RESEARCH NOTE

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The use of control group in the sports science research: the ethical challenge

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ABSTRACT

Medical ethicists have questioned the use of no-treatment controlled studies (placebo and sham procedure) of new therapies when safe and effective standard therapies are available for use as an active or "equivalence" control. Currently, ethical and conduct principles for biomedical research specifically prohibit projects that do not make or deny the "best-proven diagnosis and therapeutic treatment" to any participant in a clinical trial, including individuals who consent to randomisation into a control group. Studies of psychophysiological therapies are often criticised for not having a placebo or sham treatment control group. In sports science research, particularly in the case of clinical exercise, the use of control groups also raises ethical questions. This article briefly reviews the problem and discusses the ethical standards governing human research derived from the Nuremberg Code and the Declaration of Helsinki.

KEYWORDS: ethics of control group; placebo control; randomised controlled trial; clinical exercise.

INTRODUCTION

Recent literature has raised strong concerns about the ethical consideration of including placebo control groups in clinical trials when effective treatments are available. In contrast, others offer an alternative view that placebo control groups are necessary (Emanuel & Miller, 2001). In sports sciences research, as in clinical practice, it is clearly unethical to withhold treatment when a therapy of proven benefit is readily available. Therefore, in clinical trials, a placebo group is ethically acceptable when the therapy or therapies under investigation have not been proven to be more beneficial than a "no therapy" alternative. Proven therapeutic benefits should be designated based on the strength of the evidence rather than the conviction of the individual clinician or researcher (Kennedy & Tyson, 1999).

There is, however, a most serious issue with the use of placebo, i.e., the possibility that participants are harmed by receiving a placebo instead of an active treatment. For many conditions, not receiving an active treatment exposes the patients to higher levels of pain, aggravation of their conditions, or even the risk of death. In such situations, the use of placebos is clearly downright unethical because the patients on the placebo would be harmed for the sole benefit of third parties, namely for the scientific achievement of the trial completion (Nardini, 2014).

As noted by Freedman (2017), "The ethics of medical practice grants no ethical or normative meaning to a preference, however powerful, that is based on a hunch or on anything less than evidence publicly presented… Persons are licensed as physicians after they demonstrate the acquisition of this professionally validated knowledge, not after they reveal a superior capacity for guessing."

Allowing dishonest science to be conducted is but one step along a continuum to the conduct of cruel experiments that are conducted to yield personal rewards. Although certainly conducting dishonest science does not inevitably lead

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to unethical experiments, some of these historical examples suggest that there may be a common thread of personal advancement. Only by policing ourselves and teaching others can we truly realise the admonition of the memorial stone at the Dachau concentration camp: Nie Wieder (Never Again) (Lefor, 2005).

A little of history

Although a great deal of human experimentation has been performed to elucidate information otherwise not obtainable, there are many recorded instances of unethical human experimentation, including in the field of sports science. There is also a history of crimes that were committed and disguised as human experiments, best exemplified by the activities of some physicians in Nazi Germany from 1933 until 1945. As a direct result of these activities, a war-crimes trial after World War II resulted in the creation of the Nuremberg Code to guide future human experimentation. Despite this, unethical experiments were conducted at major academic institutions in the United States in the years after World War II by otherwise normal physicians who did not feel that the Nuremberg Code applied to them personally. There are several possible explanations for such activities, but the desire for personal advancement is prominent among these. Episodes of scientific misconduct, such as falsifying experimental data or personal qualifications, seem more commonly reported recently and have also been described in the popular press in several areas, including the sports sciences. This activity may also be motivated by a desire for personal advancement, giving it a parallel to the conduct of unethical human experimentation. Education may be the best way to prevent these activities that may have similar motivating factors (Lefor, 2005).

Until the 1980s, even fewer physicians thought that the Nuremberg Code or Helsinki Declaration had much to do with medical research or clinical practice within the United States (Butterworth, 2011). The Nuremberg Code was composed subsequent to the conviction of Nazi physicians who defended their horrific research, claiming it was similar to medical research being done all over the world (Friedmann & Sprecher, 1954). That code stated as its very first basic principle that human experimentation should involve the "voluntary consent of the subject". The World Medical Assembly meeting in Helsinki published what became known as the Declaration of Helsinki. It contained 22 "basic principles" for guiding human subject research. The Declaration was later revised in 1975 and 1983. The medical community did not develop sanctions for researchers who disregarded the Nuremberg Code or the Helsinki Declaration (Butterworth, 2011). Beecher's (2017) comments in the New England Journal of Medicine were not welcomed by some in the medical research community because prominent researchers thought his ideas about obtaining informed consent from human subjects would stifle medical research. Multidisciplinary panels that composed Federal regulations for human research had more ethicists and members of the public than physicians because US society wanted consistent treatment of human research subjects. The community of professional physicians failed to agree on the required elements of consent or enforce consistency in obtaining patient consent. Beecher (2017) himself stated that achieving truly "informed consent" was probably not possible. He acknowledged the pressure on researchers to publish combined and an explosion of research funds to coerce researchers to proceed without trying too hard to fully inform research subjects (Beechers, 2017). Federal standards were defined in the late 1970s, published in 1981, and enforced thereafter. They defined the requirements for informed consent for research subjects, which, until that time, were pretty much up to individual researchers-some of whom had more defensibly ethical practices than others (Butterworth, 2011).

