverse participants in their drug development program and reassures patients that the approved drugs were tested in trial participants like them.

Based on the potential best practices described above, ICER has developed a framework that can be used to evaluate the demographic diversity (race/ethnicity, sex, age) of clinical populations, which includes providing an overall sample diversity rating that all stakeholders can easily interpret. Specifically, on race and ethnicity, the ICER-developed framework assigns a score that ranges from 0 to 3 to each racial and ethnic category based on the estimated participation-to-prevalence ratios. Then, using the cumulative score and pre-defined cutpoints, a rating of "good," "fair," or "poor" is used to communicate the overall level of racial and ethnic diversity in a clinical trial. A detailed description of the tool and the rating guide are provided in Appendix A. The advantages of this

framework is that it is easy to implement and the ratings can easily be interpreted by all stakeholders.

One potential challenge of implementing this framework is the current trend of global trials. A recent analysis of trials included in ICER reviews over the past five years showed that about 80% of trials that inform ICER assessments are multinational.[29] The analysis further revealed that although Black or African American people and Hispanic or Latino people were underrepresented across all trials, representation in the US-based trials was significantly better. This study highlights the complexity and challenge of evaluating clinical trial diversity for multinational trials that recruit patients from locations that are likely demographically distinct from the country of interest. Given the changing US population and the current trend of global trials, it also highlights the importance of taking proactive steps to mitigate against worsening clinical trial diversity. As such, for multinational trials intended to be generalized to the US population, it would still be important to consider the racial and ethnic diversity of the overall patient population included in the trial. However, in recognition of the potential barriers for multinational clinical trials to reflect the diversity of the disease population in the US, racial and ethnic diversity ratings should only be applied to patients enrolled in the US.

Analyzing Results by Subpopulations

Racial disparity in health is a longstanding issue in the US, with racial and ethnic minority groups in the US carrying a disproportionately higher burden of a wide range of chronic conditions, including diabetes, hypertension, obesity, asthma, and heart disease, when compared to White people.[44] These health disparities are often associated with an earlier illness onset, delayed diagnosis and initial therapy intervention, greater disease severity, and worse survival. Furthermore, due to issues around cost, affordability, insurance coverage, and differential treatment by providers, racial and ethnic minority groups face a greater barrier to accessing health care in the US and tend to receive a lower quality of care than their White counterparts.[45,46] The recent COVID-19 pandemic highlighted several of these challenges, with studies showing that American Indian and Alaska Native people, Black or African American people, and Hispanic or Latino people experienced disproportionate rates of illness and death compared to White people.[47,48] To address the concern of racial disparity in health, users of HTA, including patient groups, have increasingly requested for HTA findings to be presented by subpopulation.

HTA asks important questions about the clinical- and cost-effectiveness, as well as contextual and ethical considerations of using new health technology. This question is not intended to guide individual patient care because it does not cover the individual patient characteristics, unique needs, and preferences that a clinician would assess in making recommendations for a specific patient. Instead, HTA is focused on the average effect at the population level. However, when evaluating the clinical effectiveness of an intervention, focusing on the average treatment effects alone may obscure the distinct needs, disease burden, or important treatment variations that may be present in certain subpopulations if proper consideration is not given to subgroup analysis. Broadly speaking, subgroup analyses are used to investigate if a treatment will benefit or harm a particular subpopulation more (or less), even when the treatment has a net benefit for all patients. These subpopulations may be identified by demographic characteristics, such as race/ethnicity, socioeconomic status, age, or sex, or other factors, such as severity or stage of the disease.

However, analyzing and interpreting results by subpopulations is often not straightforward due to two key methodological and statistical issues that create uncertainty about the validity and reproducibility of the findings. The first is the risk of false positive findings due to multiple comparisons, and the second is the risk of false negatives due to inadequate power. Like any other characteristic, and perhaps even more so, the use of race and ethnicity to describe a subpopulation is prone to these issues. Furthermore, race and ethnicity combine social and biological effects in complex ways, and there are often multiple and interdependent factors that cause racial variations in treatment response. As such, it can often be difficult to disentangle if a subgroup difference observed for a racial or ethnic group is truly a treatment difference by race/ethnicity or if it is due to other factors such as socioeconomic factors or the severity of the disease. Unfortunately, a lack of

clarity on this relationship in certain instances may lead to misinterpretation of evidence and, if applied to practice and policy, may lead to more harm, such as worsening health disparities.

Despite the well-founded concerns about interpreting subgroup findings, understanding if there are subpopulations with a potentially worse or better benefit-harm balance is crucial to our interpretation of the evidence on the intervention and may have important implications for health equity considerations for clinical practice, coverage decisions, and policy-making. As such, there is a need for HTA bodies to know when and how to highlight when there is a heterogeneity of intervention effects and when there are substantial differences in the evidence for a specific subpopulation to warrant a separate judgment for that group.

Recommendations:

1. **Incorporate subpopulation considerations into the HTA review scoping process by conducting a targeted literature review and interviews with patient and clinical experts on the potential scientific rationale for differential subpopulation effects.**

Discussion: From the inception of an HTA assessment, the contextual landscape of the topic should be examined, including what is known about sources of heterogeneity of intervention effect and known or concern about potential subpopulation differences for the disease area. Evaluation of the existing evidence base, consultations with clinical experts, and insights from patients, patient groups, and other stakeholders should inform defining the presumptive subpopulations of interest, including subpopulations defined by race/ethnicity and socioeconomic status/location. Decisions about which subpopulation to be evaluated should be based on careful consideration of the likelihood of a subgroup effect. Early investigations of a subpopulation during topic scoping may result in a conclusion that further consideration of that subpopulation is not warranted or that additional information is needed to proceed. The rationale and potential policy impact for including a subpopulation should be thought through and described in the scoping document and/or research protocol.

2. **Develop a consistent framework for evaluating and assessing the credibility of subgroup analyses reported in studies following the common steps of systematic literature review, including searching/identifying relevant evidence, data abstraction, critical appraisal, and synthesis of results.**

Discussion:

Searching and identifying relevant evidence: HTA evaluation of comparative clinical effectiveness is grounded in a systematic review of all available evidence. However, a barrier to identifying relevant subgroup evidence is that this information is often not reported in the primary publications with the overall clinical trial results. Therefore, it will be important for HTA bodies to develop a flexible and

inclusive approach to sources of evidence, including searching relevant databases that capture grey literature, such as conference abstracts and regulatory documents.

Data abstraction and critical appraisal: Subgroup-specific information on the subpopulations identified a priori during the scoping phase should be captured during data abstraction. Other important factors influencing outcomes uncovered during data abstraction should be considered for further evaluation if they may have important implications for policy and/or practice.

