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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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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 with 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 and 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 email questionnaire at 1 week, 6 weeks, 6 months and every 6 months thereafter, and (2) accessing linked governmental healthcare databases tracking hospital and community medical services.

Primary outcome
Composite of all-cause death, or hospitalisation for myocardial infarction/acute-coronary syndrome, stroke or congestive heart failure.

Secondary outcomes
Each primary outcome element on its own, all-cause hospitalisation or emergency department visit, long-term care admission, non-vertebral fracture, new glaucoma diagnosis, 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
Enrolment ongoing (3227 randomised to date).

Ethics and dissemination BedMed has ethics approval from six 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 generalisability 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.
- ► 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 (ie, 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 randomised controlled trial (RCT), the MAPEC trial (Monitorizacion Ambulatoria para Prediccion de Eventos Cardiovasculares, i.e. Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events), 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 eight other RCTs,[14–21] making it appear to describe a general programme of research, and not the methods of a single RCT. Following this, in 2019, the same principal investigator published another RCT favouring 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 randomisation 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 an MAPEC-like timing intervention in a hypertensive Canadian primary care population. BedMed randomises participants to take all existing BP medication (as tolerated) at bedtime, compared with 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 (Standard Protocol Items: Recommendations for Interventional Trials) 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 enrolment, prospective randomised 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 substudy).

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 (3227), and an observed 2.0% annual event rate, final analysis is anticipated in fall 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 five participating provinces (Alberta, British Columbia, Manitoba, Saskatchewan and 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 (seven at present) are also participating.

Each clinic uses their own electronic medical record 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 supplemental files 1 and 2). Interested patients call the study team where research assistants answer questions, determine eligibility and obtain consent either in real-time via email (>80% of participants opt for this) or by letter-mail for handwritten consents.

Social Media

All hypertensive residents of our five 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 and Facebook Ads) is being employed to inform the public about the trial. These Ads (online supplemental video 1) direct individuals to a landing page (https://bedmedstudy.ca/)

providing trial information, a check of eligibility and telephone/email 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 (ie, not residing in a nursing home).

Exclusion criteria

- Considered palliative or unable to consent by PCP.
- Sleep disrupting shift work (more than three 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]

Randomisation and allocation

Consenting participants receive their random allocation to bedtime vs 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 randomisation module, ensuring irreversible and 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 ACE inhibitors angiotensin receptor blockers, calcium channel blockers, beta-blockers, 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 (ie, 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 (eg, 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 minimise 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 randomisation.

Baseline: Telephone interaction to (1) obtain baseline characteristics, (2) conduct the Short-Blessed Test to assess cognitive function, and (3) randomise the participant. May be split over multiple interactions (participant's choice).

One week: Telephone interaction to troubleshoot timing change problems and encourage adherence.

Six weeks: Telephone interaction to gather information on adverse effects and outcomes.

Six months: Telephone interaction, or REDCap email survey (participant's choice), to gather adverse effects and outcomes.

Twelve months: Same as 6 months+EQ-5D-5L quality-of-life survey (EuroQol Group's health-related quality-of-life instrument).

Eighteen 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 healthcare interactions for all their residents. This includes community physician services and diagnoses (whether by specialists or generalists), prescriptions dispensed, reasons for hospitalisation and vital statistics (ie, mortality). BedMed participants consent to these datasets being accessed and analysed to support the trial, providing both outcomes and baseline characteristics.

Twenty-four-hour ambulatory BP 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 and 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

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

Secondary

1. Each component of the primary outcome individually.
2. All-cause hospitalisation/ED visit.
3. Long-term care (LTC) admission (ie, to nursing home or assisted living facility).
4. Non-vertebral fracture.
5. New glaucoma 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
   - Vision self-reported as 'much worse' compared with the last follow-up at any point, or 'slightly worse' than the last follow-up, on two 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
   - 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
   - Self-reported light-headedness, or feeling faint without loss of consciousness, in the prior month.
   - Self-reported fainting (loss of consciousness) in the prior month.
   - Self-reported falling in the prior month.
   - 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
   - Self-reported change from baseline in the number of overnight urinations per week (at 6 weeks and 6 months).
   - 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 (two times per day medications being considered as half dose in the AM and half dose in the PM for this calculation)†.
2. Sleep-time systolic BP 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 isolated 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 (ie, by administrative claims and participant self-reporting of the same events). This information will be reviewed by a panel of three 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 (eg, 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 hospitalisation/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 fall 2023.

