Ethics/Regulatory Call with Dr. Rosenthal's Demonstration Project – BPMedTime
Date: May 31, 2013
MINUTES

Participants:

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☒	Rob Califf (Duke)	☒	John Bertolatus (Univ Iowa, IRB)	☒	Denise Bonds (NIH)	☒	Tammy Reece/Cheri Janning (Coord Center)
☒	Gary Rosenthal (Univ Iowa)	☒	Julie Kaneshiro (OHRP)	☒	Catherine Meyers (NIH)	☒	Monique Anderson (DCRI)
☒	Christian Simon (Univ Iowa)	☒	Jerry Menikoff (OHRP)	☒	Wendy Weber (NIH)	☒	Jonathan McCall (Coord Center)
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These minutes were circulated to all participants on the call for two rounds of review and they reflect all corrections that were received.

AGENDA ITEMS	DISCUSSION	ACTION ITEM
Review of Demonstration Project	• Dr. Rosenthal gave an overview of the BPMedTime trial (Blood Pressure Medication Timing Study). The study will compare the risk of adverse cardiovascular events in patients who are randomized to receive instructions to take their currently prescribed once daily antihypertensive medications at bedtime vs. patients who continue to take their once daily antihypertensive medications in the morning or afternoon. • Primary endpoint: o Cardiovascular events (CV death or hospital admission for acute MI, ischemic heart disease, cerebrovascular accident,	

	heart failure, or coronary, cerebral, or peripheral revascularization) • Secondary endpoints: o Blood pressure recorded in clinic during outpatient visits o Self-reported medication adherence o Health-related quality of life o Resource utilization (counts of admissions, ED visits, and clinic visits) • Centers involved: University of Iowa and Duke University. • Eligible participants will be identified through the electronic health record (EHR) at both sites and will include adults 50–85 years of age. Potential study participants will be sent an initial packet including a letter describing the trial and informing them of their eligibility. Study endpoints will be collected from: 1) the EHR; 2) a secure, password-protected, web-based personal health record or mailed questionnaires; 3) Medicare claims data for Medicare beneficiaries; 4) hospital discharge summaries for patients who are not Medicare beneficiaries; 5) state death certificate files; and 6) the National Death Index. • No questions regarding protocol design were voiced.	
Minimal risk	• The investigators proposed that the study poses no more risk to participants for than they would experience from routine clinical care for hypertension. • Participants randomized to the intervention arm of the study will be asked to take their blood pressure medications at nighttime; there is no change to the kind of medication or dose. Participants are not exposed to any other additional risk. • In their 2013 clinical practice guidelines, the American Diabetes Association recommended that at least one hypertension	• Dr. Rosenthal will send background reference materials to OHRP representatives participating in this teleconference so that the discussion about a risk determination can continue.

	medication be given at bedtime, based on reported results from recent randomized controlled trials conducted by a single Spanish team of investigators. The International Society of Nephrology did not feel that the evidence warranted this recommendation. • A review of pharmacy prescribing data at the University of Iowa found that 92% of instructions for once-daily hypertension medications lacked specific instructions regarding what time of day to take them, leaving patients free to take medications at times they felt most convenient. • Observational studies have suggested that nighttime hypotension may be associated with ischemic optic neuropathy (a rare condition), although not specifically with nighttime dosing of antihypertensive medications. One small (n=88) Polish observational study found an association between nighttime dosing of antihypertensive medications and visual field loss in subjects with open-angle glaucoma. Because of these studies, patients with histories of ischemic optic neuropathy and/or glaucoma will be excluded. • Discussion ensued about whether the study would meet criteria for a determination of minimal risk, but no consensus was reached about this during the call.	
Consent (patient and physician)	• Informed consent will be obtained using an online interactive platform (preferred) or a mailed a consent letter that will provide identical information. • A waiver of documentation of consent (i.e., waiver of the requirement for a witnessed signing of the consent form) is requested because: 1) the study involves only minimal risk and 2) the study involves no procedures for which consent is normally required outside of a research context. • Mention was made that there is no requirement for witnessed signing of consent under 45 CFR 46; however, witnessing can be required under other guidances if they are applicable.	• Further discussion with OHRP regarding the consent process, especially issues regarding documentation of consent, is needed.

