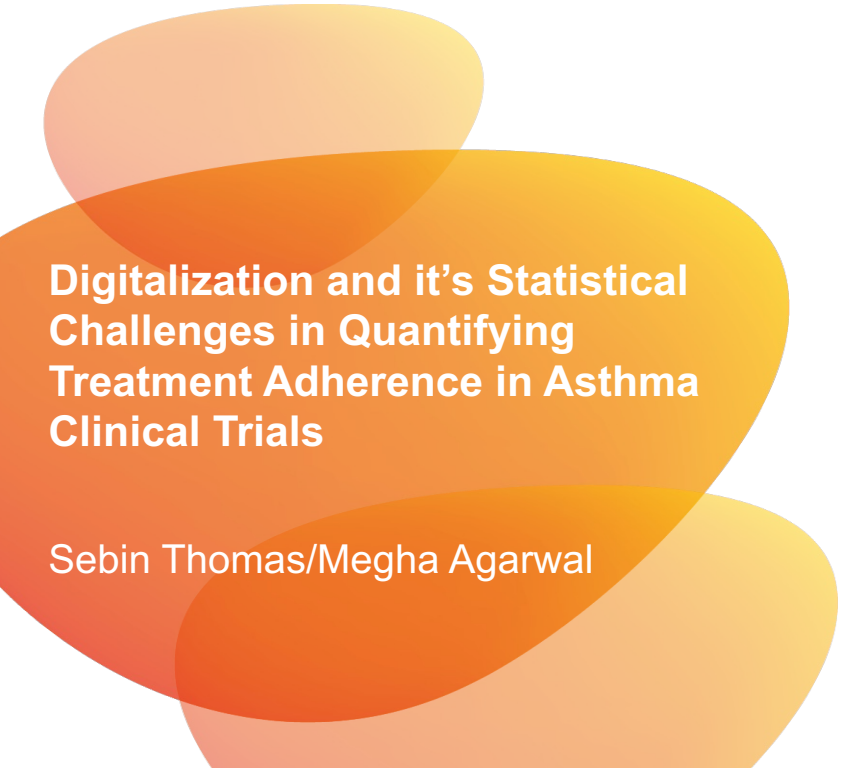


Three large, overlapping, rounded abstract shapes in shades of orange and yellow are positioned on the left side of the slide, serving as a decorative background for the title and authors.

Digitalization and it's Statistical Challenges in Quantifying Treatment Adherence in Asthma Clinical Trials

Sebin Thomas/Megha Agarwal

Disclaimer

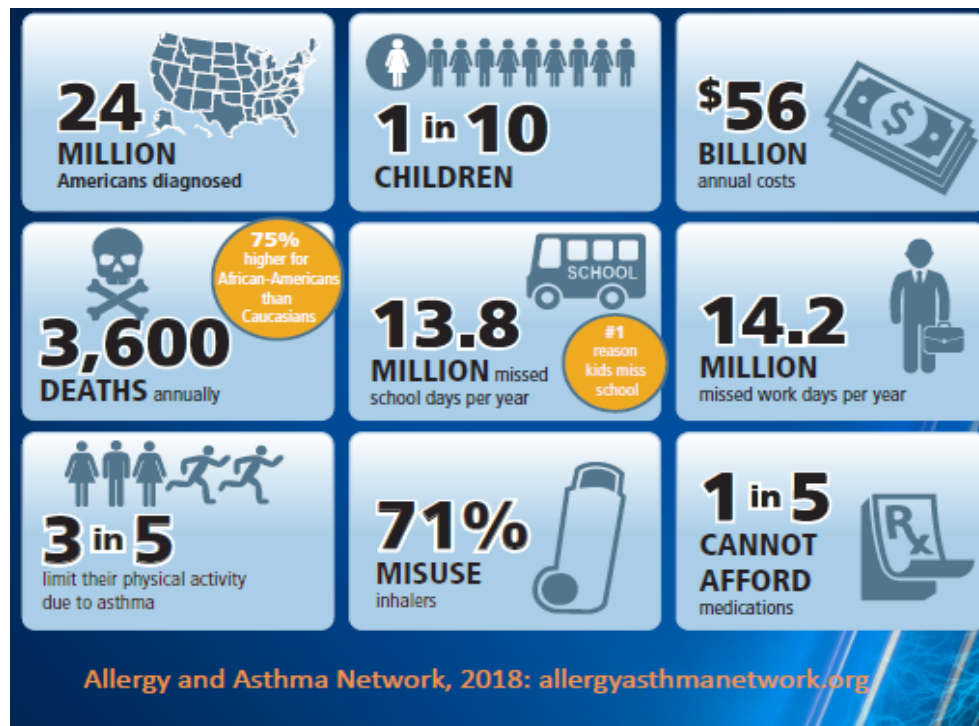
This presentation is based on the statistical challenges which can occur during the clinical trial using digital data.