Statistical analysis

Intention-to-treat assumptions

Lost 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 email 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 prioritise either minimising bias, or being conservative when bias is unavoidable (ie, biasing against benefit and towards harm, for the intervention).

Non-adherence

Non-adherence 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 (eg, assessing how nocturia differs in diuretic users switched to bedtime, compared with non-diuretic 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 randomised 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 (ie, we will not undertake stepwise addition or subtraction).

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 (coronary artery disease), stroke or TIA, sleep apnoea, 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 lost to follow-up, and compare these characteristics to those who were not 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 enrolment, 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 substudy

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 substudy 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

Table 1 Analysis plan

Outcome	Method	Covariates
Primary		
Major adverse cardiovascular events	Cox proportional hazards	Age, sex, frailty score*, current smoker, no of non-BP medications, Overall Health Score†, prior 6 months hospitalisation, CHF, diabetes, CAD, stroke or TIA, CKD‡, dialysis, BMI >35, BMI <20, sleep apnoea, exercise days§, province (four variables)
Secondary		
All-cause mortality	Cox proportional hazards	Age, frailty score*, no of non-BP medications, Overall Health Score†, prior 6 months hospitalisation, 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, no of non-BP medications, Overall Health Score†, prior 6 months hospitalisation, CHF, diabetes, CAD, stroke, TIA, Short Blessed Test score, CKD‡, dialysis, BMI >35, BMI <20, COPD, province
Non-vertebral fracture	Cox proportional hazards	Age, Overall Health Score†, BMI, no of non-BP medications, frailty score*, stroke (not TIA), sex, CHF, exercise days§, TIA, prior 6 months hospitalisation
LTC admission	Cox proportional hazards	Age ≥80, Short Blessed Test score, frailty score*
New glaucoma diagnosis	Cox proportional hazards	Age, diabetes, CAD or stroke or TIA, CHF, COPD, CKD‡, sleep apnoea, BMI, exercise days§, Short Blessed Test Score
18-month cognitive decline	Poisson regression	Age, sex, frailty score, no 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, no 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, no 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, no 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, no of non-BP medications, Overall Health Score†, prior 6 months hospitalisation, CHF, diabetes, CAD, stroke, TIA, Short Blessed Test score, CKD‡, dialysis, BMI >35, BMI <20, COPD, province
Exploratory		
Overall Health Score	Multiple linear regression	Age, sex, frailty score, current smoker, no of non-BP medications, prior 6 months hospitalisation, CHF, diabetes, CAD, stroke, TIA, Short Blessed Test score, CKD‡, dialysis, BMI >35, BMI <20, 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 min or more, vigorously enough to raise your breathing rate?'; continuous 0–7.
ACS, Acute Coronary Syndrome; BMI, body mass index; BP, blood pressure; CAD, Coronary Artery Disease; CHF, congestive heart failure; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; ED, emergency department; EQ-5D-5L, EuroQol Group's health-related quality-of-life instrument; LTC, long-term care; MI, myocardial infarction; N/A, not applicable; TIA, Transient Ischemic Attack.

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 randomised 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 randomised 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 four 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, chronic obstructive pulmonary disease, 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 postrandomisation (death, BedMed primary outcome, all-cause hospitalisation 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 randomisation, 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 hypothesised 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 3 shows the new physician letter. The added wording states: 'This study already has over 1700 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 substudy 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

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 independent data safety monitoring board, 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 UK'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 LTC 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 summarised 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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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 JB created the analysis plan. JB, SRG, AS, 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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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 #)

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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
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Sincerely,

John or Jane Doe MD