AMA Journal of Ethics®
July 2023, Volume 25, Number 7: E517-527

STATE OF THE ART AND SCIENCE: PEER-REVIEWED ARTICLE

How Should We Approach Body Size Diversity in Clinical Trials?

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Abstract

Regulatory and ethical considerations mandate that minorities affected by health disparities be included in research. Despite concerns about clinical outcomes for patients with obesity, clinical trials have reported few data about participation of and outcomes for such patients. This article examines the lack of body size diversity in clinical research participants and reviews the evidence and ethical arguments for including larger-bodied patients. Drawing on examples of improved gender diversification of trial participants, this article suggests that similar benefits would be likely from inclusion of body diversity.

Diversity in Clinical Trials

Clinical trials have historically overrepresented White male participants and underrepresented children and older adults, women, gender and sexually diverse people, and people of color.[1] Given the higher burden of disease among disadvantaged minorities,[1,2,3] their lack of representative inclusion in trials threatens to exacerbate health disparities.[4] Continued disparities in cardiovascular health demonstrate this phenomenon, as women and people of color continue to be underrepresented in clinical trials and thus benefit less from research advances.[5,6]

The NIH (National Institutes of Health) Revitalization Act of 1993 mandated the inclusion of women and minorities in clinical trials, stating that unless "substantial scientific data" exists supporting no differences in intervention effects between members of traditionally excluded demographic groups and members of demographic groups that would have been included in the trial anyway, the inclusion of the former in the clinical trial is required.[7] Mandated clinical subject diversity is effective, as increased inclusion of women in studies and subgroup analyses by gender have led to advances in our understanding of how drugs and disease states may affect women differently than men.[8,9,10,11,12,13,14] Yet more work is needed.[15] African American and Hispanic populations continue to be underrepresented and benefit less from advancements in research.[16,17] Ethical and scientific imperatives thus demand ongoing efforts to include members of diverse populations in clinical trials.

This article examines data demonstrating that patients with obesity may respond differently to some clinical interventions, thus mandating their representative inclusion in clinical trials. We argue that not only regulatory requirements but also the basic ethical principles of beneficence, nonmaleficence, and distributive justice mandate inclusion of patients with obesity in clinical trials. While we limit the scope of our discussion to clinical trials, we encourage readers to consider these principles' applications to other research programs.

Body Size Diversity

A body mass index (BMI) between 18.5 and 24.9 is categorized as "healthy weight," a BMI between 25.0 and 29.9 is categorized as "overweight," and a BMI of 30 or above is categorized as "obesity."[18] Roughly 74% of the population falls into the overweight and obesity BMI categories (otherwise referred to as higher weight and elevated BMI).[19] It should be noted that BMI has been critiqued as a poor measure of adiposity (the amount of fatty tissue in a body or region[20]) and a poor predictor of individual health,[21] making the term *obesity* inexact both biologically and medically.[21,22] We also recognize that obesity is not the preferred descriptor of many higher-weight individuals, who may use *larger-bodied* or *fat* as descriptors. Nonetheless, here we use the term *obesity* to describe these populations, as BMI is the current standard for measuring body size in medicine, and existing research uses BMI as a variable.

Larger-bodied patients remain underrepresented in clinical trials,[23] despite studies showing differences in intervention effects between people with obesity and people with normal BMI.[24,25] Underrepresentation of people with obesity occurs when researchers exclude participants above a specific BMI, fail to recruit or retain people with obesity, fail to report rates of obesity in study samples, or fail to perform relevant subanalyses. In the remainder of this paper, we discuss vaccine and dosing effects in patients with obesity and the ethical and scientific imperative to include these patients in future clinical trials to better promote health equity.[24,25]

Lessons From Vaccine Research

Studies have demonstrated that some vaccines are less effective for people with obesity than for people with normal BMIs. A 2012 study found that 12 months after administration of the influenza vaccine, patients categorized as obese had significantly decreased influenza antibody titers and $CD8^+$ T-cell activation than patients categorized with normal BMIs.[26] Similar results have been produced for rabies, tetanus, and Hepatitis B vaccines.[27,28,29,30,31] Potential explanations for the reduced effectiveness of vaccines in people with obesity include inappropriately sized needles, inadequate dosing, and altered immune responses,[31,32,33] suggesting the need for more research to optimize vaccine efficacy in larger patients.