The examples showed in the presentations are only for the purpose of illustration. The views and opinions expressed are solely those of authors and do not reflect the formal opinions and perspectives of any organization.

Burden of Asthma

What does asthma
mean to me?

Burden of Asthma



Why is Adherence important?

- ☐ Decreased **quality of life** i.e. Fatigue, reduced physical activity, missed working/school days, etc.
 - ☐ Poor symptom control i.e. Sudden and Frequent exacerbations, wheezing, chest tightness, etc.
 - ☐ More **frequent use of rescue medications** and under use of ICS
 - ☐ **Over Dose/frequency of ICS usage** than prescribed
 - ☐ Increased health care utilization
 - ☐ Increased maintenance cost
 - ☐ **Symptomatic adherence** to maintenance therapies
 - ☐ **Increase Oral Steroid Usage** like Prednisolone and associated side effects like increase in weight
 - ☐ Death
-

Poor Adherence and its evaluation

Factors contributing to Poor Adherence by Patients	Factors contributing to Poor evaluation of adherence by doctors
Beliefs and Awareness on Medication benefits • Difficulties using inhaler device • Misunderstanding about instructions • Perception that treatment is not necessary • Concerns about side effects • Inappropriate expectations Cost Asthma Management • Forgetfulness • Absence of a daily routine	Manual Assessment • Patient Diaries • Behavior Questionnaires • Dose/Pill Counters • Date of the last Prescription • Date on the last inhaler taken Difficult Access /less engagement with Health care professionals (HCP)

What if ?

- Real time and accurate Asthma Inhalation data gets recorded
- Real time HCP review occurs
- Patient gets medication reminders
- Gets awareness of the environmental triggers e.g. pollen count
- Gets easy access to demonstration of inhaler use
- Gets Asthma management suggestions e.g. to wear scarf on cold day 😊

Novel technology to assess/improve adherence i.e. Connected Inhaler System (CIS)

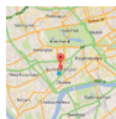


Data

Signals from Sensors added
on to Inhaler Device



+ Internet of Things



Tools



Patient support tools
(device, app, email, text)



Care team data
dashboards

Connected Inhaler System

- ❑ Medication Reminder Systems
- ❑ Asthma Action Plan (trends/schedules)
- ❑ Internet of things (air, temperature, humidity, triggers)
- ❑ Direct HCP Contacts (via email, text or phone call)

Case Study - Study Design

- ☐ This is an open-label, parallel group study in asthmatic patients
- ☐ Duration: 6 months
- ☐ Daily dose (puff)
- ☐ Daily Adherence:
 - Subjects taking one puff of treatment, within a 24-hour period, starting at 12.00 am each day
 - Not adherent if more than one puff or no puff for the day

