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Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed): Protocol for a prospective, randomised, open-label, blinded end-point pragmatic trial

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Supplementary File 3 - BedMed Social Media Ad.mp4

Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed): Protocol for a prospective, randomised, open-label, blinded end-point pragmatic trial

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Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed): Protocol for a prospective, randomised, open-label, blinded end-point pragmatic trial

ABSTRACT

Introduction: Sleep-time blood pressure correlates more strongly with adverse cardiovascular events than does daytime blood pressure. The BedMed trial evaluates whether bedtime antihypertensive administration, as compared to conventional morning use, reduces major adverse cardiovascular events.

Methods and analysis: DESIGN: Prospective randomised, open-label, blinded end-point trial. PARTICIPANTS: Hypertensive primary care patients using blood pressure lowering medication and free from glaucoma. SETTING: Community primary care providers in 5 Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario) are mailing invitations to their eligible patients. Social media campaigns (Google, Facebook) are additionally running in the same provinces. INTERVENTION: Consenting participants are allocated via central randomisation to bedtime vs morning use of all antihypertensives. FOLLOW-UP: 1) Telephone or e-mail questionnaire at 1-week, 6-weeks, 6-months, and every 6-months thereafter, and 2) accessing linked governmental health-care databases tracking hospital and community medical services. PRIMARY OUTCOME: Composite of all-cause death, or hospitalization for myocardial infarction / acute-coronary syndrome, stroke, or congestive heart failure. SECONDARY OUTCOMES: Each primary outcome element on its own, all-cause hospitalization or emergency department visit, long-term care admission, non-vertebral fracture, new or worsening glaucoma, 18-month cognitive decline from baseline (via Short Blessed Test). SELECT OTHER OUTCOMES: Self-reported nocturia burden at 6-weeks and 6-months (no, minor, or major burden), 1-year self-reported overall health score (EQ-5D-5L), self-reported falls, total cost of care (acute and community over study duration), and mean sleep-time systolic blood pressure after 6-months (via 24-hour monitor in a subset of 302 sequential participants). PRIMARY OUTCOME ANALYSIS: Cox-Proportional Hazards Survival Analysis. SAMPLE SIZE: The trial will continue until a projected 254 primary outcome events have occurred. CURRENT STATUS: Enrollment ongoing (3,227 randomized to date).

Ethics and Dissemination: BedMed has ethics approval from 6 research ethics review boards and will publish results in a peer-reviewed journal.

Trial Registration number: NCT02990663

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Recruiting through primary care providers, having minimal exclusion criteria, and reducing barriers to participation by communicating directly with participants, helps to ensure accurate data collection and good generalizability to primary care populations.
- Beyond an assessment of efficacy, multiple potential harms are being evaluated.
- Members of the public with hypertension are making substantial contributions to study design and conduct through our 10-member patient working group.
- Limitation: If we observe relative risk reductions for the primary outcome that are smaller than 17%, it is unlikely we will be able to declare those differences statistically significant with the planned sample size.

INTRODUCTION

Blood pressure (BP) normally exhibits a circadian rhythm with relatively lower pressures during sleep.[1] Lack of this sleep time "dip" correlates strongly with adverse cardiovascular events such as myocardial infarction (MI), stroke, and congestive heart failure (CHF), and BP correlates most strongly with such events when measured at night (i.e. during sleep).[2-5]

Motivated by such observations, Spanish researchers studied the effect of taking BP medication at bedtime, when the effect on nighttime BP would be greatest, versus conventional morning use.[6] The results of this randomized controlled trial (RCT), the MAPEC trial, were striking, reporting a 61% relative reduction in a composite of total mortality and cardiovascular morbidity. The same principal investigator has subsequently published another RCT reporting a similar large benefit to bedtime antihypertensives (Hygia).[7] However, calls have been made for independent confirmation of such surprising findings.[8 9]

BedMed is a large community-based RCT intended to replicate a MAPEC-like timing intervention in a hypertensive Canadian primary care population. BedMed randomizes participants to take all existing blood pressure medication (as tolerated) at bedtime, compared to conventional morning use, and tracks mortality and morbidity using regularly collected administrative health claims and participant self-report. This protocol is prepared in accordance with SPIRIT guidelines.[10]

METHODS

Objectives

Main: To determine whether a bedtime versus morning antihypertensive administration time influences mortality or cardiovascular morbidity.
Secondary: To determine whether a bedtime versus morning antihypertensive administration time adversely influences cognitive ability, visual acuity, risk of falls and fractures, or nocturia.

Trial Design

BedMed is a Phase 4 pragmatic clinical trial with an adaptive, event-driven, parallel enrollment, PROBE (prospective randomized open blinded-endpoint) design.[11] Here,

"adaptive" refers to the potential future exclusion of new participants whose only antihypertensive is a diuretic, if adherence to bedtime allocation in such individuals is poor (see *Adherence to bedtime diuretics sub-study*).

Recruitment began in March 2017, and the trial will continue until 254 primary outcome events have been observed (the number of events in MAPEC). Based on current ongoing enrollment (3,227), and an observed 2.0% annual event rate, final analysis is anticipated in early 2023.

Setting and Recruitment

Pragmatic Trials Collaborative

Most recruitment (~78%) is through community family physicians (>400) who own and operate independent clinics. These providers are spread widely across 5 participating provinces (Alberta, British Columbia, Manitoba, Saskatchewan, Ontario), but affiliated with the Pragmatic Trials Collaborative (www.PragmaticTrials.ca), a practice-based research network which is coordinating the trial. Nurse practitioners with their own practice panel (7 at present) are also participating.

Each clinic uses their own electronic medical record (EMR) to create a list of hypertensive patients and the primary care provider (PCP) removes those they consider palliative, or incapable of informed consent. The study team then provides the clinic with recruitment envelopes, which the clinic addresses and mails to these potentially eligible patients. The envelopes contain 1) a letter of introduction from the patient's PCP, and 2) a pamphlet describing the trial and providing contact information (online supplementary files 1&2). Interested patients call the study team where research assistants answer questions, determine eligibility, and obtain consent either in real-time via e-mail (>80% of participants opt for this) or by letter-mail for handwritten consents.

Social Media

All hypertensive residents of our 5 participating provinces are eligible for BedMed, whether or not their PCP is involved. While this can happen through word-of-mouth, a social media campaign (Google & Facebook Ads) is being employed to inform the public about the trial. These Ads (online supplementary file 3) direct individuals to a landing page (https://bedmedstudy.ca/) providing trial information, a check of eligibility, and telephone / e-mail contact information for the study team.

Trial Population

Inclusion Criteria

- Clinician diagnosis of hypertension (by any physician or nurse practitioner)
- Taking ≥1 BP-lowering medication once daily, or PCP willing to convert ≥1 BP-lowering medication to once daily
- ≥18 years of age
- Community-dwelling (i.e., not residing in a nursing home)

Exclusion Criteria

- Considered palliative or unable to consent by PCP
- Sleep disrupting shift work (more than 3 shifts/month during participant's regular sleeping hours)

- Glaucoma diagnosis, or using glaucoma medication (safety exclusion: nocturnal hypotension, which bedtime BP meds could worsen, has been associated with optic neuropathy in glaucoma patients).[12-14]

Randomization and Allocation

Consenting participants receive their random allocation to bedtime versus morning BP medications while dialoguing directly with a research assistant who has no preceding clinical interactions with that participant and who obtains their allocation (stratifying by province with random blocks of 10 or 12) from the central REDCap[15] server's randomization module, ensuring irreversible & concealed allocation.

Intervention

Treatment

Use of all once-daily BP-lowering medication(s) at bedtime.

Control

Use of all once-daily BP-lowering medication(s) in the morning.

Implementation

Participants choose between having their PCP assist their timing change (using the PCP's judgement on how and what to change), or being assisted by the research assistant with whom they are dialoging. Only PCPs assist with timing changes if participants describe heart disease, or if their BP medications include Tiazac XC or Diltiazem XC (which have delayed-release kinetics), furosemide, isosorbide mononitrate/dinitrate, or alpha blockers (medications whose timing decision may be more complicated). PCPs can convert twice daily medications to once daily alternatives, but this is not actively promoted.

Research assistants only change the timing of once daily medications, with a limit of one medication change per week (using the order Angiotensin converting enzyme inhibitors (ACEI) / angiotensin receptor blockers (ARB), calcium channel blockers (CCB), beta-blockers (BB), diuretic-containing medications, other). They advise participants to make the switch by delaying the next dose until the allocated time, and continuing that schedule. If bedtime use is problematic, they ask participants to try taking their BP meds with dinner. If morning use is problematic, they ask participants to try taking it with lunch. Participants with regularly reversed sleep schedules (i.e., sleeping during the day) take their BP medications when they get up, or when they go to bed, not according to the time of day.

At each follow-up, participants are asked about medication timing, and encouraged to adhere to allocation. No devices to separately monitor adherence are in use. As a memory aid, all participants are advised to place pill bottles near objects they use when transitioning to or from bed (e.g., toothbrush, denture case, alarm clock), or to use an AM/PM dosette.

Follow-up and Data Management

Research Assistant Interactions

All participant interactions with research assistants are unblinded and recorded directly into the University of Alberta's implementation of the REDCap data management platform.[15] The following interactions are scheduled relative to the date of randomization.

Baseline: Telephone interaction to 1) obtain baseline characteristics, 2) conduct the Short-Blessed Test to assess cognitive function, and 3) randomize the participant. May be split over multiple interactions (participant's choice).
1-Week: Telephone interaction to troubleshoot timing change problems and encourage adherence.
6-Weeks: Telephone interaction to gather information on adverse effects and outcomes.
6-Months: Telephone interaction, or REDCap e-mail survey (participant's choice), to gather adverse effects and outcomes.
12-Months: Same as 6-months + EQ-5D-5L quality of life survey.
18-months: Same as 6-months + follow-up Short Blessed Test (but available by telephone only).
Every 6-months thereafter: Same as 6-months.

