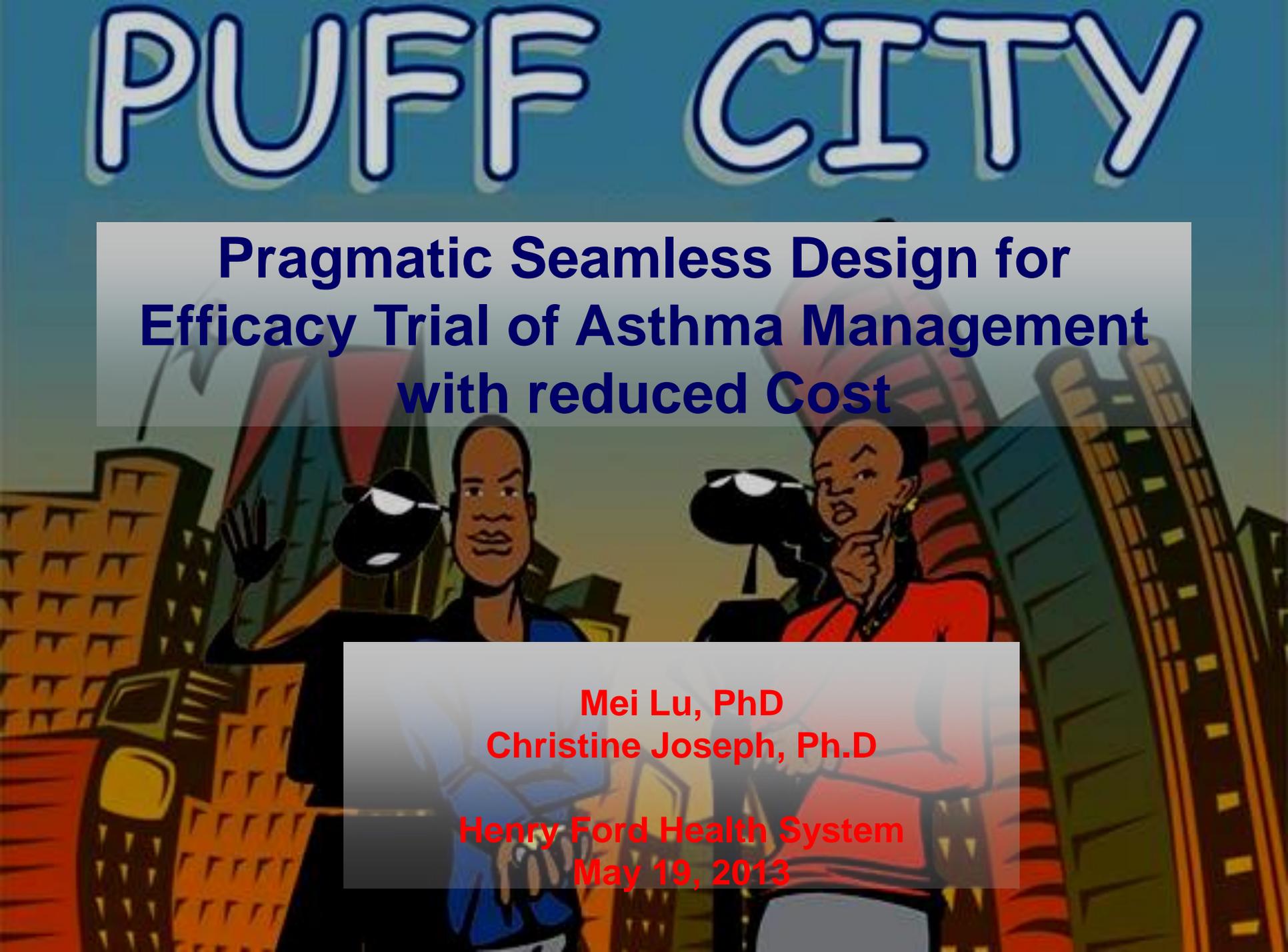


PUFF CITY

A stylized illustration of a city scene. In the foreground, a man in a black suit and a woman in a red top are looking towards the right. The background features several tall buildings and a yellow car. The overall style is reminiscent of a comic book or a graphic novel.

Pragmatic Seamless Design for Efficacy Trial of Asthma Management with reduced Cost

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Henry Ford Health System

May 19, 2013

Puff City Pragmatic RCT: Partners

- HFHS Clinical sites
 - Kaiser Permanente Georgia
 - Center for Health Communication Research
University of Michigan
 - Co-Investigators:
 - Dennis Ownby, MD (consultant/medical advisor)
Georgia Regents University
Augusta, GA
 - Douglas Roblin, PhD
Kaiser Permanente Georgia
Atlanta, GA
 - Edward Zoratti, MD
Henry Ford Health System
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Outlines

- Background:
 - The current status of clinical trials
 - Motivation - RFA-- Pilot Studies to Develop and Test Novel, Low-Cost Methods for the Conduct of Clinical Trials
 - Effectiveness of tailored asthma management in urban teens (Puff City)
 - Modifying Puff City for initiation in a clinical setting

- Study design –pragmatic approach
 - RCT parameters (inclusion/exclusion, blinding, randomization, etc)
 - Seamless phase II/III design
 - Data collection
 - Controlling cost

- Study conduct
 - Identifying eligible patients
 - Enrollment process
 - Dissemination

– Status of the trial

Current Status of Clinical Trials

Clinical Trials are critical for medical decision making, however, under the current paradigm...

...only 7% of eligible patients enroll in a clinical trial

...86% of all trials fail to meet enrollment milestones

...study populations of clinical trials often lack diversity or do not represent the targeted population

...the cost of implementation is high (e.g., recruitment and enrollment of participants, follow-up of participants, and data collection) such as using the trial visit instead routine clinical visit; using trial specific data rather than patient's medical records

...results often cannot be replicated in clinical practice

Motivations

- In 2011, RFA from NHLBI -- Pilot Studies to Develop and Test Novel, Low-Cost Methods for the Conduct of Clinical Trials
 - RFA required to test the low-cost methods the trial conduct on a fully developed study treatment or intervention.
 - Responded to the RFA with several methods to reduce the trial cost including
 - A seamless adaptive study design and pragmatic approaches
 - Puff City asthma management intervention in urban teens with asthma.
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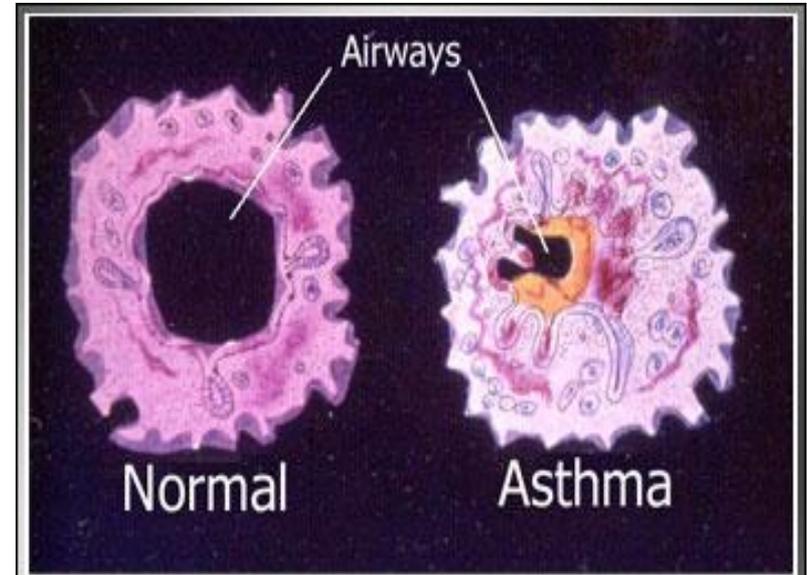
Asthma

