

Hands-on Workshop:

RWD Applications in Pharma with a Focus on Clinical Trials

Sponsored by SAS Institute

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AGENDA

01

Welcome, Intro and Agenda Overview

2.45-2.55 pm CET / 8.45-8.55 am EST

02

RWE Generation in Clinical Development

2.55-3.25 pm CET / 8.55-9.25 am EST

5 min break

03

Hands-On (break out) or Live Demo (main room)

3.30-4.30 pm CET / 9.30-10.30 am EST

04

Q&A, Quiz and Close Out

4.30-4.45 pm CET / 10.30-10.45 am EST

A photograph of a man and a young boy looking at a laptop screen. The man is on the left, smiling, and the boy is on the right, also smiling. They are both looking at the screen. The background is slightly blurred, showing a room with a blue wall and a red and white striped object.

Empower Innovation.
Improve Lives.

Our Vision

Clin

Line



**Improving and
optimizing
the clinical trial
process**

- Processes

- Technical
- Procedures
- KPIs

- Data

- Clinical Trial
- Real World

- People

- Stakeholder
Management
- Drives &
Leadership



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Trial Feasibility

Trial Feasibility Business Challenges

Designing effective clinical trials is a complex process that starts with a well-defined research question, the *generation of a hypothesis, and definition of the target patient cohort for the trial.*

This can be a **lengthy and iterative process** that requires inputs from many stakeholder groups and data sources.



Trial Feasibility

Business Challenge

The traditional ways for evaluating trial feasibility include:

- Published findings from previous studies and trials conducted in the patient population of interest
- Primary chart review studies which can be costly and resource intensive
- Seek opinions from physicians who specialize in the therapeutic area of interest

These methods don't provide extensive breadth or depth, especially when it comes to **rare diseases and less common disease subsets**.

