

Biomedical Ethics

GOING OFF THE GOLD STANDARD: PAIN RESEARCH BEYOND THE RANDOMIZED CONTROLLED TRIAL

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Abstract. *A compelling case can be made for significant compromises to the processes of the randomized controlled trial. The clinicians' and researchers' ethical responsibility to the patient must be considered if ethical practice is to be assured. An argument is made for the careful consideration of the welfare of the patient as paramount in the decisions related to changes in the original design of research protocols in pain studies.*

Descriptors. *biomedical ethics, ethics, research ethics*

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There has been a great deal of discussion in recent years about the randomized controlled trial (RCT) as the “gold standard” of medical research, both in terms of scientific methodology and ethics. With the dramatic success of the RCT, however, comes the risk that this stance is becoming dogma – an occurrence that would be particularly worrisome in the context of clinical research on pain. As a philosopher, I will concentrate on the ethical concern that arises from the conduct (or, over-conduct) of RCTs in pain research, and my hope is that this will generate interest in the development and use of alterna-

tive designs that better serve the interests of patients in pain who serve as research subjects.¹

In the era of evidence-based medicine, many researchers and ethicists believe that the RCT represents not only the best scientific methodology in clinical research, but that it is morally best as well, at least under

For a commentary on this article, see pages 66-69.

conditions of *equipose* (i.e., presumptive equality of experimental arms) (1), however that term is construed. A number of arguments can be adduced in support of this claim. First, a RCT typically is expected to yield the most reliable results by comparison with other methods, which

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1. Although many of the arguments offered here could apply to pain research that enrolls “healthy” volunteers, throughout the paper I have in mind the paradigm of clinical research involving patients who are experiencing significant pain.

improves the profile of expected benefits of the research. All other things being equal, an increase in expected benefit represents an ethical gain, as well. Of course, in comparing the RCT to other potential experimental designs, all other morally relevant things are *not* equal. (While I don't wish to quibble with the old adage that "bad science is bad ethics," that does not imply, as some seem to believe, that "better science" is better ethics.) Second, the RCT provides results faster and more efficiently than many other designs. This means that the benefits of knowledge are disseminated more quickly both to subjects in the trial and to the entire patient population, and that resources for conducting clinical research – monetary and otherwise – are conserved. Again, these are not merely gains in efficiency, but they represent tangible improvements in the welfare of subjects and patients by comparison with other potential trial designs. Third, the pairing of equipoise and randomization that characterizes well designed RCTs entails that subjects are equally likely to be assigned to what turns out to be the most beneficial experimental arm. Thus, no patient-subject, at the outset of the trial, has a higher expectation of harm or benefit than anyone treated outside of the trial.

The analysis of the ethics of RCTs, like so much in pain treatment and research, cannot be captured in such a tidy analysis, however. Research design should be determined, at least in part, by the nature of the object that is – or should be – studied, and by the ways in which patients participate – or should participate – in the trial. In other words, ethics demands that the *how* of clinical research depends on the *what* and the *who*; not the other way around. In what follows, I will suggest that there are good ethical reasons for exploring alternatives in each of these dimensions, and that this, in turn, obligates researchers to consider alternatives to RCTs.

WHAT IS STUDIED

The RCT is perhaps best suited to the investigation of pharmacologic agents in the remediation of acute or sub-acute pain resulting from identifiable, discreet organic injury or disease. As is widely recognized, however, pain

is a uniquely complex phenomenon both in terms of its causes and modulating influences as well as its effect on the person (*e.g.*, neurological, clinical, phenomenological, social) (2-4). Moreover, the sources of relief that patients seek-out are manifold. If the goal of the research endeavor – not to mention the moral justification for undertaking it – is to improve the knowledge base on which responsible medical practice is founded, then investigating all of these aspects of pain and pain management is morally incumbent and will require incorporation of a multitude of research designs. The *nature* of what is studied should be responsive to the experiences and needs of pain patients and, in many cases, simply will not be suited to elucidation by RCT, *i.e.*, the variables are too numerous, too imprecisely measurable, and otherwise too difficult to specify – at least given current understanding – to include in RCTs (2).

