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CAN WE END THE "SALT WARS" WITH A RANDOMIZED CLINICAL TRIAL IN A CONTROLLED ENVIRONMENT?

Daniel W. Jones, MD,
Departments of Medicine and Physiology, Mississippi Center for Obesity Research, University of Mississippi Medical Center

Friedrich C. Luft, MD,
The Experimental and Clinical Research Center, Max Delbrück Center for Molecular Medicine, and Charité Medical Faculty, Berlin, Germany

Paul K. Whelton, MD,
Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, Louisiana

Michael H. Alderman, MD,
Departments of Medicine and Epidemiology and Public Health, Albert Einstein College of Medicine, Bronx, New York

John E. Hall, PhD,
Department of Physiology and Biophysics, Mississippi Center for Obesity Research, University of Mississippi Medical Center

Eric D. Peterson, MD,
Department of Medicine and Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina

Robert M. Califf, MD, and
Vice Chancellor for Health Data Science, Duke University

David A. McCarron, MD
Department of Nutrition, University of California-Davis, Davis, California

The 2013 Institute of Medicine (now the National Academy of Medicine) Report: Sodium Intake in Populations recommended that "clinical trials might focus on examining the effects of a range of sodium levels on risk of cardiovascular events, stroke, and mortality among patients in controlled environments."[1] This recommendation was very specific in two regards. It recommends a cardiovascular outcomes trial of dietary sodium reduction, and it recommends this be done in persons in controlled environments. There are important reasons behind these specific recommendations.

Corresponding Author: Daniel W. Jones, MD, Mississippi Center for Obesity Research, Professor of Medicine and Physiology, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, djones@umc.edu, Phone: 601-815-8995, Fax: 601-815-3642.

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Despite the large body of data regarding the relationship between cardiovascular disease and dietary sodium from observational studies and the positive impact on blood pressure in randomized controlled clinical trials and current national guidelines recommending daily sodium intakes of 2300 mg/day or less, mean daily intake for Americans remains in the 3400-3500 mg/day range.[2] Some scientists have questioned the justification for a reduced intake of dietary sodium.[3] This disagreement within the scientific community has been reported in the lay press, leading both clinicians and some in the public to express uncertainty on the issue.[4–6]

The Institute of Medicine is not alone in calling for an outcomes clinical trial on dietary sodium. The World Heart Federation, the European Society of Hypertension, and the European Public Health Association joined together to call for a definitive clinical trial of sodium restriction.[7] Indeed, for years, leading voices in this area of research have noted the absence of evidence from an outcomes-based clinical trial and advocated for execution of such a trial.

The reason this trial has not been accomplished can be seen in the second specificity of the IOM recommendations: that the trial be performed in “patients in controlled environments.” This statement recognizes the challenges of implementing a sodium reduction clinical outcomes trial. Such a trial would require a large number of participants in the intervention arm to maintain a reduced level of sodium intake for several years. Experience from behavioral intervention trials focused on blood pressure reduction demonstrates that in free-living persons in the United States, maintaining even a modest reduction in sodium intake for longer than six months is difficult for many adults.[8–10] Adherence to an 1800-2300 mg/day level of sodium has proven difficult in behavioral change clinical trials as well as clinical practice.

The food environment for most Americans includes added sodium in processed and restaurant prepared foods, making it difficult to sustain a reduced level of sodium intake. The only strategy for maintaining low sodium intake in free-living persons over long periods is likely to be consumption of prepared meals containing set amounts of sodium by study participants. This strategy of prepared meals is not likely to be financially feasible in a long term study with a large number of free-living participants. Thus, the Institute of Medicine Committee recommended that a dietary sodium reduction trial be performed in a controlled environment. [8–10]

In May, 2017 six of the authors of this paper convened in Jackson, Mississippi to discuss the issue of dietary sodium and cardiovascular disease. The agenda called for discussion of existing evidence, evidence gaps and remaining questions, and possible next steps in research to clarify the questions. The group was carefully selected for balance on points of view regarding interpretation of existing evidence related to the role of sodium in cardiovascular disease. The group concluded that differences of opinion on existing data could only be resolved with a randomized clinical trial evaluating the impact of dietary sodium on “hard” clinical outcomes, including death, stroke, and myocardial infarction.

