PERSPECTIVE

Perspective: Guidelines Needed for the Conduct of Human Nutrition Randomized Controlled Trials

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ABSTRACT

Guidelines for designing, conducting, documenting, and reporting human nutrition randomized controlled trials (RCTs) have as yet to be developed and disseminated as reference for investigators, funders, regulators, institutions, assessors, trainees, and others involved in human nutrition research. Diet-related interventions can include diet and/or behavioral manipulation, provision of foods or entire meals, or delivery of dietary components in individual food items or supplements. This Perspective introduces a series of papers that outline core principles for the design and conduct of human nutrition RCTs, documentation and reporting of all aspects of clinical trial management, and data analysis and reporting of results. Human nutrition RCTs have unique considerations delineated in these papers. Conducting them with the highest scientific rigor is essential to the development of evidence-based dietary guidance for promoting optimal health and advancing health care. *Adv Nutr* 2021;12:1–3.

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Research rigor is essential to provide quality and reliable contributions to the knowledge base, which becomes the bedrock for the development of nutrition policy and guidance. Failure to meet methodological and ethical standards can compromise the scientific integrity of the trial outcomes. Measurable standards must be established and made available to the research community and those given responsibility for overseeing the research endeavor for it to be meaningful. Resources beyond the Code of Federal Regulations (45 CFR 46) exist for discussing and establishing the standards for research ethics and research integrity, including journals devoted to the topic such as *Ethics & Human Research* (1) and the *American Journal of Bioethics* (2), or describing the role of the institutional review board (IRB) (3). IRBs frequently have additional resources and guidance provided on their websites (4). Human nutrition RCTs have special considerations for research ethics because they involve humans. Institutional IRBs require all individuals conducting scientific investigations that involve human research to complete training before a project is initiated or prior to joining a research team, often through the Collaborative Institutional Training Initiative (CITI) Program (5). The CITI is implemented and funded by the Office of Research Integrity of the Department of Health and Human Services. However, the training for clinical research largely focuses on ethical aspects, particularly related to drugs and devices, and, in general, does not address the operational details or the special considerations encountered by investigators engaged in nutrition and other lifestyle intervention research.

From a national public health perspective, nutrition is vital to health, growth, economic development, and productivity throughout the life span of the population. Dietary risk factors surpassed tobacco use as the leading cause of death in the United States. Poor nutrition may contribute to poor health outcomes, particularly related to chronic diseases (6). The United States spends over $1 trillion annually managing diet-related chronic conditions (7). It has

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Abbreviations used: CITI, Collaborative Institutional Training Initiative; CTSI, Clinical and Translational Science Institute; IRB, institutional review board; NURISH, NUtrition InteRventIon ReSearcH working group; RCT, randomized controlled trial.

been estimated that, for cardiometabolic disorders, 10 dietary factors account for 18% of related costs in the United States (8). Rising health care costs have tremendous economic impact, which overburdens federal and state budgets, private businesses, and consumers. On an individual level, the burden of chronic diseases leads to diminished quality of life. Yet, the evidence base for making many public health dietary recommendations to improve diet quality and slow the onset of chronic diseases remains suboptimal. The standards for developing federal and professional society evidence-based dietary guidance are rigorous; guidelines and recommendations are, for the most part, based on the results from RCTs and/or systematic reviews and meta-analyses of RCTs (9–11). Studies not meeting predetermined criteria set by the working group, for example, a minimum Grading of Recommendations, Assessment, Development and Evaluations (GRADE) score, are not included in evidence reviews (12).

In pursuit of achieving scientific rigor in human nutrition RCTs, central to establishing evidence-based public health dietary guidelines and recommendations, a working group, NUtrition InteRventIon ReSearcH (NURISH), was convened under the auspices of the Tufts and Indiana Clinical and Translational Science Institutes (CTSIs). Initial topics for developing human nutrition RCT guidance were discussed during a retreat at Purdue University in February of 2018. A workshop of NURISH members was subsequently hosted at Tufts University in February of 2019. Representatives from CTSIs having a clinical nutrition program, as well as others working in the field were invited to attend. The ASN was invited as a partner to expand the community of experts to provide input.