WHO ARE THE DECISION MAKERS IN THE TRIAL

In traditional study designs, including the RCT, control over the strategy for allocating subjects to experimental arms rests with the investigators. As a way to buttress the allocation scheme against withdrawals from the trial and consequent effects on validity, to reduce bias produced by beliefs about the relative effectiveness of experimental interventions, and to avoid dilemmas concerning the therapeutic obligation of researchers to patient-subjects, RCTs typically restrict access to accumulating data and interim findings to an independent data monitoring committee that is charged with determining when to terminate the study and make its findings publicly available (5). Contrary to the perceived wisdom inherent in these practices, I will argue that in at least some cases (*i*) assignments of patients to specific experimental regimes should be made on a non-random basis or patient-subjects ought to be able to choose at the outset of the trial in which arm they will be enrolled, (*ii*) patient-subjects ought to be provided with interim findings during the course of a trial and allowed to choose their experimental arm, and (*iii*) researchers should consider setting target significance values to better fit the interests of patient-

subjects.

Non-random assignment to experimental arms. The case for non-random assignment to experimental arms rests on a mix of methodological and moral grounds, both of which are based on the observation that specific cognitive states or beliefs contribute in complex ways to the experience of pain. Thus, beliefs about treatment assignment are likely to affect outcomes. In such cases, randomization interferes both with the potential therapeutic benefit of the experimental regimens and with the comparative evaluation of those.²

Conceptual concerns with the notion of equipoise at the outset of the trial underlie an additional set of concerns about randomization. Equipoise is a much debated topic in the bioethics and clinical trials literature (6,7), and substantial questions remain about whether any one formulation – individual (8), clinical (1), “community” (9), and others – justifies randomization (10,11). If equipoise is intended as a way to bridge the tension between the researcher’s therapeutic obligation to the subject and the scientific interest in randomization, the confluence of two considerations undermines this function. The first is the fragility of equipoise as a point of genuine uncertainty about which experimental arm is likely to be best for a given subject (8), while at the same time the highly individual nature of the experience of pain and responsiveness to interventions places a heightened therapeutic obligation on the researcher to individualize care within the trial as much as possible. Appreciation of these two points should lead pain researchers to consider study designs that allow at least some degree of directed assignment to experimental regimens, including, for example, the use of historical controls or the Bayesian decision process developed by Kadane (12).

Provision of interim findings during the trial and subject choice of experimental arms. Even if one accepts the utility of equipoise in justifying randomization of subjects at the beginning of an RCT, as such a trial progresses, information about the relative superiority of different experimental arms accrues. Interim trends indicate that one arm is better than any competing one(s)

before widely accepted criteria for stopping a trial and publishing the results have been met. Arguments rooted in the therapeutic obligation would suggest that study designers and the physicians enrolling patients have a duty to use this accumulating data to benefit the patient. The current convention of agreeing to the withholding of this information, both from clinicians and from patient-subjects, constitutes a kind of culpable ignorance on the part of the health care professional. If it is information that one would seek-out and use outside the research context in determining what treatment recommendation to make to a patient, then to ignore it willfully is to consciously sacrifice the interest of the patient for the sake of the research. The evidence that, despite extensive efforts to clarify the concept of randomization, subjects in trials often believe that treatment allocation and other aspects of the research protocol are designed to benefit them (13), together with the highly individual nature of pain experience and treatment and the cascading impact of pain in the patient-subject’s life, makes a practice of favoring scientific over patient interests in pain research particularly problematic.

