Ethical Considerations of Randomized Control Trials with Human Participants in Dentistry: A Reflective Analysis

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Introduction

In 2006, clinicians from the Division of Oral and Maxillofacial Surgery at the University of Texas Southwestern Medical Center asked a common question of the dental and medical profession: what can we do to ensure the best health outcome for our patients? Specifically, these clinicians wanted to know if the administration of postoperative antibiotics would be beneficial to patients with open mandibular fractures in reducing infection. As such, these clinicians conducted a prospective randomized trial to investigate the effectiveness – and thus necessity – of postoperative antibiotic regimens in the treatment of 181 patients who presented with open mandibular fractures (Miles et al., 2006).

While all of the patients received preoperative antibiotics and intraoperative antibiotics on the day of surgery, the patients were randomly placed into two groups to determine whether or not they would receive postoperative antibiotics. Within the eight-week follow-up period, 8 infections were found in the group that did receive postoperative antibiotics, and 14 infections were found in the group that did *not* receive postoperative antibiotics. Despite this disparity, statistical analysis yielded no statistically significant difference. Therefore, the clinicians concluded within their prospective randomized study that no statistically significant benefit was found in the administration of postoperative antibiotics in their patients with mandibular fractures (Miles et al., 2006).

We currently live in a day and age where a baby born today will live a longer life on average than any other human being in the history of mankind (Center for Disease Control and Prevention, 1999; Caspari and Lee, 2004). Thanks to advancements in biotechnology, improvements in public health, and substantial gains from drug testing in human patients, human health is at its relative best than it has ever been before. Despite the fact that we have yet to find

cures to a host of diseases and despite the fact that the final years of life are plagued by diseases that significantly decrease quality of life, some say that we have no ethical and moral obligation either to discover the cures to these conditions or to ameliorate the final years of life, particularly by potentially harming humans as subjects in drug trials. Especially for placebo-controlled randomized control trials (RCTs) where the disease being drug-tested against is as terminal as many metastatic cancers not limited to the head and neck region, opponents question the ethical permissibility of using human participants if the novel drugs or treatment proves to be statistically ineffective.

Indisputably, human experimentation involves the important and ultimate questions about personal dignity and the inviolability of persons. What differentiates human experimentation from *in vitro* drug testing is that artificial substitutes designed specifically for the purpose of the experiment are no longer used; rather, we are using human beings, and this very fact alone makes RCTs far more complex and unnerving. Similarly, animal research has its limits. While it is true that up to a certain point other organisms can serve as proficient substitutes for human research, it is a fact that there are innate biological differences between *Homo sapiens* and *Drosophila melanogaster*, and even between humans and our closest primate relatives. As such, to assess the efficacy of a drug regimen designed for *Homo sapiens*, it must be argued that human subjects be used for absolute validation of medical research.

In this paper, I shall consider and compare various ethical and moral views of conducting randomized control trials with human subjects in dentistry, generating a back-and-forth dialogue where I present increasingly complex arguments *for* human research, and then attempt to refute them until I have exhausted all the arguments against the usage of RCTs. Intermixed I will offer my own thoughts of the topic at hand and will conclude with my opinion of human participation

in oral health research from a greater public health perspective. I shall assume in this paper that what is considered *primary inviolability*, or the inviolability of humans and sanctity of life, needs no justification whatsoever. Specifically, this philosophical principle does not contribute to the discussion of RCTs with human subjects in that it entirely dismisses RCTs as morally unjustifiable and thus transcends this discussion (Merritt, 2005). Therefore, in order to justify the infringement of primary inviolability – to justify the usage of human beings as research subjects and the potential harm or even death from treatment – the justification must be by certain values that not only equate but also *exceed* the values forgone with primary inviolability. Ultimately, I will attempt to do so and conclude that randomized control trials with human participants in dentistry and oral medicine for the purpose of clinical research and the advancement of human health *is* in fact ethically and morally permissible.