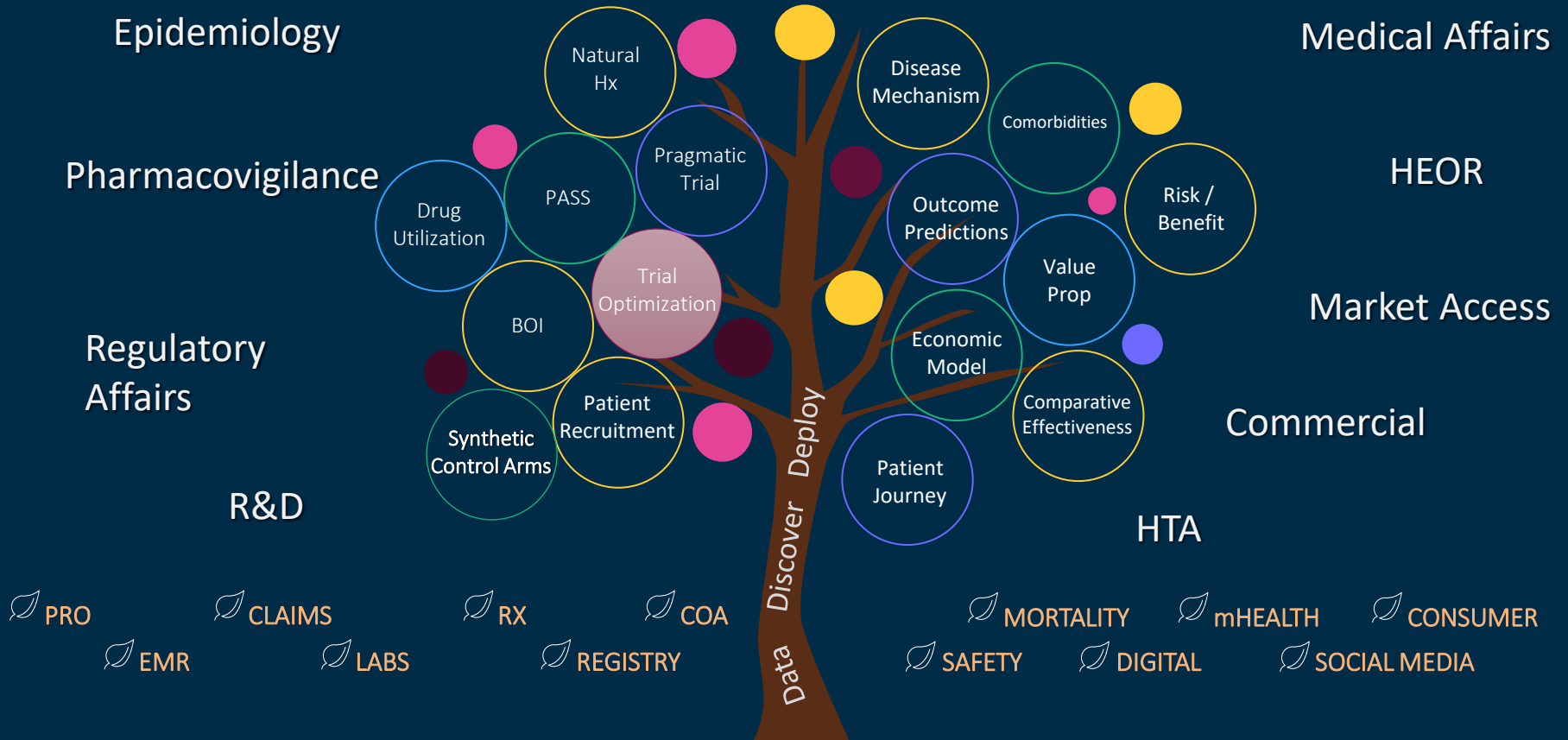
Trial Feasibility

Value of Real World Data

Real World Data has become essential *to more accurately explore target patient populations and inform robust initial trial hypotheses.*

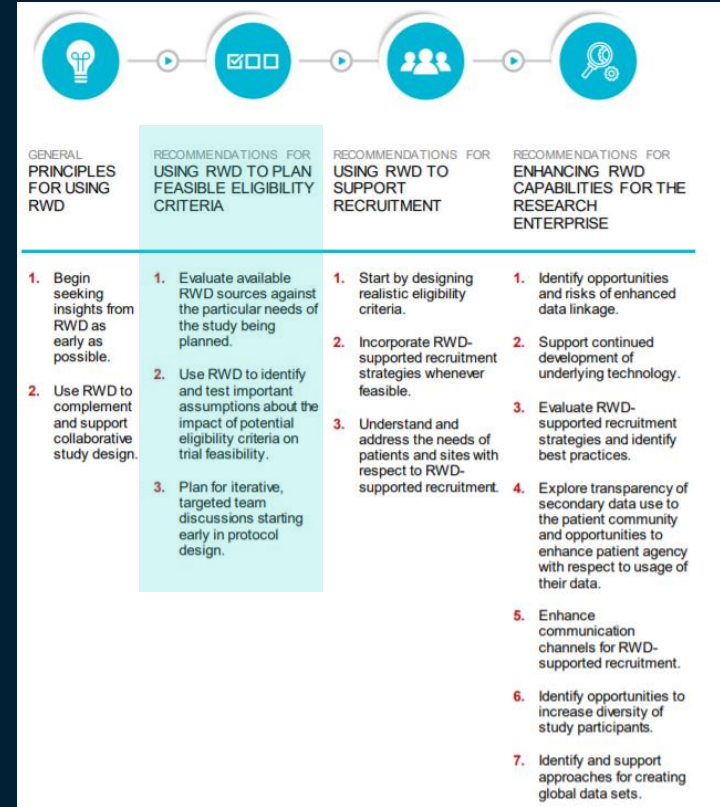
Enable organizations to create more patient-centric protocols to identify and **reduce operational risk and development costs**

Real World Evidence



Industry Recommendations (CTTI)

- Evaluate available RWD sources against the particular needs of the study being planned.
- Use RWD to identify and test important assumptions about the impact of potential eligibility criteria on trial feasibility.
- Plan for iterative, targeted team discussions starting early in protocol design



https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/rwd-recommendations_final.pdf

<https://link.springer.com/content/pdf/10.1007/s43441-020-00248-7.pdf>



Regulatory Authorities, RWD aspects to consider & Bias

Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision- Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document or the RealWorld Evidence Program, please email CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

September 2021
Real World Data/Real World Evidence (RWD/RWE)