If the therapeutic obligation were the only moral consideration pertaining to the release of interim findings, then under certain circumstances, alternate designs that provide for the selective assignment (or movement) of subjects into experimental arms that appear to be optimal for them would be sufficient. “Play-the-winner” strategies or Bayesian allocation schemes of the sort that Kadane advocates (12) are examples of designs that may satisfy such an obligation, even without explicitly disclosing interim findings. Respect for the autonomy of patient-subjects, however, may demand that they be apprised of interim findings and given the opportunity to choose for themselves whether to receive the apparent best treatment as a part of the trial (14,15). This is, of course, a very controversial and complicated claim, and I am not the first to challenge the orthodoxy of withholding interim findings from subjects (16). While the argument for this position cannot be fully elaborated and justified here, perhaps a brief sketch of it will suffice to establish some degree of initial plausibility of the view.

It is widely held that, as a matter of respect for

2. Brewin and Bradley make an analogous point about methodology in studies in which motivation is likely to affect the success of experimental regimens. See: Brewin CR and Bradley C. Patient preferences and randomized clinical trials. *BMJ*, 1989; 299: 313-315.

autonomy, patient-subjects must be given all of the available information relevant to their decisions to enroll in a given trial. Indeed, this is a principle that does not generally give way, at least in biomedical research, to the considerations of science, despite the fact that enrolling into research only those individuals who consent to do so under such information conditions clearly biases the results of clinical trials (17,18). Yet, informed consent from subjects at the outset of a trial does not satisfy the deeper obligation of genuine voluntariness that research participation requires. For this, informed consent must continue throughout the duration of the subject's participation, and this entails the need for subjects to be given all available information relevant to a decision to *remain* enrolled in a trial. It might be argued that interim findings are too unreliable to constitute "information" or to be appropriately relevant to a decision to remain enrolled, but this either misunderstands the notion of information or fails to appreciate the symmetry between the conditions constituting adequately informed *initial* and *continuing* consent. Information in clinical trials is aggregative; it stands as evidence that something is the case, not as certainty. The levels of statistical significance at which the medical and scientific communities typically discontinue trials is an artificial threshold for the accumulation of information; it is not a criterion for determining whether one has information *at all*. If the interim findings that are generated during the conduct of the trial are such that one would have been obliged to disclose them had they existed before the trial commenced, or such that a responsible clinician would consider them (though not necessarily be swayed by them) in making a treatment recommendation outside the research context, then they ought, at least *prima facie*, to be provided to subjects.

Relaxing target significance values. The possibility that there is a moral obligation to release interim findings to research subjects in pain trials as well as to participating physicians and researchers has far reaching implications for the design of experiments and, in particular, for the question of whose decision criteria should determine when a clinical trial should come to an end. At present, stopping guidelines for terminating clinical trials em-

body decision criteria dictated by the medical-scientific community. These guidelines specify a level of information on which general treatment guidelines may be based. As Gifford has pointed-out, however, the level of certainty required for establishing medical guidelines affecting large numbers of people is much different than level of certainty required for individual patients' treatment decisions (10). Providing patient-subjects with interim findings would afford them an opportunity to "vote with their feet" on the extent to which they are willing to sacrifice their interests for the sake of the community at large. If it is correct that providing interim findings to patient-subjects and enrolling physicians and researchers would result in decisions to withdraw from a trial or to migrate (as needed) into an apparently superior arm of a trial, then at the very least it should suggest that pain researchers consider ending trials when they reach significance levels that fall short of conventionally accepted *p*-values or other criteria but that still provide sufficient evidence of a difference between experimental regimens that patients in the trial would be unwilling to continue if they had the requisite information and options. To do otherwise is to conscript the service of patients in pain, withholding the information and options that would allow them either to choose, in the fullest moral sense, to serve, or to do what they believe to be in their best medical interests.