The Researcher

To begin, I will offer a view of human experimentation from the perspective of the researcher, of the quest for scientific advancement. By definition, clinical research is when medical research is conducted with human subjects to ascertain, for example, the efficacy of novel medications and treatments. And as a researcher, the goal is to determine and *scientifically* establish the best treatment. But the main issue here concerning clinical trials is that the only way for an investigator to conduct a study is to have some of the patients bear the medical burdens or risks that are *not reasonably expected* to bring direct benefit (Merritt, 2005).

For instance, in a 2009 randomized placebo-controlled study at the Department of Thoracic/Head and Neck medical Oncology at the University of Texas Anderson Cancer Center, researchers randomly assigned patients with high-risk oral premalignant lesions to receive a high dose of green tea extract, a low dose of green tea extract, or a placebo (Tsao et al., 2009). With

epidemiologic data supporting the notion of oral cancer prevention by means of green tea extract through the reduction of the angiogenic stimulus, tumor stromal vascular endothelial growth factor A, the study's methodology consisted of the placebo-group patients receiving the equivalent of no medical treatment. Consequently, the placebo-controlled patients were *not* expected to receive the purported benefit of oral cancer prevention, and thus they bore a medical burden. Ultimately, the study did not yield statistical significance between patient cohorts that received a high dose of green tea extract and those that received the placebo. However, the study did show a dose-response effect when higher amounts of green tea extract were administered and resultant oral cancer prevention, thus supporting future long-term clinical testing of green tea extract in patients with high-risk oral premalignant lesions (Tsao et al., 2009).

As seen in this example, it is imperative in a clinical trial that researchers adhere to the strict methodological procedures of research with professional integrity to validate the study and to justify human participation. Otherwise, to allow human subjects to participate in a poorly executed trial lacking sufficient statistical strength is to expose people to medical burdens, nonetheless risks, without the realistic hope of adding any valuable information to presently known knowledge (Merritt, 2005). Thus, to complete the clinical trial so as to produce scientifically valid data and to share this new information with the rest of the dental community becomes an absolutely essential criterion in ensuring that subjects are not exposed to medical risks in vain. Just as prominently, the relationship between the patient and the investigator is grounded on the shared understanding that the subject voluntarily and willfully agrees to partake in the clinical study for the purpose of aiding the scientist in this medical investigation. Further, an ultimate aim of the researcher is the betterment and progress of dental medicine – and in this one example, the prospect of a common and affordable supplement in oral cancer prevention.

The Oral Healthcare Clinician

Yet moral considerations also come in to play, and here we take into consideration the oral healthcare clinician, the healer. The clinician's duty is to place the needs of the patient above all else and to protect the patient's health in the face of all else, which may include protection from research participation that involves the hardship of medical burdens and/or risks. This is an ethical and moral obligation, particularly as a trained dental professional. With regard to dental medicine, clinicians are governed by the moral considerations of *beneficence* – removing harm or improving a patient's condition – and *non-maleficence* – mitigating harm such as refraining from providing false treatments (Beauchamp and Childress, 2001). These two principles, along with patient-autonomy, justice, and veracity in the form of truthfulness, establish the fundamental ideology that governs the professional ethics of dental medicine and our profession (American Dental Association – ADA, 2012).

However, the following is the innate conflict between the oral healthcare clinician and researcher. From the clinician's standpoint, the needs of the patient override the fact that a patient may indeed be a research subject. From the researcher's standpoint, however, the needs of the patient may not be the immediate priority; rather, it is the testing of a novel treatment such as green tea extract against a placebo to prevent oral cancer, and for the advancement of scientific and clinical knowledge. Thus, the dichotomy between clinician and researcher, between caregiver and scientist, between healer and investigator is quite stark with regard to answering to the needs of the patient. Especially for RCTs, however, both obligations – that of the clinician and that of the researcher – cannot be equally and explicitly fulfilled. As such, when can both obligations be fulfilled? Or more specifically, when is an oral healthcare clinician simultaneously allowed to be a researcher?