Administrative Claims Data

All Canadian provinces have publicly funded healthcare systems and maintain linkable healthcare databases tracking medical services rendered during health care interactions for all their residents. This includes community physician services and diagnoses (whether by specialists or generalists), prescriptions dispensed, reasons for hospitalization, and vital statistics (i.e. mortality). BedMed participants consent to these datasets being accessed and analyzed to support the trial, providing both outcomes and baseline characteristics.

24-Hour Ambulatory Blood Pressure Monitoring

To assess between-group differences in achieved BP, we intended to carry out 24-hour BP monitoring on a consecutive sample of 151 intervention & 151 control subjects residing in 6 Alberta communities at 6-months (providing 90% power to detect the difference in overnight systolic BP observed in MAPEC). Although we will be able to reach our intended sample size, the timing of these measurements has been delayed by several months for many participants due to the COVID-19 pandemic and other logistic hurdles. Participants are provided a copy of their test results, which are also faxed (if they consent) to their PCP.

Outcomes

Unless otherwise stated, all outcomes are recorded over the duration of the study.

Primary:

Major adverse cardiovascular events (MACE)

- Defined as first occurrence of either all-cause death or hospital admission / emergency department (ED) visit for acute coronary syndrome / myocardial infarction (MI), stroke, or congestive heart failure (CHF).

Secondary:

1. Each component of the primary outcome individually
2. All-cause hospitalization / ED visit
3. Long-term care (LTC) admission (i.e., to nursing home or assisted living facility)
4. Non-vertebral fracture
5. New or worsening glaucoma
    - Defined as first occurrence of either first-ever glaucoma diagnosis, first-ever glaucoma treatment, or first-ever glaucoma surgery (Note: despite our excluding participants with self-reported glaucoma, participants could conceivably have a baseline glaucoma claims diagnosis without knowing it. Such individuals can contribute to new glaucoma treatment, or new glaucoma surgery, but not to new glaucoma diagnosis, as it would not be a "first-ever" diagnosis).
6. Cognitive decline at 18 months
    - Defined as ≥ 2-point worsening in cognitive performance compared to baseline, as measured by the Short Blessed Test

Supplementary Safety Outcomes:

1. Vision
    a. Vision self-reported as "much worse" compared to the last follow-up at any point, or "slightly worse" than the last follow-up, on 2 or more occasions (Note: vision is reported, every 6-months, as either "unchanged", "slightly worse", or "much worse" than the last follow-up)
2. Cognition
    a. New "impairment consistent with dementia" at 18-months (Short Blessed Test newly ≥ 10) or new diagnosis of dementia at any point during follow-up
3. Symptomatic Hypotension
    a. Self-reported light-headedness, or feeling faint without loss of consciousness, in the prior month
    b. Self-reported fainting (loss of consciousness) in the prior month
    c. Self-reported falling in the prior month
    d. Hip fracture
    (Note: at 6-weeks, 6-months, and every 6-months thereafter, participants are separately asked whether they have felt lightheaded, fainted, or fallen in the last month)
4. Nocturia
    a. Self-reported change from baseline in the number of overnight urinations per week (at 6-weeks and 6-months)
    b. Self-reported nocturia burden in the prior month, recorded as no nocturia, or nocturia that is "no problem", "minor problem", or "major problem" (at 6-weeks and 6-months)

Cost:

1. Acute care costs (estimated from each hospital admission's resource intensity weight and length of stay)*
2. Total cost of care (acute care costs + medication costs + physician billings)*

*All cost measures are derived entirely from administrative claims data, and not from self-report. If claims data is not available for some participants, they will be excluded from this analysis.

Exploratory:

1. Self-reported overall health score (via EQ-5D-5L) at 12-months

Process:

1. Proportion of BP medication doses taken at the allocated time at 6-months (twice daily medications being considered as ½ dose in the AM and ½ dose in the PM for this calculation)
2. Sleep-time systolic blood pressure after 6-months (consecutive sample of 302 Alberta residents)

End-point Adjudication

Administrative data

Administrative data derived outcomes will be identified using established and validated coding algorithms.[16-18] Physicians providing these diagnoses are generally acute care providers (emergency physicians, hospitalists, specialists) who are unaffiliated with the BedMed trial.

Adjudication panel

Most primary and secondary outcomes are being collected in duplicate (i.e. by administrative claims and participant self-reporting of the same events). This information will be reviewed by a panel of 3 physicians blinded to allocation. If the panel deems both data sources to be concordant, those events will be considered valid, and the event date in administrative claims will be used. When events are discordant (e.g. only present in one of the two data sources, or differing in diagnoses) the participant's PCP will be contacted to provide the adjudication panel with more information, including their opinion on whether the event occurred. The exception is all-cause hospitalization, where we will preferentially use only administrative claims data, believing it to be highly accurate, and being more challenging to confirm with PCPs given the high number of such occurrences.

Sample Size Determination

BedMed is event-driven, and originally sought to observe 406 primary outcome events before stopping. We chose this event target believing this was the largest number of events a network our size could detect with 3-years of observation. However, because patients receiving recruitment packages are less likely to enrol than expected (projected enrolment 12%, actual enrolment 6%), and because the overall annual event rate is at

the low end of expectations (2.0%), we have reduced our event target for stopping to 254, which matches the number of events observed in MAPEC. Assuming meaningful covariates, 254 events should allow observed risk ratio differences of ~17% or larger to be declared statistically significant. To estimate when this number of events has likely been reached, Alberta Health Services is tracking the primary outcome event rate in Alberta BedMed participants on a quarterly basis. We then extrapolate this to the trial as a whole using the number of participant years of observation. At the current rate of events and enrolment, BedMed should conduct its final analysis in early 2023.

Statistical Analysis

Intension-to-treat assumptions

Loss to follow-up: If participants are lost to follow-up, but medical services continue to be recorded within administrative claims data, we will treat them as though they were still active in the study and censor survival data on the last date of medical services, or indication of death, whichever occurs later. If no such medical claims exist, data will be censored on the last day of successful telephone or e-mail follow-up.

Withdrawal: Participants withdrawing from the study are asked to allow us to continue to follow their administrative claims data. If they agree (as the majority do), we will continue to use administrative claims outcomes for those individuals as per the loss-to-follow-up description. If they do not agree, survival data will be censored on the date of withdrawal.

Missing data: For each analysis, we will either impute a value from subsequent or preceding follow-up visits, or exclude a participant from analysis. How we deal with missing data will be specific to each analysis and prioritize either minimizing bias, or being conservative when bias is unavoidable (i.e. biasing against benefit, and towards harm, for the intervention).

Nonadherence: Nonadherence to allocation will not exclude participants from analysis unless the outcome of interest is a harm that only makes sense to assess while on-treatment (e.g. assessing how nocturia differs in diuretic users switched to bedtime, compared to nondiuretic users making the same switch).

Selecting regression covariates

Analyses of dichotomous outcomes will use a maximum of 1 covariate per 10 outcomes, and analyses of continuous outcomes will use a maximum of 1 covariate per 20 randomized subjects. The covariate list for each analysis is predefined in table 1, and all are measured at baseline. We will always use the maximum number of covariates possible, selected in the order given (i.e. we will not undertake stepwise addition or subtraction).

Table 1 Analysis Plan

Outcome	Method	Covariates
Primary		
Major adverse cardiovascular events	Cox Proportional Hazards	Age, sex, frailty score*, current smoker, number of non-BP medications, Overall Health Score†, prior 6-months hospitalization, CHF, diabetes, CAD, stroke or TIA, CKD‡, dialysis, BMI > 30, BMI < 18.5, sleep apnea, exercise days§, province (4 variables)
Secondary		
All-cause mortality	Cox Proportional Hazards	Age, frailty score*, number of non-BP medications, Overall Health Score†, prior 6-months hospitalization, CHF, diabetes, CAD, CKD‡
Hospitalisation for stroke Hospitalisation for MI/ACS	Cox Proportional Hazards	Age, stroke or TIA, CAD, current smoker, sex, diabetes, exercise days§, BMI > 35
Hospitalisation for CHF	Cox Proportional Hazards	Age, CHF, CAD, diabetes, CKD‡
All-cause hospitalisation / ED visit	Cox Proportional Hazards	Age, sex, frailty score*, current smoker, number of non-BP medications, Overall Health Score†, prior 6-months hospitalization, CHF, diabetes, CAD, stroke, TIA, Short Blessed Test score, CKD‡, dialysis, BMI >35, BMI <18.5, COPD, province
Non-vertebral fracture	Cox Proportional Hazards	Age, Overall Health Score†, BMI, number of non-BP medications, frailty score*, stroke (not TIA), sex, CHF, exercise days§, TIA, prior 6-months hospitalization
LTC admission	Cox Proportional Hazards	Age ≥ 80, Short Blessed Test score, frailty score*
New or worsening glaucoma	Cox Proportional Hazards	Age, diabetes, CAD or stroke or TIA, CHF, COPD, CKD‡, sleep apnea, BMI, exercise days§, Short Blessed Test Score
18-month cognitive decline	Poisson Regression	Age, sex, frailty score, number of non-BP medications, Overall Health Score†, CHF, stroke, TIA, COPD, BMI, exercise days§, province
Supplementary Safety		