Relevance

- Exposure
- Outcomes
- Covariates

May '22 HMA-EMA
EU Data quality
framework

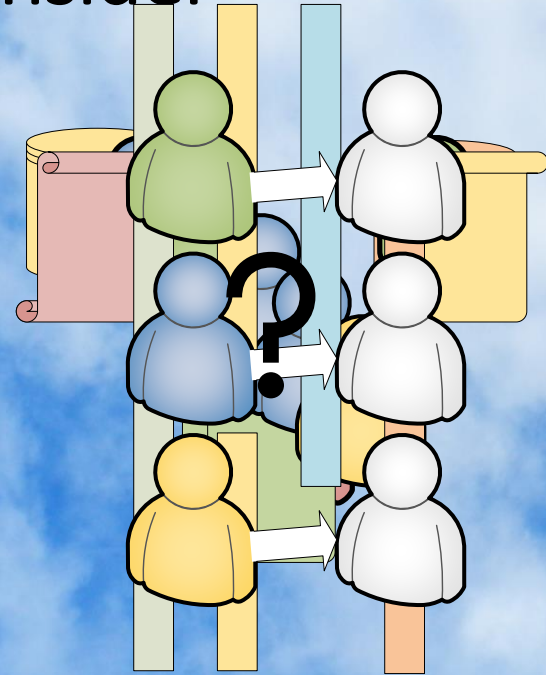
ICH9 R1 - Estimands

Reliability

- Accuracy
- Completeness
- Provenance
- Traceability

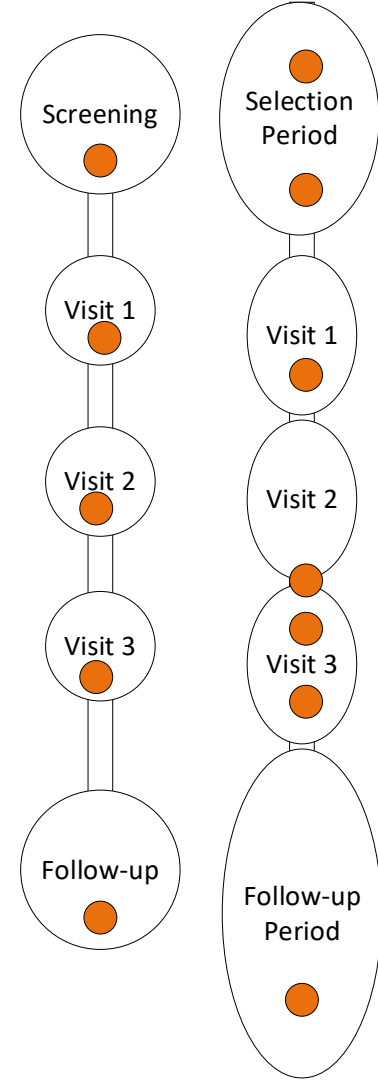
Real World Data aspects to consider

- **Availability**
- **Information System heterogeneity**
- **HCP heterogeneity**
- **Treatment protocol heterogeneity**
- **Duplications**
- **Enrolment periods**
- **Pseudo/Anonimization**



Windowing

- Match Real world visits with study visits
 - Define start – visit 1
 - Define periods
 - Define minimal periods between visits
- Define what to do when 2 visits within 1 window
- Assess potential bias
 - Bigger/smaller gaps
 - Missing window periods



Bias assessments

- Exposure definition
- Hospital / Area / Country
 - Different treatment protocols
 - Different registration requirements
 - Different populations
 - ...
- Window selection & Follow-up length
- Eligibility patient selection
- Information system
 - Entry screens and labels
 - Availability of variables

BIAS



Synthetic Control Arms

Key Considerations

Synthetic Control Arms

- Not universal replacement for conventional control arms
 - Only applicable to well-known, predictable diseases with well-defined Standard of Care
 - RWD information may be difficult to extract or lack quality
 - Design and analytics may not fully control for all systematic issues and biases
- New tools and methodologies are needed to consolidate, organize, and structure RWD to generate research-grade evidence
 - Specific analytical approaches and evolving practices may address some challenges
 - Natural language processing and machine learning can be leveraged in this space

Quality Checklist for Researchers

Data Sources & Control Methods

External Control Data Sources

- Was the original data collection process similar to that of the clinical trial?
- Was the external control population sufficiently similar to the clinical trial population?
- Did the outcomes definitions of the external control match those of that clinical trial?
- Was the synthetic control data set sufficiently reliable and comprehensive?
- Were there any other major limitations to the dataset?

Synthetic Control Methods

- Did the clinical trial include a concurrent control arm? Is the synthetic control data the only control data?
- How was the synthetic control data matched to the intervention group?
- Were the results robust to sensitivity assumptions and potential biases?
- Were synthetic control comparisons possible for all clinically important outcomes?
- Are the results applicable to your patients?
- Were there any other major limitations to the synthetic control methods?

