HHS Public Access

Author manuscript

Clin Trials. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Clin Trials. 2015 December ; 12(6): 557–563. doi:10.1177/1740774515607213.

Ethical Complexities in Standard of Care Randomized Trials: A Case Study of Morning Versus Nighttime Dosing of Blood Pressure Drugs

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Abstract

Background—Pragmatic trials comparing 'standard of care' treatments provide comparative effectiveness data to make practice of medicine more evidence-based. With electronic health records, recruiting and conducting such trials can be relatively inexpensive. But some worry that the traditional research ethics framework poses unnecessary obstacles and is not appropriate for evaluating such clinical trials. This concern is based on the view (which we call the 'Standard of Care Principle') that such research is similar to usual clinical practice and therefore does not raise significant ethical issues since everyone in the research study will receive an accepted standard of care treatment.

Methods—A case study of a pragmatic RCT (BPMedTime study) comparing morning versus nighttime dosing of antihypertensive medications. The BPMedTime study has been proposed as a paradigm example of why the Standard of Care Principle obviates the need for traditional levels of ethical scrutiny and how the current regulatory framework poses unnecessary obstacles to research. We provide an ethical analysis of the BPMedTime study drawing on empirical literature as well as normative analysis.

Results—The Standard of Care Principle is the main ethical rationale given by commentators for asserting that the BPMedTime study does not require "significant ethical debate" and by investigators for the assertion that the BPMedTime study is minimal risk and thus eligible for lessened regulatory requirements. However, the BPMedTime study raises important ethical issues, including whether it is even necessary, given the considerable RCT evidence in support of nighttime dosing, a much larger (N≈17000) confirmatory RCT already in progress, evidence for safety of nighttime dosing, and the cost-free availability of the intervention. Further, the Standard of Care Principle provides a misleading basis for analyzing the informed consent requirements, especially regarding the requirement to disclose alternative courses of treatment that "might be advantageous to the subject."

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Conflict of Interest: All authors have no conflicts of interest to report.

Disclaimer: The opinions expressed herein are the authors' and do not reflect the policies and positions of the National Institutes of Health, the United States Public Health Service, or the United States Department of Health and Human Services.

Conclusions—The Standard of Care Principle is ethically inadequate and misleading even when it is applied to the pragmatic RCT proposed as a paradigm case for its application.

Keywords

Standard of care; research ethics; pragmatic trials; comparative effectiveness research; informed consent

Comparative effectiveness randomized clinical trials (RCTs) are much needed because clinicians often face situations in which there is more than one treatment that is generally accepted, known to be efficacious, or Food and Drug Administration (FDA)-approved for their patient's condition, and it is usually not clear which is superior or how best to use the treatments. The need for more pragmatic comparative effectiveness RCTs to make clinical practice truly evidence-based is integral to the vision of a learning healthcare system.[1] The advent of a modern electronic health record system makes it feasible and relatively inexpensive to conduct these studies in the context of routine clinical practice.[2]

An important feature of comparative effectiveness research involving standard of care treatments is that every participant will receive a clinically accepted or at least commonly used intervention for his or her condition, as distinct from trials of novel or experimental interventions.[3] Thus, some commentators note that "…standard-of-care research does not expose participants to risk beyond the risk they might be exposed to outside the study."[4, 5] Indeed, some argue that within learning health care systems the traditional distinction between research and treatment is problematic and outmoded[6, 7] and that the regulations "no longer match current needs."[6] Some see the requirement of informed consent as a "critical barrier" for comparative effectiveness RCTs,[8] and others argue that some types of RCTs do not need informed consent.[9] For brevity, we will call the view that studies comparing standard of care interventions do not raise significant ethical issues since they are similar to ordinary clinical practice the "Standard of Care Principle."

According to the Standard of Care Principle, the traditional research ethics framework is not appropriate for standard of care RCTs because the subjects experience in research essentially the same care they would experience as patients. Applying the traditional framework would, on this view, be unnecessarily restrictive. Accepting the Standard of Care Principle could expedite much needed research (potentially by decreasing level of oversight, waiving or altering informed consent procedures, etc.).