Critical appraisal: Several excellent published checklists have been developed to evaluate the credibility of subgroup analyses.[49-51] HTA bodies should consider adapting these checklists while continuing to assess new tools as they become available to address and present information on the credibility of subgroup analyses in clear and consistent terms that are easily understood by all users of HTA. Specifically, credibility assessment should cover information such as the likelihood of the subgroup effect being spurious, whether the trial was powered to detect subgroup differences (when a subgroup effect is not observed), and the potential for confounding in a subgroup analysis by another study variable. An example of a best practice to present this information using an overall rating to judge the credibility of a subgroup finding was proposed by Whitlock et al., but it requires further testing and evaluation for use in the HTA context.[51]

Synthesis: In summarizing the subgroup-specific findings across trials, considerations should be given to the overall coherence of findings from the entire body of the evidence. The summary of subgroup findings should include information about the adequacy of the evidence base and the credibility of the subgroup analyses, including listing different or inconsistent evidence. Approaches such as stratified meta-analyses and meta-regression, which provide information on how treatment effect differs between groups of studies and not by subpopulations within the studies, should not be used to address racial and ethnic subgroup differences.

3. **Consider issuing a separate evidence rating/final judgment if there is robust, high-quality evidence that supports substantial differences in the magnitude of net benefit for a particular subgroup.**

Discussion: The overall judgment on the clinical effectiveness of the health technology being appraised is based on the certainty and magnitude of the available evidence. When robust, high-quality evidence supports substantial differences in the magnitude of the net benefit of the health technology for a particular subpopulation defined by race and/or ethnicity, a separate overall judgment/evidence rating should be considered. Considerations should be given to the relevance, impact on health equity, and evidence gaps before issuing a separate overall judgment/evidence rating.

In the absence of high-quality evidence that supports substantial differences in the magnitude of net benefit for a race or ethnic group, the overall judgment/evidence rating for the entire

population should be applied to that group. However, relevant considerations should still be given to where and how any available information on the subgroup of interest should be highlighted in the HTA report. For example, in situations with low-quality evidence to suggest differences in the magnitude of net benefit, HTA evaluation should highlight the potential differences in the magnitude of net benefit for that subpopulation as an area of future research need. There may be other situations where there are significant differences in disease epidemiology for a particular racial or ethnic minority group, but there are no observed differences in the magnitude of net benefit (or the question of the difference in magnitude of net benefit is not answered). In this case, HTA has a role to play in highlighting the differences in epidemiology as a contextual consideration that may impact the value of the treatment for that population and may also impact coverage decisions.

4. **Even if clinical evidence suggests differences in the magnitude of net benefit by race, ethnicity, or socioeconomic status, do not calculate cost-effectiveness estimates for subpopulations defined solely by these characteristics.**

Discussion: Although there is natural interest in exploring whether treatments have distinctive risks and benefits for different racial/ethnic groups, or for groups defined by their socioeconomic status or location, there are also important potential unintended consequences. For example, data could suggest that outcomes for African American people are worse than for White people. This kind of conclusion could be translated into cost-effectiveness analyses that would suggest that treating African Americans is "less" cost-effective. But characteristics such as race/ethnicity, as well as socioeconomic status, can be related in complex ways to other characteristics that might affect health outcomes of treatment, including differences in access to basic care, to healthy food, and to adequate transportation or other social supports. Given the concern that these other factors could easily confound subpopulation analyses of clinical data, we propose that subpopulation analyses of clinical evidence not be used to support separate cost-effectiveness analyses for subpopulations defined solely by these characteristics.

The risks of subpopulation analyses may be magnified by HTA if translated into cost-effectiveness analyses used to determine coverage or fair pricing. Suggesting a treatment is more cost-effective in one subpopulation always implies that it is less cost-effective in those not within that subpopulation. When subpopulations are clearly defined a priori by clinical characteristics it may be an important goal of cost-effectiveness analyses to examine relative cost-effectiveness, but analyses focused on subpopulations based on race/ethnicity or socioeconomic status are too vulnerable to misinterpretation and misuse.[52] HTA bodies should put forth formal guidance to inform stakeholders of this risk and for the rationale to avoid cost-effectiveness analyses of subpopulations defined by characteristics other than appropriate clinical markers of risk or outcome.

Measuring the Opportunity to Reduce Health Disparities

Decision makers may wish to give greater priority to interventions that have a potential benefit of helping reduce health disparities. Equity, along with other benefits, disadvantages, and contextual considerations, is traditionally incorporated within an HTA assessment through committee deliberations, but this approach has been criticized as lacking rigor and transparency and has been implemented inconsistently. Although equity is traditionally discussed as part of the deliberative process, evidence to inform the committee as to how the condition and/or treatments within the condition influence equity has typically not been provided. In other words, appraisal committee deliberation around equity often lacks evidence to guide the conversation.

Evidence-informed deliberative processes can help promote the rigor, transparency, and consistency of deliberation. Evidence on a condition related to the extent to which it impacts underserved populations, as well as evidence on a treatment related to the extent to which it reduces health inequities, can be provided to the HTA appraisal committees to promote evidence-informed deliberation around equity.

Evidence can be presented in various forms, from stakeholder comment, to qualitative data, to quantitative empirical measures. Some have argued that HTA bodies should make equity a quantitative endpoint of each assessment, similar to how quantitative evidence is shared for comparative effectiveness, cost effectiveness, and budget impact assessments.[53] Equity could be presented as a quantitative endpoint of each assessment through equity-informative economic evaluation methods, but each of these methods have their share of limitations, including requiring data that are typically not available. The strengths, challenges, and data requirements to implement equity-informative economic evaluation are discussed in greater detail in the following section.

Even without conducting an equity-informative economic evaluation, empirical measures of equity can still be developed and calculated to provide quantitative evidence to the appraisal committees to inform the deliberative process. These empirical measures could quantify the equity considerations within a particular clinical condition and for a particular treatment for use in HTA deliberation. Providing these empirical measures to the appraisal committee throughout the deliberative process could address some of the common critiques of HTA deliberative processes.

Recommendations:

1. **Consider whether data are available to calculate an empirical measure of distributional equity that can estimate the impact of a treatment on overall health disparities across key subpopulations.**

Discussion: Policymakers may wish to give greater priority to interventions that have a potential benefit of helping reduce health disparities. One option to consider is a recently developed methodology called aggregate Distributional Cost-Effectiveness Analysis (DCEA).[54] A detailed explanation of this method with examples can be found elsewhere.[54] Aggregate DCEA uses disease-specific prevalence data and aggregated cost-effectiveness model outcomes for the cost and health outcomes. The summary measure of the method includes a quantitative estimate of the health, inequality, and social welfare impact of a treatment. Aggregate DCEA differs from traditional DCEA in that it does not require the distribution of health benefits (health outcomes of the model) to be estimated separately for each subpopulation of interest. Rather, aggregate DCEA is a simpler, less resource-intensive approach, that takes the average health outcomes reported from the cost-effectiveness analysis, adjusts it using disease-specific prevalence numbers, and then separates the population-level numbers according to social patterns for that specific disease. Because the average health outcomes reported from the cost-effectiveness analysis are used, there are limitations when there are known disease-specific or treatment-specific differences among subpopulations. Aggregate DCEA may undervalue positive equity effects in those instances, and a DCEA might be a more appropriate method in situations with known disease-specific or treatment-specific differences among subpopulations.