DEFINITION

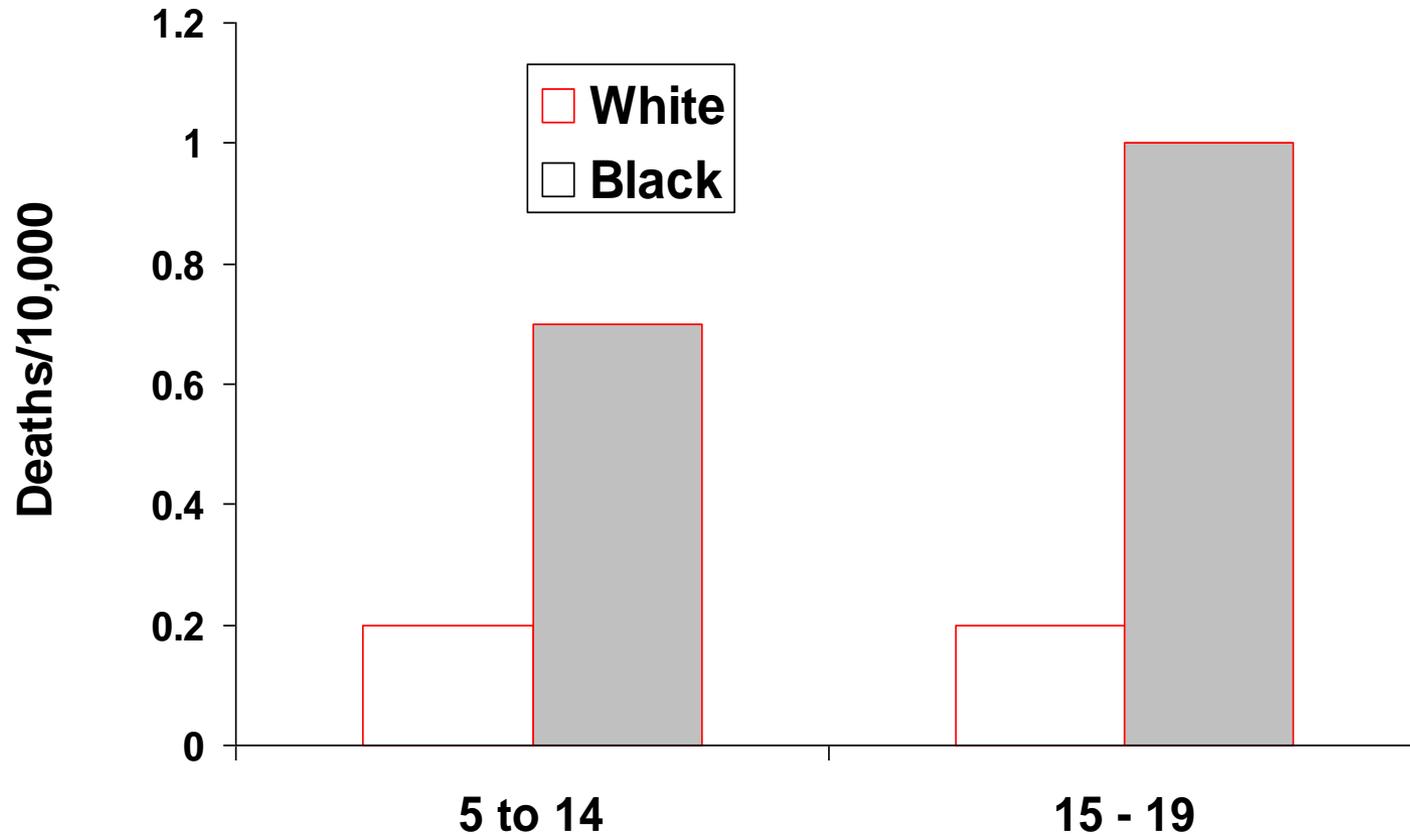
- Airway hyperresponsiveness
- Reversible airway obstruction
- Airway inflammation

TREATMENT

- Clinical Management
 - Assessment of severity
 - Identification of triggers
 - Bronchodilators (Rescue)
 - Anti-inflammatory (Controllers)
- Patient self-regulation
 - Trigger avoidance
 - Assess need for adjusting medication
 - Recognize need for emergency care
 - Partner with health care provider



Average annual number of asthma deaths per 10,000 persons with current asthma, by age and race, National Vital Statistics System, US, 2001–2003



