

# Nighttime Dosing of Anti-Hypertensive Medications

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**April 5, 2013**

# Nighttime Dosing of Anti-Hypertensive Medications

## Investigative Team

### University of Iowa

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### Duke University

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# Overview of Presentation

- Background and rationale for the proposed trial
- Overview of the trial design and unique elements
- Review major UH2 milestones and tasks
- Highlight important lessons learned
- Identify next steps and review key decisions with regard to preparing for UH3 trial

# Rationale for Pragmatic Trial

- Long known that BP exhibits circadian variability → lower during sleep (“nighttime dipping”) & increases quickly upon arising (may explain some of the excess risk of AMI during early morning hours)
- Sleptime BP stronger predictor of CV events than office BP measurements or average daily BP as captured by 24 hour ABPM
- Nighttime ***non-dipping*** (systolic BP decline < 10%) is strong predictor of CV risk in patients with HTN
- Non-dipping particularly common in DM and CKD

## Rationale (cont.)

- Increasing development and use over past 20 years of longer acting anti-hypertensives to improve patient compliance
- However, many once daily anti-hypertensives require 60-90 minutes to achieve peak plasma concentrations after ingestion & do not maintain sustained plasma concentrations for full 24 hours
- Thus, when taken in am, medication concentrations may not be high enough to fully protect against morning surge in BP that occurs in most patients

## Rationale (cont.)

- Two recent Spanish trials of patients with HTN & DM (n=448) and HTN & CKD (n=661) led by Hermida randomized patients to take 1 or more anti-hypertensives at night
- Primary endpoint was heterogeneous group of CV events → *death (all causes), AMI, angina, coronary revascularization, CHF, acute LE arterial occlusion, retinal artery thrombosis, CVA, and TIA*
- 24 hour ABPM performed annually
- Median f/u period of 5.4 years

# Rationale (cont.)

## Results of Hermida et al nighttime dosing trials

1. Nighttime dosing group had 3-fold lower risk of CV events
  - HTN + DM → Adjusted HR = 0.33
  - HTN + CKD → Adjusted HR = 0.31
2. Nighttime dosing group had similar daytime BPs but lower sleep syst BP (115 vs. 122 mm Hg)
3. Each 5 mm Hg decrease in sleep time systolic BP associated with a 12% lower risk of CV events

# Why is Nighttime Dosing an Ideal Topic for a Pragmatic Trial?

- HTN is common problem & major CV risk factor
- Patients eligible for intervention can be identified through EMR
- Key study endpoints (adverse CV events) can be captured through EMR and other extant sources
- Nighttime dosing can be implemented in practice w/o need for sophisticated infrastructure
- Intervention has high potential for sustainability if pragmatic trial confirms prior clinical trials,

# Aims of Pragmatic Trial

1. Examine the impact of nighttime dosing of anti-hypertensive medications among patients with HTN and other comorbidities on CV outcomes, self-reported medication adherence, and healthcare utilization
2. Successfully Implement approaches to increase the efficiency of subject recruitment and data collection through the use of EMRs and of web-based platforms for obtaining informed consent and for collecting patient-reported outcomes

# Overview of Trial Design

- 2 partnering study sites: Univ of Iowa & Duke Univ
- Patient identified from EMR-based eligibility criteria
  - *Diagnoses of HTN &  $\geq 1$  comorbid conditions that increase cardiovascular risk*
  - *Active prescriptions for  $\geq 1$  once-daily anti-hypertensive medications (excluding diuretics)*
  - *2 or more visits in prior 12 months to General Medicine, Family Medicine, Cardiology, or Nephrology clinics*

## Overview of Trial Design (cont.)

- Patient-level randomization → *Eligible patients randomized to: (1) nighttime dosing of  $\geq 1$  more medications or (2) control*
- Informed consent obtained through web-based interactive module (preferred) or 1-800 telephone
- Study endpoints obtained from EMR and from a web-based personal health records (to obtain PROs and to collect information on endpoints that occur outside the UI and Duke healthcare systems)

# Overview of Trial Design (cont.)

## Primary Endpoint

- CV events → *CV death or hospital encounters for AMI, ACS, CVA, CHF, or coronary, cerebral, or peripheral revascularization*

