

2010

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## Repository Citation

Bluhm, Robyn L.; Downie, Jocelyn; and Nisker, Jeff, "Dr. Cezanne and the Art of Re(peat)search: Competing Interests and Obligations in Clinical Research" (2010). *Philosophy Faculty Publications*. 43.  
[https://digitalcommons.odu.edu/philosophy\\_fac\\_pubs/43](https://digitalcommons.odu.edu/philosophy_fac_pubs/43)

## Original Publication Citation

Bluhm, R. L., Downie, J., & Nisker, J. (2010). Dr. Cezanne and the art of re(peat)search: Competing interests and obligations in clinical research. *Accountability in Research: Policies and Quality Assurance*, 17(2), 85-95. doi:10.1080/08989621003708451

# Dr. Cézanne and the Art of Re(peat)search: Competing Interests and Obligations in Clinical Research

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Clinician researchers have a number of roles, each of which carries specific obligations. There are times when these obligations may be in competition (up to and including conflict) with each other. Using a narrative case study that describes a group of colleagues discussing their clinical department's participation in an industry-sponsored research protocol, we illustrate a number of the obligations faced by clinician researchers, and discuss how competing interests and obligations can lead to ethical problems. The case study is followed by a discussion of the effect of university–industry relations on competing interests and obligations in both clinical research and the role of the university, and a suggested framework that could be used to determine when university involvement in commercial research is ethically acceptable.

**Keywords:** clinical research ethics, competing interests, conflicts of interest, research ethics, university–industry relations

## DR. CÉZANNE'S STORY

Dr. Cézanne and his colleagues sit in silence as they prepare to discuss their participation in the pharmaceutical company–sponsored clinical trial described in the pile of documents lying on the table in front of them. Only

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their signatures are required for this multicenter and multimillion-dollar, predesigned, and prepackaged proposal to proceed to their university's research ethics board (REB). Dr. Cézanne knows he will be alone in his opposition to the proposal. His colleagues know they will patiently listen to Dr. Cézanne's concerns, which he has brought to this table many times, and which they will disregard again, even though they respect Dr. Cézanne as a serious scientist and as a caring physician. It is indeed because they respect their well-intentioned but impractical friend, and because they all see themselves as "honorable men" that they patiently commence the discussion that they already know will lead to the decision to participate in the trial. It's like a game where the result has been predetermined.

One of Dr. Cézanne's colleagues plays his standard opening *scientifically-sound* card. "This study is a well-designed, placebo-controlled, double-blind, randomized trial investigating the efficacy and safety of a hormone replacement therapy. On page 7 of the drug company's proposal, you can see that the number of patients that will be recruited nationally has the statistical power to answer the scientific questions regarding whether the drug is effective and safe. The methods of data analysis described on page 28 are appropriate. The proposal is scientifically sound, and we should participate."

Dr. Cézanne knows well the cards not-so-well concealed in his colleagues' well-intentioned, science-driven, budget-responsible hands; powerful cards that compel the embrace of pharmaceutical company--sponsored research. He counters with his *re(peat)search* card. "The proposed research is not research at all. It is re(peat)search of a drug that has been approved and prescribed for 10 years in Europe and 7 years in the United States. The only justification for repeating the study on women in Canada would be if we believe physiological differences exist between women in Canada and women in the United States or Europe that might affect their tolerance of the drug or their risk of neoplasia. If physiological differences do exist, they are more likely based on ethnic origin than on country of residence. Although environment and diet are potential variables, these are more likely to vary within each country than between sides of the 49th parallel of the Atlantic Ocean.

A colleague promptly plays his *Health-Canada-insists* card. "You are correct, Dr. Cézanne, the study is re(peat)search, but it is required by the Therapeutic Products Directorate of Health Canada before patients can be prescribed this drug in Canada. The pharmaceutical companies are forced by Health Canada to spend their millions."