Aggregate DCEA uses many data elements that are already traditionally reported in HTA, including mean incremental costs, mean incremental health outcomes, and patient population estimates. Aggregate DCEA also requires data not traditionally reported in HTA, including disease-specific healthcare utilization data by sex, age, and socioeconomic distribution. Additionally, opportunity cost data on the age, sex, and socioeconomic distribution for those that would forgo health are needed. These data elements can be combined to estimate the net distributional effect of the treatment as well as the cumulative net distributional effect of the treatment. These summary measures could be used as an empirical measure of equity to inform appraisal committee deliberation if a treatment reduces health inequities.

However, there are data requirements for DCEA that create barriers to its use on a routine basis. For example, in the United States, standardized sociodemographic data are not available for the baseline population or for participants in the clinical trials. This data infrastructure should continue to be built to promote potential use of DCEA.

2. **Present for decision makers some measure of the relative prevalence of the condition across key subpopulations and any available access data that can highlight potential opportunities to reduce health disparities.**

Discussion: New treatments for populations with a greater burden of illness and/or systematic barriers to access have the potential to produce proportionately greater health gains for these populations and reduce health disparities. HTA reviews should incorporate some measure of relative prevalence and/or access differences across key subpopulations to highlight for decision makers when there may be an important opportunity to achieve this goal.

ICER has recently developed a metric called the health improvement distribution index (HIDI), that is calculated as the disease prevalence in the subpopulation of interest divided by the disease prevalence in the overall population. A HIDI above one suggests that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4% = 2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population.

It is important to note that the HIDI does not represent a full distributional analysis, in that it does not consider potential prognostic, treatment effectiveness, uptake, and access differences that may exist between subpopulations. Further, unlike DCEA methods, the HIDI does not attempt to consider the opportunity costs of adopting a treatment at a given price. However, the HIDI is not computationally complex, has minimal data requirements, and can be easily interpreted by appraisal committees. The HIDI is not a normative measure, in that it does not have specific thresholds at which certain levels of priority are suggested, and it is not a standalone measure that comprehensively measures the opportunity to reduce health disparities. HTA programs may wish to develop their own approach to presenting relative prevalence and/or access data for appraisal committees and other decision-makers, but in some way treatment reviews should include information on the relative distribution of health gains across key subpopulations so that the potential to reduce health disparities can become part of deliberation and decision-making.

3. **Avoid using any single empirical measure of health disparities or the opportunity to improve equity as a substitute for a deliberative process that should integrate multiple important equity criteria in policy decisions.**

Discussion: The causes of health disparities are multifactorial, and relative prevalence of conditions across key subpopulations reflects just one aspect of the opportunity to improve health equity. Deliberative processes are necessary within HTA to account for the complexity of these issues and the transparent integration of multiple perspectives in setting priorities for new technologies.

Promoting Health Equity Through Quantitative Methods of Cost-effectiveness Analysis

Some have argued that traditional methods for economic evaluation (e.g., cost-effectiveness analysis) facilitates equity by reducing out of pocket payments for patients[4] and providing evidence so neither patients nor society overpay for care that doesn't offer a significant benefit. In health systems that are focused on value-based care and value-based prices, the reduction in low-value care or costs results in additional resources that can then be used to support those in need.[4] Yet traditional methods for economic evaluation have been criticized by others because they are focused primarily on efficiency, while other factors such as equity may be important attributes to decision making.[52] These other factors, including equity, are traditionally incorporated through HTA committee deliberations, but this approach also has been criticized as lacking rigor and transparency and has been implemented inconsistently.

There are now novel economic methods, often called equity-informative economic evaluations, that are extensions of the traditional cost-effectiveness framework capable of quantitatively incorporating the distributional impacts of a healthcare treatment based on relevant equity stratifications.[52] There are numerous types of equity-informative economic evaluations, each of which differs based on its complexity, data requirements, generalizability, integration within cost-effectiveness analysis, and the ability to measure changes in the inequality distribution. Detailed descriptions and appraisals of each method are available in the published literature, but we will very briefly summarize each here.[1,52,55]

One method, known as equity-based weighting, uses quantitative weights to give greater or lesser weight to subgroups of the population.[55] It quantitatively incorporates equity into the cost-effectiveness analysis by adjusting the health outcome (thereby adjusting the incremental cost-effectiveness ratio) or by adjusting the threshold by some preference weight(s) for equity. Equity-based weighting might be most informative when a treatment is either cost-effective but harms equity or when a treatment is not cost-effective but improves equity.[1] Equity-based weighting then allows for the decision maker to assess these trade-offs between efficiency and equity. For this type of analysis, equity preference weights are needed, as is the ability to disaggregate the outcomes or population by the equity stratification factor (e.g., socioeconomic status, race, ethnicity).[55] If equity preference weights are not available, equity-based weighting can also be achieved by using an equity parameter that represents the degree of concern for reducing health disparities.[1] Strengths of equity-based weighting are that it is relatively simple, both analytically and conceptually, and it is able to be incorporated directly into the cost-effectiveness analysis with little to no changes to the economic model.[55] A limitation of this method is that it requires additional data, either an equity preference weight for different subpopulations or an equity

coefficient that quantifies the importance of reducing health inequity.[55] To our knowledge, these data do not exist for many countries and the elicitation of the weights are often based upon best-worst scaling or discrete choice experiments that have their own challenges and critiques. Another issue is that equity-based weighting is not capable of examining changes in the inequality distribution,[55] and a limitation common to any adjustment in the health outcomes or in the cost-effectiveness threshold is that the weighting is best suited for single attributes (e.g., equity, severity), whereas decision making typically involves multiple attributes.[56]

Another form of equity-informative economic evaluation is "extended cost-effectiveness analysis." This method considers equity through additional outcomes presented alongside the cost-effectiveness analysis, including financial risk protection and distributional consequences.[1] Decision makers can then view the cost-effectiveness findings alongside additional equity-centered outcomes. In an extended cost-effectiveness analysis, treatments are not only evaluated by their costs and health gains as is done in traditional cost-effectiveness analysis, but also in their associated financial risk protection gains (including private expenditures avoided) and distributional consequences (by some equity stratification such as race and ethnicity).[1] For this type of analysis, patient out of pocket payments and a poverty spending threshold are typically needed. Strengths of this type of analysis are that it provides additional information to decision makers beyond cost-effectiveness analysis, it is analytically simple, and it evaluates changes in the outcome inequality distribution resulting from the treatment.[55] A key limitation of this method is that it requires additional data that are not readily available and will vary dramatically between countries, health systems, payers, and patients.[55] Further, in countries where few people suffer medical impoverishment, this method may be less applicable.