One of the most controversial aspects of the Declaration of Helsinki is its insistence that proposed new treatments be compared with the best currently available option for health rather than with the response of a true control or placebo group (Joseph, 1998; Singer & Benatar, 2001). The equilibrium principle requires genuine uncertainty about which of the two treatments is preferable (Freedman, 2017). The scientific ideal is to assign participants randomly between experimental and control or placebo groups, and where possible, the type of treatment should also be hidden, for example, the controls may be given a homoeopathic dose of exercise or a fitness information sheet something that is common practice for example in the field of sports science. Such 'blinding' of treatment is often important to the reaching of scientifically valid conclusions, but it is difficult to explain to potential participants and also requires very careful discussion with an ethics review committee (Shephard, 2002). Given what is known about the substantial health benefits of exercise (Bouchard & Shephard, 1991), the policy of asking controls not to exercise or to take an ineffective dose of exercise is controversial and would seem contrary to the Declaration of Helsinki. At the University of Toronto, the research review committee generally requires that after completing a study of finite length (e.g., 1 year), any controls or placebo groups must be offered an exercise program that matches the one previously provided for experimental groups. A crossover trial might offer one possible alternative, although, with such a

design, difficulties of data interpretation could arise from a loss of the benefits of training in the group who first received the active treatment (Shephard, 2002). In some instances, it is important to include indications for halting an experiment, even when it has not run its intended course. For example, in one trial of coronary rehabilitation, the research review committee imposed a requirement that the experiment should be stopped if, at any point, it became statistically clear that the control group was faring more poorly than the exercisers (Rechnitzer, Cunningham & Jones, 1977). The Declaration of Helsinki does not specifically prohibit healthy volunteers from serving as control participants for the benefit of science or humanity. However, the declaration does distinguish clearly between such healthy volunteers and the client or patient who is so often involved in exercise science experiments (Rothman, 2000). Services or treatment to a client must not be diminished because of an individual's willingness to participate in an experiment (Medicine, 1979).

In clinical research, a gap exists between those exposed to the risk of medical intervention — the trial participants — and those who are the intended beneficiaries of the trial results — future patients and society at large. The existence of this gap has informed the conception of most ethical guidelines that are currently in use, which were created with a keen eye to protect participants from the risks and burdens of research (Nardini, 2014). For instance, the aforementioned Declaration of Helsinki requires that "the wellbeing of the individual research subject must take precedence over all other interests" (art. 6). However, this emphasised participant protection paradigm is increasingly considered inadequate. Mainly, two considerations speak against this. The first point is the realisation that the only effect of such strict regulation in developed countries has been to encourage the outsourcing of the conduct of trials to countries where the standards of protection of participants are lower (Maguire, 2014; Vargas-Mendoza, Fregoso-Aguilar, Madrigal-Santillán, Morales-González & Morales-González, 2018; Watson, Way & Hilliard, 2017). This is an issue, also due to the fact that both the national states involved and the prospective participants individually often find themselves in a situation of economic vulnerability and captivity towards the large pharmaceutical groups that are running the trial (Glantz, Annas, Grodin & Mariner, 1998; Montagne, 1985). Thus, strong protection norms prove ultimately ineffective in warranting high levels of protection to participants in a globalised setting, appearing on the contrary to foster new forms of exploitation. Negotiating the adequate level of protection that can be set as a global standard for medical research has proven challenging, as testified by the continuing effort in revising the Declaration of Helsinki (Riis, 2003). A second argument that has been raised against the current paradigm concerns the issue of paternalism (Miller & Wertheimer, 2007), i.e., the concern that the levels of protection warranted by current guidelines may conflict with the autonomous choices of participants. A patient participating in a trial might wish to take a higher level of risk for the sake of an individually gauged perceived benefit, for instance, by taking a chance with an innovative and promising treatment. Or, more controversially, a patient might wish to take part in research from which he/she knowingly stands no chance of receiving any benefit for the sake of benefiting other patients or posterity.

The use of control groups

To understand the nature of the controversy, it is necessary to first distinguish between types of control groups regularly used in sports science research. Your use is a critical aspect of randomised controlled trials that distinguishes these trials from other study designs (Lau, Mao & Woo, 2003). The main aim of using a control group is to discriminate the effects caused by the study treatment compared to other possible effects caused by other factors (EMA, 2001). Control groups are selected in a way that they should be similar to the experimental groups in all variables that could affect the outcomes, except for the study treatment. Thus, any significant differences between the two groups can be attributed to the difference between the study treatment and the placebo or the other active treatments under comparison. Failure to achieve such comparability would result in bases (EMA, 2001; Lau et al., 2003).