We have argued elsewhere that the mere fact that two standard of care treatments are being compared is not a sufficient reason to bypass careful case by case ethical analysis of RCTs.[10] In this article, we illustrate this need for careful case by case analysis by focusing on a study that is cited as a particularly good case for applying the Standard of Care Principle. In a recent article, a study comparing morning versus nighttime dosing of antihypertensive medications is offered as a prime example of why regulatory reform is needed.[6] This is an actual study within the National Institutes of Health Collaboratory (BPMedTime study),[11] an initiative whose purpose is to promote comparative effectiveness research. The authors assert that the "significant debate about appropriate ethical oversight" of such a study is a reflection of a "fundamental problem," namely, the "entrenched view

that research, including evaluation of treatments already approved and widely administered to patients, automatically creates higher risks than ordinary care."[6] Against this view, we demonstrate that "a significant debate about appropriate ethical oversight" is precisely what is needed even for this seemingly benign pragmatic trial.

BPMedTime study

Drugs for high blood pressure are taken daily by millions of patients in the U.S. Some doctors prescribe it for the morning, some for the evening, and most say nothing about timing; all three practices are "within the standard of care."[11] The BPMedTime study is a pragmatic RCT that plans to enroll over 6000 subjects from two sites in the U.S.[11, 12] Subjects will be patients with hypertension plus at least one comorbidity (such as diabetes, ischemic heart disease, renal insufficiency, cerebral or peripheral vascular disease, congestive heart failure, and hyperlipidemia) who are taking all of their medications in the morning. They will be randomized to being told to continue their daytime dosing or switch all of their once-a-day blood pressure medications to nighttime dosing, and will be followed for 36–42 months. The primary endpoints are cardiovascular events (death, admission for acute myocardial infarction, strokes, ischemic heart disease, heart failure, or coronary, peripheral, or cerebral revascularizations). Notably, the investigators have proposed the study as minimal risk.[11] The final informed consent forms and procedures are not currently publicly available.

What do we know about AM vs PM dosing of antihypertensive medications?

The designers of the BPMedTime study support this pragmatic RCT by citing an RCT conducted in Spain (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares, i.e., Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events, known as the MAPEC study[11–13]). The MAPEC study involved 2156 subjects who were randomized to taking all antihypertensive medications in the morning or taking at least one of their antihypertensive medications at bedtime. After a median follow up of 5.6 years (or about 12,000 person-years of evaluation), there were 255 cardiovascular events, consisting of 68 in the PM dosing group and 187 in the AM dosing group ($p<0.001$), with adjusted relative risk of *major* events (cardiovascular deaths, myocardial infarction, and stroke) of 0.33 [0.19–0.55; $p<0.001$].[13] Although there were no differences in awake blood pressures, there were significant differences in asleep systolic and diastolic blood pressures, as well as in the proportion of persons whose nighttime blood pressure 'dipped' (62% for PM dosing vs 34% for AM dosing, $p<0.001$), a feature previously shown to be a predictive parameter against cardiovascular events.[14, 15] Subgroup analyses of persons in MAPEC study with chronic kidney disease (n=661),[16] diabetes (n=448),[17] and resistant hypertension (n=776)[18] have also shown similar results. There were no differences in adverse events between the two arms (Hermida, personal communication). A 2011 Cochrane review meta-analysis, conducted prior to the MAPEC study, showed that although at the time of the review there had been no published studies using 'hard' clinical outcomes, nighttime dosing significantly lowered 24 hour blood pressure without any increase in adverse events.[19] A systematic review and meta-analysis of randomized trials of

antihypertensives, comparing evening dose trials with morning dose trials, also support better cardiovascular outcomes for evening dosing.[20]