## Secondary Endpoints

- Clinic BP during outpatient visits
- Self-reported med adherence (*Moriskey, Hill Bone*)
- Symptoms, health-related quality of life, & potential adverse drug events
- Resource utilization (admissions & ER visits for CV disease)

# Proposed Steps in Subject Recruitment

1. List of eligible patients for each MD generated via EMR and sent to MDs
2. MDs review list of eligible patients & identify patients who should not be approached for inclusion → *Minor source of attrition*
3. Patients receive information letter from their MD about study and are referred to website or 1-800 number to obtain additional information about how to enroll and provide informed consent

# Proposed Steps in Subject Recruitment (cont.)

4. Patients go to website or 1-800 number, asked additional eligibility questions & if eligible provide informed consent & baseline info → ***Major potential source of attrition (75-80%)***
5. Patients are then randomized to nighttime dosing and control groups
6. MDs receive Epic 'Best Practice Alert' to provide study brochure to non-respondents at their next scheduled visit and to encourage patients to consider enrolling

# Key UH2 Tasks

1. Develop online informed consent module
2. Develop PHR for collecting PROs, medication adherence, and out-of-system CV events
3. Validate EMR algorithms for identifying study patients and CV events
4. Review pragmatic trial sample size estimates
5. Engage IRB regarding design and informed consent issues
6. Engage participating physicians to determine their study design preferences & attitudes

# Task 1: Develop Interactive Online Informed Consent (IC) Module

- Modification of platform developed by faculty in UI Colleges of Medicine and Law
  - **Preliminary data** → *Compared to traditional paper-based IC process, online module improved ( $p < .05$ ) subjects' understanding of mock study & satisfaction with IC process*
- PowerPoint version of online module for pragmatic pragmatic trial developed & IRB approval obtained
- Online prototype based on PowerPoint version under development with usability testing in target population scheduled for later this month

# Interactive: Questions with Feedback

The screenshot shows a patient education interface. At the top left is the 'X-Plain PATIENT EDUCATION' logo. At the top right is the 'UNIVERSITY of IOWA HOSPITALS & CLINICS' logo with the tagline 'University of Iowa Health Care'. On the left side, there is a vertical menu with buttons for: Introduction, Purpose of the Study, Procedures, Risks & Benefits, Costs & Compensation, Confidentiality, Participation, and Contact Information. The main content area displays a question: 'What is unknown and experimental about this study? (click on the answer)'. Below the question are four multiple-choice options: A. Whether blood pressure medication works better at different times during the day. B. Whether blood pressure changes at different dosage levels. C. Whether blood pressure medications have different side effects. D. Whether people should take more blood pressure medication at night. Option D is marked with a large red 'X'. Below the options is a yellow feedback box that reads: 'Incorrect. We do not know for sure whether blood pressure medications work better when taken at certain times during the day. This study will not focus on the amount of medication you take. (click here to close)'. At the bottom of the interface, there is a control bar with a progress indicator, the text 'Slide 1 (ESC to exit)', a volume icon, a repeat icon, and navigation arrows. The footer includes 'powered by X-Plain' and 'Copyright © 1995 - 2012 The Patient Education Institute'.

# Collection of Project Data via Module

The screenshot displays the X-Plain Patient Education interface. At the top left is the X-Plain logo with the text 'PATIENT EDUCATION'. At the top right is the University of Iowa Hospitals & Clinics logo with the text 'University of Iowa Health Care'. On the left side, there is a vertical menu with buttons for: Introduction, Purpose of the Study, Procedures, Risks & Benefits, Costs & Compensation, Confidentiality, Participation, and Contact Information. The main content area shows a slide with the text: 'We will ask you to provide information about your health during the 3 years through surveys. These surveys will take less than 15 minutes to complete. You can take the surveys online, over the phone, or by mail.' Below the text are three illustrations: a woman using a laptop, a man on a mobile phone, and a woman at a desk with papers. Each illustration has a small copyright notice for 'Patient Education Institute'. At the bottom of the slide, there is a progress bar and a control panel with the text 'Slide 2 (ESC to exit)', a volume icon, a repeat icon, and navigation arrows. The footer of the interface includes the text 'powered by X-Plain' and 'Copyright © 1995 - 2012 The Patient Education Institute'.