HIPAA	• Post-consent, a full waiver of HIPAA authorization is planned. It is not practicable to obtain this authorization without losing the pragmatic nature of the trial (i.e., obtaining such authorization would substantially reduce enrollment efficiency). • No concerns about this were raised on the call.	
Monitoring and oversight	• Information will be reviewed by a data safety monitoring board that will be constituted according to NIH policies.	The study will require a Data and Safety Monitoring Plan, which will be developed by the study team, and approved by NHLBI prior to study implementation.
Issues beyond the BP MedTime Trial	• None voiced.	
Conclusion of meeting	• Follow-up needed as noted in action items.	• A case study will be drafted to provide guidance for others planning similar trials to facilitate navigation of the ethical and regulatory issues.

SUPPLEMENTARY MATERIAL FOR BPMEDTIME DISCUSSION

NIGHTTIME DOSING OF ANTIHYPERTENSIVE MEDICATIONS

Primary Goal: The goal of this randomized pragmatic trial is to compare the risk of adverse cardiovascular events and other endpoints in patients who are instructed to take their currently prescribed once daily antihypertensive medications at bedtime and patients who continue to take their once daily antihypertensive medications in the morning or afternoon.

Rationale for Trial: The rationale for the trial is that nighttime dosing may better control the early morning rise in blood pressure (BP) that occurs in most patients and that is associated with an increased risk of acute cardiovascular (CV) events. Nighttime dosing may also promote greater nighttime dipping of BP in patients with hypertension and other chronic illnesses, such as chronic kidney disease and diabetes. Such nighttime dipping has been shown to be protective of cardiovascular events.

Building on this background, Hermida et al conducted the MAPEC (*Monitorización Ambulatoria para Predicción de Eventos Cardiovasculare*s) study that randomized patients to take all of their antihypertensives on awakening or one or more agents at bedtime. The trial enrolled 2,156 individuals with hypertension from one center in Spain. CV events that were assessed included death from all causes, myocardial infarction, angina pectoris, coronary revascularization, heart failure, acute arterial occlusion of lower extremities, thrombotic occlusion of the retinal artery, hemorrhagic stroke, ischemic stroke, and transient ischemic attack. Subjects were followed for a median of 5.6 years. The study found that mean sleep time systolic blood pressure was significantly lower with bedtime dosing (111 versus 116 mm Hg, p<0.001), although no differences were observed in daytime BPs. The study further found a roughly 3-fold reduction in adverse CV events in patients who received bedtime dosing, compared to patients who took all medications on awakening (hazard ratio 0.33 [95% CI 0.19-0.55]; p<0.001).

The same authors reported two subgroup analyses from the MAPEC study of patients with diabetes (n=448) and with chronic kidney disease (n=661). Both analyses yielded nearly identical results with regard to CV risk reduction as was observed in the entire cohort. These data represent the first randomized study to directly compare nighttime and morning dosing of antihypertensive medications. While the results are encouraging, they are derived from a single medical center in Spain and observed an unexpectedly large CV risk reduction. It is important to note that the Veterans Cooperative Study conducted in the 1960s, that was a placebo controlled trial of moderate hypertension (diastolic BPs of 90 to 114 mm Hg) found a similar level of risk reduction.

Eligible Sample: The study will be conducted at two sites – The University of Iowa and Duke University. The eligible sample for this study will be identified through the electronic medical record (EMR) at both sites and will include adults 50 to 85 years of age. Eligibility criteria include:

- *One or more encounters in the prior 12 months to a general internal medicine, family medicine, cardiology, or nephrology clinic at either the University of Iowa or Duke;*
- *Diagnosis of hypertension on the EMR active problem list or diagnosis of hypertension captured on an encounter in the prior 24 months;*
- *One or more blood pressure measurements recorded in the prior 12 months;*
- *Blood pressure at most recent clinic note is less than 150/95 mm Hg;*
- *Currently taking one or more non-diuretic once daily antihypertensive medications;*