In 2013 and 2014, the American Diabetes Association Standards of Medical Care in Diabetes recommended at least one antihypertensive drug be taken at nighttime, citing 'level A' (highest level) evidence.[21] The 2015 American Diabetes Association document, which did not evaluate any new evidence, does not list PM dosing as a separate bulleted recommendation and instead says, "Consider administering one or more antihypertensive medications at bedtime" and cites the MAPEC study.[22] Other international organizations have recommended bedtime dosing,[23] although it is reported that the International Society of Nephrology did not believe the evidence was sufficient for an official guideline recommendation.[11]

Commentators have called for larger, multi-site studies. They note that the MAPEC study was a single site in one European country and that some features of the MAPEC study would not be part of practice in the United States.[12, 24] Indeed, the MAPEC study had a strong explanatory component in using 48-hour ambulatory blood pressure monitoring (in which subjects wear a portable device for 48 hours, including during sleep) and use of actigraphs (which measure movement, thus making it possible to accurately detect asleep BPs). Accordingly, the study documented the impact of dosing on overnight sleep pressures, which was the best explanatory variable for the difference in cardiovascular outcomes.[15, 23] The MAPEC investigators in January of 2008 started a large multi-site study (the HYGIA study) similar in design to the MAPEC study with a plan to enroll 15,000 subjects[25] The HYGIA study has a current enrollment of approximately 17,000 persons with median follow up of several years and an interim analysis to be performed soon. (Hermida, personal communication)

Standard of care principle in action?

In discussing the ethical aspects of the study, the investigators of the BPMedTime study rely heavily on the claim that the proposed study mirrors the standard of care. This is most evident in their discussion of the study's risks. They argue that the study is no more than minimal risk because it "exposes patients to no greater risk than they would experience from the routine clinical care of their hypertension."[11] Additional rationales given are that the study is "largely observing the outcomes that patients experience in the course of their routine care following randomization"; that "patients likely take once-daily medications at different times of the day" and that random assignment within the study "would mimic in many ways the random nature by which most patients currently time the dosing…"[11] In short, the investigators are appealing to the Standard of Care Principle, the view that emphasizes the ethical similarity between such research and clinical practice since "… standard-of-care research does not expose participants to risk beyond the risk they might be exposed to outside the study."[4, 5]

If the BPMedTime study is indeed minimal risk, then the study would be a potential candidate (under the current regulations) for less extensive IRB review and for waiver or alteration of informed consent. As we explain below, however, the fact that the Standard of

Care Principle would allow such a conclusion indicates how misleading such a principle is in analyzing the ethics of standard of care RCTs.

Alternative analysis: The ethical complexity of BPMedTime study

Is the BPMedTime study necessary?

Does the MAPEC study, an RCT involving over 2000 people with a large effect size, along with prior smaller studies as well as systematic reviews[20, 26] form a sufficient basis for physicians to tell their patients with hypertension to take their antihypertensive medication at night? Commentators who advocate additional study point out that the MAPEC trial was conducted at one site[24, 27, 28] that it was a 'small' study,[12,13] and its results may not generalize to an ethnically heterogeneous population in the United States.[11, 24, 27] Also, the use of 48-hour ambulatory blood pressure monitoring and actigraphs do not reflect current practice in the U.S.[24, 29] How important are these considerations?

The MAPEC study is indeed limited by having been conducted at one site.[28] The assertion that the study was a small study is interesting because even some commentators who argue for a multi-site study in fact note MAPEC's "large sample size" as a strength.[24] The total N of 2156 is, by standards of some cardiovascular medication studies, small.[30] But the median follow up was 5.6 years, for a total observation of approximately 12,000 person-years (assuming that the median follow up was not drastically different from the mean). In comparison, the BPMedTime study is not much larger, as it will follow 5000–6000 subjects 36 to 42 months, or 15,000 to 21,000 person-years, especially considering that as a pragmatic study one can anticipate a lower signal-to-noise ratio. Further, the existence of a very large (N=17,000) multicenter Spanish study that has already been in progress since 2008 and about to undergo interim analysis is an important factor in evaluating the need for the BPMedTime study. In view of completed and ongoing research on the timing of antihypertensive medication, it is unclear how much scientific benefit the BPMedTime holds.