Distributional cost-effectiveness analysis (DCEA), which we have described earlier in this paper, is another form of equity-informative economic evaluation. Not only does this method focus on the distribution of a treatment's health effects, but also on the distribution of the opportunity costs that occur if a treatment is adopted at a given price.[1] Key steps to DCEA involve first establishing baseline quality-adjusted life expectancy across the equity stratifications (e.g., sociodemographic groups, geographic locations), estimating cost-effectiveness outcomes for each equity stratification, estimating population outcomes for each equity stratification, and then assessing the equity impact overall through social welfare functions and health inequality aversion preferences.[57,58] Strengths of DCEA are that it measures changes in the inequality distribution, is generalizable across health systems, disease areas, and interventions, and there are well established methods of conducting such an evaluation.[55] However, DCEA also requires a significant amount of additional data beyond that traditionally needed for a cost-effectiveness analysis, can be challenging to interpret, and is conceptually complex.[55] Key data gaps in the United States that restrict the ability for DCEA to be implemented are described in detail elsewhere but include missing quality-adjusted life expectancy data by geography and subpopulations and how trade-offs between efficiency and equity are valued by patients and the public.[57]

The final method we will briefly describe is multiple criteria decision analysis (MCDA). In MCDA, multiple criteria can be evaluated (and potentially combined) in a decision-making framework. Criteria can be scored and weighted. MCDA is not a form of economic evaluation but can be thought of as an extension of economic evaluation that captures a broader set of decision-relevant factors. For example, MCDA could include the measure of health benefit from the economic model, but could also quantitatively weigh and integrate some measure of equity. A strength of MCDA is that multiple attributes, including those outside of what is traditionally captured in cost-effectiveness, can be examined.[55] However, this method is deeply challenged by requiring consensus on the range of criteria considered, on the scoring and ranking strategy for each criterion, and the exact mechanism for integrating each criterion.[55] In the literature and in real-world experiments with MCDA, it is clear that this consensus does not exist.[52]

These limitations have restricted the use of MCDA in practice. In regard to equity concerns, MCDA has not been used to showcase distributional effects, but rather as a decision-making tool that could include equity as one of the criterion.[52] Novel explorations of MCDA have explored its potential to rank the most important contextual considerations of a treatment (including equity considerations) to inform HTA deliberation. This application of MCDA as a tool for structured HTA deliberation does not require a value or weight for each criterion, and thus avoids the limitations associated with weighting, but is challenged by whether or not the people informing the criteria are appropriate for the decision context.

Although not typically considered an equity-informative economic evaluation because the equity component is separate from the economic evaluation, evidence-informed deliberative processes can be a robust and practical method to incorporate equity (among other attributes as well) into the value assessment. Deliberative procedures can be criticized for being neither rigorous nor transparent, and the specific influence of deliberation on the decisions ultimately made can only be implicitly evaluated. However, deliberation is a powerful tool to discuss important issues openly and transparently. It also enables multiple attributes which can differ dramatically, such as equity concerns and health system personnel retention, to be considered. Evidence-informed deliberative processes therefore have properties similar to MCDA but without the criteria assumptions and mathematical requirements that have numerous limitations.[59]

Ultimately, because efficiency is not the only attribute that informs decision making, there is a need for HTA bodies to have an explicit method by which to incorporate equity into assessment methodologies and/or deliberative procedures. As noted in our short summary of each method, there are potential strengths for each method, but many important challenges exist that may limit their implementation within HTA, now or in the future.

Recommendations:

1. **Advocate for the development of data necessary to consider a broad range of equity-informative economic evaluations.**

Discussion: As noted above, there are numerous equity-informative economic evaluation methods that are capable of examining inequality differences and incorporating them alongside more traditional cost-effectiveness methods. However, a limitation common to all of them is the current lack of data available to rigorously and robustly conduct such analyses. At least considering the US perspective and data landscape, the limited data available prohibit wide-spread implementation of these methods. HTA stakeholders should advocate for efforts to gather and make public the data necessary to conduct such analyses before these methods can be considered for potential integration into the HTA process. National efforts, perhaps by organizations such as the National Institutes of Health or the Agency for Healthcare Research and Quality, may be needed to allow for robust and representative collection of these data for the United States.

For equity-based weighting, either an equity preference weight for different subpopulations or a single equity coefficient that quantifies the importance of reducing health inequity is needed. For extended cost-effectiveness analysis, patient out of pocket payments and a poverty spending threshold are needed. For DCEA, standardized sociodemographic and geographic variables of the baseline population, contemporary quality-adjusted life expectancy estimates for the general population and by geography, and preferences for inequality aversion are essential. For multiple criteria decision analysis, consensus on criteria and preference weights for each criterion are needed.

There are economic methods that are developed to incorporate equity into evaluations of efficiency, but the data infrastructure has lagged behind the methodological development. This data infrastructure should continue to be built to promote potential use of these novel methods.

2. **Avoid using quantitative equity-informative economic evaluation as a substitute for a deliberative process that should integrate multiple important social values in policy decisions.**

Discussion: There are numerous criteria that inform and influence coverage and reimbursement decision making, two of which are efficiency and equity, but there are many other criteria of importance. Deliberative processes are necessary within HTA to account for these multiple criteria and bring in contextual considerations and other benefits or disadvantages of a treatment. Equity-informative economic evaluation should not be used to replace or substitute the deliberative processes of HTA that should inform all HTA decisions and subsequent coverage and reimbursement decision making. Equity-informative economic evaluation can showcase where inequalities occur within the patient journey to make this information more available and

transparent to inform decision making. These methods provide additional information related to equity that can be subsequently used to inform policy planning and decision making, but they should not make a decision in itself.

3. **If quantitative or deliberative approaches suggest higher priority be given to a treatment because of its potential to reduce health disparities, do not automatically translate that priority into endorsement of higher prices that will adversely affect patients.**

Discussion: Equity-informative economic evaluation methodologies could suggest that additional priority be given to the health gains for treatments that improve health equity by addressing health problems of greater importance to disadvantaged subpopulations. For example, equity-based weighting and DCEA can weight the clinical outcomes observed for a specific subpopulation or weight the cost-effectiveness threshold to assign more value to a treatment that reduces disparities. For new drugs or other interventions for which the price is under the control of the manufacturer, letting society's goal of reducing health disparities support pricing that exceeds common cost-effectiveness thresholds may only serve to increase barriers to care for patients with limited economic resources. If special priority due to equity considerations is considered, deliberation should address whether that priority should or should not be translated into acceptance of higher pricing based on both the short and long-term interests of patients.

