Blood Pressure Medication Timing Study (BPMedTime)

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Blood Pressure Medication Timing Study (BPMedTime)

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University of Iowa

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Overview of Presentation

- Rationale and aims of the proposed UH3 trial
- Overview of trial design
- Strategies for subject recruitment, obtaining informed consent, implementing nighttime doing intervention, and data collection
  - *Recent refinements to improve efficiency and decrease costs*
- Next steps in preparing for UH3 trial

Rationale for Pragmatic Trial

- BP exhibits circadian variability → *lower during sleep ("nighttime dipping") with increase on arising (may explain excess risk of AMI during early am)*
- 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 & is particularly common in DM and CKD

Rationale (cont.)

- Many once-daily BP meds require 60-90 minutes to achieve peak plasma levels after ingestion & do not sustain plasma levels for a full 24 hours.
- Thus, when taken in AM, plasma levels may not be high enough to protect against AM surge in BP
- Three recent Spanish trials led by Hermida found that patients randomized to take ≥1 BP meds at night had a roughly 65% reduction in CV events
  - *Death, AMI, CVA, TIA, angina, coronary revascularization, lower extremity arterial occlusion, retinal artery thrombosis*

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 the 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 BP medications on:
   - *CV events → primary endpoint*
   - *clinic BPs, self-reported medication adherence, HRQOL, and healthcare utilization → secondary endpoints*
2. Implement EMR-based approaches to increase the efficiency of subject recruitment and web-based platforms for obtaining informed consent and collecting patient-reported outcomes

Overview of Trial Design

- 2 partnering study sites: University of Iowa & Duke University
- Subjects identified from EMR eligibility criteria
  - *Diagnoses of HTN & ≥ 1 comorbid conditions that increase cardiovascular risk*
  - *Active prescriptions for ≥ 1 once-daily anti-hypertensive medications (excluding diuretics)*
  - *Prior visits to General Medicine, Family Medicine, Cardiology, or Nephrology clinics*

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Overview of Trial Design (cont.)

- Patient-level randomization → *Eligible patients randomized to: (1) nighttime dosing of ≥ 1 more BP medications or (2) control*
- Informed consent obtained using online interactive module (preferred) or mailed consent letter
- Patients followed for 36-42 months with f/u contacts every 6 months via online PHR or survey
- Primary and secondary endpoints obtained from EMR, PHR, written surveys, and extant data (Medicare claims, hospital discharge abstracts, & death certificates)

Overview of Trial Design (cont.)

Primary Endpoint

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

Secondary Endpoints

- Clinic BP during outpatient visits
- Self-reported med adherence
- Health-related quality of life
- Resource utilization (counts of admissions, ER visits, and clinic visits)

Overview of Trial Design (cont.)

Analytic Approach

- Analyses will use generalized linear models (*ie, Poisson or negative binomial regression*) for **event counts** of binary endpoints, including the primary outcome – CV events
- Independent variables in the model will include study group, study site, and baseline covariates that are found to differ between the study groups
- Models will be fit using generalized estimating equations (GEE) method to account for possible correlation of outcomes between subjects of the same MD

Overview of Trial Design (cont.)

Analytic Approach – Sample size determination

- Assumptions underlying sample size estimation of **2607 patients** per group:
  - *Attrition rate of 10% per year, resulting in average follow-up of 2.7 years*
  - *Statistical test compares Poisson rates between patients in intervention and control groups*
  - *Event rate in control group of 0.05 per-person year with power to detect 20% relative difference in event rates between intervention and control groups*
  - *2-tailed test with α = .05 and power = 0.80*

Sample Size Requirements per Group in Relation to Event Rate & Effect Size

Effect Size of Nighttime Dosing

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

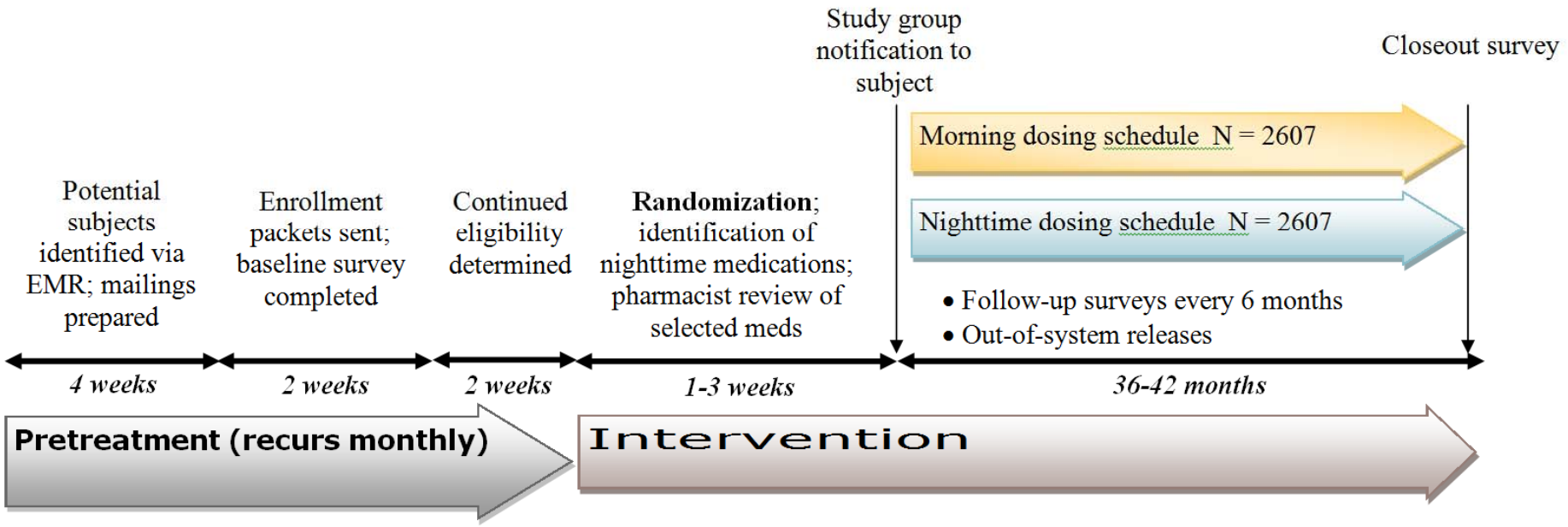
Key Modifications to Study Design and Implementation