Nevertheless, because the MAPEC investigators used 48 hour ambulatory blood pressure monitoring and actigraphs to adjust the treatments of their subjects to target nighttime BPs, there is a question of whether PM dosing without such guidance would have a similar result, in terms of both safety and efficacy.[28, 29] There is evidence that presenting clinicians in Spain with ambulatory blood pressure monitoring data has significant impact on clinical management—in both increasing and decreasing treatment—of patients when compared to those not given ambulatory blood pressure monitoring data, with difference in blood pressure control outcomes.[31] However, much of that difference was due to initiation of PM dosing when ambulatory blood pressure monitoring information is given to clinicians.[31] The use of 48 hours ambulatory blood pressure monitoring is not standard practice in the United States and the BPMedTime study would in fact test whether PM dosing would result in cardiovascular outcome benefits, even without the ambulatory blood pressure monitoring component. However, the BPMedTime study will not be comparing two management practices since neither arm in the study will use ambulatory blood pressure monitoring. Even if the BPMedTime results prove negative, it is unclear one could draw the conclusion that

nighttime dosing of antihypertensive medication guided by ambulatory blood pressure monitoring would be ineffective.

Thus, the theoretical value of BPMedTime study rests on the fact that it will be a multisite study of U.S. patients under conditions comparable to usual care. However, the study is only marginally larger, has only two sites, and does not seem to be specifically designed to answer whether subgroups of patients who are ethnically and racially different from the MAPEC cohort would benefit from PM dosing. Further, simply because a pragmatic trial includes a diverse sample does not imply that the results are generalizable to each subgroup of interest (unless a priori research design provides for it, with adequate sampling), only that average effects can be expected in the heterogeneous sample.

The value of a research study depends not only on the reduction in uncertainty gained through an RCT (i.e., the information gained) but on the *value* of that reduction in uncertainty. This reduction in uncertainty is especially valuable if the intervention at issue is invasive (with attendant potential for harm), expensive, and would take significant resources to make available to patients. How great is the need to reduce uncertainty in the current case? Consider for example those patients with type II diabetes and hypertension, one of the targeted groups for the study. For two years, the American Diabetes Association's Standards of Medical Care in Diabetes recommended PM dosing as based on level A evidence. Although it is currently recommended as a "consideration," there is a clear recognition of the value of PM dosing in persons with diabetes and high blood pressure. At a minimum, those BPMedTime patients with diabetes who are assigned to AM dosing will not be receiving due consideration regarding whether PM dosing might be better for them.

Further, the intervention at issue in the BPMedTime study—nighttime dosing—is free, non-invasive, universally available, with substantial evidence regarding lack of adverse side effects. In this case, the amount of uncertainty regarding efficacy that is tolerable from a public policy perspective should be higher—perhaps much higher—than for novel and expensive interventions. In fact, from a public health perspective, a false negative result (that is, an RCT falsely finding that PM dosing does not reduce cardiovascular events) would be a great loss since it would mean that a virtually cost-less yet effective intervention would have been missed.

In short, the current evidence—many small studies with blood pressure as outcome, a systematic review and meta-analysis comparing evening versus morning dose using data from large clinical trials, and a large single site RCT with hard outcomes—supports the superiority of evening dosing over morning dosing on balance.[26] One can make an argument that a definitive answer may require a larger, multi-site study.[28] Such a trial is already underway in Spain.[31] Thus, it is not clear what the BPMedTime study will add.

Although we believe the argument against the necessity of conducting BPMedTime is quite strong, we recognize that reasonable people might disagree about its necessity. For example, given that hypertension involves millions of people in the U.S., experts might place greater weight on the potential unknown differences between Spain and U.S. contexts than we do. But what is not disputable is that the BPMedTime study deserves close ethical scrutiny

about its necessity—scrutiny that is not obviated by the fact that the BPmedTime study is testing interventions that are 'within the standard of care.'