Promoting Health Equity through Deliberative Methods

HTA has always existed as a social construct through which evidence assessment using objective scientific methods would be integrated within a broader "appraisal" function that would allow for the consideration of scientific values (e.g. tolerance for uncertainty) and social values (e.g. the goal of improving health equity), along with other factors not captured as part of clinical evidence or cost-effectiveness analysis. Sometimes the appraisal function of HTA is performed out of public view by government staff with the responsibility of representing the values and the wishes of the public. Other HTA programs have developed a public deliberation process through which meetings are held to introduce testimony from patients and other stakeholders and to have the HTA evidence review scrutinized by an independent group of outside experts. Whether the appraisal function is performed by government staff, through an independent appraisal committee, or some combination thereof, health equity should be one of the primary factors considered. Given the challenges described in the preceding sections of the paper of adopting a formal quantitative method for weighting evidence to reflect the goal of improved health equity, qualitative or mixed methods for integrating these considerations in the appraisal function of HTA are needed.

To our knowledge, no HTA program has adopted MCDA or developed any other formal, algorithmic way to integrate considerations of equity alongside other factors within technology appraisal. Most or all international HTA programs do include equity as part of the principles underlying their efforts, but transparent decisions to lend greater priority on the basis of equity to a service than is merited by its effectiveness or cost-effectiveness alone are politically controversial, and it is not clear that HTA programs themselves, even those functioning as part of government, have the mandate to determine independently how to weigh health equity in relation to other factors.

ICER has experimented since its founding with different ways to make the consideration of factors beyond clinical effectiveness and cost-effectiveness more transparent and consequential in technology appraisal. Our historical methods, superseded by others over the years through iterative trial and error, are available on our website.[60] Our approach since 2020 has been focused on delineating a set of "potential other benefits or disadvantages" and "contextual considerations" for every technology assessed.[61] These factors have been standardized to include specific information on the relative severity of the condition (informed in part by calculations of years of healthy life lost), on the potential broader benefits beyond health that allow patients to pursue their major life goals; on the spillover effects of better health achieved by patients on the quality of life of their caregivers; and on "society's goal of reducing health disparities."

With information on each of these considerations in the assessment document, ICER public deliberation meetings include formal moderated discussion of each element with patient and clinical experts at the table to join in deliberation with the independent appraisal committee. These

discussions are capped with voting by the appraisal committee using a Likert-scale response to indicate whether the technology under discussion offers anything from a "major negative" effect to a "major positive" effect on each parameter.

These votes are not used to quantify a specific change to the operative cost-effectiveness range for the technology. Instead, the appraisal committee is charged with considering each factor as part of an overall vote on "long-term value for money at current pricing." The basis for this vote begins with a normative cost-effectiveness range of approximately $100,000-$150,000 per added equal value life year gained (evLYG) or quality-adjusted life year (QALY) gained. The committee is instructed to integrate the cost-effectiveness results with these other factors, including the potential impact on health disparities. Before a final vote is taken, moderated discussion occurs among the committee members so they can explore how others will be weighing these other factors into their final vote.

This approach rests midway between a completely qualitative, free-form discussion of factors such as health equity, and a more formalized weighting within MCDA.[62] As noted earlier, MCDA has the advantage of potentially being more transparent and consistent, but it has two major limitations. First, there is no obvious right source from which to derive the weights to be assigned to each of the potential factors in a technology appraisal decision. For example, whose judgment should be used to assign a universal weight to "health equity" among the other considerations?

Second, MCDA is complex and very time consuming. ICER attempted to implement formal MCDA with its independent committees on several occasions in the past and found the technique too complicated for reliable use. The differences between a more mathematical approach to integrating health equity considerations into appraisal versus other approaches with a greater emphasis on qualitative deliberation, should not obscure their common objective: ensuring that health equity is considered explicitly as a factor within a decision about health care value that can reflect society's broad goals to maximize population health outcomes and improve health equity.

Recommendations:

1. **Develop robust methods for highlighting equity-relavent information in every report and for integrating these considerations into determinations of value through deliberative procedures that address the potential impact of a technology on health equity.**

Discussion: As discussed above, there are different ways to try to quantify the existence and impact of health inequity, but no matter whether quantitative measures are used, all HTA programs should adopt some standardized approach to include information on epidemiologic data on prevalence in different subpopulations as well as any existing data on disparities in health access and outcomes for patients with the condition. There is a spectrum of approaches that can be considered for integrating considerations of health equity into determinations of value. As noted earlier, ICER believes that at the current time the methods for formal weighting through MCDA are not feasible for routine use in HTA, and this approach raises difficult questions about the appropriate source for normative weights to be applied to health equity across different decision-making contexts. Using an explicit yet less quantified approach, such as ICER's methods for voting on "potential other benefits" and "contextual considerations," followed by explicit integration of these factors into a summary vote on long-term value for money, has offered a way for health equity considerations to be vigorously incorporated into public deliberation to guide policy making. To foster an even more tangible and consistent approach, we will create a designated section of each report to highlight health equity considerations for our appraisal committees and policymakers.

2. **Address openly in deliberation the potential tension between assigning higher value to interventions that promote health equity when doing so could lead to higher prices and costs for individual patients.**

Discussion: As mentioned above, according more "value" to health care interventions on the basis of their potential to reduce disparities may perversely suggest higher prices for these interventions that will produce even greater disparities in the future. Admittedly, higher prices may have an indirect effect of supporting greater incentives for future investment in interventions that could help patients from racial, ethnic, and lower socioeconomic status populations. Nonetheless, deliberation should be moderated to address directly whether higher prices are the only or best way to create these incentives, and if it is likely that higher prices will produce higher costs for patients already subject to health inequities, then the appraisal should include discussion of measures to protect individual patients.

3. **Use deliberative processes to highlight structural aspects of the health care system that should be changed in order to ensure that disparities are not worsened with the introduction of new interventions.**

Discussion: Given the systemic discrimination that has molded many elements of the US health care system, including historical patterns of access inequity, many new interventions introduced into health care today will unfortunately contribute to ever greater disparities in health outcomes for many racial, ethnic, and socioeconomic subpopulations. HTA should accept a broad responsibility to provide information beyond technical analyses of evidence to policymakers. The deliberative function of HTA should therefore address potential policy interventions that could help ensure that innovations in health care reach all parts of society in a way that is equitable and that, over time, will help reduce disparities in health outcomes across all segments of the American population.

Conclusions and Next Steps

This paper should conclude with a frank acknowledgment of how early and limited our understanding is of how HTA can best support the goal of health equity. We made a conscious but difficult decision to narrow our focus to methods addressing inequity across populations defined by race, ethnicity, or socioeconomic status. It must be stated again that this in no way diminishes the importance of HTA seeking to inform policymaking that can address inequities for other people who face discrimination or neglect in our health care system.

We are also limited by our past. We are all products of the history and infrastructure of health care in the US that has been influenced by forces of racism and other forms of discrimination, and it will take concerted effort and time to unpack all the assumptions and standards that are based on that history. This is as true for us as individuals involved in HTA as it is for our organization and the organizations with which we interact. We conclude therefore with an honest openness to the likelihood that we have yet not found all our blind spots, and we will only make progress if we continue to be open to challenging our own beliefs and prerogatives.