**Centers for Disease Control and Prevention. Surveillance Summaries. MMWR 2007;56.*

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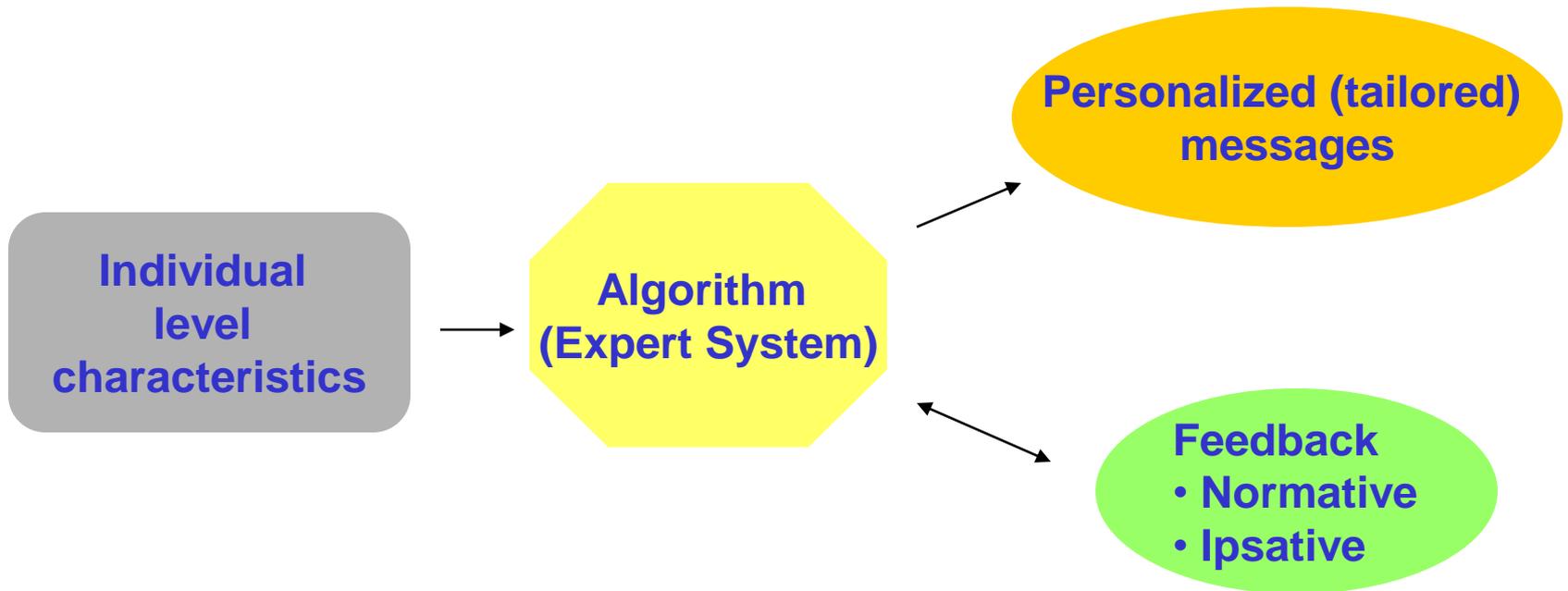


Puff City objectives: Improve asthma control

- Motivate teens to adopt positive behaviors
 - Controller medication adherence
 - Having a rescue inhaler nearby
 - Smoking cessation/reduction
 - Reduce asthma-related morbidity
 - Acute care visits (emergency department visits)
 - Hospitalizations
 - Improve functional status
 - Symptom-days, nights
 - Days of restricted activity
 - School days missed
-

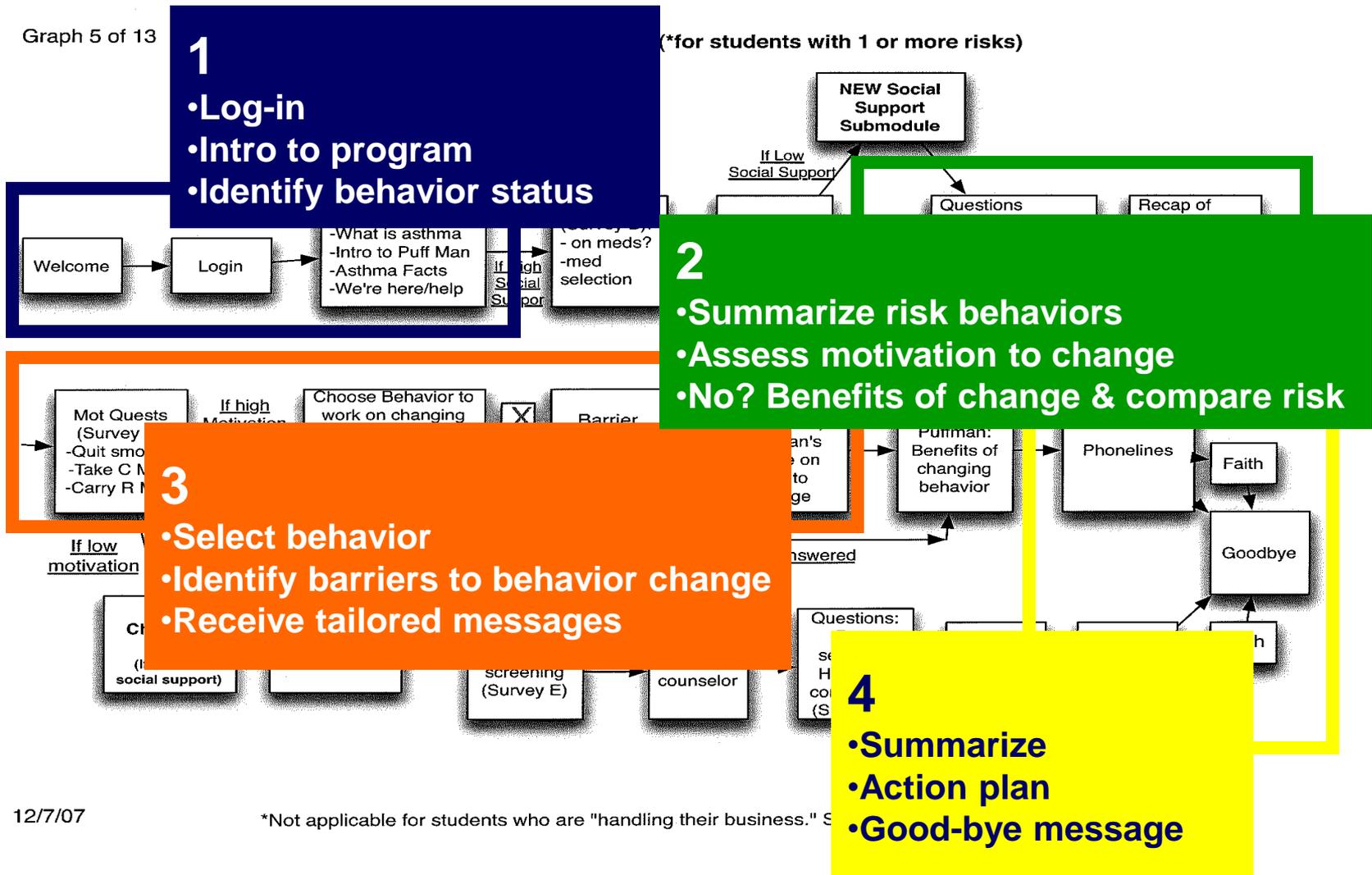
Tailoring

“...information or change strategies intended to reach one specific person, based on characteristics...unique to that person...and...derived from an individual assessment.