With regard to the COVID-19 pandemic and vaccine efforts, research has yet to produce universal data on obesity's impact on vaccine effectiveness[34] and whether obesity is significantly associated with increased morbidity and mortality from COVID-19.[35,36] While a large cohort study conducted in England found higher rates of vaccination among people with obesity than those of healthy weight as well as evidence that vaccines are effective in preventing severe COVID-19 in people with obesity,[37] it also highlights the need for replication research in other populations. However, as of May 2021, of 58 COVID-19 vaccine trials in phases III and IV, only 2 protocols indicated an intention to conduct subgroup analyses of participants with obesity; of 249 COVID-19 vaccine trials

across all 4 trial phases, 29.3% specifically excluded those with BMIs over 30, and half provided no specification of body size.[38]

While government and media messaging targeting obesity may have contributed to more higher-weight people getting vaccinated, as was demonstrated in the English study, researchers have also critiqued COVID-19 messaging focused on obesity as potentially contributing to increased weight stigma.[39] Given significant COVID-19 vaccine hesitancy among those with obesity[40] and that weight bias is attributed to delays in preventive and acute care,[41] it is important to consider the potential impact of weight stigma in public health discourse regarding COVID-19. Townsend et al concluded that "weight *stigma* and its cumulative sequalae are a prevalent and distinct vulnerability that interacts with biologic and structural risks for worse COVID-19 outcomes,"[42] highlighting the need to be attentive to issues of weight stigma when conducting public health outreach targeting higher-weight populations. Research examining the efficacy and reach of vaccination campaigns, effectiveness and dosing of COVID treatments, and the role of weight stigma in larger-bodied patients' COVID outcomes is needed.[42,43,44,45]

Different Pharmacologic Effects

Adipose tissue has different pharmacokinetic properties than lean tissue, and larger-bodied patients have demonstrated differences in activity of key enzymes and physiologic functions, leading researchers to hypothesize that drugs will function differently in patients with obesity. Natural variations in fat-to-lean mass ratios in patients with similar BMIs complicates the ability to predict drug effects. Some studies of highly lipophilic drugs in patients with obesity show differences in tissue blood flow and cardiac function, although the causes of these differences are not well characterized.[46,47]

Altered pharmacokinetics may in part explain data suggesting that standard dosing of some medications is not as effective in patients with obesity. For example, patients with obesity may be underdosed with anesthetics[48,49] and anticoagulants, such as enoxaparin.[50] In addition, studies show that antibiotics are frequently underdosed in patients with obesity due to both a lack of dosing research (in some cases) and physicians' lack of adherence to specified dosing guidelines,[51,52,53,54] suggesting a need for further research on best practices. The emergency contraceptives levonorgestrel and ulipristal acetate have reduced effectiveness in larger-bodied patients for unknown reasons, but higher dosing may not rectify this problem, suggesting additional factors may be at play.[24,55]

Body size also influences response to chemotherapeutic agents. Among patients with higher BMIs, studies have found decreased rates of complete pathologic response to neoadjuvant chemotherapy and reduced clearance of drugs (eg, doxorubicin or cyclophosphamide) compared to those of normal weight, as well as differences in overall survival.[56,57,58,59] A 2018 systematic review of 76 randomized controlled trials of obesity-related cancer types found that only one conducted a subgroup analysis and that this analysis showed less treatment success in patients with obesity.[23] Based on unpublished information, the median proportion of patients with obesity in 22 trials was only 18%.[23] These findings are concerning, given that higher weight is associated with increased incidence of multiple cancers,[60,61,62] possibly due to biological mechanisms.[63] Obesity is also correlated with social determinants of health that contribute to cancer rates, including lower socioeconomic status, residence in historically redlined neighborhoods, decreased access to fresh food, adverse childhood experiences, and

high allostatic load.[64] Additionally, weight stigma leads to reduced access to quality health care and screenings and exerts negative socioeconomic pressure on larger patients.[65,66,67] Inclusive research is needed to separate the impacts of these various factors and the clinical steps necessary to rectify disparities.

To ensure safe and effective care for higher-weight patients, studies should include a representative number of patients at the full range of higher BMIs, examine dosing and effectiveness through subgroup analysis, and explore whether other anthropomorphic measures predict medication response more accurately than BMI.

Including Higher-Weight Bodies

The principles of beneficence, nonmaleficence, and justice underlie the justification for inclusion of patients with higher BMIs in clinical trials.

- *Beneficence*. Given data showing the underrepresentation of larger bodied patients in cancer-related clinical trials, the differing efficacy of chemotherapeutic treatment in larger bodied patients, the association of obesity with cancer, and the increased cost of obesity-related cancers,[68] representative inclusion of larger-bodied patients in clinical trials is essential to maximizing benefit.