Worsening of vision	Poisson Regression	Age, diabetes, CAD or stroke or TIA, CHF, COPD, CKD‡, Overall Health Score†
New impairment consistent with dementia	Poisson Regression	Age, sex, frailty score, number of non-BP medications, Overall Health Score†, CHF, stroke, TIA, COPD, BMI, exercise days§, province
Light-headedness in last Month Syncope in last month Falling in last month	Poisson Regression	Age, frailty score, number of non-BP medications, Overall Health Score†, CHF, stroke, TIA, sex, exercise days§, BMI, province
Hip fracture	Cox Proportional Hazards	Age, Overall Health Score†, BMI, number of non-BP meds, frailty score, stroke (not TIA), sex, CHF, exercise days§
Change in overnight urinations / week	Mann-Whitney or t-test	N/A
Nocturia a major burden	Fisher's Exact Test	N/A
Cost		
Acute care costs Total cost of care	Multiple Linear Regression	Age, sex, frailty score, current smoker, number of non-BP medications, Overall Health Score†, prior 6-months hospitalization, CHF, diabetes, CAD, stroke, TIA, Short Blessed Test score, CKD‡, dialysis, BMI > 35, BMI < 18.5, COPD, province
Exploratory		
Overall Health Score	Multiple Linear Regression	Age, sex, frailty score, current smoker, number of non-BP medications, prior 6-months hospitalization, CHF, diabetes, CAD, stroke, TIA, Short Blessed Test score, CKD‡, dialysis, BMI > 35, BMI < 18.5, COPD, province
*Score on physical frailty subscale of the Tilburg questionnaire; continuous 0-8 †From EQ-5D-5L; continuous 0-100 ‡Not including dialysis §"How many days in the past week have you exercised for 30 minutes or more, vigorously enough to raise your breathing rate?"; continuous 0-7		

Subgroup Analyses

We will repeat the primary outcome analysis for those with and without the following baseline characteristics: Age ≥ 75, sex, physically frail (score ≥3 on physical frailty subscale of the Tilburg questionnaire), polypharmacy (≥ 5 medications), Overall Health

Score ≤ 75, resistant hypertension (≥3 BP-lowering medications), CHF, diabetes, CAD, stroke or TIA, sleep apnea, chronic kidney disease (with or without dialysis), sedentary (exercise 0 days per week).

Sensitivity Analyses

We will present, according to treatment group, the baseline characteristics of those whose data was censored due to withdrawal or loss to follow-up, and compare these characteristics to those who weren't censored in this way using Fisher's Exact Test.

Patient and Public Involvement

Patient Working Group

BedMed has a 10-member patient working group helping to guide the trial. The group began meeting in 2016 prior to any recruitment to review and revise 1) recruitment materials, 2) phrasing of questions, and 3) outcomes to be collected through self-report. Working group members have also assisted in hiring research staff, in further revising recruitment materials mid-study to increase enrollment, and in constructing a social media campaign. We anticipate working with our patient partners to make decisions, if needed, following our interim analysis in spring 2022, to interpret final results in 2023, and to help disseminate findings.

Patient Driven Sub-Study

The draft BedMed protocol was presented in 2015 to a group of ~25 seniors prior to study registration and grant application. Feedback from this presentation resulted in the sub-study to determine whether diuretics can be taken at bedtime without troublesome nocturia threatening adherence.

SUBSTUDIES

Adherence to bedtime diuretics

Diuretics are widely believed to promote nocturia if taken later in the day, and are typically recommended for morning use only as a result.[19 20] However this recommendation is largely opinion based. Whether or not participants will adhere to bedtime diuretic dosing is unclear. To determine this, we will examine, at 6-weeks and 6-months, self-reported nocturia burden (no, minor, major), number of overnight urinations per week, and adherence to bedtime allocation, in the first 203 AM diuretic-only users randomized to bedtime and being followed for 6-months, and compare this to all those switching a single AM non-diuretic to bedtime during the same period. Assuming equal numbers in both groups, and 75% adherence to allocation time in non-diuretic users, this should provide 90% power to detect a 20% relative reduction in adherence in diuretic users.

Volunteer bias

Concern has been raised that randomized trial participants are poorly representative of real world populations.[21-25] We will examine, using Alberta administrative claims, how baseline characteristics and preventive health behaviours differ in 4 distinct Alberta populations: 1) All BedMed-eligible patients attached to participating PCPs, 2) BedMed

participants who enrolled after a PCP-letter, 3) BedMed participants responding to social media advertisement, and 4) All BedMed-eligible Albertans. We will compare 1) Demographics (age, sex, postal code derived deprivation index, rural residence), 2) Comorbidities (diabetes, CAD, stroke, osteoarthritis, CHF, COPD, dementia, hip fracture, CKD, dialysis, hospital admission in prior 6-months plus accompanying length of stay and resource intensity weighting), 3) Preventive therapies (prior 3-years shingles vaccine, statin use, osteoporosis medication), 4) Screening tests (prior 3-years PAP smear, colonoscopy, mammogram, FIT testing, PSA testing), and 5) clinical outcomes post-randomization (death, BedMed primary outcome, all-cause hospitalization or ED visit along with length of stay and resource intensity weighting, nursing home admission, new glaucoma diagnosis / treatment / surgery, hip fracture, and new dementia diagnosis). To substitute for the date of randomization we will use the date of PCP mailout for BedMed-eligible PCP-attached patients, and the date providing the same mean number of years of observation for all BedMed-eligible Albertans.

"Nudge Sentence" Recruitment Strategy

Two years into recruiting, we hypothesized that altering the physician letter of introduction to state that a large number of people were already participating might improve the response rate. Online supplemental file 4 shows the new physician letter. The added wording (in purple here) states: "*This study already has over 1,700 Canadians with high blood pressure taking part. If you too choose to participate…*". As of March 2019, providers are given an equal number of both recruitment envelopes, sealed and shuffled together, for them to address and mail. Both letters are otherwise identical save for the date on the letter (odd numbered for the new version, even numbered for the original). Participants calling to enrol are asked the date on the letter to determine which version they are responding to, allowing a pseudorandom assessment of the ability of such a "nudge" sentence to improve enrolment. This sub-study will continue until recruitment ends, with sample size determined by the number of letters mailed during that interval.

EARLY STOPPING

Independent Data Safety Monitoring Board (IDSMB)

Outcomes from all provinces will be collected at the end of 2021. Each analysis described in this protocol will then be carried out, and presented to the Cochrane Hypertension Working Group (our IDSMB).

Stopping Rules: If p is ≤ 0.001 for primary outcome benefit (the Haybittle-Peto boundary),[26] or if p is ≤ 0.05 for harm, the IDSMB will apply clinical judgement and decide whether to recommend to the principal investigator that the trial be stopped early.

Competing Studies

A trial similar to ours, the United Kingdom's TIME trial,[27] will likely release results ahead of BedMed. If convincing benefit is demonstrated, we will ask our IDSMB to weigh this new information and consider again whether early stopping is recommended.

Our group is also conducting a separate RCT of the same antihypertensive timing intervention in hypertensive long-term care residents (BedMed-Frail).[28] As both trials share the same IDSMB, interim data from both trials could be weighed in early stopping discussions for either trial.

DISSEMINATION

Results will be published in a peer-reviewed journal, and summarized in knowledge translation vehicles targeted at PCPs, and the general public. We will also invite trial participants to a results webinar where they can directly pose questions to the principal investigator.

DISCUSSION

By working with volunteer primary care providers, and drawing trial outcomes from usual care administrative claims data, BedMed's design is low-cost, pragmatic, and minimally disruptive of provider workflow. The use of research assistants to guide participants through all stages of the trial further helps to ensure physical and cognitive barriers to participation are minimized so that a representative population can be enrolled, and so that outcomes will be accurately recorded.

We anticipate being able to validate previous work suggesting mortality and cardiovascular morbidity can be reduced if antihypertensive medications are taken at bedtime, rather than in the morning. And we anticipate being able to add new information as to whether bedtime antihypertensives might adversely affect visual acuity, cognition, falls and fractures, or nocturia.

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Authors contributions

BedMed was conceived and designed by SRG with input on specific design elements from the other authors. SRG and LSF wrote the draft manuscript, which was circulated among all authors for critical comments.

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Competing Interests

All authors declare no competing interests related to the submitted work.

Ethics Approvals

BedMed has approval from 7 university ethics boards in 5 Canadian provinces, including University of Alberta (Pro00045958), University of Calgary (REB17-1887), University of Manitoba (HS20852 [B2017:08]), University of British Columbia (H21-00523), University of Saskatchewan (1421), University of Toronto (00038892), and McMaster University (13092).

Data Sharing

An anonymized participant level dataset containing most baseline characteristics, all analytic covariates, and all trial outcomes will be freely available on the Pragmatic Trials Collaborative website (www.PragmaticTrials.ca) upon publication of the final analysis.

Dr. John/Jane Doe
Family Medicine Clinic Name
Street Address
City, Province, Postal Code
PHONE XXX-XXX-XXXX| FAX: XXX-XXX-XXXX

Today's Date

To my patients,

Our office is participating in a national blood pressure study led by the University of Alberta. We are sending this letter to all our patients with high blood pressure as an invitation to participate.

Research suggests that the ability of blood pressure pills to reduce heart attack and stroke may vary by 50% or more depending on the time of day those medicines are taken. This new study will help us to understand if altering the timing of blood pressure medicine can be used to better prevent heart attack and stroke.

The study involves randomly assigning participants to either take at least one of their current blood pressure medications either in the morning, or in the evening. Health outcomes would then be followed for up to 3 years.

If you choose to participate, our office will assist you in making and monitoring any medication changes that might be required. We believe this is an important study, but please know that your participation is voluntary. Whether or not you participate in no way affects our relationship.

For more information or to participate in the study, please call:
Toll free 1-844-492-7570
(7am-5pm Alberta time)

Email: bedmed@ualberta.ca
Website: www.pragmatictrials.ca/bedmed

Sincerely,

John or Jane Doe MD

BedMed

Pragmatic Trials Collaborative
Measuring What Matters

UNIVERSITY OF ALBERTA

The BedMed Study

Study Email Address: BedMed@ualberta.ca
Principal Investigator: Dr. Scott Garrison
Study Coordinator: Janis Cole

Toll Free Phone: 1-844-492-7570
Phone Number: (587) 785-3012
Phone Number: (780) 492-1602

Research suggests it might be possible to improve health outcomes for people living with high blood pressure. With your help, we can find out.