Practitioner Equipoise

To first evaluate the role transformation from clinician to researcher within the context of human research, let us consider the broad case of *practitioner equipoise*. In a given clinical scenario, it is true that a dental clinician may not always know the best treatment. For instance, given the physical body of evidence and symptoms, the clinician may have no reason in particular to choose one treatment over another. Thus, the clinician is in a state of *equipoise*. Given the evidence, procedure A is neither significantly better nor worse than procedure B; therefore, the dentist may just as well flip a coin to select a procedure over the other. For example, given the evidence, a clinician may have no reason to favor the usage of a conventional denture over an implant prosthesis in a particular patient. Equivalently, with respect to placebo RCTs where some patients are randomized to receive no treatment and others are randomized to receive treatment, a clinician is in equipoise with regard to what will be of greater benefit to the patient. As a result, perhaps RCTs simply formalize a dentist's individual state of equipoise by means of a clinical trial. By further eliminating selection bias in randomly controlling the trial, a dentist is therefore in equipoise and uncertain if one procedure is better than the other or if a new agent is better than the placebo, and is thus permitted to conduct a RCT.

In theory this makes sense, but there is an obvious flaw here when we consider everyday clinical situations. As I have seen from shadowing dentists, an individual dentist is often in a position with sufficient evidence so as to deduce which treatment is best suited for the patient. Importantly, even if a dentist does not have sufficient evidence to *know* for certain the best treatment, the dentist often at least has more evidence one way or another such as in deciding between a denture and an implant. Via practical reasoning, the delicate evidential balance act required for equipoise rarely occurs. By this same reasoning, an oral healthcare clinician cannot justify putting patients in RCTs based on individual practitioner equipoise.

Clinical Equipoise – Dental Amalgam

Now let's take a step further and examine *clinical equipoise* as opposed to individual equipoise. If there is genuine uncertainty in the *dental community* as to whether one treatment is better than another, then by definition the dental community is in clinical equipoise (Miller and Brody, 2003). Here, due to this disagreement over the preferred treatment, the matter cannot be settled as oral healthcare clinicians reach different conclusions given the body of evidence. In contrast to an individual dentist choosing between two procedures based upon practitioner equipoise, the entire industry is at clinical equipoise which evinces the need for RCTs. The first dentists who suspected amalgam as a potentially hazardous filling material despite its durability in comparison to resin composites, for instance, were dutifully concerned about the potential harm in the usage of mercury in dental fillings. As such, many RCTs grounded upon clinical equipoise were conducted across the world resulting in controversial results, a couple prominent cases of which I will now discuss. (Bellinger et al., 2006; Woods et al., 2007).

In 2006, researchers at Harvard Medical School conducted a randomized clinical trial with 534 children between the ages of 6 to 10 years to investigate potential neuropsychological and renal effects of the amalgam restorations as compared to children who received composite restorations (Bellinger et al., 2006). Although the study found no statistically significant adverse neuropsychological or renal effects within the five-year follow-up period for the children with amalgam restorations, a different RCT with 507 children over a seven-year follow-up period found a strong, positive correlation between mercury exposure from amalgam restorations and urinary mercury excretion with mean mercury urine concentrations of the amalgam cohort more than double the composite resin cohort (3.2 μg/L vs. 1.5 μg/L) (Woods et al., 2007). In light of clinical equipoise, I believe that genuine uncertainty in the dental industry – as shown by the great number dental amalgam studies – is a valid argument for allowing RCTs.

Resultantly, as long as the treatments and procedures being tested satisfy the requirements of clinical equipoise, then clinician-investigators are able to satisfy their therapeutic obligation to patients within the context of RCTs (Miller and Brody, 2003). Here, RCTs are not only scientific experiments designed to produce knowledge that can help enrich patient care, but also treatments administered by oral healthcare clinicians who preserve fidelity to the ideology of beneficence and non-maleficence that govern the ethics of dental medicine (ADA, 2012). Ethically, this makes it permissible for clinician-investigators to conduct RCTs *without* forfeiting therapeutic obligation in imparting treatment consistent with scientifically validated measures of care. Perhaps then, because of the genuine non-consensus of preferred treatments in the dental community as seen in the prominent case of dental amalgam usage, it is ethically permissible for clinicians to conduct RCTs with human participants in institutional settings.