From what we have learned, however, we have been able to identify important areas for improvement at ICER and, by extension, for many other HTA organizations. We have framed the findings of this paper as action statements, and ICER will immediately take each of these action statements as guides to our methods and procedures going forward. Where relevant, they will be incorporated into our general value assessment framework document scheduled for update later in 2023. And we will implement a regular process for seeking input from our Advisory Group and others on our progress and on new ideas for improvement on an annual basis.

We will disseminate this document among other HTA groups internationally, some of which have launched their own initiatives to examine equity more deeply. We will also share this work with leaders in government who are responsible for the management of groups involved in HTA, including the Agency for Healthcare Research and Quality, the United States Preventive Services Task Force, and the Medicare Evidence Development and Coverage Advisory Committee. And we will ensure that life science organizations and payers with which we interact are aware of these recommendations. We will encourage them to take aligned action on elements such as clinical trial diversity where other stakeholders own significant responsibility.

In closing, we would like to thank again all the experts and policy leaders who contributed to our understanding as reflected in this white paper. We remain responsible for any lapses in fact or perspective, but we accord to them many of the insights from which we hope to base new methods for HTA to strengthen its role in improving health equity across the US.

References

1. Cookson R, Mirelman AJ, Griffin S, et al. Using Cost-Effectiveness Analysis to Address Health Equity Concerns. *Value Health.* 2017;20(2):206-212.
2. Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. *Bmj.* 2004;329(7459):224-227.
3. Culyer AJ, Bombard Y. An equity framework for health technology assessments. *Med Decis Making.* 2012;32(3):428-441.
4. Hoch JS, Trenaman L, Hearney SM, Dewa CS. How Economic Decision Modeling Can Facilitate Health Equity. *AMA J Ethics.* 2021;23(8):E624-630.
5. Marsh K, Bhashyam SS, Le A. More Care Needed: Incorporating Equity into Health Technology Assessment. 2015.
6. Cook S, Tan R. Health disparities and health technology assessment: Current value assessment frameworks fall short. 2021.
7. Frank L, Concannon TW. Inclusion In Health Technology Assessments: The First Step Toward Equity. 2021.
8. Linthicum M, Jalowsky M, Valentine A, Ahmed R, Bright J, Chapman R. Finding Equity in Value. 2022.
9. Panteli D, Kreis J, Busse R. Considering equity in health technology assessment: an exploratory analysis of agency practices. *International Journal of Technology Assessment in Health Care.* 2015;31(5):314-323.
10. Centers for Medicare & Medicaid Services. Health equity. https://www.cms.gov/pillar/health-equity#:~:text=Health%20equity%20means%20the%20attainment,language%2C%20or%20other%20factors%20that. Published 2022. Accessed.
11. World Health Organization. Health Inequality Monitor. https://www.who.int/data/inequality-monitor/about#:~:text=Health%20equity%20is%20the%20absence,economic%2C%20demographic%20or%20geographic%20characteristics. Published 2022. Accessed.
12. ADA National Network. Health Care and the Americans With Disabilities Act. https://adata.org/factsheet/health-care-and-ada#:~:text=The%20Americans%20with%20Disabilities%20Act%20(ADA)%20is%20a%20federal%20civil,are%20covered%20by%20the%20ADA. Published 2023. Accessed.
13. Institute for Clinical and Economic Review. Cost-Effectiveness, the QALY, and the evLYG. https://icer.org/our-approach/methods-process/cost-effectiveness-the-qaly-and-the-evlyg/. Published 2022. Accessed.
14. Quality AfHRa. EHC Program Topic Nomination and Selection. 2017.
15. Hunter A, Facey K, Thomas V, et al. EUPATI Guidance for Patient Involvement in Medicines Research and Development: Health Technology Assessment. *Frontiers in Medicine.* 2018;5.
16. Gagnon MP, Desmartis M, Lepage-Savary D, et al. Introducing patients' and the public's perspectives to health technology assessment: A systematic review of international experiences. *Int J Technol Assess Health Care.* 2011;27(1):31-42.
17. Arntsen KA, Blount LG, Dickerson BJ, Koola CP, Venable Y, Wildman P. Patient-centered health technology assessment: a perspective on engagement in health technology assessment by three patient organizations and a health technology assessment body. *International Journal of Technology Assessment in Health Care.* 2022;38(1):e76.
18. Darien G, Griggs C, Hudson M, Mendenhall N, Neu D, Grammel LW. From Principles to Practice: Building Partnerships for Trust and Equity in Health Research. 2021.

19. Allen EH, Haley JM, Aarons J, Lawrence D. Leveraging Community Expertise to Advance Health Equity: Principles and Strategies for Effective Community Engagement. *Urban Institute.* 2021.
20. Agency for Healthcare Research and Quality. AHRQ Health Literacy Universal Precautions Toolkit. https://www.ahrq.gov/health-literacy/improve/precautions/index.html. Published April 2010. Updated September 2020. Accessed March 8, 2023.
21. The Literacy Project. Illiteracy by the Numbers. https://literacyproj.org/. Published 2022. Accessed March 8, 2023.
22. HTAi. HTAi Values and Quality Standards for Patient Involvement in HTA. Guidelines International Network. https://g-i-n.net/toolkit/htai-values-and-quality-standards-for-patient-involvement-in-hta. Published 2014. Accessed January 26, 2023.
23. Health Technology Assessment International. HTAi Patient and Citizen Involvement Interest Group's Current Project List: Patient Insights Research Platform. https://past.htai.org/interest-groups/pcig/projects/. Accessed March 8, 2023.
24. US Department of Health & Human Services. National Institutes of Health. NIH GUIDELINES ON THE INCLUSION OF WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH. https://grants.nih.gov/grants/guide/notice-files/not94-100.html. Published March 1994. Accessed.
25. US Department of Health & Human Services. National Institutes of Health. NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research (Updated). https://grants.nih.gov/policy/inclusion/women-and-minorities/guidelines.htm. Published 2001. Accessed.
26. U.S. Department of Health and Human Services FaDAF. Collection of Race and Ethnicity Data in Clinical Trials. Guidance for Industry and Food and Drug Administration Staff. https://www.fda.gov/media/75453/download. Published October 2016. Accessed.
27. U.S. Department of Health and Human Services FaDAF. Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. https://www.fda.gov/media/127712/download. Published November 2020. Accessed.
28. U.S. Department of Health and Human Services FaDAF. Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials. Guidance for Industry (Draft Guidance). https://www.fda.gov/media/157635/download. Published April 2022. Accessed.
29. Wright A, Herron-Smith S, Mathur D, Agboola F. An Analysis of Sample Diversity in Pivotal Clinical Trials Included in ICER Reviews. Society for Medical Decision Making (SMDM) 44th Annual Meeting; October 24, 2022, 2022; Seatle, WA USA.
30. Turner BE, Steinberg JR, Weeks BT, Rodriguez F, Cullen MR. Race/ethnicity reporting and representation in US clinical trials: a cohort study. *Lancet Reg Health Am.* 2022;11.
31. Lin GA, Whittington MD, Synnott PG, et al. Aducanumab for Alzheimer's Disease: Effectiveness and Value. Final evidence report and meeting summary. *Institute for Clinical and Economic Review.* 2021. https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf. Accessed December 16, 2022.
32. Rottas M, Thadeio P, Simons R, et al. Demographic diversity of participants in Pfizer sponsored clinical trials in the United States. *Contemporary Clinical Trials.* 2021;106:106421.
33. Adams B. Roche's Genentech launches new alliance aimed at achieving greater diversity in cancer trials. https://www.fiercebiotech.com/cro/roche-s-genentech-launches-new-alliance-aimed-at-achieving-greater-diversity-cancer-trials. Published 2021. Accessed January 24, 2023.