Dr. Cézanne quickly counters his *lack-of-clinical-equipoise*-card. "If the pharmaceutical companies must spend millions, why not spend the millions on a proper clinical trial? This study is not research, for it lacks clinical equipoise (Freedman, 1987). The Canadian philosopher, Benjamin Freedman, coined the term 'clinical equipoise' to remind us that if the results of the study are apparent before the study commences, the study is not research. We

should change the protocol to compare the drug to the current gold standard instead of placebo (Weijer, 1999; Weijer et al., 2000) and if the new product is more effective, and at least equally safe, we will learn something from the study rather than possibly causing harm to Canadian women and gaining no new knowledge. The pain from the endometrial biopsies required by the protocol and, for the women who receive placebo, the discomfort of their symptoms, would be an unjustifiable harm.”

A colleague utters, “You know we can’t change the protocol” as he plays his *participation-is-in-the-best-interests-of-the-women-who-participate* card. “A woman, by enrolling in research, can receive a drug that might better alleviate or even cure her problem years before it will be available to her by prescription. There is also evidence that patients who participate in clinical research may have better outcomes than those who do not (Braunholz et al., 2001). And don’t forget, the women in the study will get the drugs for free and that is a significant benefit.”

Dr. Cézanne plays his *non-nocere* card. “This proposal requires that all women undergo endometrial biopsy to rule out endometrial neoplasia before they can be entered in the study---all women---and these women cannot have a medical indication for endometrial biopsy or they would not have met entry criteria. Venepuncture, although less painful, is also required. Patients should not be asked by their physicians to endure painful procedures with no benefit to science. We take an oath not to harm our patients (Hippocrates, 1943) and this unnecessary pain is harmful.”

A colleague counters with his *patient-choice* card, “Our patients will not be forced to participate in this study. They will be offered the opportunity to freely choose to participate, and, if they decide to participate, they will sign a consent form indicating that they freely chose to participate. Our patients will be educated about the risks and potential benefits by the study nurse before they consent. After considering what the study nurse has said, a patient can simply say, ‘I’d rather not.’”

Dr. Cézanne counters with his *lack-of-true-choice* card: “Rare is the patient who has the courage to refuse her physician’s offer to enroll her in a clinical trial, as she perceives her refusal as threatening to her prospects for good care in the future (Baylis, 1989; Kenny, 1994; Sherwin, 1994; Nisker and White, 2005). The woman fears her physician will think less of her if she refuses to participate in a study that might forward the science that will help other women, and she is sure the study her doctor is offering is important or her doctor would not be asking. If she refuses, she feels she will offend her doctor. Further, many patients feel the study drug is another treatment option (Kass et al., 1996), the option their doctors want them to take.”

A colleague smiles and plays his *more-choice-for-women-card*. “Clinical trials, such as the one before us, are necessary to afford Canadian women the

maximum number of choices for the best drugs available. I cannot believe you of all people, Dr. Cézanne, would want to limit women's choices."

Dr. Cézanne plays his *more-marketing-than-measuring* card. "But the proposed study, designed this way, is really just a marketing tool. The motivation for the pharmaceutical company is to introduce their product to academic physicians like us, who will later introduce their product to private practice physicians at 'drug dinners,' 'drug lunches,' and 'getaway' conferences. We unknowingly advertise their product in every letter we write to referring physicians regarding their patient *qua* research subject."

A colleague plays his *let-our-research-ethics-board-decide* card. "Our university's REB is well-known for screening research. You know how seriously its members take their jobs. Why do you think you know more than the members of our REB?"

Dr. Cézanne counters with his *lack-of-REB-knowledge-of-nuance* card (Palca, 1996; Annas, 1994) "The capacity for appropriate REB review rests firmly on the shoulders of the researchers whose signatures declare not only what is required on the REB application form (carefully completed by pharmaceutical company or contract research staff), but all information relevant to the REB deliberations. It is only fair to the REB members (and especially to the women who will endure the pain) that it is clear that the proposal is re(peat)search and that the gold standard drug is not part of the study, without camouflaging these facts in creative wording, or submerging them in euphemisms extolling the importance of the research to Canadian women. REB members rely on us researchers to fully inform them of the specific ingredients and scientific worth of the study (Bok, 1995), and their study approval is inexorably linked to their confidence in our understanding and integrity. We must, therefore, appreciate that our signatures today will be interpreted by our REB as support of all aspects of the proposal; to condone, not just non-condemn."