Puff City: The intervention

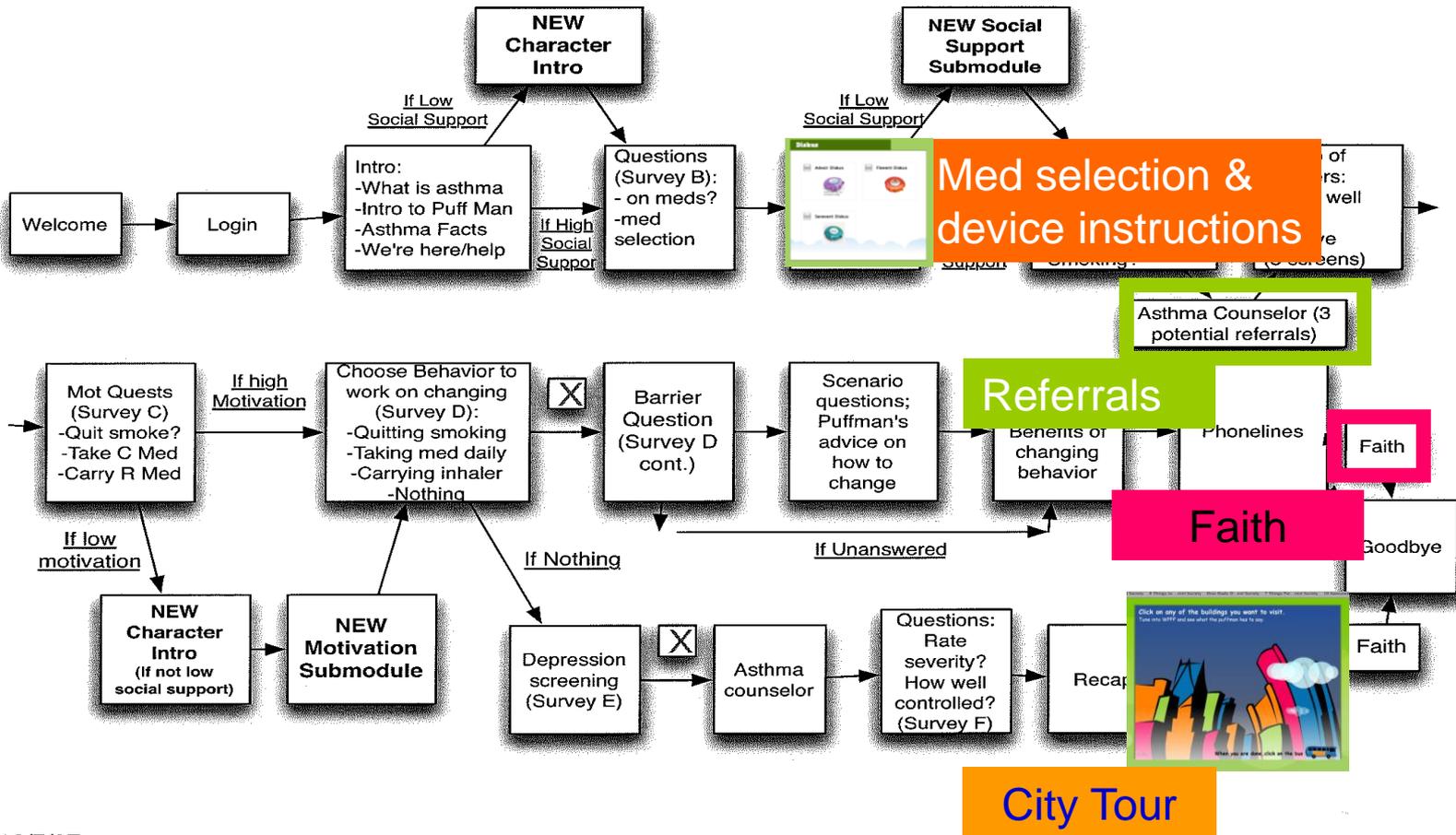
Graph 5 of 13



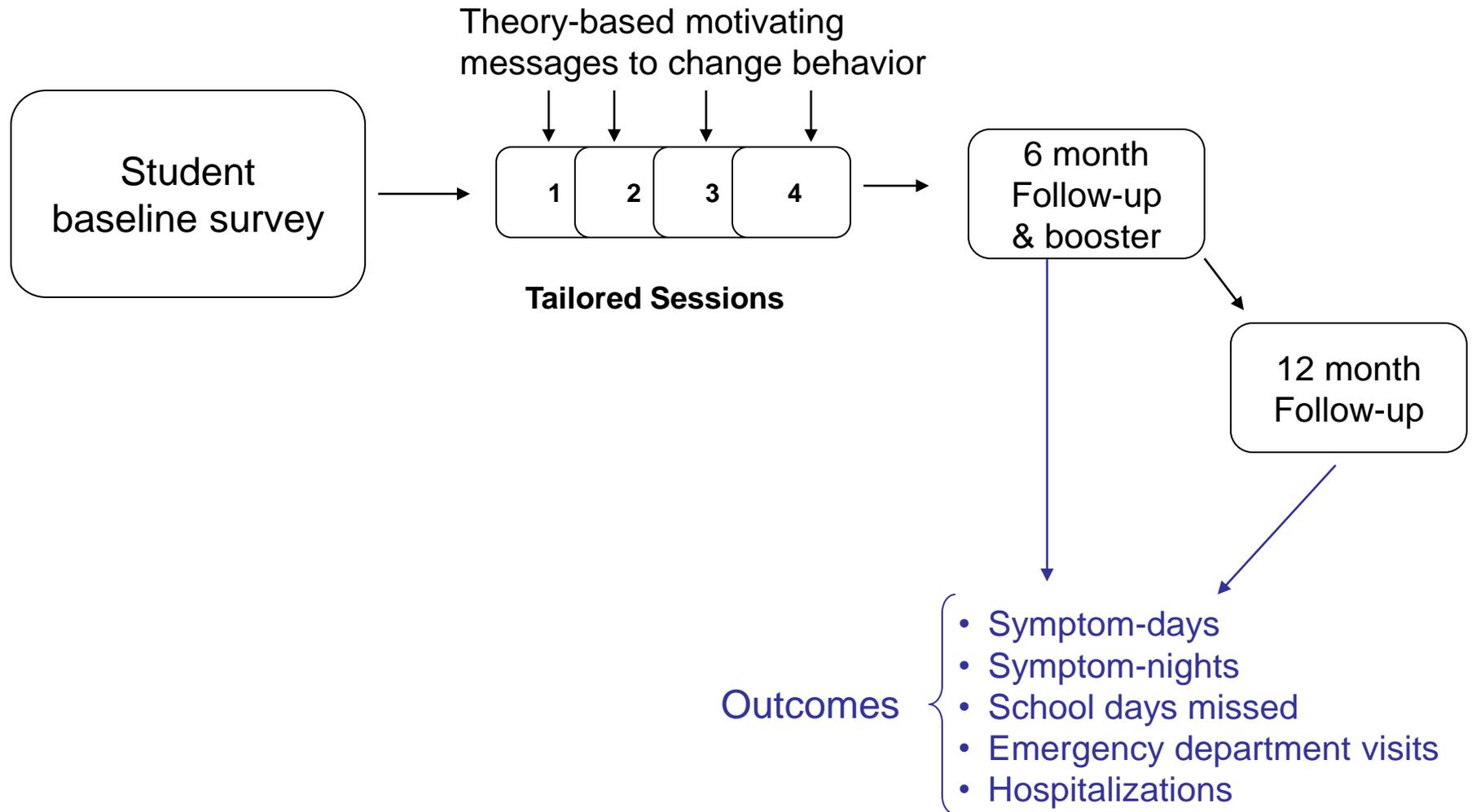
Puff City Basic: Additional features

Graph 5 of 13

Puff City Flowchart - Session 1 (*for students with 1 or more risks)