# Task 2: Develop PHR

Sign Out

April 3, 2013



IowaPHR Home Medications Tracking Messages Surveys About Me Files

Home

## Ben A. Zepiril

### Your Study Summary

Take Next Survey

Continue Survey

Completed Surveys

Tools and Updates

Next Steps

### Report Health Updates

Report a Hospitalization

Report a New Health Condition or Symptom

Record Changes to Medications

### Messages

Sort By: Date Received

< 1 - 3 of 4 >

03/20/2013 04:29 pm

Ben, We received your phone message, and we're happy to better explai ...  
Cora Dinator

03/03/2013 01:25 pm

Hi Ben, Yes, I am available to talk at 4pm today. Would you like me t ...  
Cora Dinator

02/28/2013 04:24 pm

You're welcome! We hope you find this study interesting and engaging.  
Cora Dinator

Send a New Message

### Latest Hypertension News

< 1 - 3 of 15 >

#### America: Time to shake the salt habit?

Medical researchers have written a review paper summarizing data linking excessive sodium intake to increased rates of hypertension, stroke and cardiovascular disease. Is it time for national policy? - March 26, 2013 08:17 AM

[\[view\]](#)

#### Uncontrolled hypertension could bring increased risk for Alzheimer's disease

A new study suggests that controlling or preventing risk factors such as hypertension earlier in life may limit or delay the brain changes associated with Alzheimer's disease and other age-related neurological deterioration. - March 18, 2013 05:04 PM

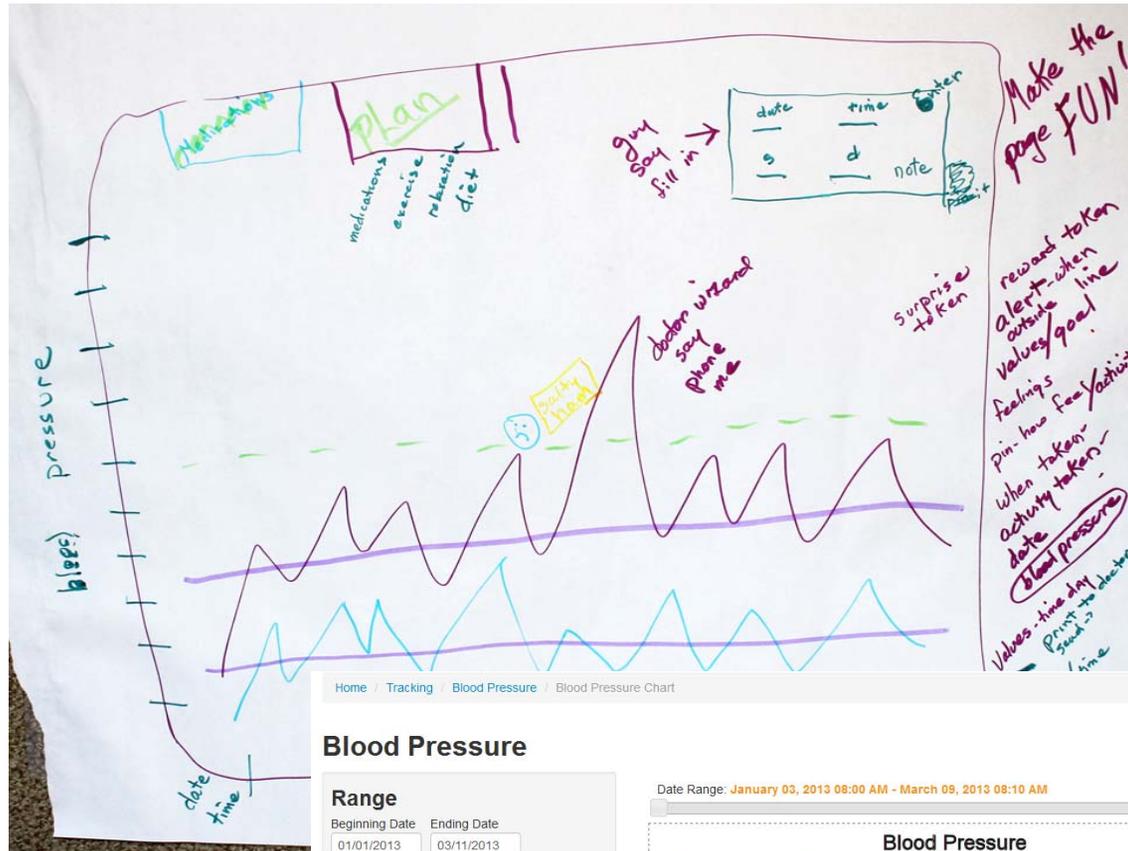
[\[view\]](#)