Arguments against Randomly Controlled Trials

I believe that it is important to acknowledge the greater implications of RCTs with human participation, as moral philosophy provides the basis of medical and dental ethics. Hans Jonas, the 20th century German philosopher who pioneered the field of bioethics, presents several interesting cases why human subjects should *not* be used for medical research. One of his strongest arguments is that "no complete abrogation of self-interest" – or in other words, *sacrifice* – can be found in the social contract, and thus human sacrifice towards the benefit of society can neither be obligatory nor morally justified (Jonas, 1969). Specifically, the theory of the *social contract* refers to 17th century political philosophical thought as propounded by Thomas Hobbes' *Leviathan* and John Locke's *Second Treatise of Government* in which all citizens of society have consented to relinquish some of their rights to the governance of society in exchange for the aegis of their remaining freedoms (Harrison, 2002).

As such, Jonas argues that the good of society alone *cannot* justify the potential sacrifice of the individual. However, Jonas agrees that at times the rights of the individual *can* in fact be trumped by the rights of society, but only in cases of utmost emergency. Specifically, Jonas draws upon the state of war when the perseverance of society temporarily supersedes individual citizen's rights; therefore, only in such an extreme case can society call upon its members to engage in combat and risk their lives (Jonas, 1969).

In RCTs, however, the cause for members of society to engage in medical research and risk their lives is a matter of *improving* and not rescuing society; medical advancement is not war. Jonas would thus harshly argue that it would not be the end of society, for instance, if a certain percentage of oral cancer patients continue to die. Along these lines, decreasing mortality rates from a disease like oral cancer or increasing quality of life through novel direct restoration treatments of caries by means of RCTs does *not* make it morally permissible to use human beings as research subjects. "Progress," Jonas claims, "is an optional goal, not an unconditional commitment," and thus sacrifice by means of human participation in RCTs goes above and beyond what should be asked of any human being (Jonas, 1969).

Reflection

I personally feel as if "sacrifice" is too strong and deceiving a word for Jonas to use in claiming that randomized control trials with human subjects are impermissible due to the absence of complete abrogation of self-interest – or sacrifice – in the social contract we have signed with society. While I agree that no one, not even society, can ask someone to sacrifice themselves as a victim in the name of science, I strongly believe that no one is a complete victim of medical research through RCTs purely for the public good. On the contrary, there are potential and concrete gains as postulated by the methodological investigation of scientific inquiry and

maintained by the supervision and compassionate care of clinicians. Moreover, I believe that much more would be at stake if society were *not* allowed to conduct RCTs. In particular, I perceive no extreme risk to be asked of individuals to voluntarily participate in RCTs than if RCTs were never conducted in the first place.

Furthermore, I believe that Jonas is wrong as to say that medical research via the social contract would result in the complete abrogation of self-interest. To highlight my point, let's consider the fact that many individuals suffer from oral cancer and subsequently experience significantly decreased quality of life. According to a recent 2012 epidemiologic review of oral and pharyngeal cancers, there are approximately 30,000 new cases of oral and pharyngeal cancers diagnosed annually in the United States alone with five-year survival rates as low as 27.6% for African-Americans (Saman, 2012). To this extent, it is in the best interest for continued research in oral cancer or else the final years in the lives of countless patients not only in the United States, but also across the world will be spent in misery, let alone cut short. Subsequently, if the argument for continued human research is not for overall good, I believe that it can be argued strongly in favor of *self-interest* so as to increase quality of life and even extend life.

Clinician Training

With regard to self-interest, I ask you to consider the analogy of the duty to accept dentists-in-training in which patients are also considered 'experimental subjects'. It is a fact that it is in our self-interest, and in society's interest, to train dental clinicians. How else, for instance, would periodontal disease be treated or impacted third molars extracted if there were no trained oral healthcare clinicians? Regardless of all else, it is also true that dentists-in-training must have to treat someone their first time, which will be the case for me and my many peers across the country when we enter the clinic and treat patients as student dentists. On what moral basis can

someone insist that *someone else* is to accept clinicians-in-training so that they themselves can avoid them? As a matter of fact, someone else in society will have to bear the burden of being the first patient of a clinician-in-training if you refuse to do so. Thus, each of us bears a shared responsibility to train future clinicians. If not, we bear a greater burden – that is, there will be no oral healthcare clinicians whatsoever to treat our oral health concerns.