It is possible that someone who strongly believes in the Standard of Care Principle may object that the BPMedTime study is in fact a poor test case. They might argue that the principle should only apply for those RCTs that are testing 'appropriate' treatments based on available evidence (even if such treatments are not widely in use). We would respond to this in two ways. First, such a move would be an acknowledgment that the BPMedTime study is ethically problematic. (Note, however, that we have not found evidence for this view in the literature or in the investigators' discussion of the study. Indeed, as we have pointed out, BPMedTime is seen as an exemplar.) Second, whether such a revised Standard of Care Principle would provide robust ethical guidance can only be answered by examining how it works in practice. As we have discussed elsewhere, there is such a wide variety of standard of care RCTs that it seems doubtful that a simple principle could be robustly action-guiding for all such studies.[10]

We now turn to the issue of informed consent for the BPMedTime study. Given that reasonably strong evidence exists for the safety and efficacy of PM dosing, complex ethical issues arise for informed consent.

Complex informed consent issues in BPMedTime study

The BPMedTime investigators' proposed informed consent document is not publicly available.[11] Accordingly, our goal here is not to critique the content of the BPMedTime's proposed informed consent disclosures but instead to provide an analysis of the ethical issues regarding informed consent that need to be addressed, given the features of the BPMedTime study. (Nor are we addressing informed consent issues regarding dose timing in the clinical setting.) We argue that there are complex ethical issues regarding informed consent that require considerable scrutiny which must go beyond a mere appeal to the Standard of Care Principle.

In light of the current informed consent framework used in the US, there are at least two important issues that must be addressed. First, the United States regulations require "a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject."(45CFR46.116a4) Second, even if the study is deemed minimal risk (defining risk as adverse events due to the intervention in question), whether the study would be eligible for waiver or alteration of informed consent would require careful consideration.

In terms of "appropriate alternative procedures or courses of treatment… that might be advantageous," the question is whether and how the current state of knowledge (reflected in the literature leading up to the MAPEC study and the MAPEC study itself) about potential benefits of PM dosing should be conveyed to the subjects. The regulatory language on its face does not require a great deal of evidence ("might be advantageous"). It mentions "appropriate" alternative procedures. Since AM and PM dosing are "within standards of care," recommending either outside the trial would probably fall under a range of "appropriate" alternative procedures.

The main question then is whether and how the research subjects should be told about the potential advantages of PM dosing. This is particularly salient for those who are assigned to the AM dosing arm. Should they be told that the best available evidence, including a study of over 2000 people, shows that people taking their medicines in the morning have almost 3 times the risk of heart attacks, strokes, angina, etc. compared to those who take their medicines at night? Or should they be told nothing since there is not yet a universally accepted treatment guideline recommending PM dosing? Or simply that "We are not asking you to do anything different than what you have been doing, so there is no additional risk to you than what you would have faced during regular course of treatment." Or should they be told that the current state of knowledge about impact of dose timing is equivocal: "… hypotheses exist for potential benefits of both nighttime and morning dosing."[6] Should people with diabetes who are recruited have special disclosure about the American Diabetes Association recommendations from 2013–2015 regarding standard medical care for diabetes?

The FDA guidance regarding this disclosure element states, "where such descriptions or disclosures can contain quantified comparative estimates of risks and benefits (e.g., from the clinical literature), they should do so."[32] This seems to fit the present case. One might reasonably infer from this that subjects should be told that the current evidence supports PM dosing because the best estimate of its benefit is that compared with AM dosing, the risk of cardiovascular events would be ½ to 1/3.