Synthetic Control Arms - Types

Potential vs. Necessity

	External Control Cohort Inception Date	Possible Types of Data Collection	
		Retrospective RWD Collection	Prospective RWD Collection
Contemporaneous External Control	On or after the first patient enrollment in the clinical trial		
Historical External Control	Before the first patient enrollment in the clinical trial		
Hybrid External Control	Varies		

Real-world evidence to support regulatory decision-making for medicines: Considerations for external control arms

Hands-on Workshop:
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**Scheduled break in progress –
the workshop will resume shortly.**

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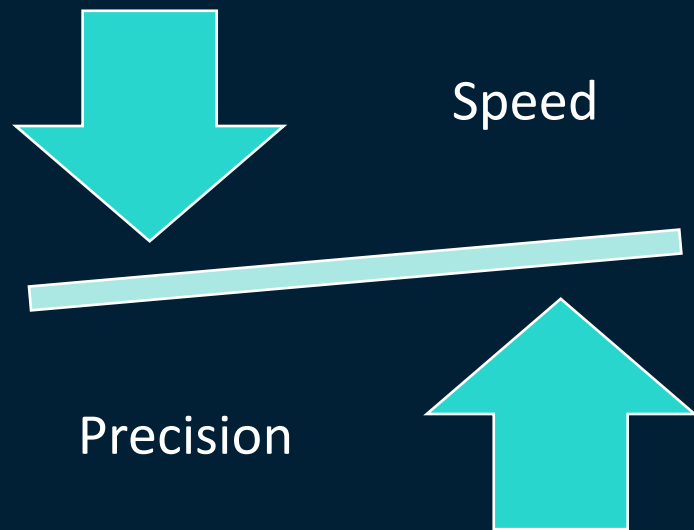
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Business Case

- Shorten Time to Market:
Faster Vs. **Better** recruitment
- Develop decision support
tools to find optimal balance



Protocol

The PRECISE Protocol: Prospective Randomized Trial of the Optimal Evaluation of Cardiac Symptoms and Revascularization (PRECISE)



The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT03702244

[Recruitment Status](#) ⓘ : Recruiting

[First Posted](#) ⓘ : October 11, 2018

[Last Update Posted](#) ⓘ : February 25, 2019

See [Contacts and Locations](#)

Sponsor:

HeartFlow, Inc.

Collaborators:

Duke Clinical Research Institute
Cardiovascular Research Foundation, New York

Information provided by (Responsible Party):

HeartFlow, Inc.

Study Description

Go to 

Brief Summary:

The study will be a prospective, pragmatic, randomized clinical trial of the comparative effectiveness of diagnostic evaluation strategies for stable CAD, to be performed in outpatient settings, including primary care and cardiology practices.

Condition or disease ⓘ	Intervention/treatment ⓘ	Phase ⓘ
Coronary Artery Disease	Diagnostic Test: cCTA with selective FFRct	Not Applicable

In & Exclusion Criteria

Criteria

Inclusion criteria (all must be present):

1. Age ≥ 18 years
2. Stable typical or atypical symptoms suggesting possible significant coronary artery disease (CAD) with further non-emergent testing or elective catheterization recommended to evaluate the presence of suspected significant CAD. Stable chest pain (or equivalent) includes those who have fully been ruled out for Acute Coronary Syndrome (ACS) and for whom elective testing is recommended, regardless of the venue in which they are seen.
3. If prior CV testing has occurred, it must have been performed greater than one year prior to randomization, and the following must be met:
 - a. cCTA or invasive coronary angiography (ICA) with stenosis $< 50\%$
 - b. Quantified coronary artery calcium (CAC) < 100 AG
4. Safe performance of cCTA:
 - a. Creatinine clearance ≥ 45 ml/min per most recent measurement within 90 days
 - b. For a female participant of childbearing potential (those who have not been surgically sterilized or are not postmenopausal), a pregnancy test must be performed with negative results known within 7 days prior to randomization
5. Willingness to comply with all aspects of the protocol, including adherence to the assigned strategy and follow-up visits
6. Ability to provide written informed consent

Exclusion criteria (all must be absent):

1. Acute chest pain (in patients who have not been ruled out for ACS)
2. Unstable clinical status
3. Noninvasive or invasive CV testing for CAD within 1 year. CV testing for CAD refers to any stress tests, invasive coronary angiography (ICA) and cCTA (including calcium scoring) only.
 - a. Resting ECG, resting echocardiogram and resting CMR (MRI) are not exclusionary regardless of when were performed
4. Lifetime history of known obstructive CAD (prior myocardial infarction, CABG or PCI, stenosis $\geq 50\%$), known EF $\leq 40\%$ or other moderate to severe valvular or congenital cardiac disease
5. Contraindications to cCTA including but not limited to creatinine clearance (GFR) < 45 ml/min as per most recent measurement taken within 90 days
6. Exceeds the site's weight or size limit for cCTA or cardiac catheterization
7. Any condition leading to possible inability to comply with the protocol procedures or follow-up
8. Any condition that might interfere with the study procedures or follow-up
9. Enrolled in an investigational trial that involves a non-approved cardiac drug or device which has not reached its primary endpoint
10. Life expectancy less than 2 years due to non-cardiovascular comorbidities

Process Flow

1.1 Build Industry
Standard Cohort
[STRINGENT]

WHY?

