Nighttime Dosing of Anti-Hypertensive Medications

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Investigative Team

University of Iowa

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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)
- Sleeptime 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 & ≥ 1 comorbid conditions that increase cardiovascular risk*
  - *Active prescriptions for ≥ 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 ≥ 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 form 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

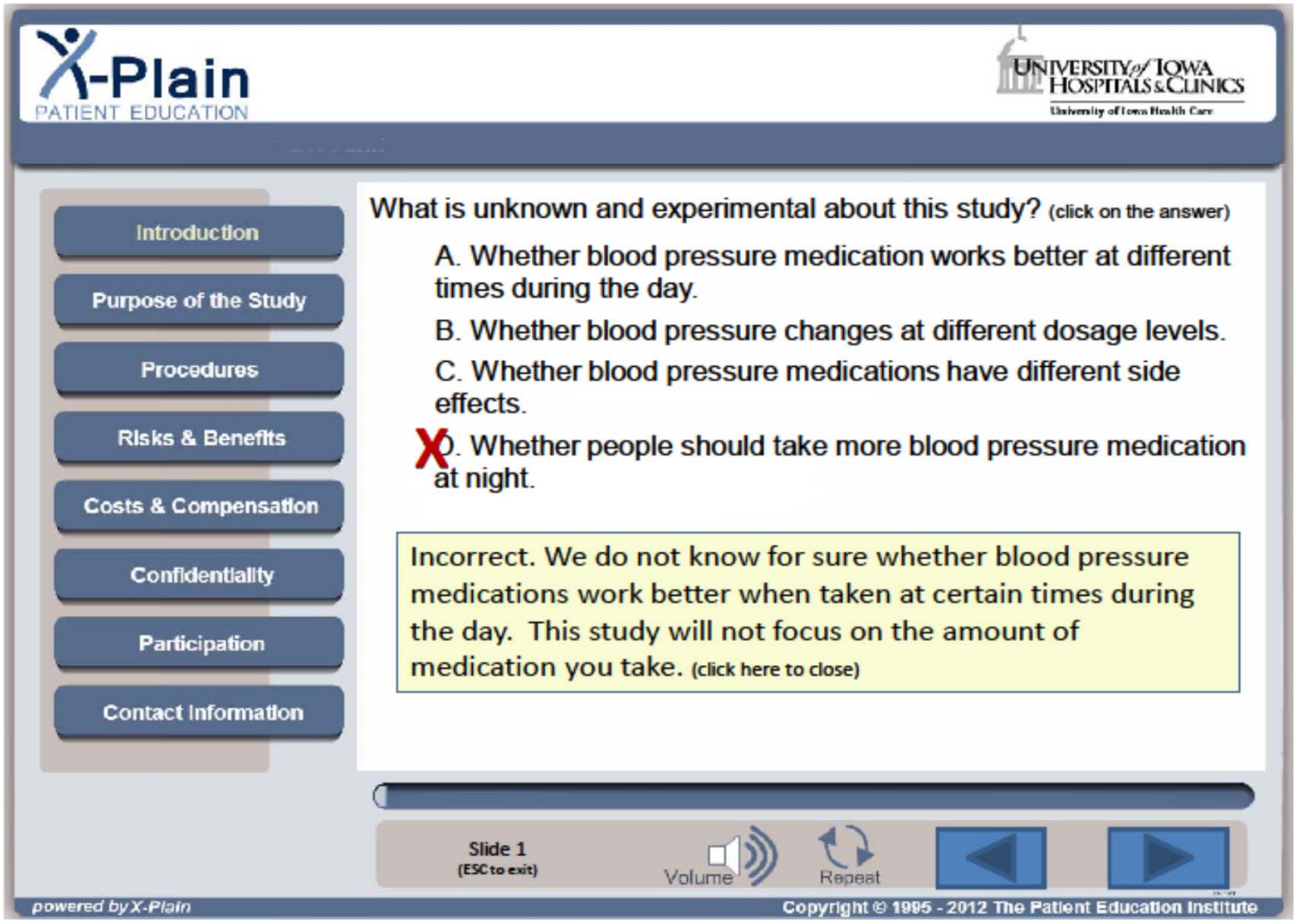
Key UH2 Tasks

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

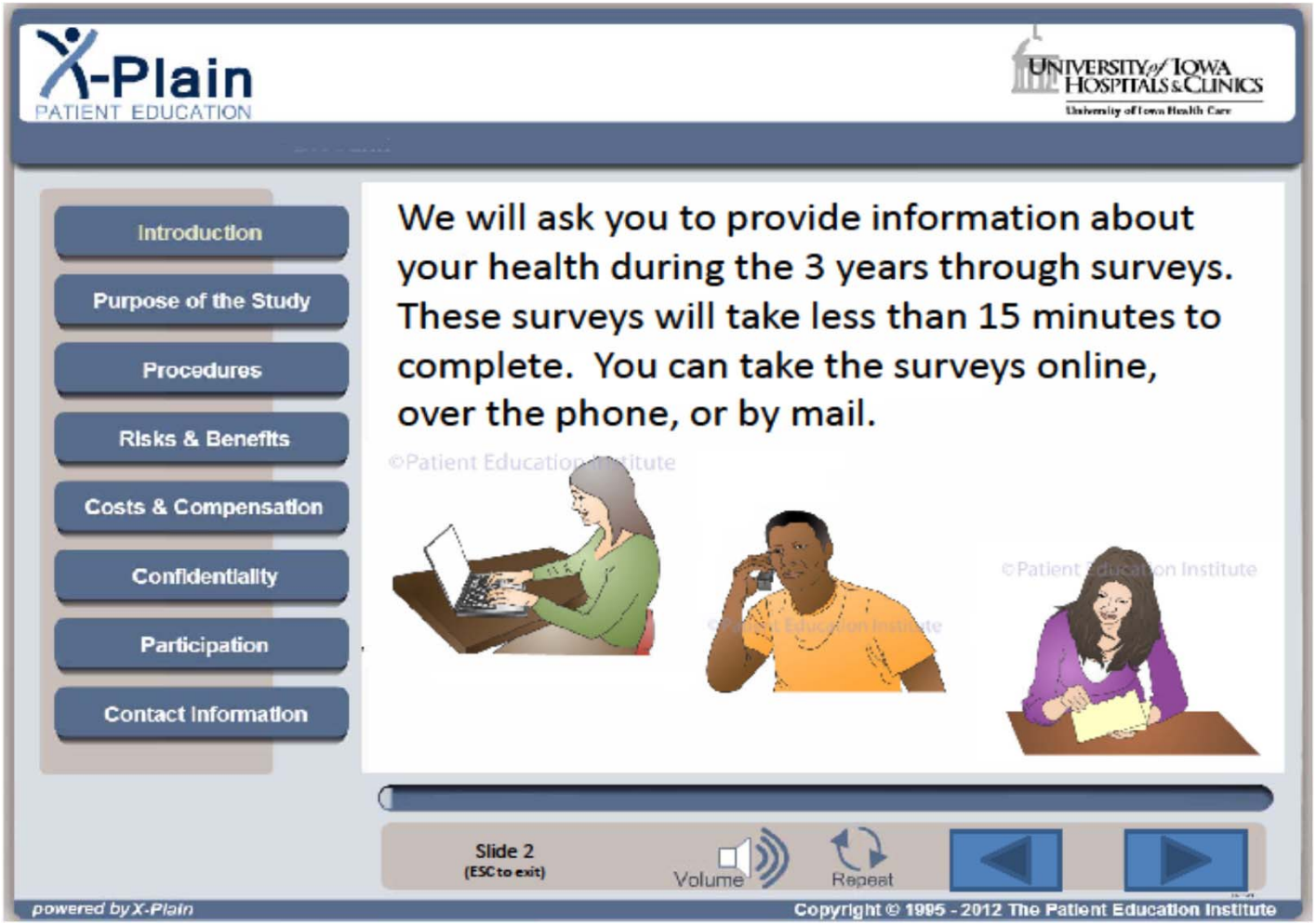
Task 1: Develop Interactive Online Informed Consent (IC) Module