34. Amgen. Improving Diversity in Our Clinical Trials for Long-term Health Equity. https://www.amgen.com/stories/2022/04/improving-diversity-in-our-clinical-trials-for-long-term-health-equity. Published 2022. Accessed January 24, 2023.
35. Genentech. Removing Barriers to Inclusion in Clinical Studies. https://www.gene.com/stories/removing-barriers-to-inclusion-in-clinical-studies?topic=diversity-and-inclusion. Published 2022. Accessed January 24, 2023.
36. Biogen. Increasing diversity in clinical trials: A collaboration with Tufts Center for the Study of Drug Development. https://www.biogen.com/stories/tufts-clinical-trial.html. Published 2020. Accessed January 24, 2023.
37. Metastatic Breast Cancer Alliance (MBCAlliance). BECOME: BLACK EXPERIENCE OF CLINICAL TRIALS AND OPPORTUNITIES FOR MEANINGFUL ENGAGEMENT. https://www.mbcalliance.org/projects/become/. Accessed December 13, 2022.
38. Centers for Medicare & Medicaid Services (CMS). Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease. Coverage with evidence development (CED). https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&ncaid=305. Published 2022. Accessed.
39. Centers for Medicare & Medicaid Services (CMS). Transcatheter Mitral Valve Repair (TMVR). Coverage with Evidence Development (CED). https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=273. Published 2014. Accessed.
40. National Academies of Sciences E, Medicine, Policy, et al. The National Academies Collection: Reports funded by National Institutes of Health. In: Bibbins-Domingo K, Helman A, eds. *Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups.* Washington (DC): National Academies Press (US) Copyright 2022 by the National Academy of Sciences. All rights reserved.; 2022.
41. Office of Information and Regulatory Affairs OoMaB, Executive Office of the President, . Initial Proposals For Updating OMB's Race and Ethnicity Statistical Standards. https://www.federalregister.gov/documents/2023/01/27/2023-01635/initial-proposals-for-updating-ombs-race-and-ethnicity-statistical-standards. Published 2023. Accessed.
42. Poon R, Khanijow K, Umarjee S, et al. Participation of women and sex analyses in late-phase clinical trials of new molecular entity drugs and biologics approved by the FDA in 2007-2009. *J Womens Health (Larchmt).* 2013;22(7):604-616.
43. Eshera N, Itana H, Zhang L, Soon G, Fadiran EO. Demographics of clinical trials participants in pivotal clinical trials for new molecular entity drugs and biologics approved by FDA From 2010 to 2012. *Am J Ther.* 2015;22(6):435-455.
44. Center for Disease Control and Prevention (CDC). What is Health Equity. https://www.cdc.gov/healthequity/whatis/index.html. Published 2022. Accessed December 16, 2022.
45. Mahajan S, Caraballo C, Lu Y, et al. Trends in Differences in Health Status and Health Care Access and Affordability by Race and Ethnicity in the United States, 1999-2018. *Jama.* 2021;326(7):637-648.
46. Radley DC, Baumgartner JC, Collins SR, Zephyrin L, Schneider EC. Achieving Racial and Ethnic Equity in U.S. Health Care. A Scorecard of State Performance. https://www.commonwealthfund.org/publications/scorecard/2021/nov/achieving-racial-ethnic-equity-us-health-care-state-performance#7. Published 2021. Accessed December 16, 2022.

47. Magesh S, John D, Li WT, et al. Disparities in COVID-19 Outcomes by Race, Ethnicity, and Socioeconomic Status: A Systematic Review and Meta-analysis. *JAMA Network Open.* 2021;4(11):e2134147-e2134147.
48. Centers for Disease Control and Prevention (CDC). Risk for COVID-19 Infection, Hospitalization, and Death By Race/Ethnicity. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. Published 2022. Accessed January 24, 2023.
49. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. *Ann Intern Med.* 1992;116(1):78-84.
50. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *Bmj.* 2010;340:c117.
51. Whitlock EP, Eder M, Thompson JH, et al. An approach to addressing subpopulation considerations in systematic reviews: the experience of reviewers supporting the U.S. Preventive Services Task Force. *Syst Rev.* 2017;6(1):41.
52. Avanceña ALV, Prosser LA. Examining Equity Effects of Health Interventions in Cost-Effectiveness Analysis: A Systematic Review. *Value Health.* 2021;24(1):136-143.
53. Cookson R, Mirelman AJ. Equity in HTA: what doesn't get measured, gets marginalised. *Isr J Health Policy Res.* 2017;6:38.
54. Love-Koh J, Cookson R, Gutacker N, Patton T, Griffin S. Aggregate Distributional Cost-Effectiveness Analysis of Health Technologies. *Value Health.* 2019;22(5):518-526.
55. Ward T, Mujica-Mota RE, Spencer AE, Medina-Lara A. Incorporating Equity Concerns in Cost-Effectiveness Analyses: A Systematic Literature Review. *Pharmacoeconomics.* 2022;40(1):45-64.
56. Round J, Paulden M. Incorporating equity in economic evaluations: a multi-attribute equity state approach. *Eur J Health Econ.* 2018;19(4):489-498.
57. Xie R, dosReis S, Kowal S, Garrison L. Addressing Health Inequity in Value Assessments: A New Role for HEOR? *Value and Outcomes Spotlight.* 2022;Vol. 8.
58. Kowal S, Ng CD, Schuldt R, Sheinson D, Cookson R. The Impact of Funding Inpatient Treatments for COVID-19 on Health Equity in the United States: A Distributional Cost-Effectiveness Analysis. *Value in Health.* 2022.
59. Baltussen R, Jansen MPM, Bijlmakers L, et al. Value Assessment Frameworks for HTA Agencies: The Organization of Evidence-Informed Deliberative Processes. *Value Health.* 2017;20(2):256-260.
60. Institute for Clinical and Economic Review. Overview of the ICER value assessment framework and update for 2017-2019. https://icer.org/wp-content/uploads/2020/10/ICER-value-assessment-framework-Updated-050818.pdf. Published 2017. Accessed.
61. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_2023_VAF_013120-4.pdf. Published 2020. Accessed.
62. Mendola ND, Oehrlein E, Perfetto EM, Westrich K, McQueen RB. Stakeholder perception of pharmaceutical value: A multicriteria decision analysis pilot case study for value assessment in the United States. *J Manag Care Spec Pharm.* 2022;28(10):1190-1196.