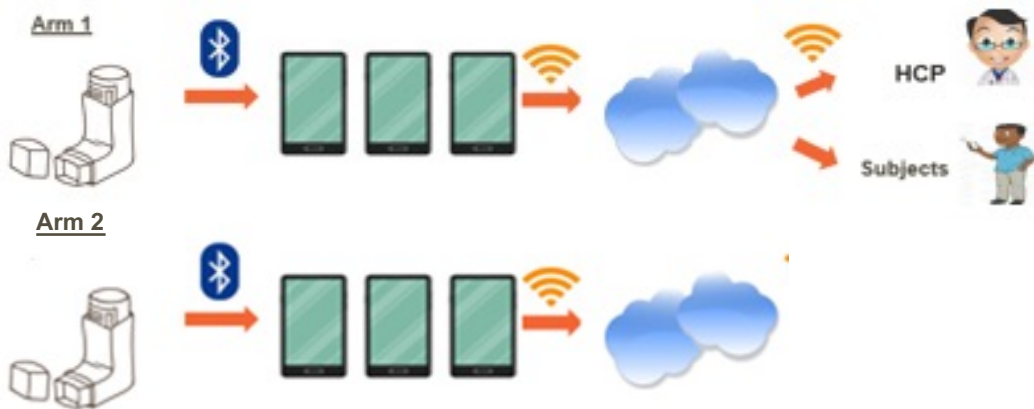
Primary Objective

- ❑ To compare the effect of 6 months use of the CIS on adherence to maintenance therapy when both the subject and the health care professional (HCP) are supplied with data from the maintenance sensor (**Arm 1**)

versus

no data supplied to the subject and HCP (**Arm 2**)

- ❑ Primary Endpoint: **Percentage of doses taken** (daily adherence) between the beginning of month 4 and the end of month 6



Statistical Analysis Method

- ❑ The mean difference in daily adherence between Arm 1 and Arm 2 will be estimated from an Analysis of Covariance (ANCOVA) model

This is in normal scenario... what are the challenges can occur in a study which has internet of things??

- ❖ Withdrawal of study
 - ❖ Discontinuation of treatment
 - ❖ Bluetooth issues - Discontinuation of eSensor
 - ❖ Hub issues
 - ❖ Network issues
 - ❖ Mobile problems
- } Discontinuation of feedback

Intercurrent Events and Estimands

- ❑ There are lot of challenges which results in the missing data in analysis
- ❑ Intercurrent events: Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation.
- ❑ The frame work which handles the intercurrent events is called estimand framework