1. Changes to study protocol changes to allow for increased sample size (1,160 → 5,200) to reflect the smaller effect size (i.e., 20%).
   - *Result is a more efficient, pragmatic design*
   - *Take advantage of expanded primary care sites via new UI Health Alliance ACO*
2. Protocol changes to collect documentation of consent (due to ongoing OHRP deliberation about minimal risk determination)
   - *Potential decrease in efficiency*

Key Modifications to Study Design and Implementation (cont.)

3. Strategies to enhance data collection efficiency
   - *Events for primary endpoint (admissions for AMI, CVA, IHD, CHF, and revasc) determined from billing codes in lieu of clinical adjudication of event as originally planned*
     - *EMR & billing data as source for events at UI & Duke*
     - *Medicare claims data for out of system events for fee for service Medicare beneficiaries*
     - *Hospital discharge summaries for out of system events events in non-Medicare patients and events in Year 4 for Medicare beneficiaries*
   - *Scaled back PHR & survey data collection for secondary endpoints (HRQOL, adherence, and adverse events)*

Protocol for Recruitment & Implementation of Nighttime Dosing



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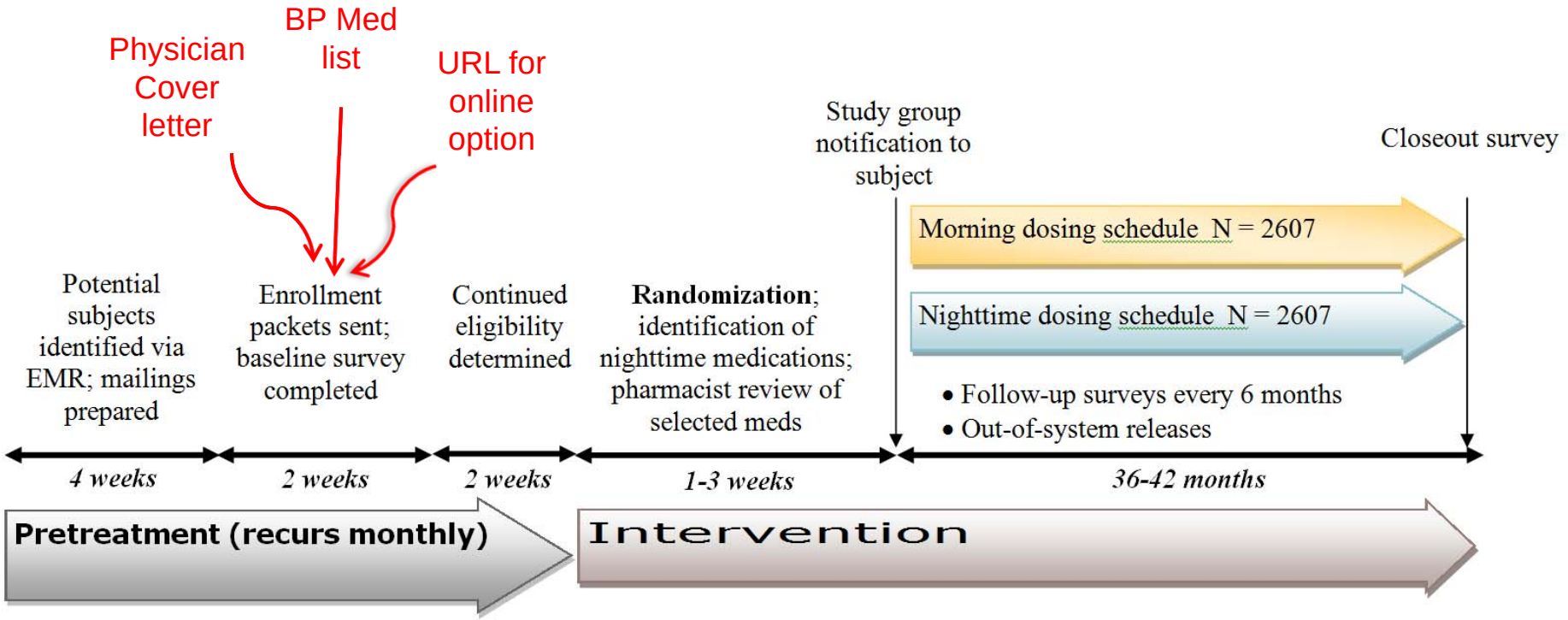