Why is this study being conducted?

For those with high blood pressure, medications reduce the risk of heart attack and stroke. How effective these medications are may depend on the time of day they're taken. A European study suggests that taking blood pressure pills at bedtime, instead of in the morning, may reduce heart attacks and strokes by more than 50%. The BedMed Study is designed to determine if this is true.

Where will this study take place?

Wherever you are. Initial contact with the study team is by phone. Consent and follow up interviews can be done either by phone or online survey.

What is involved if I participate?

You may be asked to change the time you take your blood pressure medication. You'll be randomly assigned to take those medications (as tolerated) either in the morning or at bedtime for the duration of the study - up to 3 years. If you take medications at both times, you are still eligible to participate.

Which medications you use, and all other decisions regarding changes to these medications, will stay between you and your health care provider. If you need to change back to your original medication timing, you are able to do so. Whether you choose to participate or not will have no impact on your relationship with your healthcare team.

When will the study start?

The study begins after you speak with the study team by phone. Please don't change the time of day that you take your blood pressure medications before talking with your healthcare provider. Participation in this study is voluntary and you may withdraw at any time without having to give a reason.

Call the study team toll free at: **1-844-492-7570** (M-F, 7am – 5pm MST)
Email the study team at: BedMed@ualberta.ca
Visit the study website at: **pragmatictrials.ca/BedMed/**

The study will involve these steps:

1 Call: 1-844-492-7570

Our study staff will talk with you to see if the study is a good fit for you and answer any questions.

2 Consent

Consent can be done through mail or online survey. The study team will also collect medical history questions from you over the phone.

3 Randomization

A) You will be randomly placed into either the morning or evening group. You will record this on the "Medication Worksheet" at the back of this package, along with a list of your blood pressure medications.
B) You might see your health care provider if you need to change the time of one or more medications.

4 Follow-ups

The study team will call you one week later if there is the possibility of medication timing being changed. After this, follow-up interviews are at six weeks, six months, and every six months thereafter until the study is done. Interviews from month six onward are by phone or online survey if you prefer.

What are the Benefits?

One in five adult Albertans has high blood pressure. Whether or not we confirm benefit to bedtime prescribing, your participation will help answer an important question surrounding medications used by millions of people worldwide.

What are the Risks?

Morning Medication use

According to previous research, it's possible that there 's a higher risk of heart attack and stroke for those who take their blood pressure medications in the morning (compared to those who use them at bedtime). We don't know if this is true, which is why we're conducting this study.

Bedtime medication use

There are **no established risks** to using blood pressure pills at bedtime but we're closely watching for three possibilities:

1. Best evidence suggests it's not the case, but certain blood pressure pills might increase the number of overnight trips to the bathroom to urinate.
2. Having lower blood pressure overnight may lead to dizziness and potential for falls and fractures.
3. Lower blood pressures overnight might lead to reduced blood flow to the back of the eye in patients with glaucoma, and this may adversely affect vision. For this reason, those with glaucoma are excluded from participating.

Study Confidentiality

All information you provide is confidential. It will be kept in a locked cabinet in a locked research office or on an encrypted computer that's password protected, and only accessible to study investigators and staff. We will do everything we can to keep this data private. No study-related data that includes your name will ever be released outside of the study doctor's office. We will make every legal effort to make sure that your health information is kept private.

Throughout the study, we will be collecting your health data during our phone interviews with you. We will also use your Personal Health Number (PHN) to link this study data to relevant records from your hospital, emergency room, physician office visits, and pharmacy data. The personal health information that we get from these records will be limited to what is needed for the study. If you leave the study, we will not collect new health information about you, but we will need to keep the data that we have already collected.

After you have completed the study, all of the identifying information (i.e. name and contact information) will be removed and your record will be labeled with a study ID that doesn't resemble your name. Your information will be stored in an encrypted, password protected electronic file. We will keep a separate list (in a locked cabinet) that links your name to the study ID number if it's ever necessary to relink you to your data. We will store this data for a minimum of 5 years after the end of the study. The results of this study will be used for publication, but will not identify any participants in any way. To maximize the value of this study after our analysis is complete, we will make our raw data available over the Internet (with all identifying information removed) so that other research groups can verify our findings and explore questions of their own.

For any concerns about your treatment or rights as a research subject in Alberta, contact the Research Ethics Office, University of Alberta at 780-492-2615 or e-mail them at reoffice@ualberta.ca). These offices have no direct involvement with this project.

Medication Worksheet

Your interviewer will help you fill out this table. Please keep this sheet for your records.

For the duration of the study, my blood pressure medication(s) have been assigned to:

A) Morning *B) Bedtime*

My current medications:

Drug Name	Strength	Number of Tablets (example ½, 1, 2)			
		Morning	Noon	Dinner	Bedtime

Interview Dates: You will have telephone follow-up interviews with our study team at one week, six weeks, six months, and every six months after your initial medication review visit. At month six, you may choose to continue with telephone follow-ups or switch to email. If you choose email follow-ups, your interviewer will provide you with a five-digit code and explain the process.

Online survey access information
(Applicable for online follow-ups)

Five-digit code: _____

Interviewer name: _____

For questions regarding the study or how to use this form please contact us:

Call the study team toll free at: **1-844-492-7570** (M-F, 7am – 5pm MST)

Email the study team at: BedMed@ualberta.ca
Visit the study website at: **pragmatictrials.ca/BedMed/**

Dr. John/Jane Doe
Family Medicine Clinic Name
Street Address
City, Province, Postal Code
PHONE XXX-XXX-XXXX| FAX: XXX-XXX-XXXX

Date (ODD #)

To my patients,

Our office is participating in a national blood pressure study led by the University of Alberta. We are sending this letter to all our patients with high blood pressure as an invitation to participate.

Research suggests that the ability of blood pressure pills to reduce heart attack and stroke may vary by 50% or more depending on the time of day those medicines are taken. This new study will help us to understand if altering the timing of blood pressure medicine can be used to better prevent heart attack and stroke.

The study involves randomly assigning participants to take at least one of their current blood pressure medications either in the morning, or at bedtime. Health outcomes would then be followed for up to 3 years.

This study already has over 1,700 Canadians with high blood pressure taking part. If you too choose to participate, our office will assist you in making and monitoring any medication changes that might be required. We believe this is an important study, but please know that your participation is voluntary. Whether or not you participate in no way affects our relationship.

For more information or to participate in the study, please call:
Toll free 1-844-492-7570
(7am-5pm Alberta time)

Sincerely,

John or Jane Doe MD

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Page	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2	Trial identifier and registry name. If not yet registered, name of intended registry
	-	All items from the World Health Organization Trial Registration Data Set
Protocol version	-	Date and version identifier
Funding	16	Sources and types of financial, material, and other support
Roles and responsibilities	1	Names, affiliations, and roles of protocol contributors
	1	Name and contact information for the trial sponsor
	16	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	8,13	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	3	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	3	Explanation for choice of comparators
Objectives	3	Specific objectives or hypotheses
Trial design	3	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	4	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	4	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	5	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	5	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	5	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	5	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	6	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	6	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	8	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	4,12	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	5	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	5	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	5	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	6,8	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	6,8	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	6	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	9	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	6	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	9	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	12	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	9	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	13	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	13	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	7,13	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	-	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	17	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	-	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	4	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	6	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	17	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	17	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	17	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	-	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	14	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	-	Authorship eligibility guidelines and any intended use of professional writers
	17	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	S1,2, 4	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	-	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed): Protocol for a prospective, randomised, open-label, blinded end-point pragmatic trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-059711.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Jan-2022
Complete List of Authors:	Garrison, Scott; University of Alberta, Family Medicine Kolber, Michael; University of Alberta, Family Medicine Allan, G. Michael; University of Alberta, Family Medicine Bakal, Jeffrey; Alberta Health Services, Provincial Research Data Services Green, Lee ; University of Alberta, Family Medicine Singer , Alexander; University of Manitoba College of Medicine, Family Medicine Trueman, Darryl; BedMed Patient Working Group McAlister, Finlay ; University of Alberta, Medicine Padwal, Raj S ; University of Alberta, Medicine Hill, Michael; University of Calgary, Clinical Neurosciences Manns, Braden; University of Calgary, Nephrology McGrail, Kimberlyn; University of British Columbia, Centre for Health Services and Policy Research O'Neill, Braden; University of Toronto, Family and Community Medicine Greiver, Michelle; University of Toronto, Family and Community Medicine Froentjes, Liesbeth; University of Alberta, Family Medicine Manca, Donna; University of Alberta, Family Medicine Mangin, Dee; McMaster University, Family Medicine Wong, Sabrina T.; University of British Columbia, Centre for Health Services and Policy Research MacLean, Cathy; University of Saskatchewan, Academic Family Medicine Kirkwood, Jessica; University of Alberta, Family Medicine McCracken, Rita; Providence Health Care, Family Medicine; University of British Columbia Faculty of Medicine, Family Practice McCormack, James; University of British Columbia, Faculty of Pharmaceutical Science Norris, Colleen; University of Alberta, Faculty of Nursing Korownyk, Tina ; University of Alberta, Family Medicine
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Hypertension < CARDIOLOGY, CLINICAL PHARMACOLOGY, Cardiology < INTERNAL MEDICINE, PRIMARY CARE, Clinical trials < THERAPEUTICS

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.
Supplementary Video 1 - BedMed Social Media Ad.mp4

Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed): Protocol for a prospective, randomised, open-label, blinded end-point pragmatic trial