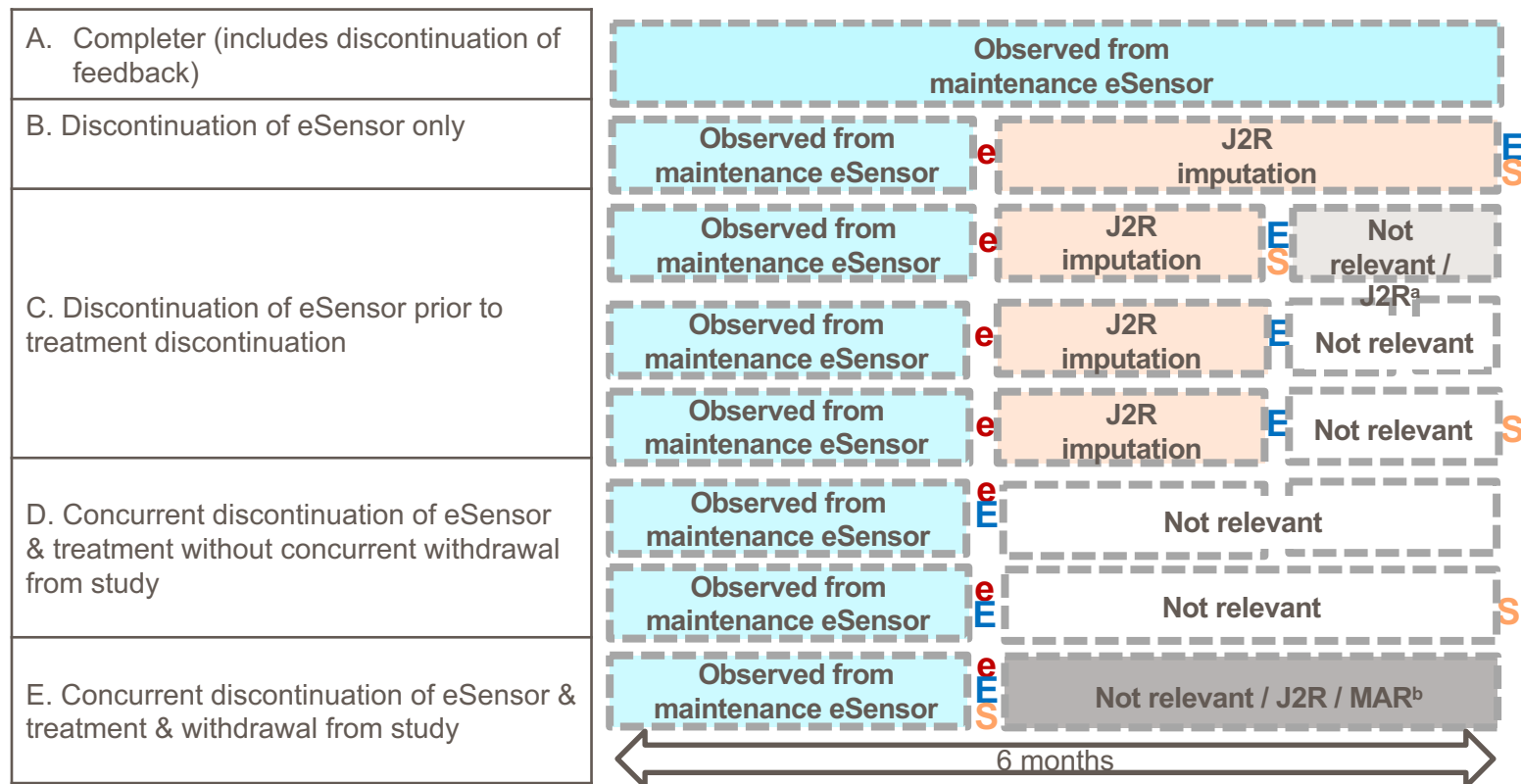
Estimand Strategy



Intercurrent event	Strategy	Estimation Method
None (completed as randomised, or discontinued CIS feedback only)	<u>Treatment policy:</u> Directly assessed using observed adherence data while maintenance eSensor is in use, regardless of whether the CIS feedback is discontinued.	Data are available; no imputation required
Discontinuation of eSensor only	<u>Treatment policy:</u> Without the eSensor, no CIS feedback is possible ⇒ assume subjects continue to take treatment as they would have without the CIS intervention ⇒ assume adherence will be like that in the control (no CIS feedback) group	Jump to reference (J2R) Imputation
Discontinuation of treatment	<u>Whilst on treatment:</u> treatment adherence is only a relevant measure while treatment treatment is appropriate.	Follow-up after treatment discontinuation is excluded; adherence is weighted by proportion of months 4 to 6 for which data is included
Withdrawal unrelated to treatment or CIS	<u>Hypothetical:</u> When study withdrawal is unrelated to treatment or the CIS then reasonable to assume that subject would have continued with treatment and their CIS intervention, had the unrelated event not occurred	Missing at random (MAR) Imputation

Intercurrent Event - Rules

e Discontinuation of maintenance eSensor
 E Discontinuation of Treatment
 S Withdrawal from study



a. Not relevant if withdrawal related to treatment; J2R if withdrawal not related to treatment

b. Not relevant if withdrawal related to treatment; J2R if withdrawal related to CIS; MAR if withdrawal not related to treatment or CIS

-
- ❑ In respiratory related diseases, **inadequate control of asthma symptoms continues to be a serious problem**, and despite advancements in therapeutics for the treatment of asthma, adherence rates to the therapy remain less than optimum.
 - ❑ With all the new technology outbreaks, it is high time to switch from a **traditional path to a digitalized one** in health care.
 - ❑ Digitalization can pose new challenges to the data analysis, **a clinical and statistical strategies has to be framed** to handle the different sources and patterns of missing data that can arise.