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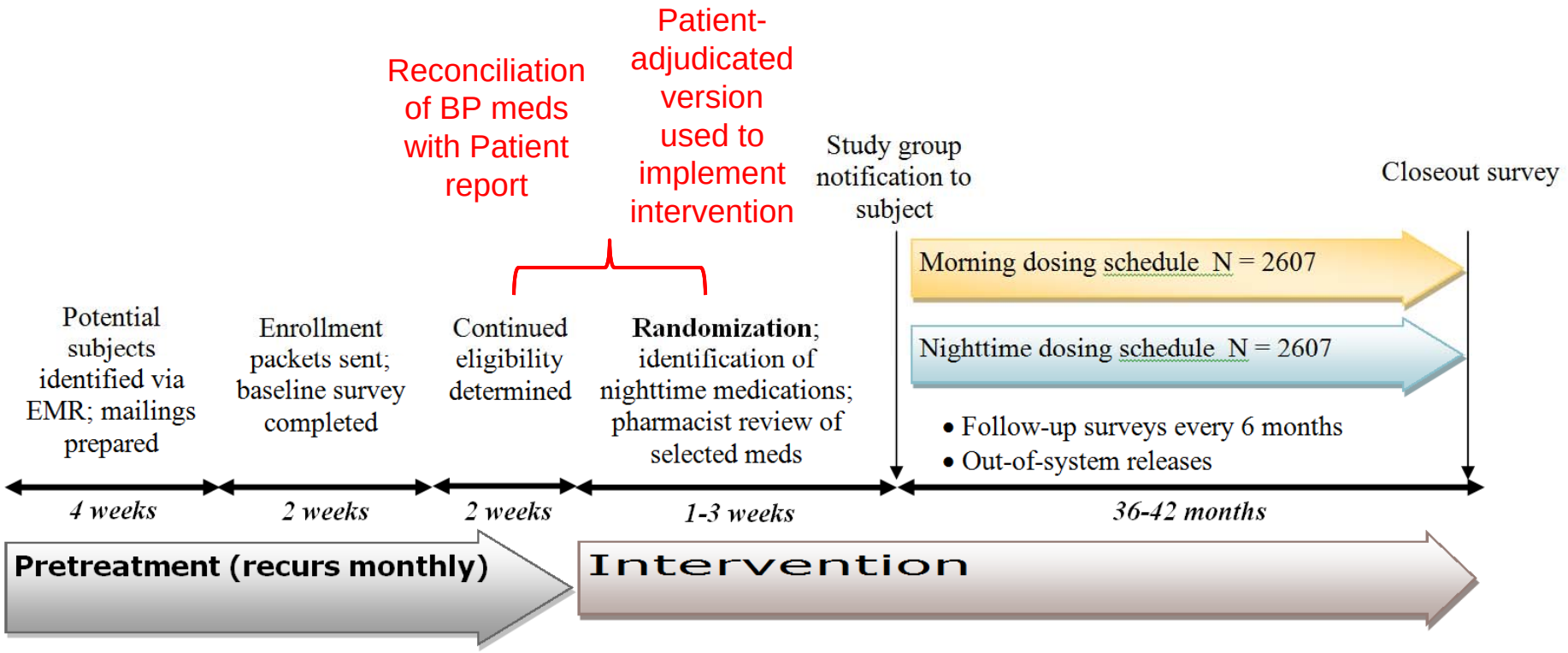

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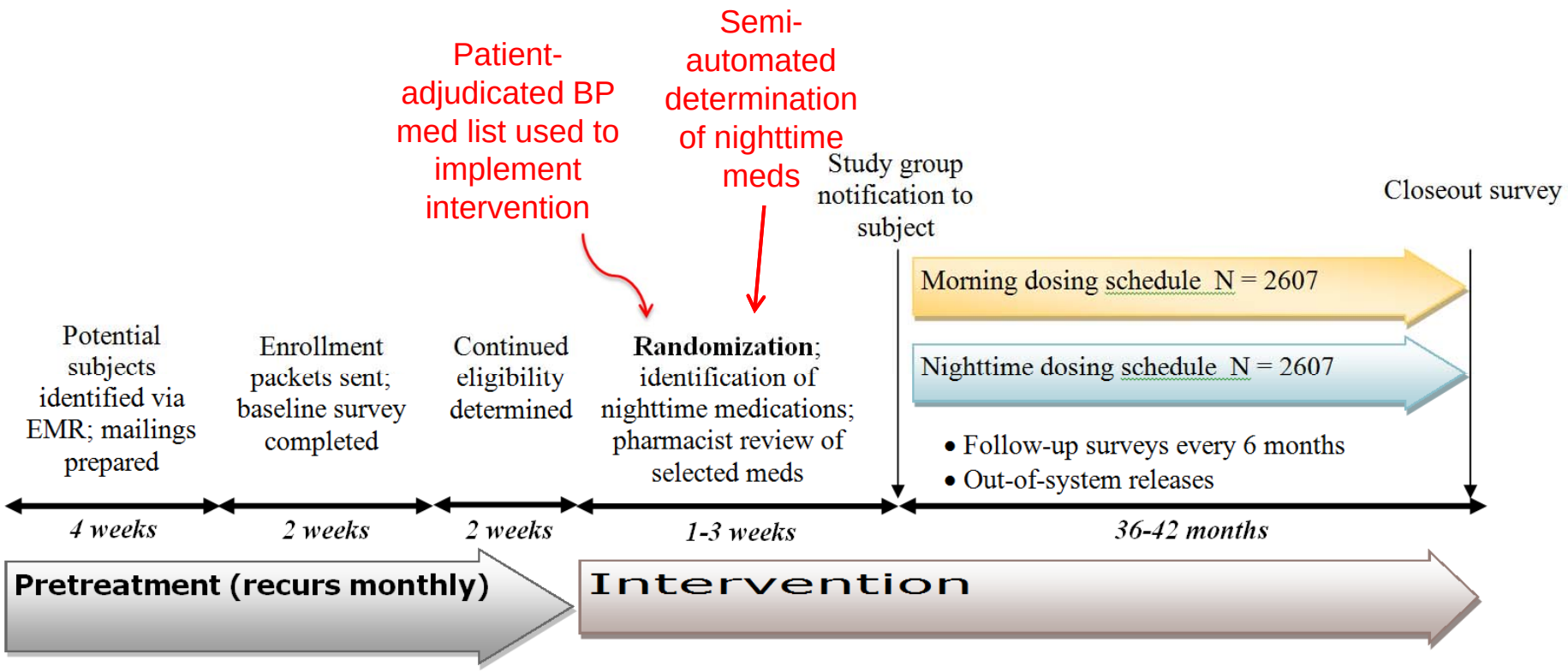