If these arguments are to be taken seriously, they present a challenge to researchers to develop or explore alternative study designs that permit the release of information and yield some decisional authority to patient-subjects who enroll in pain trials without sacrificing the important moral features of RCTs mentioned at the outset – reliability of results, speed and efficiency in the production of those results, and fair treatment of study subjects. Even when adoption of alternative designs would yield less information than a RCT or would do so more slowly or at higher cost, there is simply a point at which we must accept this as the cost of doing such trials ethically. The choice, in some cases, ought to be posed not as whether to undertake a RCT or to use an alternative design. When a RCT would maximize the resulting information but sacrifice the interests and dignity of

individual patient-subjects in the process, the choice clearly becomes that of whether to use a non-RCT design or forgo the research altogether. Put in this light, the alternative designs clearly are a gain over no information at all.

CONCLUSION

Pain plays a uniquely powerful role in the lives of patients, modulating every aspect of their experience of the world and of themselves. Pain practice and the research it is founded upon must take account of this fact if it is to manifest appropriate respect for the patient-subject. As pain undermines both the sense of and the actual capacity for control over oneself and one's surroundings, researchers must, both in their interactions with subjects and in the design of experiments, strive to facilitate and restore such control or autonomy. And in so far as researchers must acknowledge the pervasiveness of pain in patient-subjects' lives, they must also acknowledge the diversity and complexity of influences that create and that ameliorate pain and its effects. The design of experiments to elucidate the causes and treatment of pain should take account of all these things, which will, in turn, require creativity and flexibility in their design. Neither the RCT nor any other single design could represent a gold standard in this field, morally or scientifically, because an optimal design for any given research question is one that is responsive to all these factors.

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Commentary

GOOD AS GOLD? THE RANDOMIZED CONTROLLED TRIAL: PARADIGMATIC REVISION AND RESPONSIBILITY IN PAIN RESEARCH

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“Fixity of purpose requires flexibility of method” – HG Wolff (1)

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Knowledge is prevenient to understanding, and understanding is a basis for action. In science, knowledge is gained through experience and experimentation. By examining outcomes and mechanisms, we seek to know *what works*, and *why*. This pattern of discovery reflects the paradigmatic evolution of scientific research (and more recently biomedical investigation) from an enterprise of passive observation to one of active manipulation and control (2). At the zenith of the contemporary scientific paradigm is the randomized controlled trial (RCT). Originally implemented some sixty years ago, the foundational elements of the RCT seek to eliminate bias and thus solidify objectivity in experimental com-

parisons of treatment(s) and effect(s).¹

The RCT has undeniably led to a greater understanding of the neural basis of pain and to the development of pharmacologic and certain non-pharmacologic therapeutics; and it rightfully occupies an important role in pain research. Yet perhaps we must also ask whether the decade of pain control and research has shed new light not just upon mechanisms of pain, but on our research methods themselves.

As Julia Pedroni notes in this issue (*see the previous article*), the use of the RCT may provide an object lesson in the pragmatic limitations and ethical implications of research methods, intentions, and consequences. The

1. Namely, these elements being randomization of subjects into treatment or control groups, and the use of some sort of stable control against which the effects of the independent variables can be assessed. The benefits of the RCT cannot be denied, yet, as with any methodology, there is opportunity for modification, improvement, and the need to recognize inherent strengths, weaknesses, and/or limiting and de-limiting factors. See: Lindley R, Warlow CP. *Why and how should trials be conducted?* In: Zeman A, Emanuel L (editors). *Ethical dilemmas in neurology*. London: Saunders, 2000:73-86 and Sheldon T, Oakley A. *Why we need randomized controlled trials*. In: Duley L, Farrell B. (editors). *Clinical trials*. London: BMJ Books, 2002:13-24.

increasing fusion of neurobiology with other disciplines of the sciences as well as the humanities has led to studies of the combined mechanistic and experiential domains of pain. These studies have re-addressed questions of *what is pain, what are its effects, and how is pain manifested in individual persons.*² Professor Pedroni proposes that there is both a practical necessity and moral obligation to develop research techniques and strategies that are built upon this progressively expanding knowledge base and which best meet these intellectual challenges.

