Did someone push Lucy out of the tree?

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Dr Behrents' editorial, "Lucy fell from a tree and plunged 40 feet to her death" in the November 2016 issue of the *American Journal of Orthodontics and Dentofacial Orthopedics*, is a concise, clear essay on proper science that should be read by anyone trying to find a true answer to a research question.[1] It is important because it provides the background for the policy of an esteemed professional journal. Dr Behrents referred to a notorious article in which Kappelman et al[2] concluded that Lucy—name given to one of the world's most famous fossils—died from a fall from a tree. Lucy's discoverer, Donald Johanson, was skeptical and labeled the conclusion "unprovable."[3]

My purpose in selecting the above title was to call attention to a different aspect of the scientific process described by Dr Behrents. It would have been highly unethical if someone had pushed Lucy out of the tree! However, we will never know.

Dr Behrents' delightful editorial requires further amplification and is therefore incomplete. An increasingly important and intrinsic issue of the research process was not mentioned: the ethical aspect of designing and conducting an experiment involving human subjects—in casu—orthodontic patients and controls. Or, differently put by Tony Judt,[4] one of the world's most esteemed historians: "We cannot continue to evaluate our world and the choices we make in a moral vacuum".

The aims of my comment are to call attention to the ethical aspect of research and to briefly discuss how current and future orthodontic research is influenced. Although I do have the advantages of hindsight, it is not so easy to bring up the ethical aspect of research. I admit to feeling humble and hesitant to do so. I am at the end of my career; I have been an orthodontic researcher, teacher, and clinician in the last century, but I am not a professional bioethicist. That is the reason I refer to Carlson et al,[5] who cited bioethicist Tristram Englehardt:

> He speaks of the potential offensiveness of ethics. Aspects of his discussion could be paraphrased along these lines; to say someone is in the wrong factually has the potential to create a certain degree of offence, but to say that someone is in the wrong ethically is to criticize at a much deeper level and may cause a much more profound level of offence.

My comments should therefore not be seen as a critical attack at persons, but as an effort to contribute to the future of orthodontic research.

Ethical issues have expanding consequences for future orthodontic research. The orthodontic journals of which I am aware all declare that they follow the Declaration of Helsinki on human experimentation and ask authors to report approval of an independent ethics committee in their research reports. The initial historical text of the Declaration of Helsinki dates from 1964, and it has been 7 times revised, after controversies, intensive debates, and searches for consensus.

Ethical viewpoints are thus continually subject to change. This refers particularly to the protection of subjects participating in a randomized controlled trial (RCT). Version 2013 is extremely carefully worded by the World Medical Association.[6] It is for that specific reason that I will cite from the numbered articles of the Declaration of Helsinki.

Good science

In the first paragraph of his editorial, Dr Behrents listed 7 steps authors can take; number 4 reads: "testing the hypothesis by designing and conducting an experiment."

The Declaration of Helsinki, however, requests the research protocol for the design of an experiment involving human subjects to:

22. "…contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed."

23. "…be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins."

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The effect of this development is that the prime goal of the experimental procedure is not only that "the whole process be objective (free of bias)," as Dr Behrents stated, but also that it be ethical.

The need for continuity of research

Dr Behrents wrote: "each experimental trial builds direction for the next inquiry."[1] This idea, although apparently evident and straightforward, raises doubt. The following observation may serve as an example of such doubt with possible far-reaching consequences for future orthodontic clinical trials.

In reaction to the acclaimed results of the 2016 Class III early facemask trial by Mandall et al,[7] several ethical concerns were expressed.[8] The 2010 and 2016 publications showed that these authors carefully applied a number of restrictions for ethical reasons.[7,9] The objections focus on the fact that the control subjects received no treatment during the test. Some of these subjects were given the option of orthognathic surgery after the experimental period.

Interestingly, in 2 of these comments, it was feared that new research protocols would find increasing objections by ethics committees.[8] In other words, ethical concerns could make repetition of the experiment impossible.

Such circumstances are, of course, not new. By far the best example of that phenomenon is the frequent revision of the Declaration of Helsinki since 1964 by the World Medical Association. An example in our field is longitudinal craniofacial growth research using radiographic cephalometry, which has come to a complete stop.[10] Within the context of this comment, it is of interest to consider that the earliest and most well-known of these growth studies by Broadbent et al[11] was intended to serve as the control group for clinical studies. The RCT by Mandall et al[9] started in 2003 and is best seen as a placebo-controlled trial. In that time period, the Declaration of Helsinki 2000 (version 6) was valid. However, trials with a placebo or no-treatment control group had evoked fierce controversial views in the medical world for quite some time. The successive revisions of the Declaration of Helsinki since the 2000 version are testimony to the changing views as the trial participants' safety and prevention of harm or risks have become much more explicit.

With hindsight, applying the Declaration of Helsinki 2013 (version 8), one must conclude that the trial participants were exposed to additional risks; this was a violation of articles 8 and 33.

In the impressive article by Emanuel and Miller[12] dating from 2001 entitled "The ethics of placebo controlled trials—a middle ground," the authors opposed the rigor of the 2 contrasting views as "placebo orthodoxy" and "active control orthodoxy." They considered both viewpoints indefensible and proposed "a middle ground"

> …in which placebo-controlled trials are permitted but only when the methodologic reasons for their use are compelling, a strict ethical evaluation has made it clear that patients who receive placebo will not be subject to serious harm, and provisions have been made to minimize the risks associated with the receipt of placebo [loc. cit. p 918].

National or international regulations?

Within the context of the above, it is important to quote the following regarding research ethics committees.

23. "…must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration."

This sentence also has consequences for the editorial board of a journal publishing reports of international origin. Currently, journals appear to have the policy to request a specific statement about the report of an ethical committee. However, a journal's editorial board is part of the research process and is placed in a position of judgment, because:

36. "Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research."

In my opinion, it is not always clear how these obligations for editors and publishers are met.

The review process

It is within the scope of my comments to consider the ethical aspects of the review process. Consider the following case example. A team of experienced clinical researchers reported on a long-term prospective clinical trial of an innovative dentofacial orthopedic treatment in young children. At the end of the report, they declared a limitation of conclusions: they considered it impossible and unethical to establish a relevant and adequate control (ie, no alternative treatment) group.[13]

The request by anonymous reviewers for an "untreated control group" would result in the recommendation to reject or retract the manuscript.

This request is questionable if the task of the reviewer and the editor is to make such a judgment. It even