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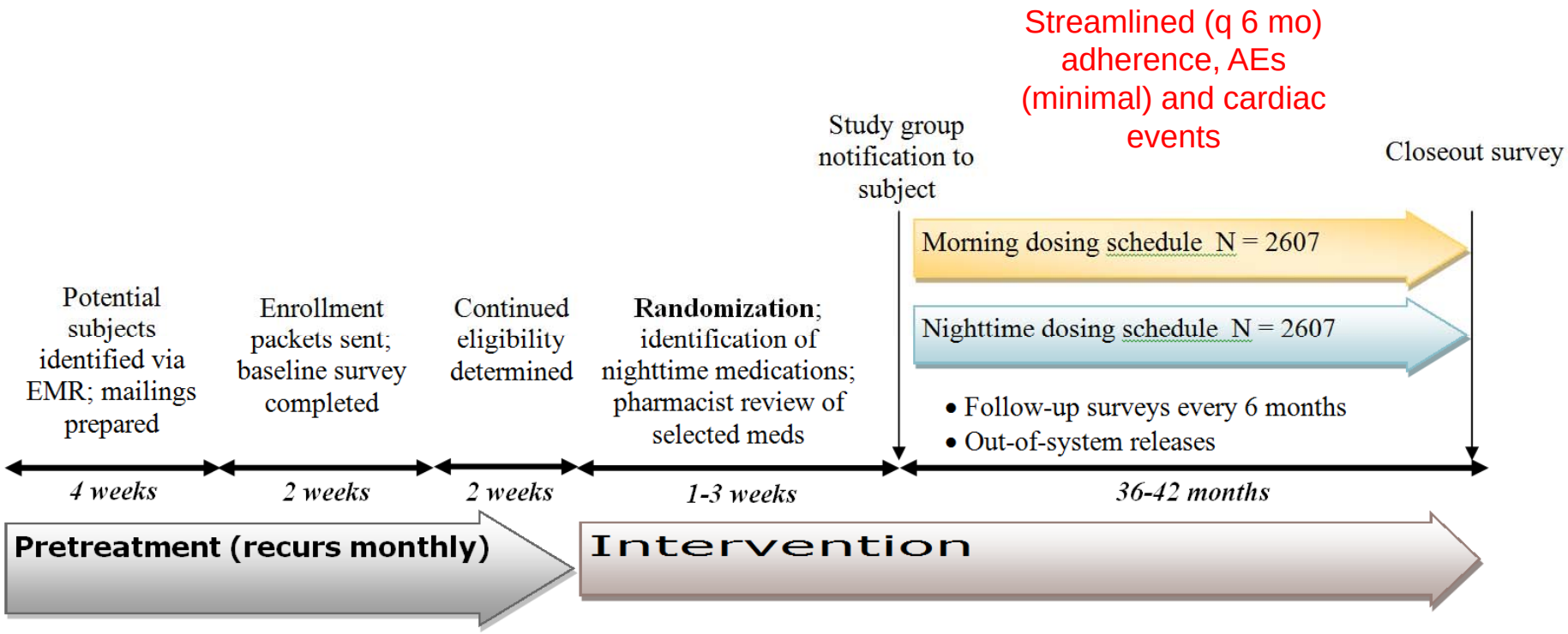