Scott R Garrison;[1,2] Michael R Kolber;[1,2] G Michael Allan;[1,2] Jeffrey A Bakal;[3] Lee A Green;[1,2] Alexander G Singer;[4] Darryl R. Trueman;[5] Finlay A McAlister;[6] Raj S Padwal;[6] Michael D. Hill;[7] Braden Manns;[7] Kimberlyn McGrail;[8] Braden G. O'Neill;[9] Michelle Greiver;[9] Liesbeth S Froentjes;[2] Donna P Manca;[2] Dee A Mangin;[10] Sabrina T. Wong;[11] Cathy MacLean;[12] Jessica EM Kirkwood;[1,2] Rita McCracken;[13] James McCormack;[14] Colleen Norris;[15] Christina S Korownyk[1,2]

[1]Pragmatic Trials Collaborative, University of Alberta, Edmonton, Canada; [2]Dept of Family Medicine, University of Alberta, Edmonton, Canada; [3]Provincial Research Data Services, Alberta Health Services, Edmonton, Canada; [4]Dept of Medicine, University of Manitoba, Winnipeg, Canada; [5]Patient Partner, BedMed Patient Working Group, Edmonton, Canada; [6]Dept of Medicine, University of Alberta, Edmonton, Canada; [7]Dept of Medicine, University of Calgary, Calgary, Canada; [8]Centre for Health Services and Policy research, Vancouver, Canada; [9]Dept of Family and Community Medicine, University of Toronto, Toronto, Canada; [10]Family Medicine, McMaster University, Hamilton, Canada; [11]School of Nursing, University of British Columbia, Vancouver, Canada; [12]Academic Family Medicine, University of Saskatchewan, Saskatoon, Canada; [13]Family Practice; [14]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada; [15]Faculty of Nursing, University of Alberta, Edmonton, Canada

WORD COUNT 3,778

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Bedtime versus morning use of antihypertensives for cardiovascular risk reduction (BedMed): Protocol for a prospective, randomised, open-label, blinded end-point pragmatic trial

ABSTRACT

Introduction: Sleep-time blood pressure correlates more strongly with adverse cardiovascular events than does daytime blood pressure. The BedMed trial evaluates whether bedtime antihypertensive administration, as compared to conventional morning use, reduces major adverse cardiovascular events.

Methods and analysis: DESIGN: Prospective randomised, open-label, blinded end-point trial. PARTICIPANTS: Hypertensive primary care patients using blood pressure lowering medication and free from glaucoma. SETTING: Community primary care providers in 5 Canadian provinces (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario) are mailing invitations to their eligible patients. Social media campaigns (Google, Facebook) are additionally running in the same provinces. INTERVENTION: Consenting participants are allocated via central randomisation to bedtime vs morning use of all antihypertensives. FOLLOW-UP: 1) Telephone or e-mail questionnaire at 1-week, 6-weeks, 6-months, and every 6-months thereafter, and 2) accessing linked governmental health-care databases tracking hospital and community medical services. PRIMARY OUTCOME: Composite of all-cause death, or hospitalization for myocardial infarction / acute-coronary syndrome, stroke, or congestive heart failure. SECONDARY OUTCOMES: Each primary outcome element on its own, all-cause hospitalization or emergency department visit, long-term care admission, non-vertebral fracture, new or worsening glaucoma, 18-month cognitive decline from baseline (via Short Blessed Test). SELECT OTHER OUTCOMES: Self-reported nocturia burden at 6-weeks and 6-months (no, minor, or major burden), 1-year self-reported overall health score (EQ-5D-5L), self-reported falls, total cost of care (acute and community over study duration), and mean sleep-time systolic blood pressure after 6-months (via 24-hour monitor in a subset of 302 sequential participants). PRIMARY OUTCOME ANALYSIS: Cox-Proportional Hazards Survival Analysis. SAMPLE SIZE: The trial will continue until a projected 254 primary outcome events have occurred. CURRENT STATUS: Enrollment ongoing (3,227 randomized to date).

Ethics and Dissemination: BedMed has ethics approval from 6 research ethics review boards and will publish results in a peer-reviewed journal.

Trial Registration number: NCT02990663

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Recruiting through primary care providers, having minimal exclusion criteria, and reducing barriers to participation by communicating directly with participants, helps to ensure accurate data collection and good generalizability to primary care populations.
- Beyond an assessment of efficacy, multiple potential harms are being evaluated.
- Members of the public with hypertension are making substantial contributions to study design and conduct through our 10-member patient working group.
- Limitation: If we observe relative risk reductions for the primary outcome that are smaller than 17%, it is unlikely we will be able to declare those differences statistically significant with the planned sample size.

INTRODUCTION

Blood pressure (BP) normally exhibits a circadian rhythm with relatively lower pressures during sleep.[1] Lack of this sleep time "dip" correlates strongly with adverse cardiovascular events such as myocardial infarction (MI), stroke, and congestive heart failure (CHF), and BP correlates most strongly with such events when measured at night (i.e. during sleep).[2-5] Given some antihypertensive medications might lower sleep time BP more effectively when administered at bedtime,[6] administration time could conceivably alter the degree of cardiovascular risk reduction these medications provide.

In 2010, Spanish researchers published the first hypertension trial to compare bedtime with morning antihypertensive administration and examine mortality and morbidity outcomes.[7] The results of this randomized controlled trial (RCT), the MAPEC trial, were striking, reporting a 61% relative reduction in a composite of major adverse cardiovascular events (MACE). Despite the obvious clinical importance of this finding, however, hypertension guidelines have yet to endorse bedtime prescribing.[8-11] This presumably relates to concern over irregularities in the reporting of MAPEC's results and methods.[12 13] The MAPEC trial registry, for instance, was attributed to at least 8 other RCTs,[14-21] making it appear to describe a general program of research, and not the methods of a single RCT. Following this, in 2019, the same principal investigator published another RCT favoring bedtime over morning antihypertensives, the Hygia trial, which reported a 45% relative reduction in MACE.[22] Again however, irregularities in the reporting of Hygia's results and methods, including a lack of clarity over how randomization and allocation were carried out, has led to calls for independent confirmation of these findings before bedtime prescribing of antihypertensives is embraced.[13 23-25]

BedMed is a large community-based RCT intended to replicate a MAPEC-like timing intervention in a hypertensive Canadian primary care population. BedMed randomizes participants to take all existing blood pressure medication (as tolerated) at bedtime, compared to conventional morning use, and tracks mortality and morbidity using regularly collected administrative health claims and participant self-report. This protocol is prepared in accordance with SPIRIT guidelines.[26]

Objectives

Main: To determine whether a bedtime versus morning antihypertensive administration time influences mortality or cardiovascular morbidity.
Secondary: To determine whether a bedtime versus morning antihypertensive administration time adversely influences cognitive ability, visual acuity, risk of falls and fractures, or nocturia.

METHODS

Trial Design

BedMed is a Phase 4 pragmatic clinical trial with an adaptive, event-driven, parallel enrollment, PROBE (prospective randomized open blinded-endpoint) design.[27] Here, "adaptive" refers to the potential future exclusion of new participants whose only antihypertensive is a diuretic, if adherence to bedtime allocation in such individuals is poor (see *Adherence to bedtime diuretics sub-study*).

Recruitment began in March 2017, and the trial will continue until 254 primary outcome events have been observed (the number of events in MAPEC). Based on current ongoing enrollment (3,227), and an observed 2.0% annual event rate, final analysis is anticipated in early 2023.

Setting and Recruitment

Pragmatic Trials Collaborative

Most recruitment (~78%) is through community family physicians (>400) who own and operate independent clinics. These providers are spread widely across 5 participating provinces (Alberta, British Columbia, Manitoba, Saskatchewan, Ontario), but affiliated with the Pragmatic Trials Collaborative (www.PragmaticTrials.ca), a practice-based research network which is coordinating the trial. Nurse practitioners with their own practice panel (7 at present) are also participating.

Each clinic uses their own electronic medical record (EMR) to create a list of hypertensive patients and the primary care provider (PCP) removes those they consider palliative, or incapable of informed consent. The study team then provides the clinic with recruitment envelopes, which the clinic addresses and mails to these potentially eligible patients. The envelopes contain 1) a letter of introduction from the patient's PCP, and 2) a pamphlet describing the trial and providing contact information (online supplementary files 1&2). Interested patients call the study team where research assistants answer questions, determine eligibility, and obtain consent either in real-time via e-mail (>80% of participants opt for this) or by letter-mail for handwritten consents.

Social Media

All hypertensive residents of our 5 participating provinces are eligible for BedMed, whether or not their PCP is involved. While this can happen through word-of-mouth, a social media campaign (Google & Facebook Ads) is being employed to inform the public about the trial. These Ads (online supplementary video 1) direct individuals to a landing page (https://bedmedstudy.ca/) providing trial information, a check of eligibility, and telephone / e-mail contact information for the study team.

Trial Population

Inclusion Criteria

- Clinician diagnosis of hypertension (by any physician or nurse practitioner)
- Taking ≥1 BP-lowering medication once daily, or PCP willing to convert ≥1 BP-lowering medication to once daily
- ≥18 years of age
- Community-dwelling (i.e., not residing in a nursing home)

Exclusion Criteria

- Considered palliative or unable to consent by PCP
- Sleep disrupting shift work (more than 3 shifts/month during participant's regular sleeping hours)
- Glaucoma diagnosis, or using glaucoma medication (safety exclusion: nocturnal hypotension, which bedtime BP meds could worsen, has been associated with optic neuropathy in glaucoma patients).[28-30]

Randomization and Allocation

Consenting participants receive their random allocation to bedtime versus morning BP medications while dialoguing directly with a research assistant who has no preceding clinical interactions with that participant and who obtains their allocation (stratifying by province with random blocks of 10 or 12) from the central REDCap[31] server's randomization module, ensuring irreversible & concealed allocation.

Intervention

Treatment

Use of all once-daily BP-lowering medication(s) at bedtime.

Control

Use of all once-daily BP-lowering medication(s) in the morning.