To justify this, the reasoning follows that not everything we are permitted to do we ought to do; although we are permitted *not* to engage in the training of student dentists, we ought to do it. And we do so for reasons of self-interest and societal benefit in the continuation of the dental professions. Thus, in my opinion the grounds upon which to reject a clinician-in-training to save yourself are similar to those upon which to reject participation in a clinical trial to save yourself, which in this light seems rather foolish. Moreover, I believe that one of the strongest arguments against RCTs with human subjects, that citizens have no obligation in the social contract to subject themselves to research and endure potential risks, is flawed. Opponents such as Hans Jonas argue that the good of society cannot justify the good of the individual. But I am *not* arguing from a Consequentialist perspective to maximize utility in the form of societal benefits outweighing individual harms. More importantly, I believe that human participation in medical research is a matter of *fairness* as will be explained next.

Rawlsian Fair Play

In the case of Rawlsian fair play, I will examine RCTs in light of the certain obligations we have to society in relation to leading American philosopher John Rawls' veil of ignorance. Rawls' most renowned work, *A Theory of Justice*, popularized the *veil of ignorance* – an approach of investigating the morality of an institution or action based upon the thought experiment of randomly redistributing societal roles and not knowing what role you will be

assigned (Rawls, 1999). Consequently, we can debate the way a particular issue will impact each member of society through the lens of reasonable impartiality. To begin, as citizens of the United States we have certain obligations to social contracts, and as a dental student at the UCLA School of Dentistry I must also abide by certain regulations as a member of the university. We have these obligations, and we have all consented. Although most people have never consented *explicitly*, all of us have done so *implicitly*. As members of these societies, if we each receive the fair share of benefits, then *fairness* demands that we receive the fair share of burdens as well.

I will now re-examine and apply this credence to the case of clinician training in relation to the veil of ignorance. Established is the veil of ignorance, where you might easily be born an individual with syndromic cleft lip and cleft palate, an individual with Crouzon syndrome and bilateral coronal craniosynostosis, or perhaps an individual where your chief oral concerns are Class I caries on tooth #19. We have all benefited from experienced clinicians in dentistry by virtue of them once being trained as students, a cohort of which I am currently a member of as a student dentist. In corollary, someone else, also a member of the society to which we each have tacitly consented, once bore the burden to train the clinicians that we benefit from today. And they bore this burden because someone before them bore the identical burden in training a previous generation of clinicians.

Therefore, as free beneficiaries and not coerced beneficiaries of trained clinicians and – more importantly – as a distinct principle of fairness under the veil of ignorance where one may or may not be in dire need of oral care, I believe that the moral permissibility of subjecting ourselves to the same burden begins to take form. In fact, *fairness* in the form of justice, alongside autonomy, beneficence, non-maleficence, and veracity constitute the dogma that governs dental medicine. Although the ADA manual states that “the dentist has a duty to treat

people fairly," its corollary – that we should be expected to be treated fairly ourselves – rings true in light of accepting clinicians-in-training under the veil of ignorance (ADA, 2012).

Now applied to human participation in RCTs, we are simultaneously considered beneficiaries of clinical research from other members of society who were once subjects and bore this previous burden. Bone graft procedures to establish dental implants and inferior alveolar nerve blocks in dental anesthesia, for instance, are concrete products arising from clinical studies with human subjects in dentistry and oral health (Esposito et al., 2006). The efficacy of fluoride toothpaste in reducing dental caries is yet another example of the power and therapeutic value of RCTs in dentistry (Davies et al., 2002). As a matter of fairness in relation to John Rawls' veil of ignorance, I believe that RCTs with human subjects for the purpose of research in dentistry *is* in fact ethically and morally permissible.