- *Stable antihypertensive drug regimen, as indicated by the absence of medication changes within one month prior to study;*
- *One or more of the following comorbidities: diabetes, hyperlipidemia, ischemic heart disease, congestive heart failure, cerebral vascular disease, renal insufficiency, or peripheral vascular disease on the EMR active problem list or on the diagnoses recorded on two or more encounters in the prior 24 months*
- *Prescriptions for one or more once-daily antihypertensive medications from the following classes: beta blockers, ACE inhibitors, angiotensin II receptor blockers (ARBs) or calcium channel blockers, alpha blockers or prescriptions for once daily clonidine or reserpine.*

Potentially eligible subjects will be excluded for the following reasons:

- *Presence of a serious comorbidity that would decrease life expectancy independent of CV disease (metastatic cancer, cirrhosis or hepatic insufficiency [as identified from a problem list or a recent total bilirubin > 2.5 mg/dl], dementia, or severe pulmonary disease requiring home oxygen therapy).*
- *Prior history of ischemic optic neuropathy, open angle glaucoma, or visual loss. ,*
- *Currently taking one or more antihypertensive medications in the evening or at bedtime.*
- *Employed in a job requiring night shifts (due to the impact on circadian blood pressure patterns).*
- *Expressed intent to relocate to another area and/or to transfer care to another healthcare system.*

Subject Recruitment and Randomization: Prior to study implementation, the investigators will review the study protocol with physicians in the relevant clinics at both sites. The physician engagement activities will ensure that the involved clinical services approve of the study protocol. Subject recruitment and randomization will involve a number of discrete steps.

1. Eligible subjects will be identified from information in the electronic medical record (EMR) (and/or a clinical research data warehouse that includes EMR data) at each institution.

2. The patients identified in Step 1 will be sent an initial packet including a letter describing the trial and informing them of their eligibility.

3. The letter will include a weblink to a secure portal with an online interactive multi-media informed consent module through which patients will be informed of the potential risks and benefits of participating in the study and what will be required if they elected to participate with regard to providing follow-up information over the course of the study. In addition to obtaining consent, the web module will collect the following additional information:
   - *information about study exclusion criteria; and*
   - *a baseline study questionnaire, including questions to verify understanding of study procedures and information from the EMR about current antihypertensive and/or CV medications that patients will be asked to review and correct if their medication regimen was different than what was indicated in the EMR (including medications that the patient believes he/she is not taking and medications not listed that the patient believes he/she is taking for BP control or for heart or circulation problems).*

4. The introductory letter will also include a packet of material containing the same information that will be provided through the online informed consent module and the baseline questionnaire for patients who do not have access to a computer and/or who prefer not to provide information through the study web portal. Patients preferring to respond by mail will be provided a stamped self-addressed return envelope. To be comparable with the online module, the returned material will include a "checkbox" indicating that the subject was agreeing to participate in the study and understood that their return of the study material indicated their informed consent.

5. For both groups, consent will not be documented by collection of a signed witnessed consent form.

6. Information obtained through the online module and the returned questionnaires will be screened to identify patients who are not eligible, based on the exclusion criteria. In addition, differences that are found between EMR medication regimens and patient-reported regimens will be conveyed to patients' physicians.

7. Subjects who did not respond to the initial letter and packet of information will be sent a limited number of reminder mailings. Subjects who didn't respond to the letters will be provided a brochure about the study by their physician at their next clinic visit.

8. Individuals who do not meet the additional exclusion criteria will be informed by mail that they were not eligible to participate for the reasons noted on their returned material. All other individuals will then be randomized to either nighttime dosing or to continue their daytime dosing of antihypertensive medications. Patients will be randomized in a 1:1 ratio to the two groups. Randomization will be stratified by study site (UIHC or Duke) and whether the patient has diabetes (because diabetic patients have lower target BPs and tend to have higher nighttime BP).

9. Patients randomized to the nighttime dosing regimen will receive instructions by mail and/or email to take all once-daily medications in the following classes at bedtime: beta blockers, ACE inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, alpha blockers, and other centrally acting agents (e.g., clonidine, reserpine). The instructions will be customized for each patient based on the most up-to-date medication list available. Physicians will also be notified of the specific medication changes. Patients randomized to the control group will be instructed to continue to take their once-daily antihypertensives at their current dosing times.