A colleague plays his *imperative-to-do-research* card. "If our center participates in this study, large amounts of the administrative money that will be accrued by the Department will fund new research projects of yours, and many clinicians and trainees will have the opportunity to develop clinical research skills, write papers, and ultimately apply for funding to be independent investigators. Research is an imperative of our center, and studies like this one are an important source of research funding."

Dr. Cézanne plays his *obligation-to-financial-transparency* card: "Our center receives hundreds of thousands of dollars for this 'imperative,' and we researchers personally receive a thousand dollar 'finder's fee' for each patient who becomes a participant. Our patients have the right to know that we benefit financially. But by telling a patient we will receive a thousand dollars if they consent to participate in the research, we may further confine her choice in favor of 'volunteering,' as she may believe that she will

hurt her physician's opinion of her if she refuses, and also hurt her physician's bank account and the bank account of the institution that is providing her care."

One of Dr. Cézanne's colleagues exclaims: "Why do you always focus on the negative features of every clinical trial that lands on this table?" while he proudly plays his *no-restriction-to-publication* card. "There are so many positive features of this study. For example, nowhere in the 35 pages in front of you will you find any encumbrance on our ability to publish the results of this study, no matter if the results declare the drug we are testing to be clinically useless or even harmful."

Dr. Cézanne nods that no clause inhibits publication of the findings, which is irrelevant for this type of study. There will be no possibility for publication because there will be no new findings. Though his colleagues have seen the recent media stories and medical journal warnings (Gibson et al., 2002; Davidoff et al., 2001) in this regard, Dr. Cézanne is concerned that his colleagues do not go deep enough, so he counters with his *International-Council-of-Medical-Journal-Editors (ICMJE)* card.

"Although the pharmaceutical company may not be prohibiting publication of the results, the ICMJE will not allow its publication, as we will be breaking their rules. The pharmaceutical company designed the study, will analyze and interpret the data, and have a large part in writing the results—and this means that many reputable journals will refuse to publish it. We owe it to our students, our patients, our research participants, and indeed ourselves to participate only in studies of adequate merit to be publishable in ICMJE journals."

Dr. Cézanne sees the shoulders slump around the table, like heavy rocks around a smoldering campfire. No "Kumbaya" warms this communal contemplation. Rather all are chilled by the silence. Finally, trying to move the card game to its inevitable conclusion, the Department Chair plays his *why-can't-you-compromise* card. He notes that, "Many other physicians, in many other Canadian centers have already agreed to participate in this study. Seven university REBs have already approved this study. Are you suggesting they are not moral physicians? Are the members of those REBs not moral? Are we, in our Department, by choosing a road other than your high road, not moral men? I can't believe you believe that. Can't you compromise a little?"

Dr. Cézanne plays his final card, his *ethics-is-not-compromisable* card. He knows his Department's Chair colleague means "compromise" as a "balancing equation" or "arbitration process to synthesize individual viewpoints to a group viewpoint." But Dr. Cézanne hears "compromise" as "adjust by concessions," "expose to risk, suspicion, or disrepute," "imperil." Dr. Cézanne hears "compromise" with increasing frequency, increasingly branding his concerns as strident idealism inconsistent with modern research realism. Dr. Cézanne is concerned his views separate him from his colleagues.

Philosophers have often been isolated for their positions: Socrates with hemlock, Spinoza with excommunication, Voltaire with spending his life on the border of France and Switzerland near rapid retreat from whichever government he had most recently enraged. But Dr. Cézanne is not a philosopher. He is a caring physician, and he doesn't want to be cut off from their colleagues for caring.

### **Post-Cards**

Dr. Cézanne still sits at that table. So do his colleagues and other physicians in his and other institutions. Dr. Cézanne feels sorry for colleagues who cannot feel the fears that drive his argument. He understands “we can be ethical only in relation to something we can feel, understand, love, or otherwise have faith in” (Leopold, 1962). He feels sorry that through their training in “miles of medical ink” and “consuming call schedules,” his colleagues no longer maintain the idealism of their youth (Nisker, 1997, 2003), or the calling to caring (Kenny, 2002) that carried them to medical school. But if his colleagues' views have become out-of-focus through wearing the multiple professional lenses of clinician and researcher, should he not keep trying to re-refract their view?