There are different types of control groups used in clinical trials, each trial type addressing different objectives and possessing inherent limitations (Miller & Wertheimer, 2007). A clinical trial may employ a placebo group as its control group, in which subjects receive a pharmaceutically inert treatment, keeping all other aspects the same. Blinding is always built to remove effects arising from the fact that the researcher knows that the 'drug' is only a placebo that may affect both the outcomes and the compliance. Such trials are all subsumed under superiority trials. Another type of control group is the 'no treatment' group. No treatment controls are similar to placebo controls, except that blinding is not possible. The third type of control gives an active treatment to the subjects. These trials can be either superiority or non-inferiority trials depending on the objectives of the study. Control groups may also be given different dosages of the same treatment (dosage controls) if the aim is to test for dosage effects. An add-on control group could be included when stopping a treatment is not ethical. This type of study is a placebo-controlled trial

of a new agent conducted with patients who also receive the existing active treatment (EMA, 2001).

Only the use of dosage controls allows for comparisons of dosage effects. Studies involving an active treatment control group can allow for comparison between different therapies, something that often occurs in the field of sports sciences. Studies using a placebo control group and an active treatment control group with a superiority design allow for measurement of the 'absolute' effect and test for relative efficacy between two treatments. Non-inferiority trials only using an active treatment control group cannot achieve these two important objectives (Lau et al., 2003).

Pre-post with non-equivalent control group

Conducting pre-post investigations with non-equivalent control group uses a control group in the absence of randomisation. Ideally, the control group is chosen to be as similar to the intervention group as possible (e.g., by matching on factors such as clinic type, patient population, geographic region, physical characteristics, etc.) (Maguire, 2014). Theoretically, both groups are exposed to the same trends in the environment, making it plausible to decipher if the intervention had an effect. Measurement of both treatment and control conditions classically occurs pre- and post-intervention, with differential improvement between the groups attributed to the intervention. This design is popular due to its practicality, especially if data collection points can be kept to a minimum. It may be especially useful for capitalising on naturally occurring experiments such as may occur in the context of certain policy initiatives or rollouts—specifically, rollouts in which it is plausible that a control group can be identified (Miller, Smith & Pugatch, 2020). For example, Kirchner et al. (2014) used this type of design to evaluate the integration of mental health services into primary care clinics at seven US Department of Veterans Affairs (VA) medical centres and seven matched controls.

One overarching drawback of this design is that it is especially vulnerable to threats to internal validity (Anderson-Cook, 2005) because pre-existing differences between the treatment and control group could erroneously be attributed to the intervention. While unmeasured differences between treatment and control groups are always a possibility in healthcare and sport science research, such differences are especially likely to occur in the context of these designs due to the lack of randomisation. Similarly, this design is particularly sensitive to secular trends that may differentially affect the treatment and control groups (Cousins, Connor & Kypri, 2014; Pape, Millett, Lee, Car & Majeed, 2013), as well as regression to the mean confounding study results (George & Johnson, 1992). For example, if a study site is selected for the experimental condition precisely because it is underperforming in some way, then regression to the mean would suggest that the site will show improvement regardless of any intervention; in the context of a pre-post with non-equivalent control group study, however, this improvement would erroneously be attributed to the intervention itself (Type I error).

There are, however, various ways that implementation scientists can mitigate these weaknesses. First, as mentioned briefly above, it is important to select a control group that is as similar as possible to the intervention site(s), which can include matching at both the healthcare network and clinic level (Kirchner et al., 2014). Second, propensity score weighting (Morgan, 2018) can statistically mitigate internal validity concerns, although this approach may be of limited utility when comparing secular trends between different study cohorts (Dimick & Ryan, 2014). More broadly, qualitative methods (e.g., periodic interviews with staff at intervention and control sites) can help uncover key contextual factors that may be affecting study results above and beyond the intervention itself (Miller et al., 2020).