Public Health

Philosophy aside and back to ethics, the significance of population needs through public health are equally important as fairness examined through the veil of ignorance. Here, I challenge Jonas' claim that progress is an optional goal of society. Recall the dentists who first suspected amalgam as a potentially hazardous filling material and were dutifully concerned with the public health implications of the usage of mercury in dental fillings. As a result, many RCTs were conducted across the world resulting in controversial results, (Bellinger et al., 2006; Woods et al., 2007). Although dentists worldwide today still maintain conflicting views on amalgam usage, with countries such as Norway, Sweden, and Denmark banning its usage and countries such as Germany restricting its usage in children and pregnant women, it is important to recognize that RCTs have been rightfully conducted to address worldwide dental public health concerns. I find it salient that RCTs must have sufficient statistical power to provide both useful

and reliable knowledge for the dental community, and as an effect, the progress of dental medicine and the advancement of society in light of public health. Understandably, this knowledge must be of valuable and meaningful concern such as the potential risks of amalgam usage, and be applied with due diligence towards prospective improvements not only for the advancement of the dental field, but also for the promotion of public health and safety.

From the greater public health standpoint, I believe that both the research and clinical communities have the prevailing responsibility to safeguard the world population from threats to health and quality of life. Here lies our ethical obligation as dental professionals to cultivate ample data regarding the efficacy and safety of innovative treatments before they are made publicly available; simultaneously, here is where RCTs provide the best measure for ensuring such progress. Likewise, as Dr. Franklin Miller of the Department of Bioethics at the National Institutes of Health argues, "It is socially irresponsible to hasten new pharmaceutical products to market or validate new medical or surgical procedures if a conservative burden of proof has not been met and reasonable doubts persist about their therapeutic merit" (Buchanan and Miller, 2006). Fortunately, and after myriad trials over decades of research, the scientific burden of proof has been met regarding the safe and effective merit of dental amalgam in the United States.

Conclusion – Justice

Ultimately, I believe that it is unjust to discount legitimate public health concerns when conducting RCTs with human participants in the study of novel treatments and procedures in dentistry. As I have previously discussed in the case of dental amalgam usage and potential renal effects from mercury exposure, and in the case of administering green tea extract in oral cancer prevention, RCTs provide the strictest and superlative methodology in the development of novel health interventions for patients' self-interest and public health. Harkening back to the very first

RCT case regarding the administration of postoperative antibiotics in patients with mandibular fractures, that particular study concerned not only the necessity of an additional round of antibiotics, but also the implicit cost. As such, I believe it is imperative that we – as dental professionals – give due consideration to the greater ramifications of research and invest with vigor in valuable, cost-effective dental interventions that exceed the scientific burden of proof.

If we briefly consider a society without randomized control trials, how exactly would its people benefit from – and learn to trust – novel treatments and procedures? Most importantly, how would such a society be fair towards its people if no strict methodology were used to determine the efficacy and safety of innovative healthcare interventions before making them publicly available? Although my views may label me Consequentialist, I am *not* simply endorsing a modified hedonic calculus that would exploit the citizens of our society. To me, the public health concern is more of a matter of *justice*. This is a matter ultimately about allocating resources and responsibilities fairly as examined through John Rawls' veil of ignorance, particularly in meeting the healthcare needs of the socially disadvantaged. It is in fact *justice* that champions the development of viable interventions and worthwhile solutions to the inequalities that disproportionately affect the health of the world's underprivileged.

Above all, as dental professionals we bear the professional and clinical responsibility not only to honor our patients with respect to autonomy, beneficence, non-maleficence, veracity, and justice, but also to provide them the best care possible. And it is by virtue of randomized control trials with human participants that we can provide our patients with the most scientifically just, clinically sound, and ethically fair methodology in the development of novel health interventions for their self-interest as well as for the interest of population and public health.

Empowered by the trust of our patients and the societies in which we serve, we must – as dental professionals – honor the invaluable contributions of our forebears and educators, impart our patients with the best standard of oral health care possible, and always uphold a sensitivity to the ethical complexity of serving in our esteemed yet humbled profession.

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