Ethical decisions must be looked at within the context of their society, and particularly relationships between individuals and institutions within their society. As governments reduce research sponsorship, as hospitals face insolvency, and as universities fear for their future, will fiscal pressure force fracture between fiscally-based and ethically-based medical research? Dr. Cézanne believes that the REB process is but a fabric, the tightness of weave largely dependent on the pens of the researchers. Dr. Cézanne hopes national and international explorations will help sensitize researchers submitting proposals to their REBs, to not only play by national and international rules, but to play within their spirit.

### **DISCUSSION**

In the analysis of the story, we draw on the literatures on conflicts of interest, clinical equipoise, and the commercialization of research in public institutions to explore the issues raised by Cr. Cézanne's story.

Although one might argue that enlisting patients to participate in the study could be considered a conflict of interest for the clinical researchers involved, and thus no further discussion is required, this would be an oversimplification of the problem. The Institute of Medicine defines a conflict of interest as “a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest” (IOM, 2009). Because the researchers participating in the study

would receive a “finder’s fee” for enrolling patients in the study, a conflict of interest might arise if they have patients whose best interests would not be served by participation in the study. But there still seem to be problems with the study even if the researchers do not accept a finder’s fee, and these problems stem from the fact that factors other than personal income are at stake. If we broaden the discussion from one of conflicts of interest to one of competing obligations, it becomes easier to see these factors and the problematic role they play and, ultimately, to come to a position on the proposed research.

As clinicians, with primary obligations to their patients, Dr. Cézanne and his colleagues are obligated to act in accordance with their patients’ wishes and in their patients’ best interests (according to their patients’ conception of their best interest). As scientists, they are obligated to increase medical knowledge for the benefit of others in the future. As employees (or as individuals with university appointments and hospital privileges), they are required to participate in the training of students, to contribute to the generation of knowledge, and, increasingly, to contribute to their institutions’ financial well-being. We suggest that a closer look at the challenge of managing these competing obligations provides clues as to how to resolve the dispute between Dr. Cézanne and his colleagues.

Participation in a clinical trial may be beneficial to a patient, in that it may give her the opportunity to try a new and promising treatment well before the therapy is available in regular clinical care. At the same time, however, by enrolling in the trial, the patient also runs the risk that she will not benefit and she also gives up the relative certainty of the benefits of regular clinical care. At the very least, this creates an obligation for the clinician-researcher to fully explain the potential benefits and harms of participation in the trial and the alternative of receiving standard therapy.

It is important to note here, however, that society has placed restrictions on how much risk a patient can be asked or allowed to assume (or, conversely, how much benefit she can ethically be asked or allowed to forego) through participation in a clinical trial. Specifically, a state of clinical equipoise must obtain in order for a trial to be ethically justifiable. Benjamin Freedman (1987) defined clinical equipoise as a state of honest, professional disagreement among the relevant medical community as to the best treatment. It must be unclear to the experts whether the experimental intervention will be as or more safe and effective than the currently accepted standard of care (or, where there is none or where the standard of care has not been shown to be better than placebo, as or more effective than placebo).

These rules do place limits on the physicians’ obligations to act in accordance with the wishes of their patients but they do so, in part, to correct for a power imbalance between participants on the one hand and research sponsors on the other. Potential participants have an interest in accessing a drug that they believe may benefit them. Research sponsors have an interest in conducting

research in the cheapest way possible with the greatest chance of being able to claim superiority for their drug (e.g., placebo vs. active controls). Without the rules, the research sponsors could force participants to accept inferior control arms (i.e., placebo over standard of care) in order to gain even the possibility of access to the drug.

Given the rules, the most the physician could have an obligation to do (under obligations to patients), is to offer them the opportunity to participate in a trial where clinical equipoise exists and where standard therapy is the control. Neither of these conditions applies in this scenario. Therefore, the physicians do not have any obligation under obligations to patients to offer this trial to their patients.