The use of placebo in randomized clinical trail

The use of placebo in a randomised clinical trial is widely considered to be the most rigorous method of evaluating the efficacy of treatment or prevention interventions. To be ethical, clinical research requires balancing rigorous science with the protection of human subjects (Millum & Grady, 2013). Randomised clinical trial generates an intense debate and is considered an ethical dilemma. As in any ethical dilemma, benefits in one area can automatically imply shortcomings in another area. A central ethical tension is whether the researcher-clinician should be guided by the ethics of therapeutic medicine or the one underlying research. In this context, the clinical investigator has a different role as compared to a clinician. These two roles need to be differentiated (Benson, Roth & Winslade, 1985). In 1987, Freedman (2017) proposed the concept of equipoise, arguing that "the requirement is satisfied if there is genuine uncertainty within the expert medical community — not necessarily on the part of the individual investigator — about the preferred treatment". Therefore, there must be a real need to determine the efficacy or safety of a new treatment if this active treatment in the given condition being investigated does not cause any serious or irreversible harm (Benson et al., 1985). Another important aspect of randomised clinical trial is that the sample sizes are usually smaller than when an active intervention

is used in the control group, therefore, the number of subjects exposed to an experimental intervention is reduced. Leon (2000) showed that a study comparing an investigational drug with placebo needs a smaller number of subjects resulting in a smaller number of non-responders compared to the alternative of using an active control. However, some researchers consider that statistical arguments should not be used to justify ethical issues. Kraemer (2000) commented on the premise that patients do not have full comprehension of the type of medical support they will have when participating in a placebo-controlled study. The debate becomes more intense when the placebo-controlled group is not an inert placebo but an active one, such as surgical procedures or pills that mimic some of the side effects of the pharmacological therapy under evaluation. Edward, Stevens, Braunholtz, Lilford and Swift (2005) discussed this issue by considering what they called "three ethical hurdles". For these authors, the "evaluation methods must be the best or only scientific option available to get valid data; acceptable to participants in terms of a utilitarian calculation of risks and benefits; and respectful of the needs of individuals and communities to control their own destinies".

For Millum and Grady (2013), the ethical analysis and international ethical guidance permit the use of placebo controls in randomised trials when scientifically indicated in four cases: (i) when there is no proven effective treatment for the condition under study; (ii) when withholding treatment poses negligible risks to participants; (iii) when there are compelling methodological reasons for using placebo, and withholding treatment does not pose a risk of serious harm to participants; and, more controversially, (iv) when there are compelling methodological reasons for using placebo.

Some concrete cases

Many fundamental ethical issues and principles in animal research are similar to those in human research. In both cases, the governance system assumes that research is acceptable if it benefits humans or animals or advances knowledge, as long as the work is achieved in an ethically appropriate manner; this included meeting substantive standards related to potential harm, benefit and social value, as well as procedural standards such as independent ethical review (Schuppli & Fraser, 2007).

What level of evidence should be required as adequate proof of benefit? In all areas of sports sciences, many ineffective or even hazardous therapies have initially been considered beneficial and have been widely used on the basis of uncontrolled or nonrandomised studies. Masked randomised trials provide the greatest protection against biased results in clinical research. For these reasons, narcotics can be considered a proven and ethically mandatory therapy for infants receiving mechanical ventilation only if the value has been established in one or more masked randomised trials with sufficient numbers of infants to assess all important potential benefits and hazards (Tyson, 1995).

In Brazil, resolution 196/96 and its complements regulate the preservation of the rights, respect and dignity of human beings involved in research. In order to analyse the adequacy of the free communications presented during the XVIII Pernambuco Congress of Cardiology to resolution 196/96, of the 90 papers analysed for Lima et al. (2010), only 23.1% were submitted to the assessment of a Research Ethics Committee, and 15.4% of them used a Free and Informed Consent Form. Among the authors whose studies were not assessed by the research ethics committee, 65.6% stated that this conduct was not necessary, and 18% of them were unaware of the need to submit the study to such assessment. The written authorisation given by the institution where the free communications were carried out was not obtained in 56.6% of the studies. Most of the authors (80%) stated that they had never read Resolution 196/96. It is noteworthy that, according to that resolution, case reports and case series studies, as long as they involve human beings in some way, must therefore be evaluated by a research ethics committee (Lima et al., 2010).

For more than three decades, clinical research in the United States has been explicitly guided by the idea that ethical considerations must be central to the design and practice of the research. Possible conflicts between the standards of scientific research and those of ethics are particularly salient in relation to study design (de Melo-Martín, Sondhi & Crystal, 2011). Specifically, choosing a control arm is an aspect of essay design in which ethical and scientific issues are deeply intertwined. Although ethical dilemmas related to choosing control arms can arise when conducting any type of clinical trials, they are visible in the early stages of gene transfer trials that involve highly innovative approaches and surgical procedures and have children like the research subjects. Because of the vulnerabilities of children and their parents in trials investigating therapies for rare fatal diseases that affect minors, scientific and ethical concerns related to the choice of appropriate controls are particularly significant (de Melo-Martín et al., 2011).