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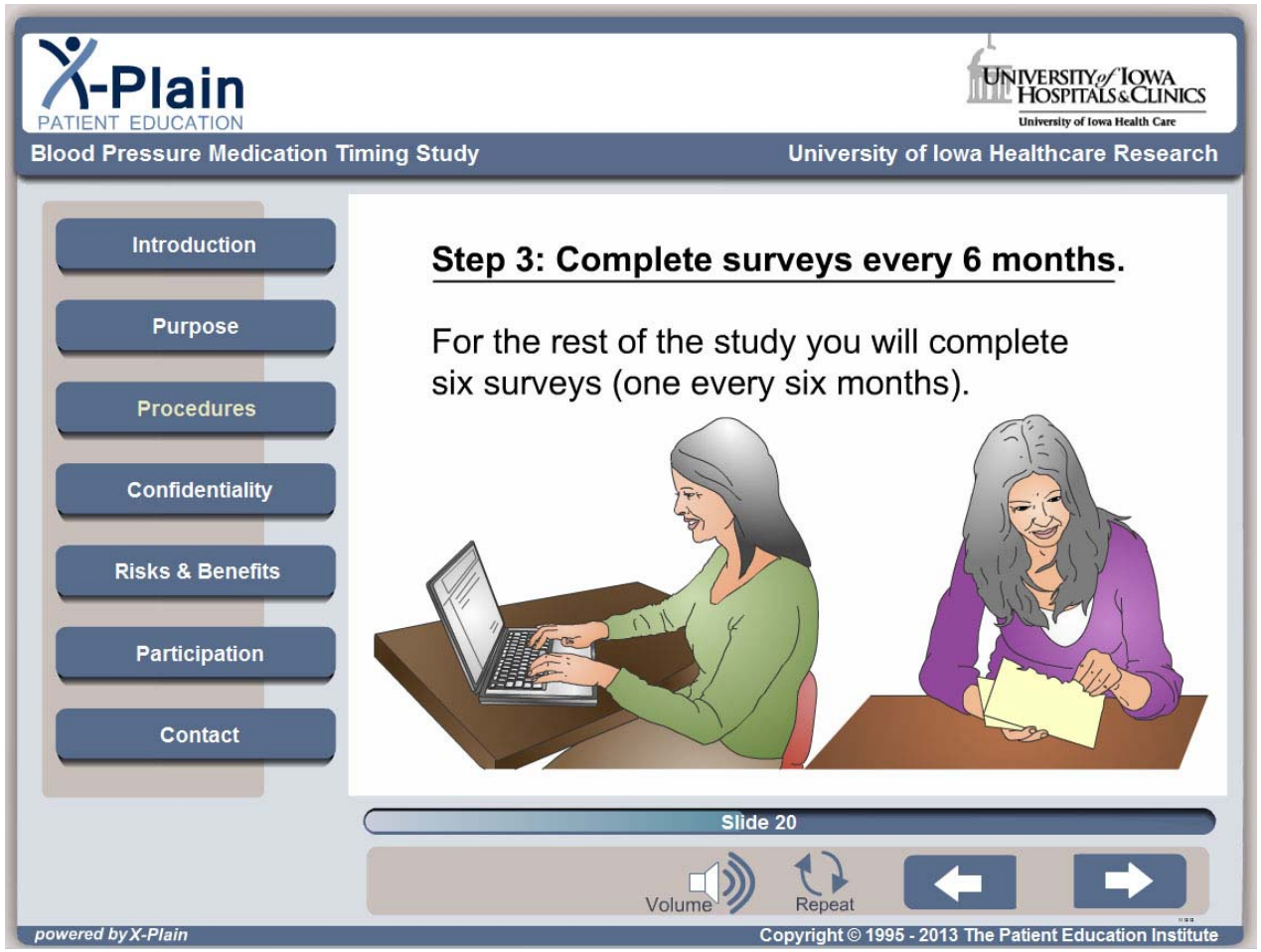
Updates on Other UH2 Tasks

- ✓ Detailed study protocol submitted to NHLBI for formal review by Protocol Review Committee on August 13th
- ✓ Online informed consent module developed
- ✓ PHR developed for collecting PROs, medication adherence, and out-of-system CV events
- ✓ Engagement of participating physicians to determine their study design preferences & attitudes

Status of Interactive Online Informed Consent (IC) Module

- Preliminary data → Compared to traditional paper-based IC process, online module improved ($p<.05$) subjects' understanding of mock study & satisfaction with IC process
- Initial PowerPoint version
  - *developed and tested for usability and comprehension with 5 people with hypertension, age 50-85.*
- Revisions incorporated into online module
- Testing of the active module set to begin
  - *One-on-one observations (with think-aloud) and structured questionnaire*
  - *Two focus groups (hi and lo SES) after users work with online and paper versions*

The IC Module Today



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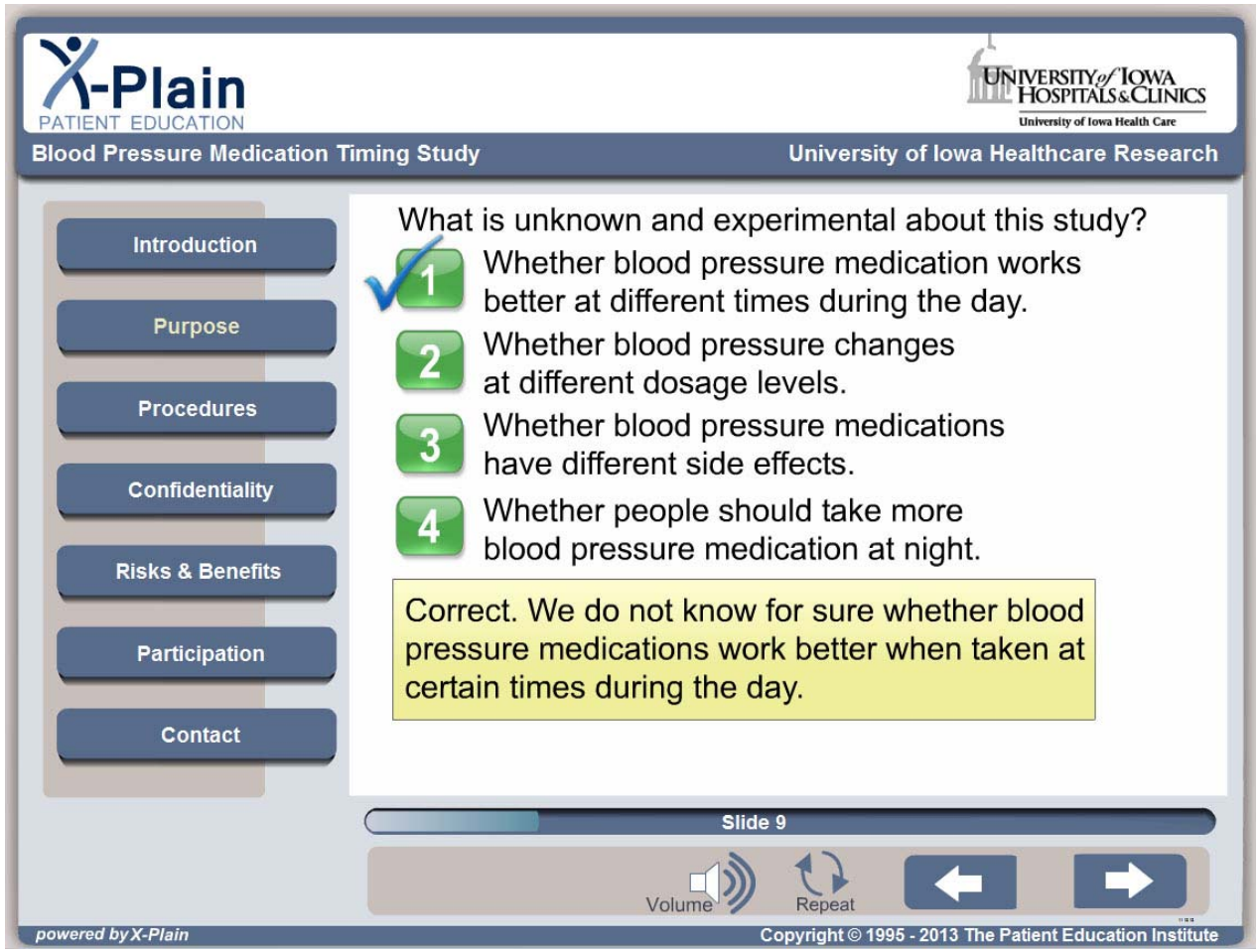
Interactive: Feedback on understanding reason for the study