I agree and believe that this reflects an important epistemic construct – simply, *what we learn about pain should influence how we study pain, and how we conduct pain studies may then provide critical insights into new types of knowledge.*³ At the crux of the matter, at least in part, is a need to re-conceptualize pain as a spectral disorder that exists along a continuum of disease and illness which affects brain and mind. Thus, the use of a solely reductionistic approach to research (and therapeutics) is insufficient. Indeed, Rees states that any study of brain function is committed to an inquiry on many levels “...from synapses to social groups” (3). It is undeniable that such research must rigorously adhere to the scientific method. Research must be valid, reliable, elucidative, and applicable. But it is equally critical to note that the scientific method is grounded upon a philosophical foundation that compels self-evaluation, self-revision and anti-dogmatism (4). This speaks to the necessity to develop research that is based upon our current epistemic capital so as to appreciate better the

reciprocity of body, brain, mind, behavior, and environment as parts of a complex, hierarchical system acting within a particular individual.

To be sure, the physiological event of pain occurs as a subjective experience that is individually variable (5). This variation can occur on numerous levels. For example, genotypic variation between individuals can produce phenotypic distinctions in the structure and function of diverse systems (*e.g.*, enzymes, ion channels, signaling and structural proteins) that can affect physiological processes ranging from metabolism to cognition (6,7). As well, the event and experience of pain can induce epigenetic effects within the central nervous system. These attributes may create individual differences in (i) susceptibility and sensitivity to types of pain, (ii) expression and manifestations of pain as illness, and (iii) responsiveness to particular types of treatment.⁴ These are factors that the RCT may miss by design (at least in its most restrictive iteration). Such attributes need to be recognized for their potential effects upon mechanisms and treatment outcomes, such that subjects might be pre-selected or stratified into representative groups that could then be randomized within the arms of the RCT. Furthermore, given the phenomenal and individually variant nature of pain, the use of qualitative approaches, or mixed methodologic designs are of significant value in bridging levels of inquiry and generating knowledge that is meaningful for both the basic sciences and the clinical encounter (8).

Such complex interactions of persons, circumstances, and environments are contributory to expectations,

2. Under the rubric of neurophilosophy, these questions have spawned considerable inquiry into the nature of pain as consciousness, and the concepts of self, dignity, and free will relative to the constructs of brain and mind. From these arise additional questions concerning the existential impact and value of suffering and the limits and parameters of scientific investigation and medical intervention that have become the focus of the somewhat incipient discipline of neuroethics.

3. This may also reflect other epistemic issues in evidence-based medicine, as well as prompting review of the general pattern and historicity of scientific and medical epistemology. See: Ashcroft RE. Current epistemological problems in evidence-based medicine. *J Med Ethics* 2004; 20:131-135 and Fuller S. Kuhn vs. Popper: The struggle for the soul of science. New York: Columbia University Press, 2004.

4. Considerations and use of individual variations have seen practical applications in pharmacogenomics and attempts at a socio-culturally oriented practice medicine, although in both circumstances, additional ethical issues have been raised regarding the possibilities for biases, discrimination, and relative value-ladenness. See: Bartfai T, Lees GV. Drug discovery from bedside to Wall Street. Burlington, MA: Elsevier Academic Press, 2006 and Allmark P. Should research samples reflect the diversity of the population? *J Med Ethics* 2004; 30:185-189.

mechanistic effects, and responses. In light of this, it may be important not simply to fit a particular subject (or group of subjects) into a research design, but to design specific study protocols that best “fit” subjective experiences and manifestations of pain to allow objective evaluation of hierarchies of evidence that have meaning to different audiences at various levels (9,10). Implicitly, this addresses the *why* question of pain research. Obviously, the goal of any clinical research endeavor is the acquisition of new knowledge contributory to decision-making and the resolution of equipoise (11).⁵ Ultimately, such knowledge upholds the fiduciary nature of the clinical encounter in that it enables the clinician and empowers the patient.⁶ But while this may be a realistic and ethically tenable end, pain research is not simply a means to acquire knowledge, but an end unto itself. Clinical research involves the participation of autonomous subjects, not objects, and there are well-known and equally important fiduciary obligations that are inherent to the researcher-subject relationship (12).