Thoughts of the group on the rationale for an event-based clinical trial fell into two categories. Some members of the group thought that existing observational data on sodium and cardiovascular disease and clinical-trial evidence on sodium and blood pressure were insufficient to support existing guidelines on sodium restriction. They expressed an opinion that a clinical trial with cardiovascular morbidity and mortality outcomes was necessary to resolve the issue. Others in the group submitted that existing data were sufficient to support current guidelines on sodium restriction to 2300 mg/day or less but thought that stronger evidence from an outcomes trial would convince more clinicians, patients, and policy makers to accomplish better implementation of these guidelines. There was consensus that a well-designed and executed randomized clinical trial was desirable, if feasible.

Next, the group considered how a trial might be accomplished. There was agreement with the Institute of Medicine committee recommendation that a controlled environment would be essential for conduct of a successful events outcome trial in the United States. The ability to control the amount of sodium in prepared foods was considered an essential element in selecting a population and setting. Several populations living in a controlled environment were considered. In theory, study of active military personnel might provide a context where diet could be controlled. But this was ruled out because of the relatively young age of many active military personnel and concerns related to sodium restriction in individuals who might be losing large amounts of sodium through intense physical activity, especially those deployed in regions with very hot climates. Residents of nursing homes would also offer an opportunity to control the sodium intake. Concerns with this option centered on the likelihood that a large number might have medical conditions requiring a prescribed sodium diet. Residents of retirement communities where group dining is available were also considered as a possibility. The concern with this group was the limited percentage of food intake that could be controlled.

The group eventually arrived at a consensus that a clinical trial in a prison population (particularly federal prisons) might provide the best setting to conduct the trial. Positives for this approach included: potential to control a large portion of dietary intake; a large population with multiple locations; possibility for use of a randomized cluster design; diversity of age and ethnicity; an existing research infrastructure including an Institutional Review Board and; the existence of a large literature on the ethics of research in prisoners and the likelihood of benefitting future prisoners by demonstrating the level of dietary sodium that optimizes their health outcomes. Negatives considered included concern regarding the sensitivity of prison research, heterogeneous views of the ethics of prison research, and uncertainty as to whether enough prison sites could be enrolled.

Several ethical issues must be addressed when considering a study in a prison population.[11] One key principle is that any study to be performed must benefit the prisoners, not just the general population. In the case of dietary sodium, if one acknowledges that until an outcomes trial is performed there remains uncertainty about the ideal sodium intake for prisoners, it would seem imperative to ascertain the ideal intake for a group of people unable to make decisions regarding the sodium content of their food. Free-living individuals may make that choice for themselves, but prisoners depend on prison system leadership to assure an ideal sodium intake.

Preliminary conversations with leadership of prison systems have been enlightening and helpful. A review of the idea by a prisoner rights ethics expert and initial engagement with potential funders have been encouraging. Similarly, we brought into our initial group two scientists with experience in complex randomized controlled trials and in federal policy (RC and EP). There are many issues to consider before moving forward in this direction. A first step is a formal proposal of a pilot study to assess current dietary sodium intake for some prison locations and to assess the feasibility of managing the level of sodium intake in these locations. Both the pilot phase and the long-term study will involve a representative group of prisoners in the concept and design of the study.

The primary purpose of this communication is to notify the community of scientists interested in dietary sodium that we intend to explore the potential for conducting an event-based clinical trial that would help determine the value of a reduced dietary intake of sodium in preventing major cardiovascular events. We are cognizant of our need to seek advice and engagement from a wide range of professionals from the scientific community. That input will be welcomed. We believe it is time to move beyond the call for a clinical trial to exploration of the feasibility of such a study. Our hope is that we will prove the feasibility of a full scale trial. Results from such a study would inform decisions by policy makers, guideline groups, clinicians, patients, and the general public and will result in better health for all Americans and for people around the world.

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