Implementation

Participants choose between having their PCP assist their timing change (using the PCP's judgement on how and what to change), or being assisted by the research assistant with whom they are dialoging. Only PCPs assist with timing changes if participants describe heart disease, or if their BP medications include Tiazac XC or Diltiazem XC (which have delayed-release kinetics), furosemide, isosorbide mononitrate/dinitrate, or alpha blockers (medications whose timing decision may be more complicated). PCPs can convert twice daily medications to once daily alternatives, but this is not actively promoted.

Research assistants only change the timing of once daily medications, with a limit of one medication change per week (using the order Angiotensin converting enzyme inhibitors (ACEI) / angiotensin receptor blockers (ARB), calcium channel blockers (CCB), beta-blockers (BB), diuretic-containing medications, other). They advise participants to make the switch by delaying the next dose until the allocated time, and continuing that schedule. If bedtime use is problematic, they ask participants to try taking their BP meds with dinner. If morning use is problematic, they ask participants to try taking it with lunch. Participants with regularly reversed sleep schedules (i.e.,

sleeping during the day) take their BP medications when they get up, or when they go to bed, not according to the time of day.

At each follow-up, participants are asked about medication timing, and encouraged to adhere to allocation. No devices to separately monitor adherence are in use. As a memory aid, all participants are advised to place pill bottles near objects they use when transitioning to or from bed (e.g., toothbrush, denture case, alarm clock), or to use an AM/PM dosette. If participants report a new diagnosis of glaucoma, they are advised to take their BP medications in the morning, regardless of allocation, to minimize the risk of optic neuropathy.

Follow-up and Data Management

Research Assistant Interactions

All participant interactions with research assistants are unblinded and recorded directly into the University of Alberta's implementation of the REDCap data management platform.[31] The following interactions are scheduled relative to the date of randomization.

Baseline: Telephone interaction to 1) obtain baseline characteristics, 2) conduct the Short-Blessed Test to assess cognitive function, and 3) randomize the participant. May be split over multiple interactions (participant's choice).
1-Week: Telephone interaction to troubleshoot timing change problems and encourage adherence.
6-Weeks: Telephone interaction to gather information on adverse effects and outcomes.
6-Months: Telephone interaction, or REDCap e-mail survey (participant's choice), to gather adverse effects and outcomes.
12-Months: Same as 6-months + EQ-5D-5L quality of life survey.
18-months: Same as 6-months + follow-up Short Blessed Test (but available by telephone only).
Every 6-months thereafter: Same as 6-months.

Administrative Claims Data

All Canadian provinces have publicly funded healthcare systems and maintain linkable healthcare databases tracking medical services rendered during health care interactions for all their residents. This includes community physician services and diagnoses (whether by specialists or generalists), prescriptions dispensed, reasons for hospitalization, and vital statistics (i.e. mortality). BedMed participants consent to these datasets being accessed and analyzed to support the trial, providing both outcomes and baseline characteristics.

24-Hour Ambulatory Blood Pressure Monitoring

To assess between-group differences in achieved BP, we intended to carry out 24-hour BP monitoring on a consecutive sample of 151 intervention & 151 control subjects residing in 6 Alberta communities at 6-months (providing 90% power to detect the difference in overnight systolic BP observed in MAPEC). Although we will be able to reach our intended sample size, the timing of these measurements has been substantially delayed for many participants due to both logistic hurdles, and the COVID-

19 pandemic. Participants are provided a copy of their test results, which are also faxed (if they consent) to their PCP.

Outcomes

Unless otherwise stated, all outcomes are recorded over the duration of the study.

Primary:

Major adverse cardiovascular events (MACE)

- Defined as first occurrence of either all-cause death or hospital admission / emergency department (ED) visit for acute coronary syndrome / myocardial infarction (MI), stroke, or congestive heart failure (CHF).

Secondary:

1. Each component of the primary outcome individually
2. All-cause hospitalization / ED visit
3. Long-term care (LTC) admission (i.e., to nursing home or assisted living facility)
4. Non-vertebral fracture
5. New or worsening glaucoma
    - Defined as first occurrence of either first-ever glaucoma diagnosis, first-ever glaucoma treatment, or first-ever glaucoma surgery (Note: despite our excluding participants with self-reported glaucoma, participants could conceivably have a baseline glaucoma claims diagnosis without knowing it. Such individuals can contribute to new glaucoma treatment, or new glaucoma surgery, but not to new glaucoma diagnosis, as it would not be a “first-ever” diagnosis).
6. Cognitive decline at 18 months
    - Defined as ≥ 2-point worsening in cognitive performance compared to baseline, as measured by the Short Blessed Test

Supplementary Safety Outcomes:

1. Vision
    a. Vision self-reported as “much worse” compared to the last follow-up at any point, or “slightly worse” than the last follow-up, on 2 or more occasions (Note: vision is reported, every 6-months, as either “unchanged”, “slightly worse”, or “much worse” than the last follow-up)
2. Cognition
    a. New “impairment consistent with dementia” at 18-months (Short Blessed Test newly ≥ 10) or new diagnosis of dementia at any point during follow-up
3. Symptomatic Hypotension
    a. Self-reported light-headedness, or feeling faint without loss of consciousness, in the prior month
    b. Self-reported fainting (loss of consciousness) in the prior month
    c. Self-reported falling in the prior month
    d. Hip fracture

(Note: at 6-weeks, 6-months, and every 6-months thereafter, participants are separately asked whether they have felt lightheaded, fainted, or fallen in the last month)

4. Nocturia
    a. Self-reported change from baseline in the number of overnight urinations per week (at 6-weeks and 6-months)
    b. Self-reported nocturia burden in the prior month, recorded as no nocturia, or nocturia that is "no problem", "minor problem", or "major problem" (at 6-weeks and 6-months)

Cost:

1. Acute care costs (estimated from each hospital admission's resource intensity weight and length of stay)*
2. Total cost of care (acute care costs + medication costs + physician billings)*

*All cost measures are derived entirely from administrative claims data, and not from self-report. If claims data is not available for some participants, they will be excluded from this analysis.

Exploratory:

1. Self-reported overall health score (via EQ-5D-5L) at 12-months

Process:

1. Proportion of BP medication doses taken at the allocated time at 6-months (twice daily medications being considered as ½ dose in the AM and ½ dose in the PM for this calculation)†
2. Sleep-time systolic blood pressure after 6-months (consecutive sample of 302 Alberta residents)†

†Although blinded to individual participant process outcomes, investigators are unblinded to the aggregated results for adherence to allocation time, and to the aggregated results from the 24-hour BP assessments. This allows for consideration of protocol alterations should the intervention appear poorly applied. Investigators are otherwise fully blinded to all trial outcomes.

End-point Adjudication

Administrative data

Administrative data derived outcomes will be identified using established and validated coding algorithms.[32-34] Physicians providing these diagnoses are generally acute care providers (emergency physicians, hospitalists, specialists) who are unaffiliated with the BedMed trial.

Adjudication panel

Most primary and secondary outcomes are being collected in duplicate (i.e. by administrative claims and participant self-reporting of the same events). This information will be reviewed by a panel of 3 physicians blinded to allocation. If the panel deems both

data sources to be concordant, those events will be considered valid, and the event date in administrative claims will be used. When events are discordant (e.g. only present in one of the two data sources, or differing in diagnoses) the participant's PCP will be contacted to provide the adjudication panel with more information, including their opinion on whether the event occurred. The exception is all-cause hospitalization / ED visits, where we will preferentially use only administrative claims data, believing it to be highly accurate, and being more challenging to confirm with PCPs given the high number of such occurrences.

Sample Size Determination

BedMed is event-driven, and originally sought to observe 406 primary outcome events before stopping. We chose this event target believing this was the largest number of events a network our size could detect with 3-years of observation. However, because patients receiving recruitment packages are less likely to enrol than expected (projected enrolment 12%, actual enrolment 6%), and because the overall annual event rate is at the low end of expectations (2.0%), we have reduced our event target for stopping to 254, which matches the number of events observed in MAPEC. Assuming meaningful covariates, 254 events should allow observed risk ratio differences of ~17% or larger to be declared statistically significant. To estimate when this number of events has likely been reached, Alberta Health Services is tracking the primary outcome event rate in Alberta BedMed participants on a quarterly basis. We then extrapolate this to the trial as a whole using the number of participant years of observation. At the current rate of events and enrolment, BedMed should conduct its final analysis in early 2023.

Statistical Analysis

Intension-to-treat assumptions

Loss to follow-up: If participants are lost to follow-up, but medical services continue to be recorded within administrative claims data, we will treat them as though they were still active in the study and censor survival data on the last date of medical services, or indication of death, whichever occurs later. If no such medical claims exist, data will be censored on the last day of successful telephone or e-mail follow-up.

Withdrawal: Participants withdrawing from the study are asked to allow us to continue to follow their administrative claims data. If they agree (as the majority do), we will continue to use administrative claims outcomes for those individuals as per the loss-to-follow-up description. If they do not agree, survival data will be censored on the date of withdrawal.

Missing data: For each analysis, we will either impute a value from subsequent or preceding follow-up visits, or exclude a participant from analysis. How we deal with missing data will be specific to each analysis and prioritize either minimizing bias, or being conservative when bias is unavoidable (i.e. biasing against benefit, and towards harm, for the intervention).

Nonadherence: Nonadherence to allocation will not exclude participants from analysis unless the outcome of interest is a harm that only makes sense to assess while on-

treatment (e.g. assessing how nocturia differs in diuretic users switched to bedtime, compared to nondiuretic users making the same switch).

Selecting regression covariates

Analyses of dichotomous outcomes will use a maximum of 1 covariate per 10 outcomes, and analyses of continuous outcomes will use a maximum of 1 covariate per 20 randomized subjects. The covariate list for each analysis is predefined in table 1, and all are measured at baseline. We will always use the maximum number of covariates possible, selected in the order given (i.e. we will not undertake stepwise addition or subtraction).