Puff City intervention framework



Puff City Effects on asthma control in Urban Teens (School-based studies)

All	aOR	95% CI	p
≥ 2 days/wk/30 days	0.52	0.2-0.8	0.006
≥ 3 symptom nights	0.68	0.4-1.0	0.074
> 2 school days missed	0.7	0.4-1.1	0.090
> 2 school days missed (asthma)	0.8	0.5-1.5	0.52
> 4 days of restricted activity	0.5	0.3-0.9	0.010
> 4 days had to change plans	0.8	0.4-1.7	0.58
Rebellious			
≥ 2 days/wk/30 days	0.3	0.1 – 0.8	0.016
≥ 3 symptom nights	0.3	0.1 – 0.6	0.002
> 2 school days missed	0.4	0.2 – 0.8	0.007
> 2 school days missed (asthma)	0.5	0.2 – 1.2	0.12
> 4 days of restricted activity	0.2	0.1 – 0.5	0.001
> 4 days had to change plans	0.4	0.1 – 1.1	0.068

(JAH, 2013)

PUFF CITY



Putt City Asthma Management is ready to be disseminated into different settings such as at the clinic

Designing a Cost-effective Efficacy Trial in a “Real World” Setting

- Seamless Adaptive Design
 - Phase II/III trial

 - Pragmatic Approaches
 - Trial should reflect routine practice and patient selection criteria should be broad

 - Controls should be standard care vs. placebo

 - Outcomes should include broad measures of health-related quality of life from the patient’s point of view
-

Why Seamless Adaptive Design?

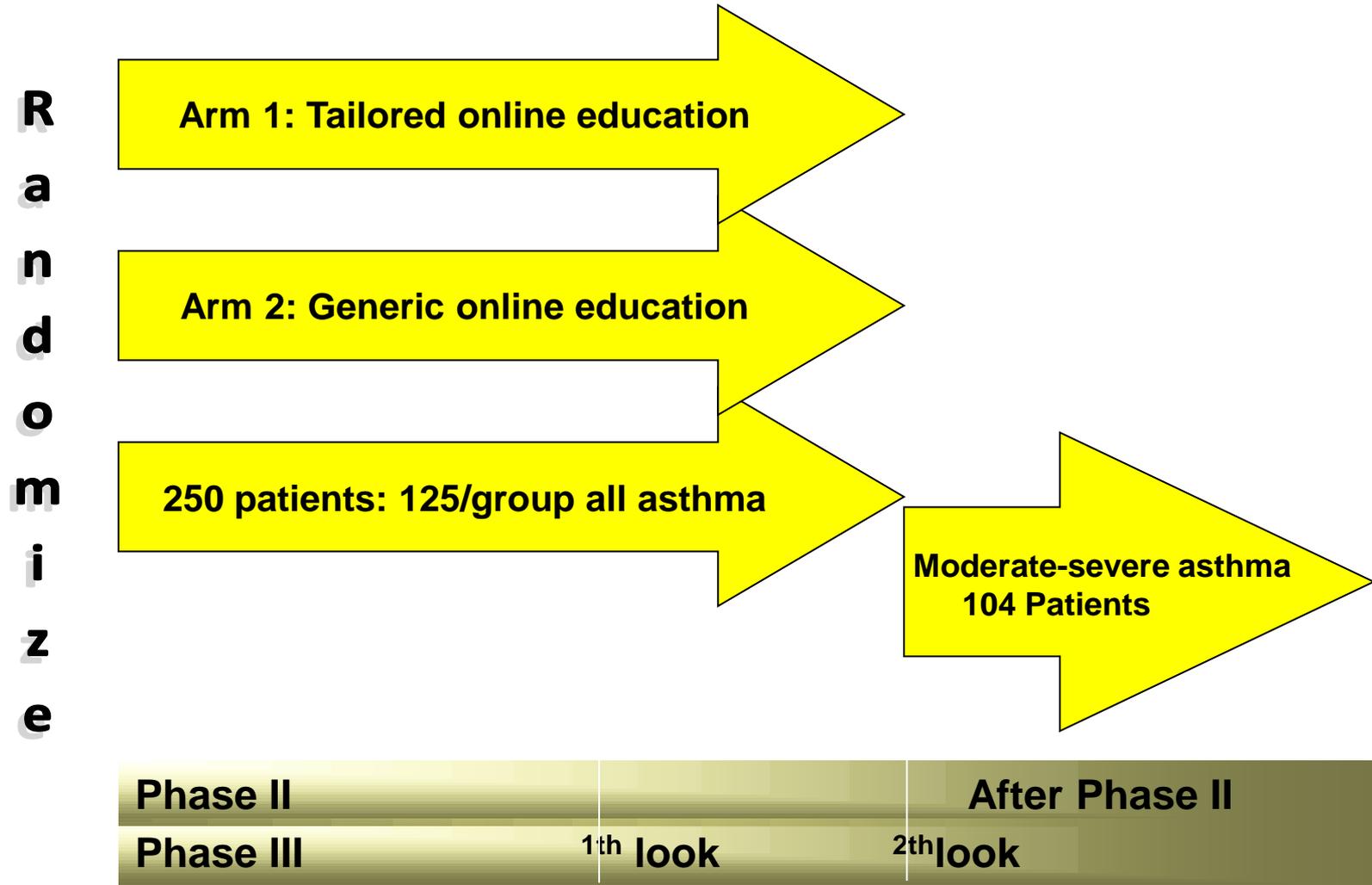
Combines the traditional II and III phases and includes patients enrolled before, and after, adaptation in the final analysis for intervention efficacy.

Advantage

- A reduction of the required sample size and study duration,
- A time and cost saving: the trial may stop early at Phase II when
 - there are toxicity concerns,
 - there is no evidence of drug activity (i.e., futility analysis)
 - a drug has a dramatic effect leading to early termination due to a high certainty of efficacy.