10. The study will enroll a total of 6000 patients, including 3000 patients at each site, over a 9-12 month period.

Data Collection: Study endpoints will be collected from: (1) the EMR; (2) a secure password-protected web-based personal health record or mailed questionnaires; (3) Medicare claims data for Medicare beneficiaries; (4) hospital discharge summaries for patients who are not Medicare beneficiaries; (5) state death certificate files; and (6) the National Death Index.

Information will be obtained from patients on a semi-annual basis. Patients will be sent a mail or email reminder to log in to the personal health record at the appropriate intervals. Patients who are unable to access the Internet will be sent mailed questionnaires.

The primary endpoint will include the occurrence of one or more CV events for which elevated BP is a primary contributing factor, including: 1) CV death; 2) hospital admissions for acute myocardial infarction (AMI), stroke, acute coronary syndromes, or congestive heart failure (CHF), based on the principal diagnosis; and 3) operative or percutaneous procedures for coronary, cerebral, or peripheral revascularization.

Endpoints will be determined from information in the EMR for events that occur within the University of Iowa or Duke healthcare systems. Events that patients report through the personal health record or IVR interviews will be verified using two approaches. For patients with Medicare, the events will be corroborated using Medicare claims data. For patients with other forms of health insurance, the discharge summary or face sheet from the encounter will be requested from the relevant hospital. State death certificate records will be used to determine cause of death for patients who have died. The National Death Index (NDI) will be used to search for information on patients who are lost to follow-up.

Secondary study endpoints include the following:

- *BPs routinely obtained in outpatient clinics and captured in the EMR (although we do not expect clinic BPs to differ between intervention and control groups;*
- *Self-reported medication adherence, as measured by a standardized instrument such as the 4-item Morisky self-reported adherence or the 8-item Medication Adherence Subscale of the Hill-Bone Blood Pressure Therapy Compliance Scale;*
- *health-related quality of life, as measured by a standardized instrument such as the EuroQOL 5-item health state classification and feeling thermometer; and*
- *inpatient hospitalizations and ambulatory procedures.*

In addition to the above endpoints, at each survey interval, patients will be asked about the time of day that each antihypertensive was taken. Lastly, several baseline covariates will be collected and will be used to assess balance achieved through randomization include. These covariates include: age, gender, race, ethnicity, family history of AMI, current smoking status, body mass index, baseline EMR BP prior to randomization, CV comorbidity (diabetes, ischemic heart disease, cerebral vascular disease, or peripheral vascular disease), hemoglobin A1C (if diabetic), active CV medications, and total, LDL, and HDL cholesterol. All measures with the exception of smoking status will be obtained form the EMR.

Analyses: Analyses will compare primary and secondary endpoints in patients taking nighttime doses of antihypertensive medications (i.e., intervention patients) and patients taking morning doses of all antihypertensives (i.e., control patients). Analyses will use Poisson or negative binomial regression for binary endpoints, including the primary outcome (occurrence of CV events), and linear mixed models for continuous or ordinal endpoints. Analyses will be conducted on an intent-to-treat basis, with comparisons between patients initially randomized to intervention and control groups. Additional analyses will compare patients based on the dosing strategy that patients utilized for a majority of the study period, recognizing that treatment crossover may occur in this pragmatic trial. The analysis will use “pattern mixture” approaches for conducting analyses assuming alternative possible dropout patterns. Analyses will examine trends in the effect of the intervention across dropout times; weighted average of the conditional effects over the distribution of dropout times provides an overall estimate of the intervention effect. The sample size of 6000 patients would provide 80% power to detect a 20% difference in the risk of CV endpoints in intervention and control groups, assuming an event rate of roughly 5% per year of follow. This sample size also allows for a 10% attrition rate during each year.

Procedures for Informed Consent: The study will obtain informed consent from participants using an online platform or consent letter that will provide identical information.

A waiver of documentation of consent (i.e., waiver of the requirement for a witnessed signing of the consent form) is requested because: (1) the study involves only minimal risk (see below for the rationale for a minimal risk determination); and (2) the study involves no procedures for which consent is normally required outside of a research context.