# PHR Design Sessions: Methods

## **Purpose:** Elicit ideas for engaging PHR design

- Participants aged 50-85; taking  $\geq 1$  anti-hypertensives; current computer users.
- Two groups of 10 adults met for a total of seven 90-minute sessions over five weeks
- 4-5 team members in attendance to facilitate sessions, field questions, assist with small group activities
- Open discussion, sketches, “sticky notes,” ranking exercise

From their designs.....



...to the web application

Home / Tracking / Blood Pressure / Blood Pressure Chart

print your blood pressure records

### Blood Pressure

**Range**

Beginning Date: 01/01/2013, Ending Date: 03/11/2013

Beginning Hour: 1, Ending Hour: 24

Last: Days or Last: Months

**Chart Display**

Systolic (top number)  
 Show Guideline  
 Diastolic (bottom number)  
 Show Guideline  
 Pulse  
 Show Guideline

Guideline values:  
Systolic (top number): 140 [reset]  
Diastolic (bottom number): 90 [reset]  
Pulse: 100 [reset]

[Update Chart]

Date Range: January 03, 2013 08:00 AM - March 09, 2013 08:10 AM

### Blood Pressure

Legend: ○ systolic, ○ diastolic

Jan 06 13 Jan 13 Jan 20 13 Jan 27 13 Feb 03 13 Feb 10 13 Feb 17 13 Feb 24 13 Mar 03 13

[Unlock Line]

- February 09, 2013 02:33 AM [Update Notes](#)
  - Blood Pressure : 127 over 65
  - Notes: Kids came to visit with the grandkids. We had a great few days together. Just left last night. House is a mess!

# What Did Patients Want in a PHR?

- A way to measure, track and send BP info
- Feedback on information entered
- A place to enter and store personal health information
- Easy access to their medical record
- A way to communicate with their physicians
- A way to improve inter-provider communication

# Engaging Patients as Partners in a Pragmatic trial (No \$ Compensation)

- Participants want:
  - *To know that their time and effort was genuinely appreciated, that their info matters*
  - *Occasional updates on study progress / findings*
  - *An authentic human connection*
- Study should be vetted by their physician

## Task 3: Validation of EMR Strategies to Identify Eligible Subjects & CV Events

- Algorithms to define eligibility and outcome events developed
- Sites worked with local IT groups to apply algorithms to EMR and billing data
- Upcoming:
  - *Comparison of algorithm results between sites*
  - *EMR record review of 100 positive and 100 negative eligibility screens*
  - *Adjudication of 150 outcome events*

# Subject Eligibility Validation (Duke Example)

Number of Patients	Category
117,310	HTN diagnosis (code 401-405), age 50-85 as of visit date and visit date 1/1/09 – 12/6/12
98,707	At least one comorbidity risk factor
38,763	2 encounters in past year (12/6/11 – 2/6/12)
31,392	Not meeting any exclusion criteria (metastatic cancer, cirrhosis, hepatic insufficiency, dementia, bilirubin > 2.5)
25,665	At least 2 BP measurements in past year