Table 1 Analysis Plan

Outcome	Method	Covariates
Primary		
Major adverse cardiovascular events	Cox Proportional Hazards	Age, sex, frailty score*, current smoker, number of non-BP medications, Overall Health Score†, prior 6-months hospitalization, CHF, diabetes, CAD, stroke or TIA, CKD‡, dialysis, BMI > 30, BMI < 18.5, sleep apnea, exercise days§, province (4 variables)
Secondary		
All-cause mortality	Cox Proportional Hazards	Age, frailty score*, number of non-BP medications, Overall Health Score†, prior 6-months hospitalization, CHF, diabetes, CAD, CKD‡
Hospitalisation for stroke Hospitalisation for MI/ACS	Cox Proportional Hazards	Age, stroke or TIA, CAD, current smoker, sex, diabetes, exercise days§, BMI > 35
Hospitalisation for CHF	Cox Proportional Hazards	Age, CHF, CAD, diabetes, CKD‡
All-cause hospitalisation / ED visit	Cox Proportional Hazards	Age, sex, frailty score*, current smoker, number of non-BP medications, Overall Health Score†, prior 6-months hospitalization, CHF, diabetes, CAD, stroke, TIA, Short Blessed Test score, CKD‡, dialysis, BMI >35, BMI <18.5, COPD, province
Non-vertebral fracture	Cox Proportional Hazards	Age, Overall Health Score†, BMI, number of non-BP medications, frailty score*, stroke (not TIA), sex, CHF, exercise days§, TIA, prior 6-months hospitalization
LTC admission	Cox Proportional Hazards	Age ≥ 80, Short Blessed Test score, frailty score*
New or worsening glaucoma	Cox Proportional Hazards	Age, diabetes, CAD or stroke or TIA, CHF, COPD, CKD‡, sleep apnea, BMI, exercise days§, Short Blessed Test Score
18-month cognitive decline	Poisson Regression	Age, sex, frailty score, number of non-BP medications, Overall Health Score†, CHF, stroke, TIA, COPD, BMI, exercise days§, province
Supplementary Safety		

Worsening of vision	Poisson Regression	Age, diabetes, CAD or stroke or TIA, CHF, COPD, CKD‡, Overall Health Score†
New impairment consistent with dementia	Poisson Regression	Age, sex, frailty score, number of non-BP medications, Overall Health Score†, CHF, stroke, TIA, COPD, BMI, exercise days§, province
Light-headedness in last Month Syncope in last month Falling in last month	Poisson Regression	Age, frailty score, number of non-BP medications, Overall Health Score†, CHF, stroke, TIA, sex, exercise days§, BMI, province
Hip fracture	Cox Proportional Hazards	Age, Overall Health Score†, BMI, number of non-BP meds, frailty score, stroke (not TIA), sex, CHF, exercise days§
Change in overnight urinations / week	Mann-Whitney or t-test	N/A
Nocturia a major burden	Fisher's Exact Test	N/A
Cost		
Acute care costs Total cost of care	Multiple Linear Regression	Age, sex, frailty score, current smoker, number of non-BP medications, Overall Health Score†, prior 6-months hospitalization, CHF, diabetes, CAD, stroke, TIA, Short Blessed Test score, CKD‡, dialysis, BMI > 35, BMI < 18.5, COPD, province
Exploratory		
Overall Health Score	Multiple Linear Regression	Age, sex, frailty score, current smoker, number of non-BP medications, prior 6-months hospitalization, CHF, diabetes, CAD, stroke, TIA, Short Blessed Test score, CKD‡, dialysis, BMI > 35, BMI < 18.5, COPD, province
*Score on physical frailty subscale of the Tilburg questionnaire; continuous 0-8 †From EQ-5D-5L; continuous 0-100 ‡Not including dialysis §"How many days in the past week have you exercised for 30 minutes or more, vigorously enough to raise your breathing rate?"; continuous 0-7		

Subgroup Analyses

We will repeat the primary outcome analysis for those with and without the following baseline characteristics: Age ≥ 75, sex, physically frail (score ≥3 on physical frailty subscale of the Tilburg questionnaire), polypharmacy (≥ 5 medications), Overall Health

Score ≤ 75, resistant hypertension (≥3 BP-lowering medications), CHF, diabetes, CAD, stroke or TIA, sleep apnea, chronic kidney disease (with or without dialysis), sedentary (exercise 0 days per week).

Sensitivity Analyses

We will present, according to treatment group, the baseline characteristics of those whose data was censored due to withdrawal or loss to follow-up, and compare these characteristics to those who weren't censored in this way using Fisher's Exact Test.

Patient and Public Involvement

Patient Working Group

BedMed has a 10-member patient working group helping to guide the trial. The group began meeting in 2016 prior to any recruitment to review and revise 1) recruitment materials, 2) phrasing of questions, and 3) outcomes to be collected through self-report. Working group members have also assisted in hiring research staff, in further revising recruitment materials mid-study to increase enrollment, and in constructing a social media campaign. We anticipate working with our patient partners to make decisions, if needed, following our interim analysis in spring 2022, to interpret final results in 2023, and to help disseminate findings.

Patient Driven Sub-Study

The draft BedMed protocol was presented in 2015 to a group of ~25 seniors prior to study registration and grant application. Feedback from this presentation resulted in the sub-study to determine whether diuretics can be taken at bedtime without troublesome nocturia threatening adherence.

SUBSTUDIES

Adherence to bedtime diuretics

Diuretics are widely believed to promote nocturia if taken later in the day, and are typically recommended for morning use only as a result.[35 36] However this recommendation is largely opinion based. Whether or not participants will adhere to bedtime diuretic dosing is unclear. To determine this, we will examine, at 6-weeks and 6-months, self-reported nocturia burden (no, minor, major), number of overnight urinations per week, and adherence to bedtime allocation, in the first 203 AM diuretic-only users randomized to bedtime and being followed for 6-months, and compare this to all those switching a single AM non-diuretic to bedtime during the same period. Assuming equal numbers in both groups, and 75% adherence to allocation time in non-diuretic users, this should provide 90% power to detect a 20% relative reduction in adherence in diuretic users.

Volunteer bias

Concern has been raised that randomized trial participants are poorly representative of real world populations.[37-41] We will examine, using Alberta administrative claims, how baseline characteristics and preventive health behaviours differ in 4 distinct Alberta populations: 1) All BedMed-eligible patients attached to participating PCPs, 2) BedMed

participants who enrolled after a PCP-letter, 3) BedMed participants responding to social media advertisement, and 4) All BedMed-eligible Albertans. We will compare 1) Demographics (age, sex, postal code derived deprivation index, rural residence), 2) Comorbidities (diabetes, CAD, stroke, osteoarthritis, CHF, COPD, dementia, hip fracture, CKD, dialysis, hospital admission in prior 6-months plus accompanying length of stay and resource intensity weighting), 3) Preventive therapies (prior 3-years shingles vaccine, statin use, osteoporosis medication), 4) Screening tests (prior 3-years PAP smear, colonoscopy, mammogram, FIT testing, PSA testing), and 5) clinical outcomes post-randomization (death, BedMed primary outcome, all-cause hospitalization or ED visit along with length of stay and resource intensity weighting, nursing home admission, new glaucoma diagnosis / treatment / surgery, hip fracture, and new dementia diagnosis). To substitute for the date of randomization we will use the date of PCP mailout for BedMed-eligible PCP-attached patients, and the date providing the same mean number of years of observation for all BedMed-eligible Albertans.

"Nudge Sentence" Recruitment Strategy

Two years into recruiting, we hypothesized that altering the physician letter of introduction to state that a large number of people were already participating might improve the response rate. Online supplementary file 3 shows the new physician letter. The added wording (in purple here) states: "*This study already has over 1,700 Canadians with high blood pressure taking part. If you too choose to participate…*". As of March 2019, providers are given an equal number of both recruitment envelopes, sealed and shuffled together, for them to address and mail. Both letters are otherwise identical save for the date on the letter (odd numbered for the new version, even numbered for the original). Participants calling to enrol are asked the date on the letter to determine which version they are responding to, allowing a pseudorandom assessment of the ability of such a "nudge" sentence to improve enrolment. This sub-study will continue until recruitment ends, with sample size determined by the number of letters mailed during that interval.

EARLY STOPPING

Independent Data Safety Monitoring Board (IDSMB)

Outcomes from all provinces will be collected at the end of 2021. Each analysis described in this protocol will then be carried out, and presented to the Cochrane Hypertension Working Group (our IDSMB).

Stopping Rules: If p is ≤ 0.001 for primary outcome benefit (the Haybittle-Peto boundary),[42] or if p is ≤ 0.05 for harm, the IDSMB will apply clinical judgement and decide whether to recommend to the principal investigator that the trial be stopped early.

Competing Studies

A trial similar to ours, the United Kingdom's TIME trial,[43] will likely release results ahead of BedMed. If convincing benefit is demonstrated, we will ask our IDSMB to weigh this new information and consider again whether early stopping is recommended.

Our group is also conducting a separate RCT of the same antihypertensive timing intervention in hypertensive long-term care residents (BedMed-Frail).[44] As both trials share the same IDSMB, interim data from both trials could be weighed in early stopping discussions for either trial.

DISSEMINATION

Results will be published in a peer-reviewed journal, and summarized in knowledge translation vehicles targeted at PCPs, and the general public. We will also invite trial participants to a results webinar where they can directly pose questions to the principal investigator.

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Authors contributions

BedMed was conceived and designed by SRG with input from MRK, GMA, JAB, LAG, AGS, FAM, RSP, MDH, BM, KM, DPM, STW, RM, JM, CN and CSK. Each of these authors also participated as co-applicants on the grants that fund the trial, with SRG as the nominated principal applicant. Family physicians were recruited by SRG with help from MRK, GMA, CSK, AGS, BGO, MG, DPM, DAM, CM, STW and JEMK. DRT participates on the BedMed Patient Working Group and helped to revise recruitment materials, and to design the social media campaign. SRG and JAB created the analysis plan. JAB, SRG, AGS, FAM, and KM are coordinating access to administrative claims data. SRG and LSF wrote the draft manuscript, with all authors providing critical feedback.