Limitation- requires a well-understood efficacy endpoint

Seamless Adaptive Phase II/III Trial for Asthma Management



Notices, the award only supports up to Phase II Component of the trial

Study Population: inclusion/exclusion criteria

Inclusion criteria

- Using modified HEDIS protocol (denominator) to identify teens with “persistent” asthma using EMR
 - Teens aged 13-19 years who meet at least 1 of the following criteria
 - > 1 Emergency Department visit with asthma as principal diagnosis
 - > 1 acute inpatient claim/encounter with asthma as principal diagnosis
 - > 4 outpatient visits on different dates of service with asthma listed as one of the diagnoses and at least 2 asthma medication dispensing events
 - > 4 asthma medication dispensing events

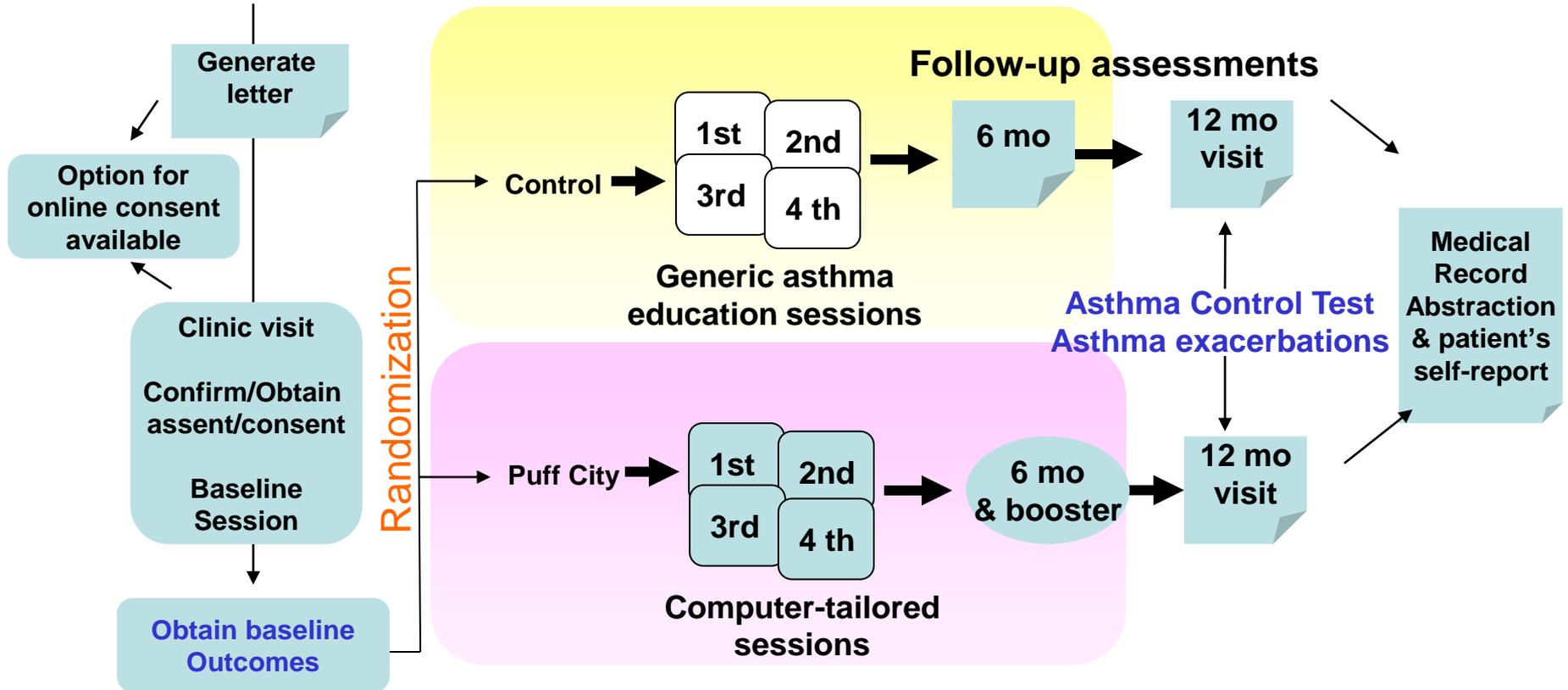
Exclusion criteria

- Patient does not meet eligibility criteria for asthma,
- Not proficient in English (Puff City is currently only available in English)*
- Patient or caregiver is unable to complete assent/consent even with help; and
- patients have been previously enrolled in Puff City trials.

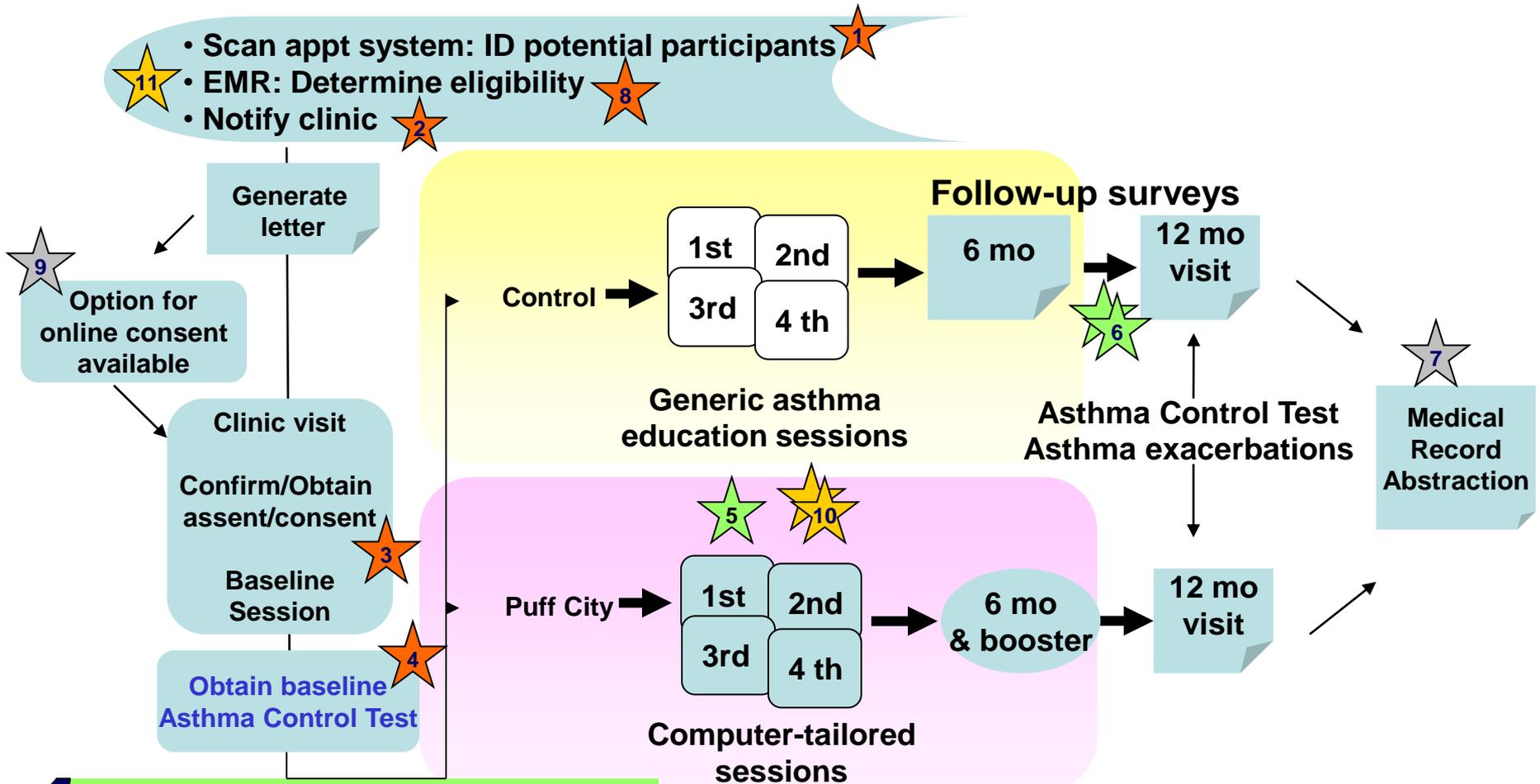
**To accommodate caregivers with limited English proficiency, consent forms will be available in Spanish and Arabic.*