Another way to determine the appropriate disclosure would be to consider how valuable the MAPEC and other data (or some layperson summary of it) would be to a person trying to decide whether to enroll in the BPMedTime Study. Given that patients can readily change when they take their medications (a change that is without cost and with evidence of little risk), how would people feel, especially for those assigned to the AM dosing arm, if they were not told of the MAPEC study's main results and were simply told "If you enroll, risks and potential benefits will be no different than it would have been if you hadn't entered the study"? If one were told to take one's medications in AM, even if he were already taking the medication in AM, and if one later found out that MAPEC results were withheld from him, how would that person feel? In sum, because the intervention is universally available, cost free, with little risk of adverse effects, the failure to disclose information that "might be advantageous" to the subjects seems ethically objectionable.

The preceding discussion makes it clear that a waiver of informed consent would be ethically problematic. The regulations require that for waivers of informed consent, the research must be minimal risk, the waiver will not adversely affect the rights and welfare of the subjects, and the research would be impracticable without the waiver.(45CFR46.116d) If the patients are not given an opportunity to consent and the healthcare system's doctors instructed all of their patients to take their medications at different times (based on randomization unbeknownst to the patients), given the significant implications for outcomes between the two arms based on the MAPEC and other data, a waiver of consent would be highly problematic. It seems essential that, for example, a patient who has hypertension and diabetes be given the chance to explicitly volunteer for the study since they are being asked to forgo (if assigned to AM arm) a likely benefit. It cannot be assumed that patients do not

have a right to such information. Patients have a right to know and to be given an opportunity to make their own decisions about giving up a potential good (reduced risk of major cardiovascular event during the course of the study). Note that this point does not rely on an empirical assumption about what the person would have received outside the study. It merely speaks to what the person is entitled to know and to decide, when he is serving as a research subject. It also seems unlikely that the study could be deemed impracticable without a waiver, since a much larger study comparing AM and PM dosing is already being conducted with informed consent.[25]

For the same reasons it would be ethically problematic to conduct this study with an "alteration" of informed consent, such as a simplified consent procedure that did not adequately disclose alternative courses of treatment that "might be advantageous." Specifically, the prospective subjects should be informed about the potential advantages of bedtime dosing.

Conclusions

This paper has focused on the BPMedTime study because it has been put forward by commentators as a particularly fitting example for applying the Standard of Care Principle to justify lessened ethical scrutiny of some types of RCTs.[6] What our analysis shows is that in fact there are fundamental ethical questions involving the BPMedTime study that require thorough debate. There must be a close ethical analysis of whether the existing evidence that is not currently being incorporated into practice is such that a new, larger RCT is warranted. And even if, upon close ethical and scientific analysis, a new RCT is deemed to be warranted, there is still a need for a thorough analysis of how the potential subjects of such an RCT should be told about the significance of the existing evidence. Appealing to de facto practice ('being in this study is no different than what would happen outside the study') in such cases is not only irrelevant but misleading.

Our analysis of the BPMedTime study illustrates only one way in which the Standard of Care Principle can be a misleading basis for analyzing the ethics of standard of care RCTs. As we have argued elsewhere,[10] there are a variety of standard of care RCTs with many varying features that have wide-ranging ethical implications: such studies vary considerably in the evidence base for the risks, burdens, and relative efficacy of the interventions that are being compared, in their study design (e.g., superiority vs non-inferiority), in the nature of outcome variables, and in the motivating factors for conducting them (e.g., cost-containment), among other factors.[10] It may be that for some standard of care RCTs, certain alterations in some of the ethical requirements may be appropriate.[33] However, we should resist relying on a broad and general principle such as the Standard of Care Principle to fundamentally change the way we analyze the ethics of RCTs.

Acknowledgements

Authors thank Neal Dickert, David Wendler, Alan Wertheimer, and Rahul Nayak for helpful comments on earlier versions and RA Hermida for unpublished information cited in the MS.

Funding: Supported by Intramural Research Program, National Institutes of Health Clinical Center Department of Bioethics.

Role of the Sponsors: The sponsors had no role in the design of the study; analysis, interpretation, preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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