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Competing Interests

All authors declare no competing interests related to the submitted work.

Ethics Approvals

BedMed has approval from 7 university ethics boards in 5 Canadian provinces, including University of Alberta (Pro00045958), University of Calgary (REB17-1887), University of Manitoba (HS20852 [B2017:08]), University of British Columbia (H21-00523), University of Saskatchewan (1421), University of Toronto (00038892), and McMaster University (13092).

Data Sharing

An anonymized participant level dataset containing most baseline characteristics, all analytic covariates, and all trial outcomes will be freely available on the Pragmatic Trials Collaborative website (www.PragmaticTrials.ca) upon publication of the final analysis.

Dr. John/Jane Doe
Family Medicine Clinic Name
Street Address
City, Province, Postal Code
PHONE XXX-XXX-XXXX| FAX: XXX-XXX-XXXX

Today's Date

To my patients,

Our office is participating in a national blood pressure study led by the University of Alberta. We are sending this letter to all our patients with high blood pressure as an invitation to participate.

Research suggests that the ability of blood pressure pills to reduce heart attack and stroke may vary by 50% or more depending on the time of day those medicines are taken. This new study will help us to understand if altering the timing of blood pressure medicine can be used to better prevent heart attack and stroke.

The study involves randomly assigning participants to either take at least one of their current blood pressure medications either in the morning, or in the evening. Health outcomes would then be followed for up to 3 years.

If you choose to participate, our office will assist you in making and monitoring any medication changes that might be required. We believe this is an important study, but please know that your participation is voluntary. Whether or not you participate in no way affects our relationship.

For more information or to participate in the study, please call:
Toll free 1-844-492-7570
(7am-5pm Alberta time)

Email: bedmed@ualberta.ca
Website: www.pragmatictrials.ca/bedmed

Sincerely,

John or Jane Doe MD

The BedMed Study

Study Email Address: BedMed@ualberta.ca
Principal Investigator: Dr. Scott Garrison
Study Coordinator: Janis Cole

Toll Free Phone: 1-844-492-7570
Phone Number: (587) 785-3012
Phone Number: (780) 492-1602

Research suggests it might be possible to improve health outcomes for people living with high blood pressure. With your help, we can find out.

Why is this study being conducted?

For those with high blood pressure, medications reduce the risk of heart attack and stroke. How effective these medications are may depend on the time of day they're taken. A European study suggests that taking blood pressure pills at bedtime, instead of in the morning, may reduce heart attacks and strokes by more than 50%. The BedMed Study is designed to determine if this is true.

Where will this study take place?

Wherever you are. Initial contact with the study team is by phone. Consent and follow up interviews can be done either by phone or online survey.

What is involved if I participate?

You may be asked to change the time you take your blood pressure medication. You'll be randomly assigned to take those medications (as tolerated) either in the morning or at bedtime for the duration of the study - up to 3 years. If you take medications at both times, you are still eligible to participate.

Which medications you use, and all other decisions regarding changes to these medications, will stay between you and your health care provider. If you need to change back to your original medication timing, you are able to do so. Whether you choose to participate or not will have no impact on your relationship with your healthcare team.

When will the study start?

The study begins after you speak with the study team by phone. Please don't change the time of day that you take your blood pressure medications before talking with your healthcare provider. Participation in this study is voluntary and you may withdraw at any time without having to give a reason.

Call the study team toll free at: **1-844-492-7570** (M-F, 7am – 5pm MST)
Email the study team at: BedMed@ualberta.ca
Visit the study website at: **pragmatictrials.ca/BedMed/**

The study will involve these steps:

1 Call: 1-844-492-7570

Our study staff will talk with you to see if the study is a good fit for you and answer any questions.

2 Consent

Consent can be done through mail or online survey. The study team will also collect medical history questions from you over the phone.

3 Randomization

A) You will be randomly placed into either the morning or evening group. You will record this on the "Medication Worksheet" at the back of this package, along with a list of your blood pressure medications.
B) You might see your health care provider if you need to change the time of one or more medications.

4 Follow-ups

The study team will call you one week later if there is the possibility of medication timing being changed. After this, follow-up interviews are at six weeks, six months, and every six months thereafter until the study is done. Interviews from month six onward are by phone or online survey if you prefer.

What are the Benefits?

One in five adult Albertans has high blood pressure. Whether or not we confirm benefit to bedtime prescribing, your participation will help answer an important question surrounding medications used by millions of people worldwide.

What are the Risks?

Morning Medication use

According to previous research, it's possible that there 's a higher risk of heart attack and stroke for those who take their blood pressure medications in the morning (compared to those who use them at bedtime). We don't know if this is true, which is why we're conducting this study.

Bedtime medication use

There are **no established risks** to using blood pressure pills at bedtime but we're closely watching for three possibilities:

1. Best evidence suggests it's not the case, but certain blood pressure pills might increase the number of overnight trips to the bathroom to urinate.
2. Having lower blood pressure overnight may lead to dizziness and potential for falls and fractures.
3. Lower blood pressures overnight might lead to reduced blood flow to the back of the eye in patients with glaucoma, and this may adversely affect vision. For this reason, those with glaucoma are excluded from participating.

Study Confidentiality

All information you provide is confidential. It will be kept in a locked cabinet in a locked research office or on an encrypted computer that's password protected, and only accessible to study investigators and staff. We will do everything we can to keep this data private. No study-related data that includes your name will ever be released outside of the study doctor's office. We will make every legal effort to make sure that your health information is kept private.

Throughout the study, we will be collecting your health data during our phone interviews with you. We will also use your Personal Health Number (PHN) to link this study data to relevant records from your hospital, emergency room, physician office visits, and pharmacy data. The personal health information that we get from these records will be limited to what is needed for the study. If you leave the study, we will not collect new health information about you, but we will need to keep the data that we have already collected.

After you have completed the study, all of the identifying information (i.e. name and contact information) will be removed and your record will be labeled with a study ID that doesn't resemble your name. Your information will be stored in an encrypted, password protected electronic file. We will keep a separate list (in a locked cabinet) that links your name to the study ID number if it's ever necessary to relink you to your data. We will store this data for a minimum of 5 years after the end of the study. The results of this study will be used for publication, but will not identify any participants in any way. To maximize the value of this study after our analysis is complete, we will make our raw data available over the Internet (with all identifying information removed) so that other research groups can verify our findings and explore questions of their own.

For any concerns about your treatment or rights as a research subject in Alberta, contact the Research Ethics Office, University of Alberta at 780-492-2615 or e-mail them at reoffice@ualberta.ca). These offices have no direct involvement with this project.

Medication Worksheet

Your interviewer will help you fill out this table. Please keep this sheet for your records.

For the duration of the study, my blood pressure medication(s) have been assigned to:

A) Morning *B) Bedtime*

My current medications:

Drug Name	Strength	Number of Tablets (example ½, 1, 2)			
		Morning	Noon	Dinner	Bedtime

Interview Dates: You will have telephone follow-up interviews with our study team at one week, six weeks, six months, and every six months after your initial medication review visit. At month six, you may choose to continue with telephone follow-ups or switch to email. If you choose email follow-ups, your interviewer will provide you with a five-digit code and explain the process.

Online survey access information
(Applicable for online follow-ups)

Five-digit code: _____

Interviewer name: _____

For questions regarding the study or how to use this form please contact us:

Call the study team toll free at: **1-844-492-7570** (M-F, 7am – 5pm MST)

Email the study team at: BedMed@ualberta.ca
Visit the study website at: **pragmatictrials.ca/BedMed/**

Dr. John/Jane Doe
Family Medicine Clinic Name
Street Address
City, Province, Postal Code
PHONE XXX-XXX-XXXX| FAX: XXX-XXX-XXXX

Date (ODD #)

To my patients,

Our office is participating in a national blood pressure study led by the University of Alberta. We are sending this letter to all our patients with high blood pressure as an invitation to participate.

Research suggests that the ability of blood pressure pills to reduce heart attack and stroke may vary by 50% or more depending on the time of day those medicines are taken. This new study will help us to understand if altering the timing of blood pressure medicine can be used to better prevent heart attack and stroke.

The study involves randomly assigning participants to take at least one of their current blood pressure medications either in the morning, or at bedtime. Health outcomes would then be followed for up to 3 years.

This study already has over 1,700 Canadians with high blood pressure taking part. If you too choose to participate, our office will assist you in making and monitoring any medication changes that might be required. We believe this is an important study, but please know that your participation is voluntary. Whether or not you participate in no way affects our relationship.

For more information or to participate in the study, please call:
Toll free 1-844-492-7570
(7am-5pm Alberta time)

Sincerely,

John or Jane Doe MD

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Page	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2	Trial identifier and registry name. If not yet registered, name of intended registry
	-	All items from the World Health Organization Trial Registration Data Set
Protocol version	-	Date and version identifier
Funding	16	Sources and types of financial, material, and other support
Roles and responsibilities	1	Names, affiliations, and roles of protocol contributors
	1	Name and contact information for the trial sponsor
	16	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	8,13	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	3	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	3	Explanation for choice of comparators
Objectives	3	Specific objectives or hypotheses
Trial design	3	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	4	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	4	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	5	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	5	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	5	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	5	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	6	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	6	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	8	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	4,12	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	5	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	5	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	5	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	6,8	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	6,8	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	6	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	9	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	6	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	9	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	12	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	9	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	13	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	13	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	7,13	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	-	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	17	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	-	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	4	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	6	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	17	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	17	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	17	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	-	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	14	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	-	Authorship eligibility guidelines and any intended use of professional writers
	17	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	S1,2, 4	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	-	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.