Puff City Phase II/III Trial: Study Design

- Scan appt system: Id potential participants
- EMR: Determine eligibility
- Notify clinic



Pragmatic Approache and Cost Reduction



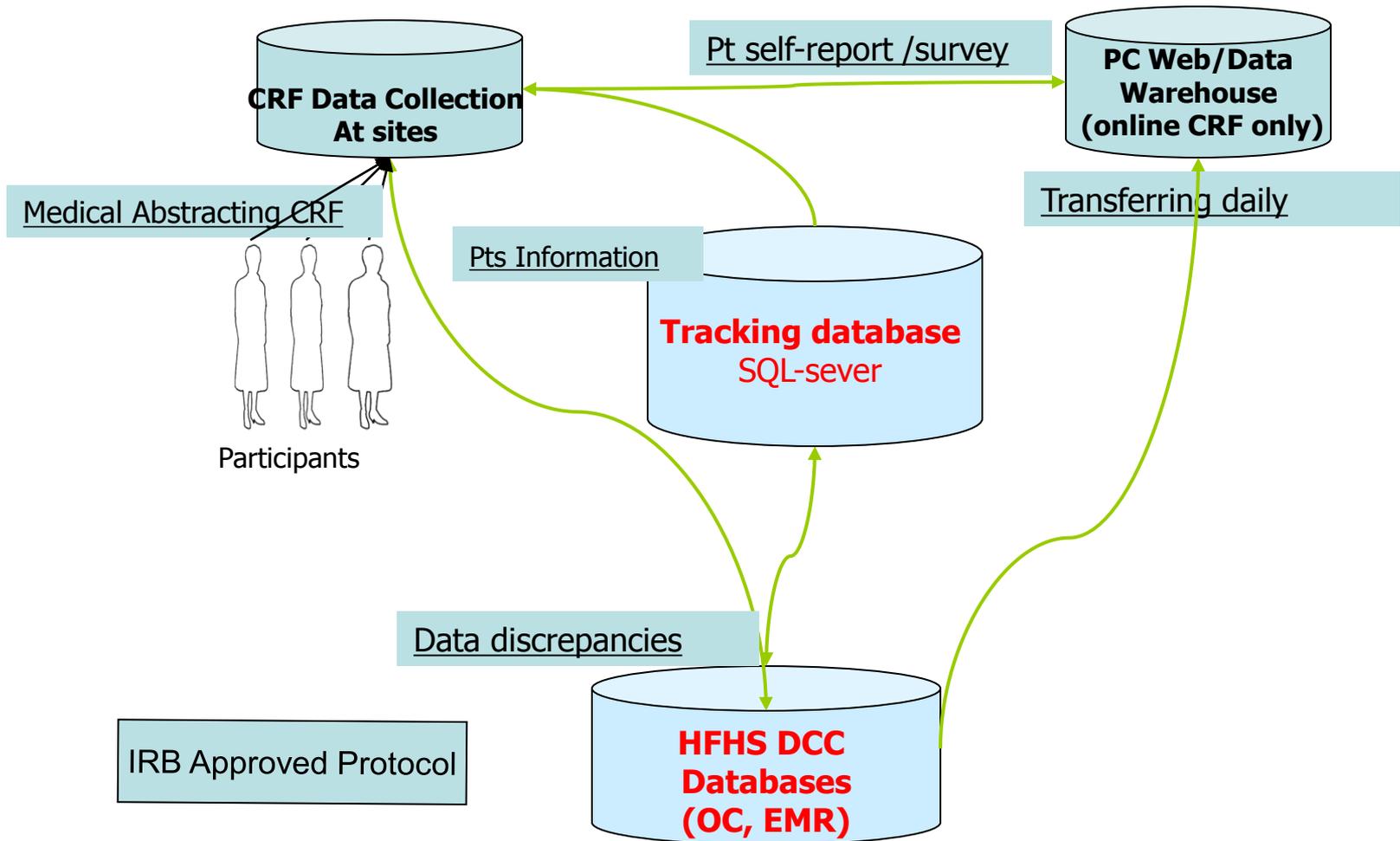
1 Minimize visits designed solely for the purpose of retrieving trial measurements (1,2,3,4)

2 Minimize specialized infrastructure developed solely for conduct of the clinical trial (1-4, 5,6,7, 8)

3 Explore novel methods of obtaining patient consent, minimizing need for specialized staff ...while still meeting ethical/legal requirements. (9)