*\*Patients identified from Duke Decision Support Repository using Iowa codes*

# Subject Eligibility Validation (Duke)

<b>Patients</b>	<b>Risk Factors</b>	<b>ICD9 or CPT Codes</b>
<b>83,958</b>	Hyperlipidemia	272.0, 272.2, 272.4
<b>42,248</b>	Diabetes	250, 362.0x, 366.41, or 357.2
<b>33,416</b>	Other IHD	411, 413, or 414, but not 414.1x
<b>18,586</b>	CKD	582, 583, 585, 586, 587, 403, 404, 274.10, 440.1, 442.1, 453.3, 581, 593, 753.0, 753.3, 866.00, 866.01, or 866.1
<b>17,995</b>	CHF	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4 – 425.9, or 428
<b>13,016</b>	AMI	410 or 412
<b>11,821</b>	PAD	442 or 443
<b>11,310</b>	Stroke	430, 431, 434, 435, 436, or 433.x1

**\* No. of patients with each risk factor included in 98,707 on previous slide**

# CV Event Validation (Iowa Example)

- Retrospective analysis
- Study population:
  - *HTN diagnosed prior to 1/1/2011, alive and age 50-85 on 1/1/2011*
  - *Seen in system and on once daily medication in 2010*
  - *Any comorbidity risk factor prior to 1/1/2011*
- Two-year CV event rate:
  - *Among the study population, the proportion with  $\geq$  CV event during 2011 – 2012*

# CV Event Validation (Iowa Example)

- Eligible study population = 11,485
- Incidence of CV event during 2-year window = 1,220 (10.6%) or 5.3% per year
- Event types:
  - *Admissions for AMI, CVA, Other IHD, or CHF from ICD9 diagnosis codes = 638*
    - *CHF > AMI > IHD > CVA*
  - *Revascularizations (Epic) = 651*
  - *Deaths (Epic) = 548*

# Task 4: Review Sample Size Estimates (Sample Sizes Requirements per Group)

## Effect Size

Event Rate	10%	15%	20%	25%	30%	35%	40%
10%	16,509	7,145	3,910	2,433	1,642	1,378	869
15%	11,006	4,763	2,607	1,622	1,095	919	580
20%	8,255	3,573	1,955	1,217	821	689	435
25%	6,604	2,858	1,564	974	657	552	348

# Task 4a: Develop Robust Estimate of Effect Size

- Hermida RCTs → 65-70% reduction
- Benefits of HTN treatment in early placebo trials of treating moderate HTN (diastolic BPs 90-114)
  - *VA Coop Study (1970) → 65-70% reduction*
- Convene panel of experienced HTN trialists and obtain consensus estimate
- Identify prior RCTs that collected timing of dosing & conduct post hoc analyses to determine effects

## Task 4b: Develop Robust Estimate of Event Rate

- Identify EMR-based cohort of eligible patients as of 1/1/2011 & identify 2-year event rates → *5.3% per year for UI*
- Identify eligible cohort from Medicare claims data and estimate proportion of events occurring outside of UI and Duke
- Estimates of event rates from national cohorts of patients with HTN and prior RCTs
  - *ALLHAT combined CV event rate → 5.5% / year*
  - *CONVINCE CV event rate → 4.3% / year*

# Task 5: IRB Engagement r.e. Subject Recruitment & Informed Consent (IC)

- UI IRB agreed to use IRBshare, to an abbreviated IC document & to waiver of IC documentation → *obtain IC via web platform or 1-800 w/o signature*
- Because of patient randomization, trial could not be performed without IC process (even if MD or clinic-level clustered design was used)
- UI IRB was not favorable to “opt-out” approach → *subjects receive info letter & told they would be enrolled unless they opt out by returning postcard*
- Duke IRB might be more favorable to opt out

# Task 6: MD Engagement

## Key findings from large & small group meetings with GIM, FM, Nephrology, & Cardiology faculty

- *MDs unanimously thought study was important*
- *MDs across all practices unanimously preferred having a central PharmD contact patients and implement nighttime dosing protocols*
- *Opinion split on whether it was worthwhile for MDs to review eligible patients & make exclusions*
- *All practices emphasized importance of minimizing practice burdens & interruptions → use of Epic BPAs as enrollment prompt met with mixed reviews*

# Next Steps and Key Decisions

1. Refine online consent module and PHR based on the results of usability testing
2. Finalize sample size estimates → *decisions about estimates of effect size and event rate*
3. Review key design elements in light of sample size that may be required
  - *Continue dialogue with IRB and MD groups r.e. opt out consent strategy*
  - *Consider identifying additional study sites*