Ethical concerns about schizophrenia research have been raised, for the most part, because of concerns about the decision-making capacity of the potential research participants. Schizophrenia is a disorder of disturbed thinking, so it was reasoned that if thinking is disturbed, capacity to consent is

likely to be compromised (Wilson & Stanley, 2006). In the late 1970s and early 1980s, ethicists and clinicians began to question the capacity of patients with psychotic disorders as a function of their illness severity (Stone, 1979). Patients with mental illnesses were viewed as generally lacking the capacity to make informed decisions about participation in research protocols, and capacity to consent was conceptualised as a static epiphenomenon of the illness syndrome (Grisso & Appelbaum, 1995). Some issues remain, however, even with the strides that have been made. For example, although there is a relative agreement on the minimum requirements for a determination of competency (Grisso, Appelbaum & Hill-Fotouhi, 1997; Zapf & Roesch, 2005), there are few reliable and valid methods for its assessment (Dijkers, 2010).

The withdrawal of treatment in psychiatric placebo-controlled studies is often cited to emphasise possible unethical situations that may cause greater risk or harm to patients in placebo groups. In fact, most European countries do not allow for placebo controls to be used in trials of antidepressant medications (Lau et al., 2003). A study reviewing 19,639 patients from the FDA database of seven new antidepressant trials performed between January 1987 and December 1997 showed that the incidence of suicide for patients in the placebo group, the active control group, and the test drug group were .4, .7, and .8%, respectively; similarly, the percentages of attempted suicide were 2.7, 3.4, and 2.8%, respectively (Khan, Khan, Leventhal & Brown, 2001). Neither set of data were of statistical significance. The percentages of patients with symptom reduction were 30.9, 41.7, and 40.7%, respectively. Hence, no evidence indicates that patients in the placebo group were exposed to a greater risk of developing serious adverse events or deriving no benefit from the study. These data do not support arguments for unethical research using these patients. A similar study (Storosum, Van Zwieten, Van den Brink, Gersons & Broekmans, 2001) that reviewed placebo controlled trials for the treatment of major depression found that, in 77 short-term studies with 12,246 patients, the incidences of suicide were .1% in both the placebo group and the active treatment group, and the incidences of attempted suicide were also identical (.4%) in both groups. Similarly, the incidence of suicide (0% for the placebo group and .2% for the active treatment group) and attempted suicide (.7% for the placebo group and .7% for the active treatment group) were not higher for the patients in the placebo groups compared with patients in the active treatment groups in eight long-term studies of 1,949 patients (Storosum et al., 2001).

For hypertension trials, there is compelling evidence that patients benefit from long term antihypertension treatment (Collins et al., 1990). A meta-analysis of 25 short-term randomised controlled trials (*n*= 6,409) conducted during 1997 and 1998, using death, stroke, myocardial infarction, and congestive heart failure as outcomes, showed that the difference in incidence between the placebo group and the antihypertension treatment group was between 0 and 6 per 10,000 subjects, however (Al-Khatib et al., 2001). Hence, short term placebo-controlled studies may still be ethical, even though a long-term study might not be safe. The study duration is, therefore, an important consideration in determining whether placebo-controlled studies are ethical or not. Similar arguments have been made for short-term studies of type 2 diabetes that are believed to be safe for patients in the placebo group, while longer trials (which may take at least 6 months to complete) will have adverse effects on the patients' quality of life and may result in microvascular complications (MacKenzie & Paget, 2015).

There are still many studies in which the development of some children is enhanced in relation to others. This happens more specifically in cases where some of them benefit from a treatment that turns out to be effective, compared to children who only benefit from the placebo. For example, in a study of adolescents aged 12 to 18 years, those who were treated with dupilumab for atopic dermatitis had a higher incidence of conjunctivitis than patients treated with placebo, while the overall rates of conjunctivitis among adolescents in the asthma study were lower than those treated with placebo in atopic dermatitis studies (Bansal et al., 2021). Another study that aimed to evaluate the effectiveness of honey for acute cough in children on an outpatient basis concluded that it relieves cough symptoms more than no treatment, diphenhydramine, and placebo but may make little or no difference compared to dextromethorphan (Briosa, Sousa & Fernandes, 2019). Honey probably shortens the duration of coughing better than placebo and albuterol.

FINAL REMARKS

Although a repetition of the worst atrocities of the Nazi death camps is unlikely, given adherence to the provisions of the Nuremberg Code and the Declaration of Helsinki, many areas of human research remain where ethical standards could be enhanced.

The use of placebo groups is common when conducting trials in the field of sports science. To date, the Declaration of Helsinki is the most widely recognised document guiding ethical considerations for human research. A heated debate has been ongoing in the US and Europe, and the arguments for the two sides are summarised in this paper. Since the fifth revision of the Declaration stated that journals should not

publish papers that are not in accordance with the Declaration, ethical issues related to the use of placebo controls are likely to be questioned more frequently and critically by the entire medical research community.

A key issue in the ethical justification of placebo-controlled trials, especially for categories in which non-treatment poses more than negligible risk, is what counts as a compelling methodological reason supporting placebo use. Here, Lau et al. (2003) argued that any additional risks of using placebo must be justified by the additional social value gained relative to other trial designs and suggested some important considerations for evaluating whether these reasons are sufficiently compelling to justify a placebo-controlled design.