Clinical equipoise is also an important principle in the analysis of the clinician-researchers' obligations to advance medical knowledge for the benefit of others in the future. Resources spent on this trial will not be available to spend on other trials. These resources include clinic facilities time as well as scarce human resources. If clinical equipoise does not exist, then surely better uses for these resources could be found. The study in Dr. Cézanne's scenario will not enable the players to advance medical knowledge and so, at best, will not contribute to them meeting their obligations; it will, at worst, interfere with their ability to meet their obligations (by distracting them from studies that could actually advance medical knowledge).

In sum, so far, we have seen that for Dr. Cézanne and his colleagues, proceeding with this clinical trial will not help them to attend to their obligations as clinicians (who must act according to their patients' wishes and in their patients' best interests as seen by the patients) and as scientists (who must conduct research that is both ethical and of scientific value) within the limits society has placed on those obligations. A "re(peat)search" study, such as the one described here, being of questionable scientific value and requiring patients to accept worse care than they would receive in regular clinical practice in order to access the experimental intervention, fails with respect to both of these sets of obligations.

However, Dr. Cézanne and his colleagues have another set of obligations that may seem to push them in the direction of approving the study. These are their obligations to the institution where they work. As employees (or individuals with appointments and privileges), they are required to participate in the training of students, contribute to the generation of knowledge, and, increasingly, to contribute to their institutions' financial well-being.

If Dr. Cézanne and his colleagues participate in the study, their institution will receive funding that can be used to support trainees and to cover infrastructure costs. In fact, it is increasingly common that research institutions receive a significant portion of their operating funds from industry-sponsored research. This research may be contracted by the industry partner, or may be a joint venture undertaken with the hope of commercializable results. The

increase in such research is due both to the hope of profitable research and to the fact that government funding of universities and other research institutes (both directly and through granting programs) has not kept pace with the increasing costs of running the institution or with the costs of research itself. These changes in the way in which universities are funded have resulted in changes to obligations that researchers have toward them. Increasingly, researchers' time is spent trying to attract funding for their own research, a portion of which is kept by the university to cover its costs. This study will, of course, help with all of this and so contribute to Dr. Cézanne and his colleagues meeting their obligations with respect to the financial well-being of their institution.

However, the study will undermine their ability to meet their other obligations which arise as a result of their relationship with the institution: teaching and creating new knowledge. At first blush, it might appear otherwise. Students who work on the study will certainly learn about research and some knowledge will be produced through the research. But will the lessons the students learn be good ones, and will the knowledge gained be new and useful for science or medicine?

We would argue that the duty of the university is actually broader than the mere teaching and the mere acquisition of knowledge. We would argue that universities have a duty to educate students and to develop knowledge in ways that can be used to benefit society. Universities should not simply become a source of researchers for hire for corporations. Universities should not simply become factories for knowledge that serves the marketing purposes of industry. Requiring that studies undertaken by academic institutions have social or scientific value prevents these consequences from being realized.

The study debated by Dr. Cézanne and his colleagues fails the test of social or scientific value both in terms of teaching and knowledge generation: the students will learn to devote their time and intellectual energy to the highest bidder rather than the health of their patients and future patients; and a number of other effective treatments are already available, and the study's purpose is not to answer a scientific question (it is already known that the drug is effective). Therefore, while the obligation to generate resources can be met through this study, the clinician-researchers' obligations to their institution in respect of teaching and knowledge generation cannot.

In sum, agreeing to run this clinical trial will *not* serve the clinician-researchers' obligations as clinicians or as researchers. Nor will it serve two of their three kinds of obligations as employees (or as individuals with appointments and privileges)—it will enable them to generate funds but not to meet the teaching and knowledge generation mandates of a university. Thus, the competition is relatively easy to resolve—money against all else—and they should not agree to run the study.



Figure 1: Paul Cézanne: The Card Players (Les joueurs de cartes) 1890–1892.

## ACKNOWLEDGMENTS

J. N. wrote the story of Dr. Cézanne. All of the authors contributed to the writing analysis of the case and the editing of the entire article. None of the authors has any conflicts of interest to report with regard to the article.

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