We are also requesting a post-consent full waiver of HIPAA authorization. This is because it is not practicable to obtain this authorization without losing the pragmatic nature of the trial (i.e., obtaining such authorization would dramatically reduce enrollment efficiency.

Rationale for a Minimal Risk Determination: We believe that the proposed study poses no more than minimal risk to participants for the reasons articulated below and exposes patients to no greater risk than they would experience from the routine clinical care of their hypertension.

1. The proposed study involves adjustment in the timing of administration of antihypertensive medications that patients are taking, but not in the dose of antihypertensives.
2. The study is largely observing the outcomes that patients experience in the course of their routine care following randomization.
3. Most national guidelines for the treatment of hypertension do not indicate that patients should take medications at a particular time of day. The one exception we are aware of (2013 Standards of Medical Care in Diabetes published by the American Diabetes Association) recommends that that one or more antihypertensive medications be administered at bedtime. In contrast, the 2013 guidelines of the International Society of Nephrology determined that the evidence was not sufficient to recommend for or against nighttime dosing.
4. Our preliminary analysis of pharmacy data from the University of Iowa indicated that a large majority (92%) of prescriptions for once daily antihypertensive medications instruct patients to take the medication once daily (i.e., " q day"), without specifying a particular time of the day (i.e., "q AM", "q PM", or "q HS"). In the absence of specific instructions, patients likely take once-daily medications at different times of the day.
5. Thus, the random assignment of patients to nighttime or morning dosage would mimic in many ways the random nature by which most patients currently time the dosing of their antihypertensive medications.
6. Data collection for the study will involve review of patients' EMR data that were collected during routine health care encounters, review of other extant data sources (e.g., Medicare claims data), and collection of patient survey data through a secure web-based personal health record or mailed questionnaire. Survey data will include information about CV hospitalizations that occur outside of the University of Iowa and Duke, timing of medication dosing, self-reported medication adherence, and health related quality of life. None of this information would be considered sensitive.
7. Physicians have an opportunity to request a patient be excluded if they perceive safety concerns for an individual patient.

Safety Monitoring: Although the study meets criteria for minimal risk, the study is not restricted to patients with proven elevated nighttime blood pressure (i.e. "nondippers"), which is not typically determined in the routine clinical management of hypertension. Thus, it is possible that nocturnal dosing may induce symptomatic hypotensive events. While a Cochrane Collaboration

review found no significant difference in adverse events between morning dosing of antihypertensives compared to dosing in the evening or at bedtime, a prior observational study found that nocturnal hypotension was associated with rare ocular vascular disorders such as ischemic optic neuropathy. A second observational study of 88 patients found an association between nighttime dosing of antihypertensive medications and visual field loss in patients with open-angle glaucoma.

Thus, the current study will exclude patients with a known history of ischemic optic neuropathy and open angle glaucoma. In addition, the study will collect survey information on self-reported episodes of vision loss . This information will be reviewed by a Data Safety Monitoring Board that will be constituted on the basis of NIH rules. The DSMB will develop an operational plan during the first six months of the study. The plan will include conflict of interest disclosure statements for each member, frequency and location of meetings, policies and procedures and dissemination of meeting materials, notification of NIH staff, data to be reviewed and procedures for evaluating data and reporting findings.

Justification for a Health Insurance Portability and Accountability Act (HIPAA) Waiver:
The University of Iowa IRB has granted the investigators a waiver of authorization to search the EMR to identify eligible patients and a post-consent full waiver of HIPAA authorization.

The waiver for identifying eligible patients was granted based on the IRB's determination that the study satisfied the following criteria:

- *the use or disclosure of protected health information to identify patients involves no more than a minimal risk to the privacy of individuals, based on: (1) an adequate plan to protect the identifiers from improper use and disclosure and to destroy the identifiers at the earliest opportunity consistent with conduct of the research; and (2) adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;*
- *patients could not practicably identified without the waiver; and*
- *the research study could not practicably be conducted without access to and use of the protected health information.*

The waiver for post-consent full HIPAA waiver was granted because is it is not practicable to obtain this authorization without losing the pragmatic nature of the trial.