The NURISH working group was divided into 3 subgroups to prepare the 3 articles in this series. The first article addresses issues related to study design and conduct (13). The second article focuses on documentation and regulation (14). The third article addresses best practices for ensuring data quality and integrity (15). The guidance proposed in the accompanying 3 articles was developed for investigative teams of researchers for the purposes of planning, conducting, and reporting on human nutrition RCTs. This guidance also may be used by institutions and funding agencies to identify and engage partners who need to be involved in this type of research. A healthy research environment that fosters reproducible and safe research practices involves the investigative team, institution(s) in which the research is conducted, the community within which the research is conducted, funding agencies and venues reporting the results, along with all other parties engaged in any aspect of the research.

Robust, independent research in nutritional science is an urgent public health priority (7). This series of articles reflects current thinking on the conduct of clinical nutrition research for the highest quality of rigorous science given current rules and best practices. Our objective is to provide a platform that facilitates the conduct of high-quality human nutrition RCTs. The tools for recruiting from larger pools of participants and monitoring participation and safety are changing and offer new opportunities. Yet, there are basic core principles that must be followed to achieve scientific rigor. A call for new guidelines that can be adopted for many types of trials and the removal of obstacles to clinical trials was recently published (16). A note of caution was included against focusing on adherence to rules rather than on scientific principles underpinning clinical trials in the interest of advancing health care. Here we attempt to answer this call for human nutrition RCTs.

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References

1. Ethics & Human Research [Internet]. [cited 2019 Nov 11]. Available from: https://www.thehastingscenter.org/publications-resources/ethics-human-research/.
2. American Journal of Bioethics [Internet]. [cited 2019 Nov 11]. Available from: https://www.tandfonline.com/toc/uajb20/current.
3. US Food and Drug Administration. Regulatory information search for FDA guidance documents, learn about the laws enforced by FDA, and more. [Internet]. [cited 2019 Nov 11]. Available from: https://www.fda.gov/regulatory-information.
4. Penn State College of Medicine. Clinical research guidebook [Internet]. [cited 2019 Nov 14]. Available from: https://research.med.psu.edu/research-support/guidebook/.
5. CITI Program. Research ethics and compliance. [Internet]. [cited 2019 Nov 11]. Available from: https://about.citiprogram.org/en/homepage/.
6. Mokdad AH, Ballestros K, Echko M, Glenn S, Olsen HE, Mullany E, Lee A, Khan AR, Ahmadi A, Ferrari AJ. The state of US health, 1990–2016: burden of diseases, injuries, and risk factors among US states. JAMA 2018;319(14):1444–72.
7. Yun J. The case for a National Institute of Nutrition. The Hill [Internet]. [cited 2019 Nov 11]. Available from: https://thehill.com.
8. Jardim TV, Mozaffarian D, Abrahams-Gessel S, Sy S, Lee Y, Liu J, Huang Y, Rehm C, Wilde P, Micha R. Cardiometabolic disease costs associated with suboptimal diet in the United States: a cost analysis based on a microsimulation model. PLoS Med 2019;16(12):e1002981.
9. Eckel R, Jakicic J, Ard J, Hubbard V, de Jesus J, Lee I, Lichtenstein A, Loria C, Millen B, Miller N, et al. Guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation 2014;25(Suppl 2):76–99.
10. National Academies of Sciences Engineering Medicine. Dietary Reference Intakes for sodium and potassium. Washington (DC): National Academies Press; 2019.

11. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G. The 2011 report on Dietary Reference Intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96(1):53–8.
12. British Medical Journal Best Practice—what is GRADE? [Internet]. [cited 2019 Nov 11]. Available from: https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade.
13. Lichtenstein AH, Petersen K, Barger K, Hansen KE, Anderson CAM, Baer DJ, Lampe JW, Rasmussen H, Matthan NR. Perspective: Design and conduct of human nutrition randomized controlled trials. Adv Nutr 2021;12(1):4–20.
14. Weaver CM, Fukagawa NK, Liska D, Mattes RD, Matuszek G, Nieves JW, Shapses SA, Snetselaar LG. Perspective: US Documentation and regulation of human nutrition randomized controlled trials. Adv Nutr 2021;12(1):21–45.
15. Maki KC, Miller JW, McCabe GP, Raman G, Kris-Etherton PM. Perspective: Laboratory considerations and clinical data management for human nutrition randomized controlled trials: Guidance for ensuring quality and integrity. Adv Nutr 2021;12(1):46–58.
16. Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. N Engl J Med 2020;382(7):674–8.