However, the use of placebo remains an ethical problem, as the possibility that participants will be harmed by receiving it rather than active treatment is a reality. Thus, it is suggested that studies carried out in the field of sports sciences take into account the following recommendations: i) place the interest and well-being of the human being above the interest in science; ii) avoid burdens and risks that are beyond the potential benefits of research; iii) reduce the physical and/or psychological suffering of the participants to the minimum necessary; iv) always carry out an informed consent where the participants are aware of the potential known risks to health as a consequence of the application of the study procedures; v) whenever the intervention is carried out in participants who present some type of pathology, the control groups can receive a standard training/intervention program instead of receiving no stimulus, thus avoiding unethical principles.

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REFERENCES

Al-Khatib, S. M., Califf, R. M., Hasselblad, V., Alexander, J. H., McCrory, D. C., & Sugarman, J. (2001). Placebo-controls in short-term clinical trials of hypertension. *Science*, *292*(5524), 2013-2015. https://doi.org/10.1126/science.1057783

Anderson-Cook, C. M. (2005). Experimental and Quasi-Experimental Designs for Generalized Causal Inference. *Journal of the American Statistical Association*, *100*(470), 708. https://doi.org/10.1198/jasa.2005.s22

Bansal, A., Simpson, E. L., Paller, A. S., Siegfried, E. C., Blauvelt, A., de Bruin-Weller, M., Corren, J., Sher, L., Guttman-Yassky, E., Chen, Z., Daizadeh, N., Kamal, M. A., Shumel, B., Mina-Osorio, P., Mannent, L., Patel, N., Graham, N. M. H., Khokhar, F. A., & Ardeleanu, M. (2021). Conjunctivitis in Dupilumab Clinical Trials for Adolescents with Atopic Dermatitis or Asthma. *American Journal of Clinical Dermatology*, *22*(1), 101-115. https://doi.org/10.1007/s40257-020-00577-1

Beechers, H. K. (2017). Ethics and clinical research. In H. K. Beechers (ed.), *Medical Law and Ethics* (pp. 381-388). Springer. https://doi.org/10.4324/9781315209692-2

Benson, P. R., Roth, L. H., & Winslade, W. J. (1985). Informed consent in psychiatric research: Preliminary findings from an ongoing investigation. *Social Science and Medicine*, *20*(12), 1331-1341. https://doi.org/10.1016/0277-9536(85)90388-0

Bouchard, C., & Shephard, R. J. (1991). Physical activity, fitness, and health: The model and key concepts. In C. Bouchard, R. J. Shephard, & T. Stephens (Eds.), *Physical activity, fitness, and health: International proceedings and consensus statement* (pp. 77-89). Human Kinetics Publishers.

Briosa, F., Sousa, R., & Fernandes, R. M. (2019). Honey for acute cough in children. *Portuguese Journal of Pediatrics*, *50*(4), 289-292. https://doi.org/10.25754/pjp.2019.18542

Butterworth, J. F. (2011). Ethics and human experimentation. *Anesthesiology*, *114*(4), 1001-1002. https://doi.org/10.1097/aln.0b013e31820d84fb

Collins, R., Peto, R., MacMahon, S., Godwin, J., Qizilbash, N., Hebert, P., Eberlein, K. A., Taylor, J. O., Hennekens, C. H., & Fiebach, N. H. (1990). Blood pressure, stroke, and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *The Lancet*, *335*(8693), 827-838. https://doi.org/10.1016/0140-6736(90)90944-Z

Cousins, K., Connor, J. L., & Kypri, K. (2014). Effects of the Campus Watch intervention on alcohol consumption and related harm in a university population. *Drug and Alcohol Dependence*, *143*, 120-126. https://doi.org/10.1016/j.drugalcdep.2014.07.015

de Melo-Martín, I., Sondhi, D., & Crystal, R. G. (2011). When ethics constrains clinical research: Trial design of control arms in "greater than minimal risk" pediatric trials. *Human Gene Therapy*, *22*(9), 1121-1127. https://doi.org/10.1089/hum.2010.230

Dijkers, M. (2010). Re: challenges and recommendations for placebo controls in randomized trials in physical and rehabilitation medicine: a report of the International Placebo Symposium Working Group. *American Journal of Physical Medicine & Rehabilitation*, *89*(12), 1045-1046. https://doi.org/10.1097/phm.0b013e3181fc7c20

Dimick, J. B., & Ryan, A. M. (2014). Methods for evaluating changes in health care policy: The difference-in-differences approach. *Journal of the American Medical Association*, *312*(22), 2401-2402. https://doi.org/10.1001/jama.2014.16153