- 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



Collection of Project Data via Module



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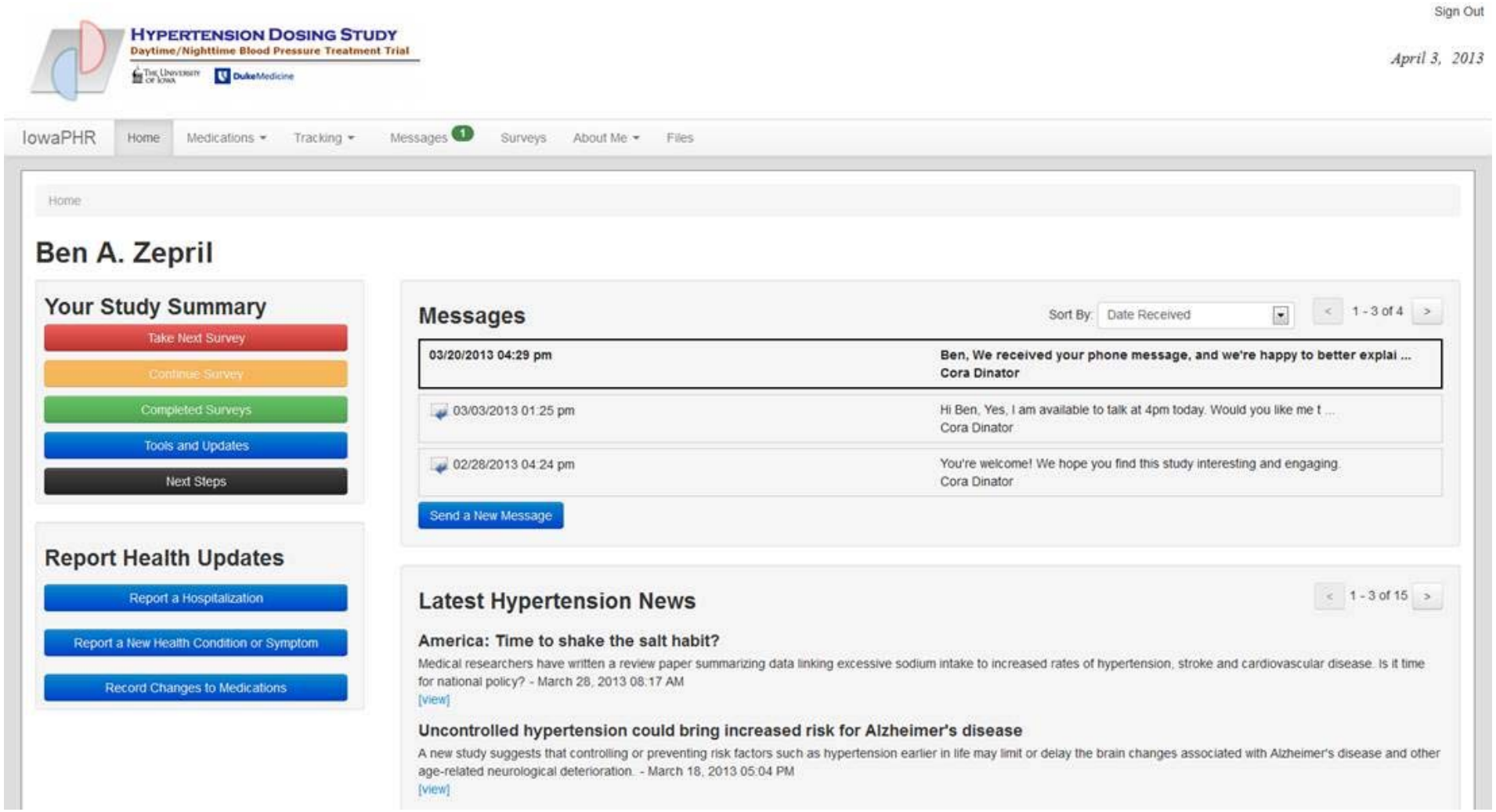
Task 2: Develop PHR