- *Nonmaleficence*. Harm could be prevented by conducting research on larger-bodied patients for whom vaccines have been shown to be less effective. Patients with obesity have been shown, in some studies, to have higher risk for COVID-19 morbidity and mortality.[35] Given the lack of conclusive data on COVID-19 outcomes for higher-weight individuals, as well as the concern that weight stigma could increase delays in care, more large-scale research is needed. In an effort to avoid jeopardizing the whole community by having a population that is potentially not adequately vaccinated, we need more population-specific research on delays in care and usage of preventive measures like vaccines. More generally, inadequate dosing of medications can lead to progression of disease and increased health care costs.[69,70,71,72]

- *Justice*. Ethical research demands that we address the historical issue of unduly burdening stigmatized groups with risks of research without full access to its benefits.[70] Given the multiple stigmas faced by patients with obesity,[73] it is fitting that researchers ensure that participants with obesity are not manipulated into participation. Concurrently, the principle of justice also requires that patients with obesity have equal access to the benefits of research participation.

In sum, while greater inclusiveness is important for research rigor (eg, generalizability, statistical power for subgroup analysis), it is ethically mandated as well.

A Path Forward

The Table provides an overview of various considerations for researchers when including higher-weight participants in clinical research. Moving forward, larger-scale legislative measures, such as an amendment to the NIH Revitalization Act to include participants with a full range of BMIs, would provide an enduring incentive for change. In addition, researchers should thoughtfully consider the ethical and methodological implications of including body diversity in study samples and subgroup analyses, even in the absence of legal mandates. While mandating body diversity inclusion may be outside the scope of

most institutional review boards (IRBs), IRBs could provide statements of "best practice" regarding body diversity inclusion to aid researchers in making study design decisions. Aside from study design, community engagement has been proven to be the most effective way to recruit subjects and maintain participation in clinical trials among minority groups.[74] Building rapport and trust, understanding community needs, being transparent about research protocol, including community input in research endeavors, and cultivating ongoing community relationships are all important not only for recruitment and retention but also for more ethical, responsible research. Likewise, addressing issues of access to trial participation, such as geographic availability of trials; introducing public health initiatives to address health literacy; and hiring community members in the research workforce all help to increase research participation as well as to empower minority communities to develop agency regarding their health.[75,76] The responsibility of research institutions also includes robust education of researchers and diversity among research personnel.[76]

Table. Considerations for Including Higher-Weight Participants in Clinical Research

When to include subgroup analysis	Critical questions to ask of published research	Sensitivity to ethical issues
Target disease has different prevalence in larger-bodied patients.	Were there any BMI restrictions for study inclusion? What range of BMIs was included in the study? Was this range representative of population BMIs?	Be attentive to potential issues of weight stigma in the research design or language; consider consulting a weight stigma expert for review of participant materials.
Target disease has different presumed mechanisms in larger-bodied patients.	Was there a subgroup analysis of higher-weight patients?	Develop more specific and biologically relevant measures of adiposity (than BMI).
Target medication depends on volume of distribution, fat mass, or liver/kidney clearance for metabolism and effect.	Did results differ for those with higher BMI? What explanations were explored?	The conclusion should not automatically be drawn that adiposity is the cause of differing results.
Target disease is known to be correlated with allostatic load, which is increased in larger-bodied patients.[64]	Did the study design control for the effects of weight stigma and weight cycling?	Weight loss should not be recommended as a solution for differing outcomes unless weight loss specifically was the intervention studied, it was studied in all participants regardless of BMI, and short- and long-term side effects were tracked as with any other intervention.
Medication is administered intramuscularly.	What was the dropout rate of higher-weight patients? Did dropout rates differ by BMI?	Given the prevalence of dieting among larger-bodied people, assessment of nutritional status will likely be important to fully understand results.
Disease or intervention is believed to be impacted by experiences of weight stigma.	Did the study control for social determinants of health?	Conduct research into barriers to participation for higher-weight patients.

Conclusion

As we have shown, lack of body diversity in medical research creates methodological and inferential challenges (eg, lack of generalizability) and ethical concerns (eg, beneficence, nonmaleficence, justice). Based on data suggesting that higher-weight individuals may respond differently to some clinical interventions, we suggest that body size diversity should be included under the NIH Revitalization Act. Compliance should be overseen by grantors and facilitated through education of researchers and in partnership with communities and IRBs. We urge the biomedical community not only to support such legislative efforts, but also to adopt representative inclusion of patients at the full range of higher BMIs in clinical trials to better promote health equity.

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Citation
AMA J Ethics. 2023;25(7):E517-527.

DOI
10.1001/amajethics.2023.517.

Acknowledgements
In the spirit of healing, we would like to acknowledge that this work was produced on the unceded land stewarded by the Chumash, Tongva, Kizh, Salish, Duwamish, Ute, Arapahoe, Apache, Comanche, and Cheyenne Nations.

Conflict of Interest Disclosure
The author(s) had no conflicts of interest to disclose.

The viewpoints expressed in this article are those of the author(s) and do not necessarily reflect the views and policies of the AMA.

ISSN 2376-6980