4 Employ low-cost methods of monitoring study conduct such as adherence (10,11)

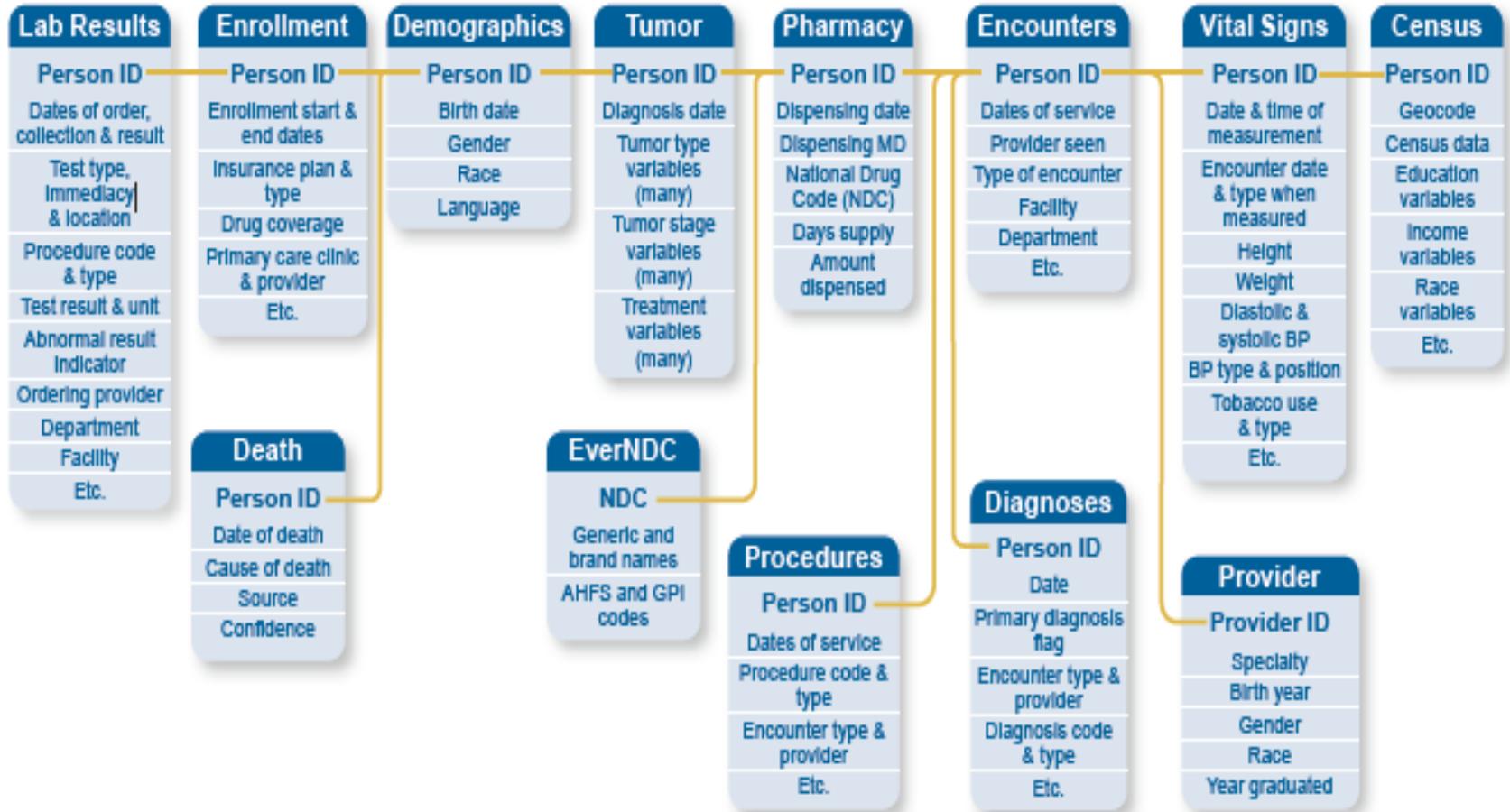
CRF Data Collection Processes



Pragmatic Approach: Data Collection

- **Eligibility form (OC)**
 - **Baseline**
 - Teen baseline (on PC web)
 - Asthma medicine (OC)
 - **Session surveys (participant on UM web)**
 - **Follow-up**
 - Participant 6 and 12 month FU (on PC web)
 - Caregiver 12 month survey (OC chart Review/Telephone)
 - Adverse Event data collection (OC)
 - **EMR data in VDW structure formats – Both HFHS and KPGA have VDW EMR data**
-

VDW e-data Tables-HMORN



EMR data: Demographic, pharmacy; Census; Encounter data

Endpoints at year 1 and Analyses:

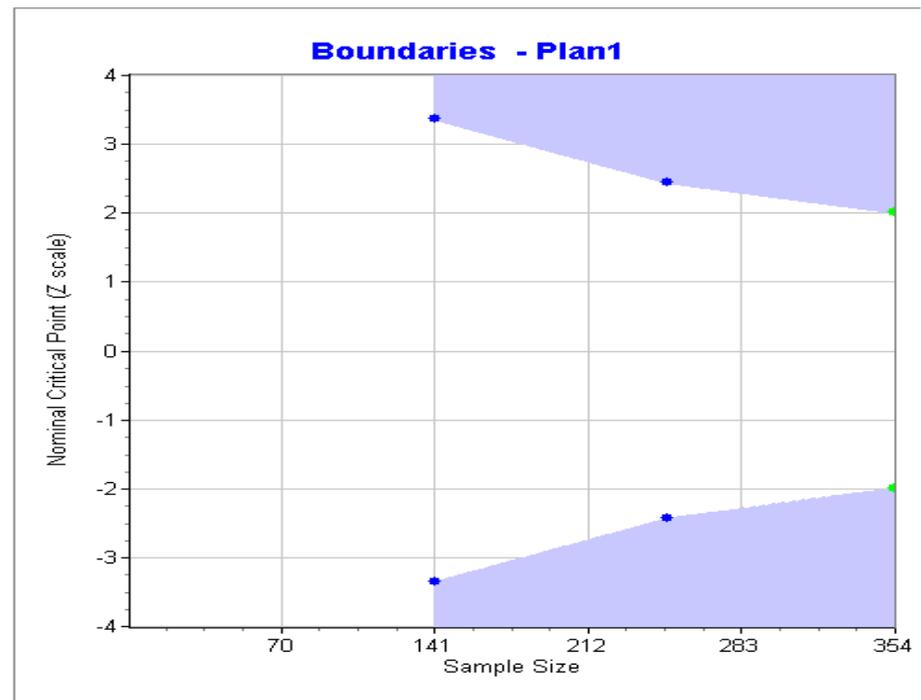
- Primary (**P1**) ACT (0-19)
 - Secondary:
 - **S1**: Asthma exacerbations
 - **S2**: self-report of symptom-days,
 - **S3**: symptom-nights,
 - **S4**: days of restricted activity, and
 - **S5**: school/work days missed.
 - **S6**: ED visits and hospitalization
 - Exploratory:
 - **E1**: the cost;
 - **E2**: cost effectiveness of Puff City
 - **E3**: reliability of EMR data collection
-

Interim Analyses and DSMB

- Planning to have 2 DSMB meetings /conference calls when 40% and 70% (the end of Phase II component) of patients complete 1 year endpoints
 - DSMB agenda items:
 - 1)Recruitment and retention
 - 2)Patient safety
 - 3)Protocol deviation
 - 4)Study endpoints
 - Seek DSMB recommendation to stop or continue the trial
-

Interim analyses and Sample Size Calculation

Assuming effect size of 0.3 (0.33 -0.54), two-sided test, 354 subjects in total, 2 interim unequal looks when 40% and 70% (250 for Phase II component of the trial) of patients have complete year 1 follow-up , we will have 80% power to detect a significant intervention effect if test statistic or p-value is ± 3.3569 or 0.0008 at 1th look, ± 2.4341 or 0.0149 at 2th look or ± 2.0017 or 0.0453 at the final analysis.



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Thank You



Questions?