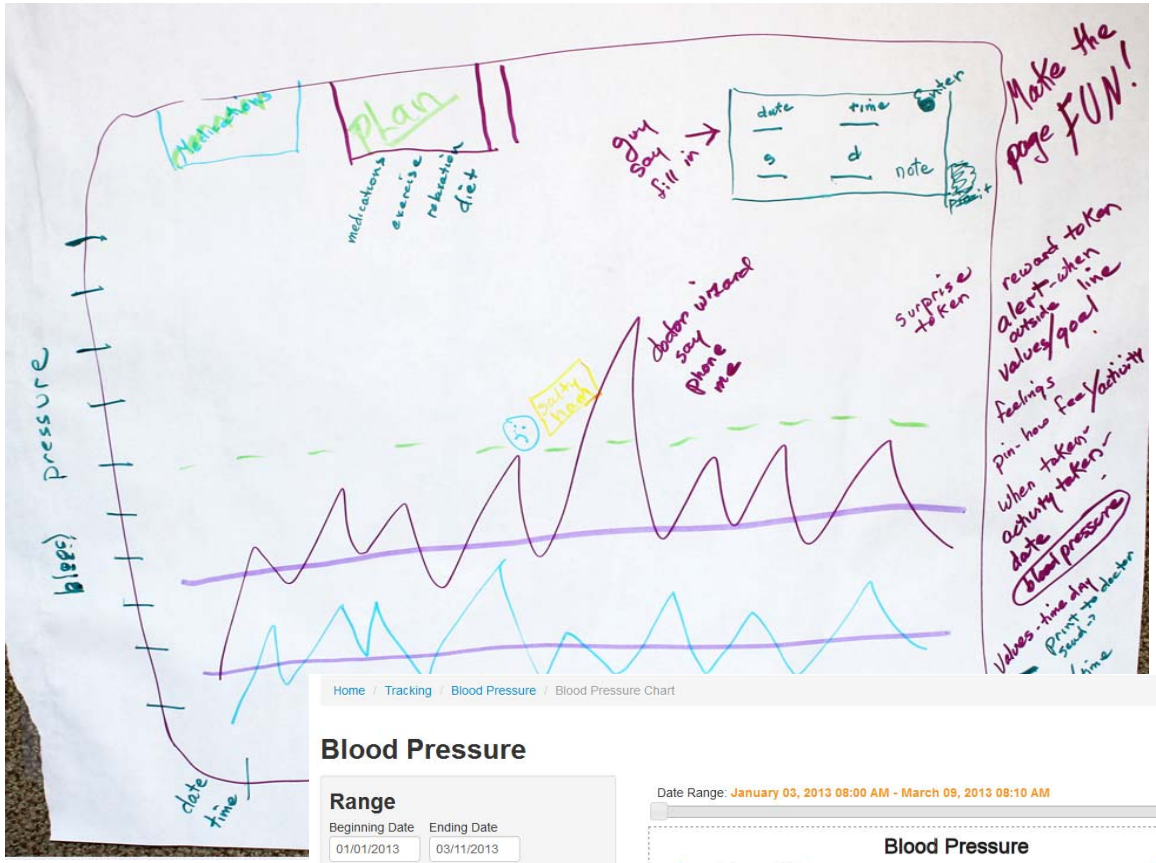


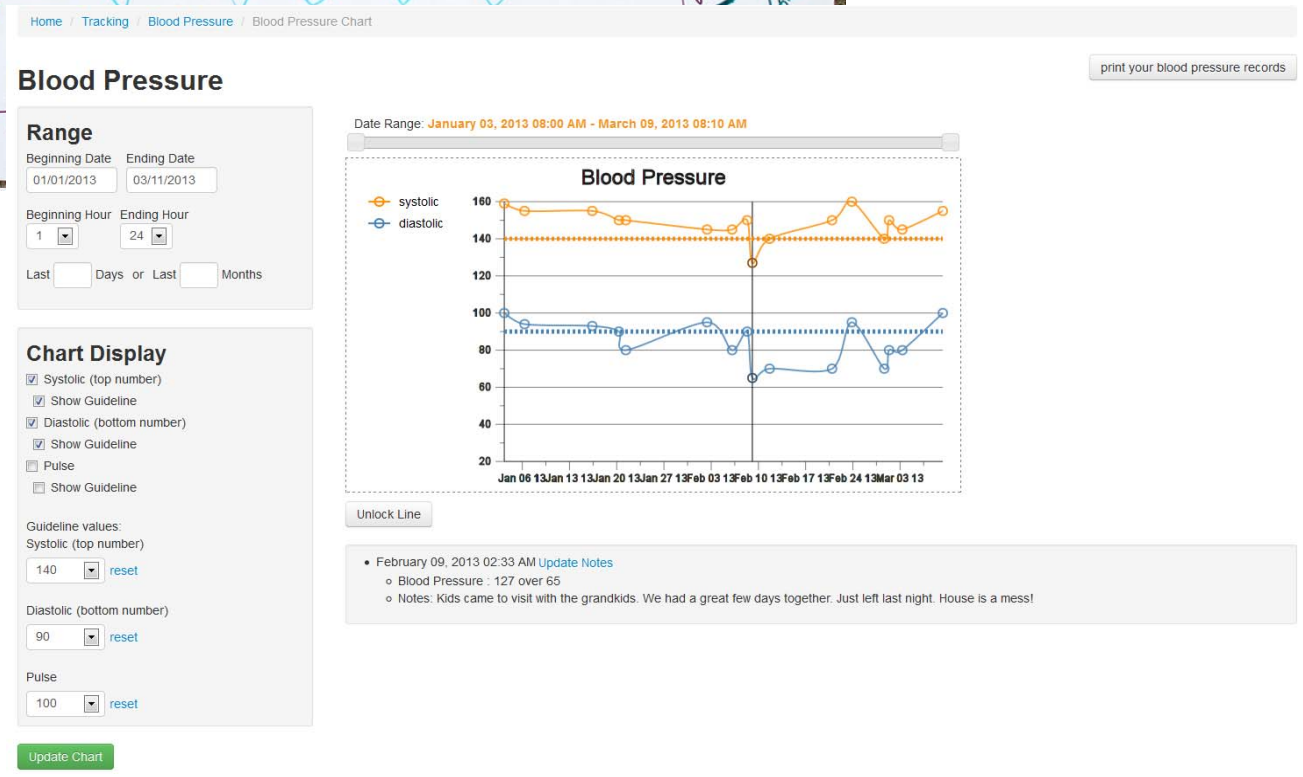
PHR Design Sessions: Methods

Purpose: Elicit ideas for engaging PHR design

- Participants aged 50-85; taking ≥ 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

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)

Patients	Risk Factors	ICD9 or CPT Codes
83,958	Hyperlipidemia	272.0, 272.2, 272.4
42,248	Diabetes	250, 362.0x, 366.41, or 357.2
33,416	Other IHD	411, 413, or 414, but not 414.1x
18,586	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
17,995	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
13,016	AMI	410 or 412
11,821	PAD	442 or 443
11,310	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 ≥ 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*