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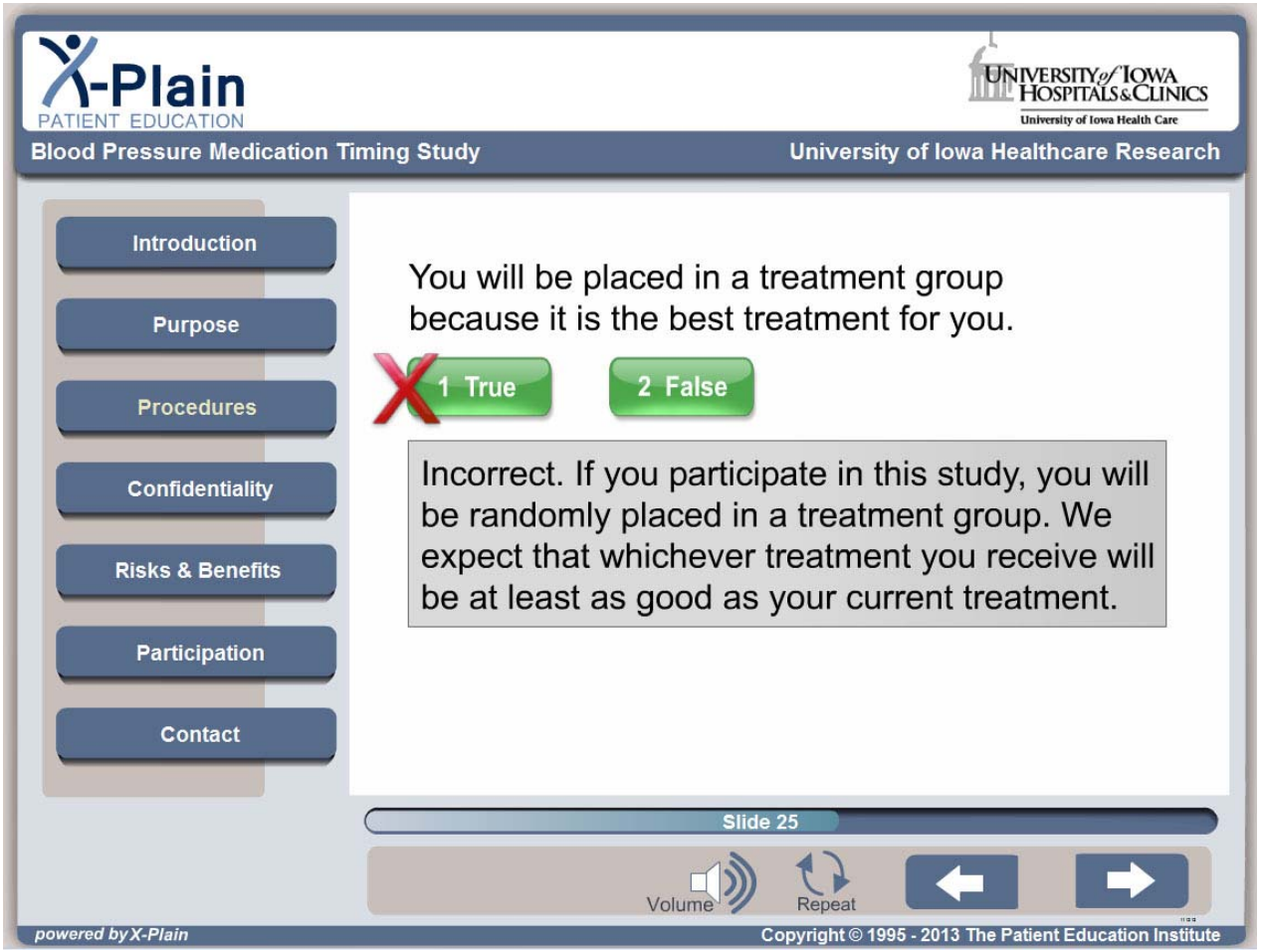
Interactive: Feedback on understanding study procedures



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Status of PHR

- Elicited ideas for an engaging PHR design
  - 2 groups of 10 patients, 7 90-minute sessions
- Patients wanted
  - A way to measure, track and send BP info
  - Feedback on information entered
  - A place to enter and store personal health information
  - Occasional updates on study progress/findings
  - To know their information matters
  - The feel of a human connection
  - Study vetted by their physician
- Revised PHR web application ready for usability testing