Edward, S. J. L., Stevens, A. J., Braunholtz, D. A., Lilford, R. J., & Swift, T. (2005). The ethics of placebo-controlled trials: A comparison of inert and active placebo controls. *World Journal of Surgery*, *29*(5), 610-614. https://doi.org/10.1007/s00268-005-7621-7

Emanuel, E. J., & Miller, F. G. (2001). The Ethics of Placebo-Controlled Trials — A Middle Ground. *New England Journal of Medicine*, *345*(12), 915-919. https://doi.org/10.1056/nejm200109203451211

European Medicines Agency (EMA). (2001). ICH Guideline E10: Choice of Control Group and Related Issues in Clinical Trials. *Choice, 10*, E10. Retrieved from: http://www.gcpunion.org/web/static/articles/catalog_ff8080815702574c01570866f936002a/article_5b6a8512677d-5f680167c5def06f0393/5b6a8512677d5f680167c5def071039d.pdf

Freedman, B. (2017). Equipoise and the ethics of clinical research. In K. D. Pimple (ed.), *Human Experimentation and Research* (pp. 427-431). Routledge. https://doi.org/10.4324/9781315244426-17

Friedmann, W., & Sprecher, D. A. (1954). Trials of War Criminals before the Nuernberg Military Tribunals under Control Council Law No. 10. Nuernberg Military Tribunals. Vol. III. *Harvard Law Review*, 67(7), 1284-1291. https://doi.org/10.2307/1337041

George, V. T., & Johnson, W. D. (1992). Effect of regression to the mean in multivariate distributions. *Communications in Statistics: Theory and Methods*, *21*(2), 333-350. https://doi.org/10.1080/03610929208830782

Glantz, L. H., Annas, G. J., Grodin, M. A., & Mariner, W. K. (1998). Research in developing countries: taking" benefit" seriously. *The Hastings Center Report*, *28*(6), 38-42.

Grisso, T., & Appelbaum, P. S. (1995). MacArthur Treatment Competence Study. *Journal of the American Psychiatric Nurses Association*, *1*(4), 125-127. https://doi.org/10.1177/107839039500100405

Grisso, T., Appelbaum, P. S., & Hill-Fotouhi, C. (1997). The MacCAT-T: A clinical tool to assess patients' capacities to make treatment decisions. *Psychiatric Services*, *48*(11), 1415-1419. https://doi.org/10.1176/ps.48.11.1415

Joseph, K. S. (1998). Ethics in clinical research: searching for absolutes. *CMAJ*, *158*(10), 1303-1305.

Kennedy, K. A., & Tyson, J. E. (1999). Narcotic analgesia for ventilated newborns: Are placebo-controlled trials ethical and necessary? *Journal of Pediatrics*, *134*(2), 127-129. https://doi.org/10.1016/S0022-3476(99)70399-9

Khan, A., Khan, S. R., Leventhal, R. M., & Brown, W. A. (2001). Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: A replication analysis of the Food and Drug Administration Database. *International Journal of Neuropsychopharmacology*, *4*(2), 113-118. https://doi.org/10.1017/S1461145701002322

Kirchner, J. A. E., Ritchie, M. J., Pitcock, J. A., Parker, L. E., Curran, G. M., & Fortney, J. C. (2014). Outcomes of a Partnered Facilitation Strategy to Implement Primary Care–Mental Health. *Journal of General Internal Medicine*, *29*(4), 904-912. https://doi.org/10.1007/s11606-014-3027-2

Kraemer, H. C. (2000). Statistical analysis to settle ethical issues? *Archives of General Psychiatry*, *57*(4), 327-328. https://doi.org/10.1001/archpsyc.57.4.327

Lau, J. T. F., Mao, J., & Woo, J. (2003). Ethical issues related to the use of placebo in clinical trials. *Hong Kong Medical Journal*, *9*(3), 192-198.

Lefor, A. T. (2005). Scientific misconduct and unethical human experimentation: Historic parallels and moral implications. *Nutrition*, *21*(7-8), 878-882. https://doi.org/10.1016/j.nut.2004.10.011

Leon, A. C. (2000). Placebo protects subjects from nonresponse: A paradox of power. *Archives of General Psychiatry*, *57*(4), 329-330. https://doi.org/10.1001/archpsyc.57.4.329

Lima, S. G., de Lima, T. A. G., de Macedo, L. A., Sa, M., Vidal, M. D., Gomes, R. A. F., Oliveira, L. C., & Santos, A. M. A. (2010). Ethics in Research with Human Beings: from Knowledge to Practice. *Arquivos Brasileiros de Cardiologia*, *95*(3), 289-294.

MacKenzie, C. R., & Paget, S. A. (2015). Ethics in clinical trials. *Rheumatology: Sixth Edition*, *1*, 204-208. https://doi.org/10.1016/B978-0-323-09138-1.00027-9

Maguire, J. (2014). *Social sciences in sport*. Human Kinetics.