Appendix A. ICER Sample Diversity Rating Tool: A User's Guide

A1. Introduction

The lack of diversity in clinical trial populations has implications for generalizability, fairness, and public trust, particularly as new therapeutic agents are regularly being approved. As a Health Technology Assessment (HTA) organization that provides evidence-based information on the clinical effectiveness, cost-effectiveness, and ethical and contextual considerations associated with new therapies, the Institute for Clinical and Economic Review (ICER) focuses on many of the most important therapies coming into the market, often representing the newest technologies with the greatest benefits. In order to elevate the conversation on clinical trial diversity, enhance transparency and accountability and promote equity in clinical trials of new drugs being evaluated, ICER has developed a sample diversity rating tool. The tool presents a framework for evaluating the demographic diversity of clinical trial populations in a consistent, transparent manner leading to an overall diversity rating. The three demographic characteristics evaluated with the tool are listed in Table A1.1. below.

Table A1.1. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity (Also see Table A1.2.)	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

Table A1.2. Definitions of Racial and Ethnic Categories

OMB-defined Racial and Ethnic Categories	Definition/More Granular Categories
White	A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.
Black or African American	A person having origins in any of the Black racial groups of Africa.
Asian	A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.
American Indian and Alaskan Native	A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.
Native Hawaiian and Other Pacific Islanders	A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
Hispanic or Latino	A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race.

OMB: office of management and budget

A2.The Rating Process

A2.1 Data Elements Needed for Rating

Evaluating the diversity of clinical trial population ratings using the ICER rating tool requires two important data types. The first data type covers the clinical trial-specific demographic characteristics - race/ethnicity, sex, and age. For example, for race, data is extracted on the percentage of the trial population who were White, Black or African American, Asian, American Indian or Alaska Native, Hawaiian or Pacific Islander. This data type is extracted from the clinical trial manuscript and supplemental materials and may be supplemented by clinical trial information on the clinicaltrials.gov database (when available). In addition, for multinational clinical trials, race and ethnicity data on the subpopulation of patients enrolled from the US should also be extracted separately. The second data type entails the disease-specific prevalence estimates. Reliable sources for prevalence estimates include the Centers for Disease Control and Prevention (CDC) website and the Global Burden of Disease (GBD) database, a comprehensive epidemiologic dataset by country supported by the World Health Organization. If prevalence data are unavailable through these sources, a comprehensive literature search should be conducted to obtain peer-reviewed journal articles that estimate the prevalence of US disease by sex, age, race, and ethnicity.

A2.2 Demographic Characteristics Included

Table 1 outlines the three demographic characteristics included in the diversity rating. When a trial evaluates a demographic-specific population, e.g., a clinical trial on sex-specific conditions, such as ovarian cancer or endometriosis, that demographic characteristic is excluded from the rating process and not evaluated.

A2.3. Categories Included

Table 1 provides information on the categories included for each demographic characteristic. Importantly, for the racial and ethnic diversity rating, although six categories are evaluated, only the four racial and ethnic categories representing greater than 5% of the US population - Asian, Black or African American, White, and Hispanic or Latino - are factored into the overall judgment on diversity rating. There are two main rationales for limiting the overall rating to these four racial and ethnic groups. First, a recent evaluation conducted by ICER showed that we often do not have disease-specific prevalence estimates for the other two races (American Indians or Alaska Natives and Native Hawaiian or Other Pacific Islanders) and, when available, are often unreliable, making it challenging to evaluate the representation of these groups reliably. Secondly, based on the most recent US census estimate (2021), the American Indians or Alaska Natives and the Native Hawaiian or Pacific Islanders represent 1.3% and 0.2% of the US population, respectively. Therefore, recruitment for these patient populations may likely present different challenges for clinical trial developers. As such, we have opted to evaluate the representation of these two racial groups separately.

A2.4. Rating Steps

Once the data elements described above are extracted, the rating process is straightforward and follows the three steps described below.

1. Representation of each demographic category is evaluated using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR)

$$\frac{Proportion\ of\ trial\ participants\ in\ demographic\ category}{Disease\ specific\ prevalence\ estimates}$$

2. Next, a score is assigned based on the PDRR estimate. The score for each demographic category ranges from 0 to 3 based on the PDRR cut points presented in the table below:

Table A2.1. Representation Score

PDRR	Representation Score
0 or Information on Demographic Category Not Reported	0
>0 and Less than 0.5	1
0.5 to 0.8	2
≥0.8	3

3. Finally, based on the total score of the demographic characteristics (e.g., Race and ethnicity), the categories "good," "fair," or "poor" are used to communicate the overall level of diversity of a clinical trial. The rating description of the rating categories for each demographic characteristic is provided below.

Table A2.2. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

A2.4. Multinational Trials

In recognition of the potential barriers for multinational clinical trials to reflect the racial and ethnic diversity of the disease population in the US, the racial and ethnic diversity rating should focus only on the subgroup of patients recruited exclusively in the US. Trials conducted exclusively in other countries will not be rated on race and ethnicity, as they are unlikely to be representative of the racial and ethnic diversity of the US population.

A3. Examples

Table A3.1. Diversity Rating For Two Clinical Trials: Race and Ethnicity

Race and Ethnicity								
Condition: X Disease	White	Black or African American	Asian	Hispanic or Latino	Total score	Diversity Rating	AIAN	NHPI
Prevalence	72.10%	16.97%	4.55%	20.71%			1.09%	0.5%
Trial 1 Participants	94.55%	3.11%	1.17%	3.11%			0%	0%
PDRR	1.31	0.18	0.26	0.15			0.00	0.00
Score	3	1	1	1	**6**	**Poor**	--	--
Trial 2 Participants	76.90%	2.60%	16.90%	12.90%			0.11%	0.06%
PDRR	1.07	0.15	3.71	0.6			0.10	0.12
Score	3	1	3	2	**9**	**Fair**	--	--

AIAN: American Indian or Alaska Native, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Table A3.2. Diversity Rating for Two Clinical Trials: Sex and Age

Condition: X Disease	**Sex**				**Age**	
	Male	Female	Score	Rating	Older adults (≥65 years)	Rating
Prevalence	38.40%	61.60%			95%	
Trial 1 Participants	48%	52%			60%	
PDRR	1.26	0.84			0.63	
Score	3	3	**6**	**Good**	2	**Fair**
Trial 2 Participants	47.70%	52.30%			64%	
PDRR	1.24	0.85			0.67	
Score	3	3	**6**	**Good**	2	**Fair**

PDRR: Participant to Disease-prevalence Representation Ratio