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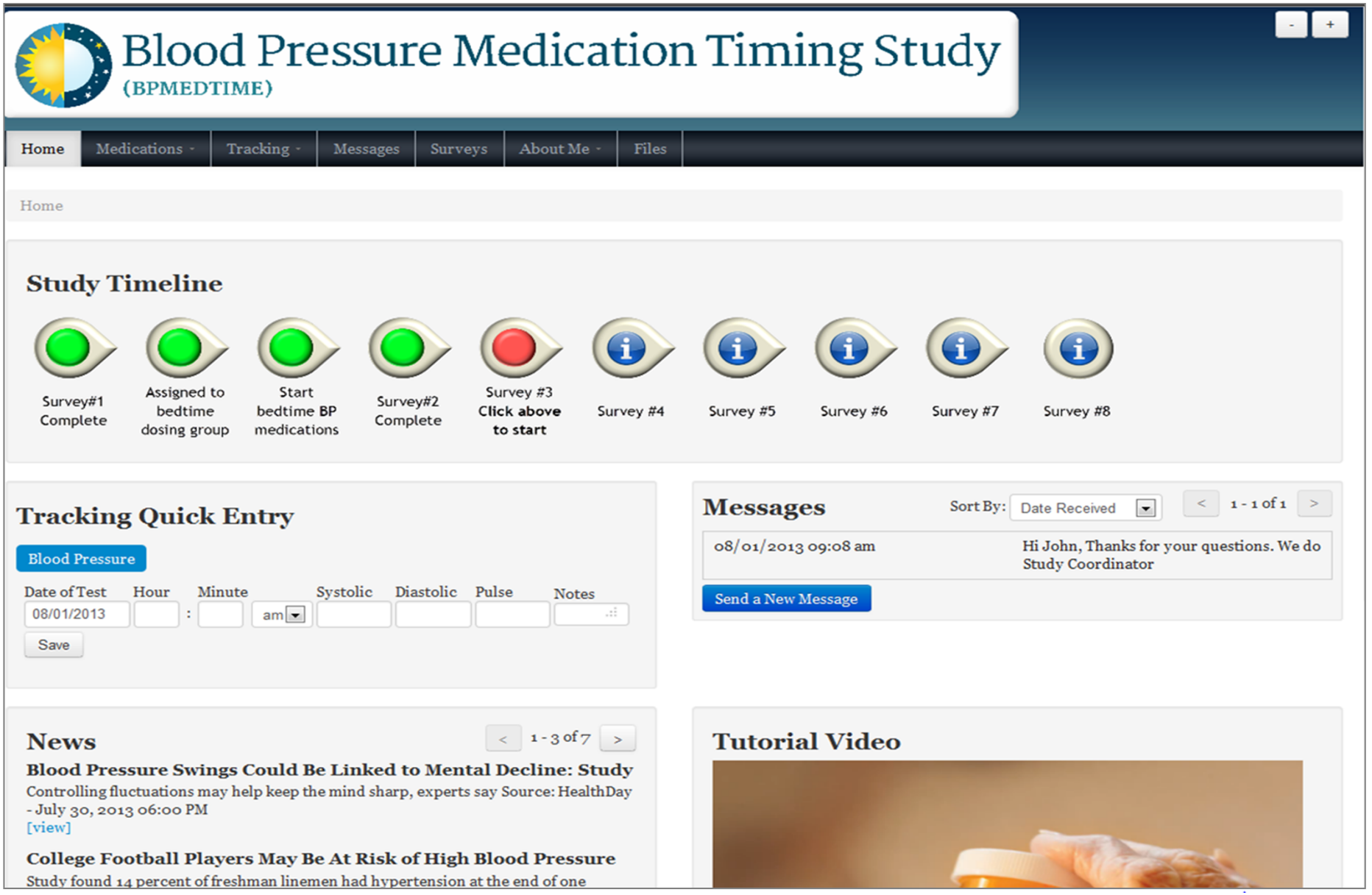
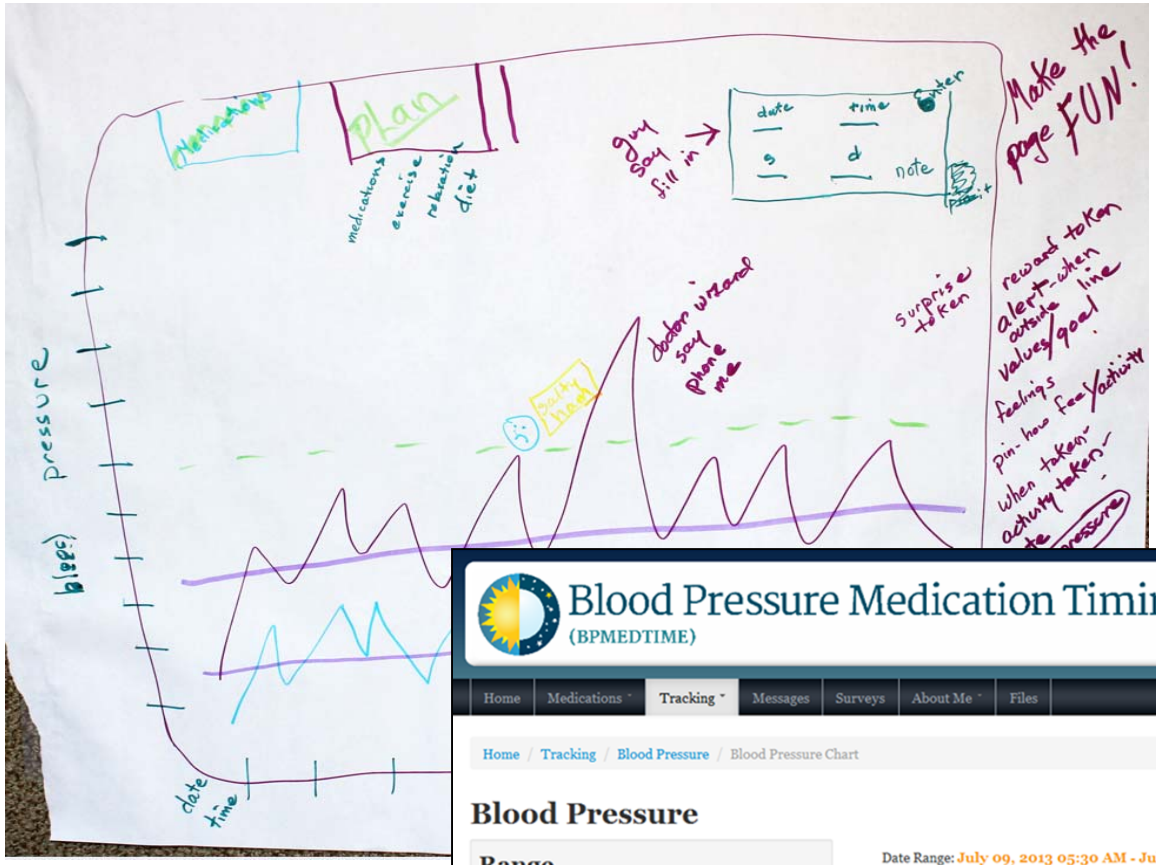
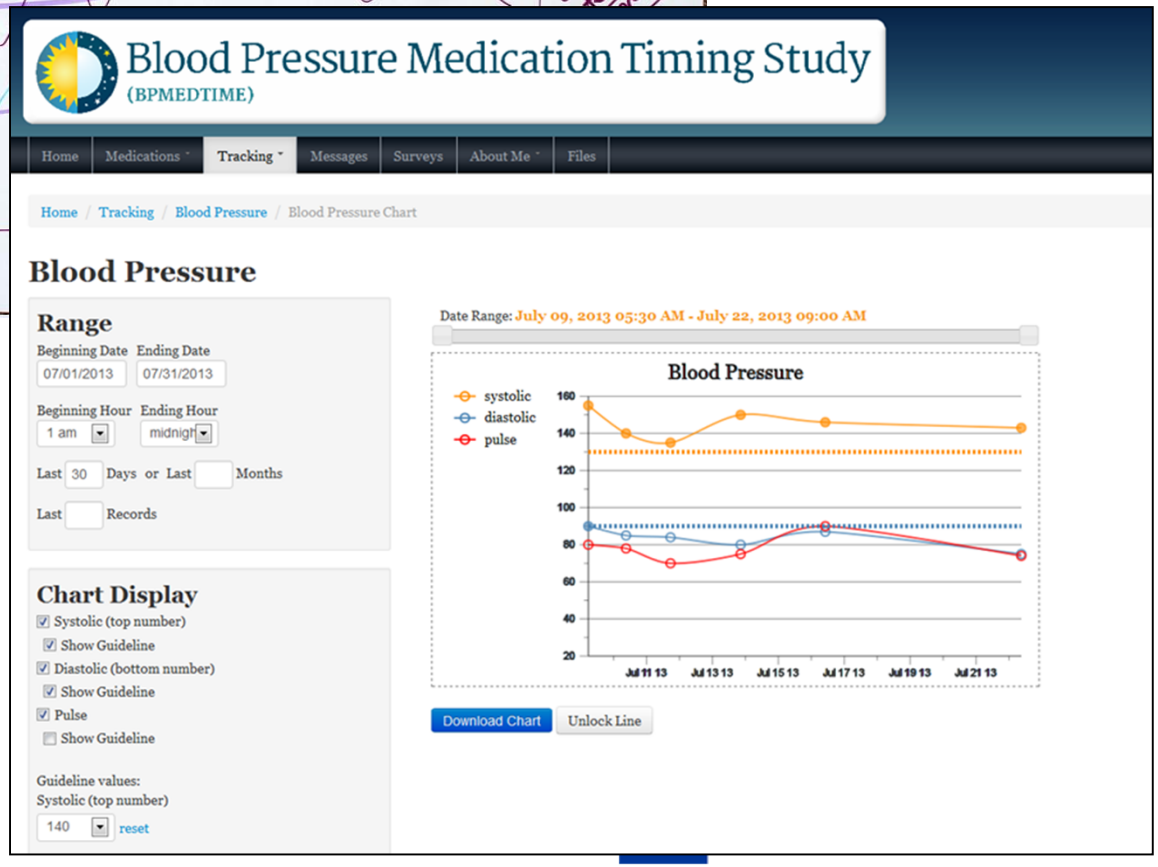
The PHR Today



From their designs…..





…to the web application

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MD Engagement and Integration of MD Preferences into Study Design

Findings from small & large group meetings with MDs

- *MDs unanimously thought study was important*
- *All practices preferred having central mechanism for implementing nighttime dosing and preferred pharmacist oversight*
- *Most MDs did not feel it was worthwhile for MDs to review eligible patients & make exclusions*
- *All practices emphasized minimizing practice burdens & interruptions → use of Epic BPAs as enrollment prompt met with mixed reviews*

Next Steps to Prepare for UH3 Trial

1. Incorporate recommendations from NHLBI PRC (meets August 13)
2. Field test algorithms for generating patient instructions for implementing nighttime doing intervention from EMR data
3. Make final refinements to PHR and online consent module based on second round of usability testing
4. Identify definitive approach for documenting consent if required by OHRP review
5. Capitalize on UI ACO with integrated EMR to expand UI study sample base