While many of these are explicit, Professor Pedroni recognizes that some are more subtle and proposes that the aforementioned pragmatic issues also have considerable moral implications. Persons who participate in clinical trials very likely have some expectation of benefit, even though they consent to the possibility of random assignment into a control group. In many ways, this is based upon the justificatory criteria for conducting the trial in the first place, as it is likely that at least some subjects will have positive therapeutic outcomes (13). Given that (i) there is a moral obligation to treat pain

(14); and (ii) this obligation is instantiated upon a philosophical basis of medicine, in general, or pain medicine more specifically (15,16,17), then it follows that everyone under the aegis of pain medicine (*i.e.*, including its research endeavors) should expect and receive pain relief. Is it sufficient simply not to violate research subjects’ rights by informing them of the possibility of non-treatment and obtaining their consent to participate, given that we are aware that patients have some expectation of therapeutic benefit?⁷

Thus, Pedroni asks not only if the RCT is pragmatically effective, but whether it is ethically acceptable to randomize pain patients into non-treatment groups. Of course, there are practical ways to avoid this problem (*e.g.*, cross-over design, comparative, active controlled trials, historical controls), but such methods are not always used. This prompts the question of whether the use of these methods should be mandatory. Yet, even these approaches are laden with potential ethical issues. If a cross-over design is used, should patients be switched from a working, active treatment to a sham intervention that is recognized to be ineffective in producing pain relief? What if patients in a sham-treated group experience significant placebo effects? Should they be told or should these treatments be deceptively continued? What if the statistical review-points of a study are insufficient to warrant continuing the trial, but the enrolled patients report positive subjective effects that are outside of the intended therapeutic parameters? Or, on the contrary, should surrogate end-points be used to maintain a trial in which patients’ subjective effects may be nominal, and

5. *Equipoise as an operational psychological construct differs from purely mathematical equipoise and is defined as an indifference to, or relative uncertainty of one treatment being superior to another. As cited in the text, Freedman (11) further differentiates equipoise into theoretical (i.e., individual) and clinical (i.e., collective) equipoise, with the latter form being operative in the weighing of relevant medical evidence and in clinical decision-making. It is this clinical or collective equipoise that is an important requirement in clinical trials. However, as Pedroni notes, even clinical equipoise generates particular ethical issues. See: Freedman B (11) and Johnson N, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical? J Med Ethics 1991; 17:30-34.*

6. *It enables the clinician to weigh the risk-benefit ratio of a particular intervention, provides mechanistic knowledge, and fortifies clinical decisional process. It empowers the patient by allowing for more information to be provided by the clinician so as to allow for enhanced judgment of whether or not to consent to treatment. But this also speaks to the need for veracity, intellectual honesty, and communicative competence in the patient-physician relationship.*

7. *For a more detailed discussion, see: Brody B. The ethics of biomedical research. New York: Oxford University Press, 1998.*

should these mid-point data be used to inform patients, given their interests and expectations (18-21)? Professor Pedroni argues that these issues may force re-examination of both the pragmatic methods and ethical goals of current paradigms of pain research.

Dr. Pedroni reminds us that research is a moral enterprise. The circumstances and conduct of clinical pain research are dependent upon the intentions and acts of the agents who are involved as experimenters, as relevant to those who are subjects. Ultimately, the questions are not just how and what we study about pain, but if we are using this knowledge in ways that best uphold pain medicine's moral obligations to the patient.

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