Medicine, A. C. S. (1979). Policy statement regarding the use of human subjects and informed consent. *Medicine and Science in Sports*, *11*(4). https://doi.org/10.1249/00005768-198103000-00013

Miller, C. J., Smith, S. N., & Pugatch, M. (2020). Experimental and quasi-experimental designs in implementation research. *Psychiatry Research*, *283*, 112452. https://doi.org/10.1016/j.psychres.2019.06.027

Miller, F. G., & Wertheimer, A. (2007). Facing up to paternalism in research ethics. *Hastings Center Report*, *37*(3), 24-34. https://doi.org/10.1353/hcr.2007.0044

Millum, J., & Grady, C. (2013). The ethics of placebo-controlled trials: Methodological justifications. *Contemporary Clinical Trials*, *36*(2), 510-514. https://doi.org/10.1016/j.cct.2013.09.003

Montagne, M. (1985). Issues in the design and conduct of clinical trials. *Clinical Research and Regulatory Affairs*, *3*(1), 23-44. https://doi.org/10.3109/10601338509051047

Morgan, C. J. (2018). Reducing bias using propensity score matching. *Journal of Nuclear Cardiology*, 25(2), 404-406. https://doi.org/10.1007/s12350-017-1012-y

Nardini, C. (2014). The ethics of clinical trials. *Ecancermedicalscience*, *8*(1). https://doi.org/10.3332/ecancer.2014.387

Pape, U. J., Millett, C., Lee, J. T., Car, J., & Majeed, A. (2013). Disentangling secular trends and policy impacts in health studies: use of interrupted time series analysis. *Journal of the Royal Society of Medicine*, *106*(4), 124-129. https://doi.org/10.1258/jrsm.2012.110319

Rechnitzer, P. A., Cunningham, D. A., & Jones, N. (1977). A controlled prospective study of the effect of endurance training on the recurrence rate of myocardial infarction. The Ontario exercise heart collaborative trial. An interim report. *Cardiology*, *62*(2), 358-365.

Riis, P. (2003). Thirty years of bioethics: the Helsinki Declaration 1964-2003. *New Review of Bioethics*, *1*(1), 15-25. https://doi.org/10.1080/1740028032000131396

Rothman, K. J. (2000). For and against: Declaration of Helsinki should be strengthened FOR AGAINST Rothman and Michels' riposte. *BMJ*, *321*(7258), 442-445. https://doi.org/10.1136/bmj.321.7258.442

Schuppli, C. A., & Fraser, D. (2007). Factors influencing the effectiveness of research ethics committees. *Journal of Medical Ethics*, *33*(5), 294-301. https://doi.org/10.1136/jme.2005.015057

Shephard, R. J. (2002). Ethics in exercise science research. *Sports Medicine*, *32*(3), 169-183. https://doi.org/10.2165/00007256-200232030-00002

Singer, P. A., & Benatar, S. R. (2001). Beyond Helsinki: A vision for global health ethics. *British Medical Journal*, 322(7289), 747-748. https://doi.org/10.1136/bmj.322.7289.747

Stone, A. A. (1979). Informed consent: Special problems for psychiatry. *Hospital and Community Psychiatry*, *30*(5), 321-327. https://doi.org/10.1176/ps.30.5.321

Storosum, J. G., Van Zwieten, B. J., Van den Brink, W., Gersons, B. P. R., & Broekmans, A. W. (2001). Suicide risk in placebo-controlled studies of major depression. *American Journal of Psychiatry*, *158*(8), 1271-1275. https://doi.org/10.1176/appi.ajp.158.8.1271

Tyson, J. E. (1995). Use of unproven therapies in clinical practice and research: How can we better serve our patients and their families? *Seminars in Perinatology*, *19*(2), 98-111. https://doi.org/10.1016/S0146-0005(05)80030-8

Vargas-Mendoza, N., Fregoso-Aguilar, T., Madrigal-Santillán, E., Morales-González, Á., & Morales-González, J. A. (2018). Ethical concerns in sport: when the will to win exceed the spirit of sport. *Behavioral Sciences*, *8*(9), 78. https://doi.org/10.3390%2Fbs8090078

Watson, J. C., Way, W. C., & Hilliard, R. C. (2017). Ethical issues in sport psychology. *Current Opinion in Psychology*, *16*, 143-147. https://doi.org/10.1016/j.copsyc.2017.05.008

Wilson, S. T., & Stanley, B. (2006). Ethical concerns in schizophrenia research: Looking back and moving forward. *Schizophrenia Bulletin*, *32*(1), 30-36. https://doi.org/10.1093/schbul/sbj023

Zapf, P. A., & Roesch, R. (2005). An investigation of the construct of competence: A comparison of the FIT, the MacCAT-CA, and the MacCAT-T. *Law and Human Behavior*, *29*(2), 229-252. https://doi.org/10.1007/s10979-005-2194-4