Commentaries on Viewpoint: Control arms in exercise training studies: transitioning from an era of intervention efficacy to one of comparative clinical effectiveness research

PHYSICAL ACTIVITY—WHAT DO WE REALLY KNOW?

TO THE EDITOR: It was with great interest that I read the Journal of Applied Physiology Viewpoint on control arms in exercise training studies: transitioning from an era of intervention efficacy to one of comparative clinical effectiveness research (1).

I believe, as do the authors, in the importance of discussing continuously the code of ethics while we continue to do research. The Viewpoint(s), however, opens up for debate.

WHO (3) states that “…a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs…” In addition, clinical equipoise (true uncertainty that one arm of an intervention is superior to another) must be mandatory (as stated in the Viewpoint) with regard to these clinical trials.

However, with support from the Medicines for Human Use (Clinical Trials) Regulations 2004 (2), I would like to suggest that human mechanistic studies, which are performed to identify physiological responses to provide direct proof of causation, thereby increasing the insight into human physiology, are not necessarily defined as clinical trials.

So, as long as questions regarding causality remains, it is ethical to do studies also aiming at investigating efficacy of an intervention (e.g., exercise making humans inactive) as long as the subjects are completely informed and possibly followed up after the study.

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A PROPOSED ALTERNATIVE TO AN INACTIVE CONTROL ARM: LOW-IMPACT EXERCISE GROUPS

TO THE EDITOR: In a recent Viewpoint (3), the ethics of using an inactive control group in exercise trials was challenged. While we agree that it is not ideal to withhold exercise because of its multiple benefits, many individuals in North America are inactive. Despite the recommendation of 150 min/wk of physical activity for optimal health (1), only 35% of adults engage in regular exercise while 65% are sedentary or not regularly active (2). Thus an inactive control group may not cause harm because it reflects the participants’ usual lifestyle.

We highlight that a control group of low-impact/intensity exercises is an attractive and viable option to an inactive control group. We have successfully implemented this option in past trials of exercise (4).

Our suggested alternative is also consistent with the goal of economic evaluations—to determine which interventions provide the best value for money. The most compelling comparator (i.e., control group) is one that receives an intervention that is widely available and thereby enabling us to make conclusions regarding cost effectiveness. Currently, most community-based programs for older adults include only low-impact/intensity exercises.

Despite the well known benefits of exercise (5), it is still unclear what specific prescriptions will provide maximal benefit for different outcomes. Hence, exercise trials should shift their focus toward understanding what type(s) of exercise are most advantageous and the dose-response relationship. This will allow health care practitioners to make specific recommendations for policy and prescriptions at the individual level, thereby facilitating individuals to engage in regular exercise.

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CONTROL ARMS IN EXERCISE INTERVENTION STUDIES SHOULD REFLECT TRAINING OPTIONS AVAILABLE IN THE “REAL WORLD”

TO THE EDITOR: Huffman et al. (2) appropriately recommend that clinical trials investigating health benefits of physical activity be designed to examine comparative clinical effectiveness. It is frequently recommended that individuals participate in a wide array of fitness activities to optimize adherence and physiological benefits (1). However, such freedom is often not offered in RCTs when individuals are assigned to a group that performs a specific type/intensity of exercise in a strictly regimented
manner to minimize confounders. Control arms of future large-scale RCTs should borrow a feature from observational studies through creating a setting that allows participants to self-select each training session from a variety of options to meet recommended standards for physical activity (e.g., various supervised group fitness classes or structured ergometry protocols). This allows participants freedom to adjust exercise type and intensity throughout the study period to their personal preference, resembling a “real world” scenario. Exercise duration and intensity could still be quantified through onsite monitoring. Outcomes from more regimented protocols (e.g., specific interval training programs) would then be compared to this control arm to determine if a given protocol is indeed superior to preference-based “real world” training. Continued research could then examine voluntary long-term adherence to each intervention beyond the time frame of required participation as a further measure of potential for true clinical effectiveness.

While this approach sacrifices strict uniformity in exercise prescription of the control arm, it provides a comparative “real world” scenario without violating clinical equipoise as assigned inactivity or delayed-entry control arms do.

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