Reply

Response to Commentary by Giuseppe Mancia

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We appreciate the commentary by Prof. Mancia on our manuscript [1].

He argues that randomized trials are not feasible to certain areas, particularly epidemiology, diagnosis, and patients' follow-up [2]. We agree that in the current climate, randomized trials of such topics are not feasible. However, all observational studies are subject to confounding; there are numerous examples in the literature of observational studies or expert opinion being contradicted by the results of well-conducted randomized clinical trials [3,4]. Acquiescing to the status quo, accepting that clinical trials are expensive and difficult to conduct, and lowering our standards for high-quality evidence will not provide patients and physicians with the quality evidence they deserve to make decisions about their healthcare.

Rather, we believe our manuscript should serve as the impetus to revamp the clinical trials enterprise such that questions of importance to physicians and patients can be answered by rapid, less expensive randomized clinical trials, and that the importance of the question to patients' health should primarily drive decisions to conduct trials, rather than only the likelihood of the trial returning a positive return on investment to an industry funding partner [5]. The potential trials Prof. Mancia describes—examining frequency of follow-up for patients with hypertension, methods of screening for hypertension and assessing cardiovascular risk—have the potential to tremendously affect global health and resource utilization, and should not be dismissed as unfeasible.

Routine digital collection of healthcare data is creating an environment where, with coordination, pragmatic clinical trials should be able to be conducted with limited investment in data collection, enabling rapid, less costly evidence generation from randomized clinical trials. Registry-based clinical trials in Sweden, which leverage data collected for quality improvement and administrative purposes, have successfully enrolled high proportions of eligible patients in pragmatic clinical trials such as oxygen versus no oxygen in patients with acute myocardial infarction [6]. These types of trials should serve as a model for the rest of the world, and a call for governments to invest in high-quality, comprehensive, longitudinal, real-world data sources to which investigators can apply randomization. Further, by enrolling patients in trials during the course of routine practice and limiting patients' trial-specific contact with

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investigators, such pragmatic clinical trials also afford an opportunity to study therapeutic inertia and adherence with medications [7].

With the advent of digital data, there is a tremendous opportunity to reshape a portion of the clinical trials enterprise to put patients' needs at the center. Physicians and clinical trialists should think not of what evidence *can* be generated, but what evidence *should* be generated.

CONFLICTS OF INTEREST

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