1. Test hypothesis and enrollment factors

Process Flow

1.1 Build Industry
Standard Cohort

[STRINGENT]

1.2 Build Subject
Matter Expert
(SME) Cohort

[RELAXED]

WHY ?

1. Challenge current industry standard
2. Test enrollment factors
3. Test scientific robustness after introducing noise

Process Flow

1.1 Build Industry
Standard Cohort

[STRINGENT]

1.2 Build Subject
Matter Expert
(SME) Cohort

[RELAXED]

1.3 Build Machine
Learning assisted
and SME Cohort

[ML/SME]

WHY ?

1. Challenge current industry standard
2. Test enrollment factors
3. Test scientific robustness after introducing noise
4. Enhance precision of industry standard

Process Flow

1.1 Build Industry
Standard Cohort

[STRINGENT]

1.2 Build Subject
Matter Expert
(SME) Cohort

[RELAXED]

1.3 Build Machine
Learning assisted
and SME Cohort

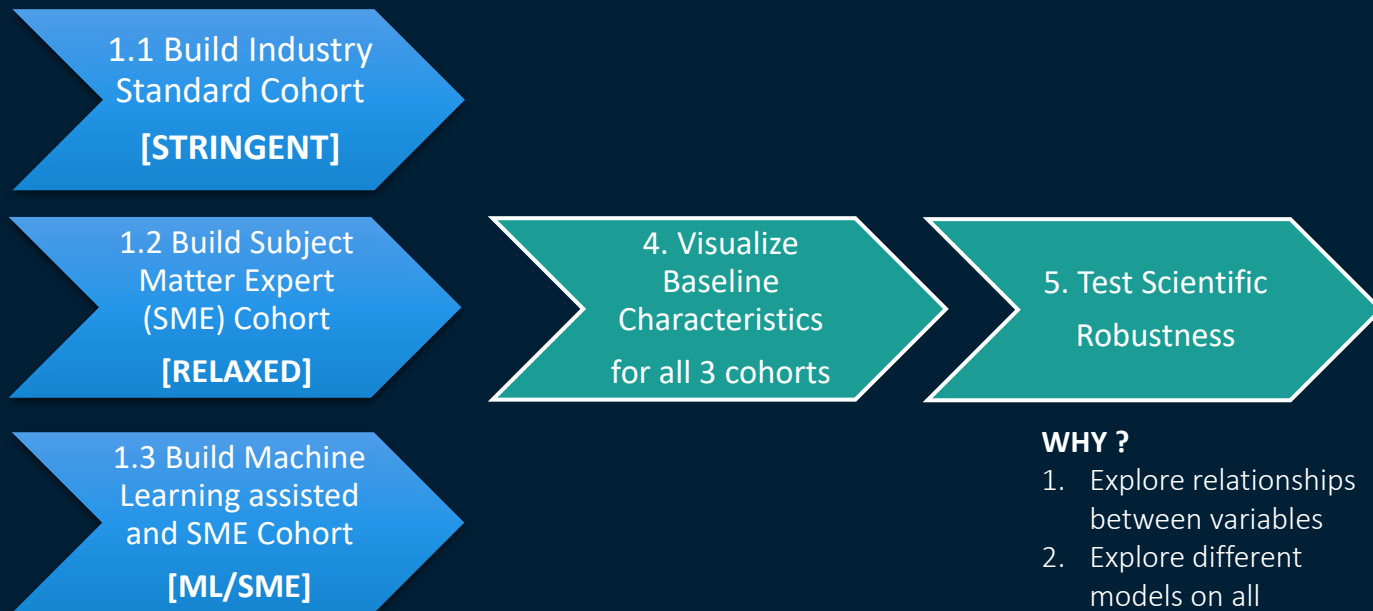
[ML/SME]

4. Visualize
Baseline
Characteristics
for all 3 cohorts

WHY ?

1. Testing shifts in baseline characteristics

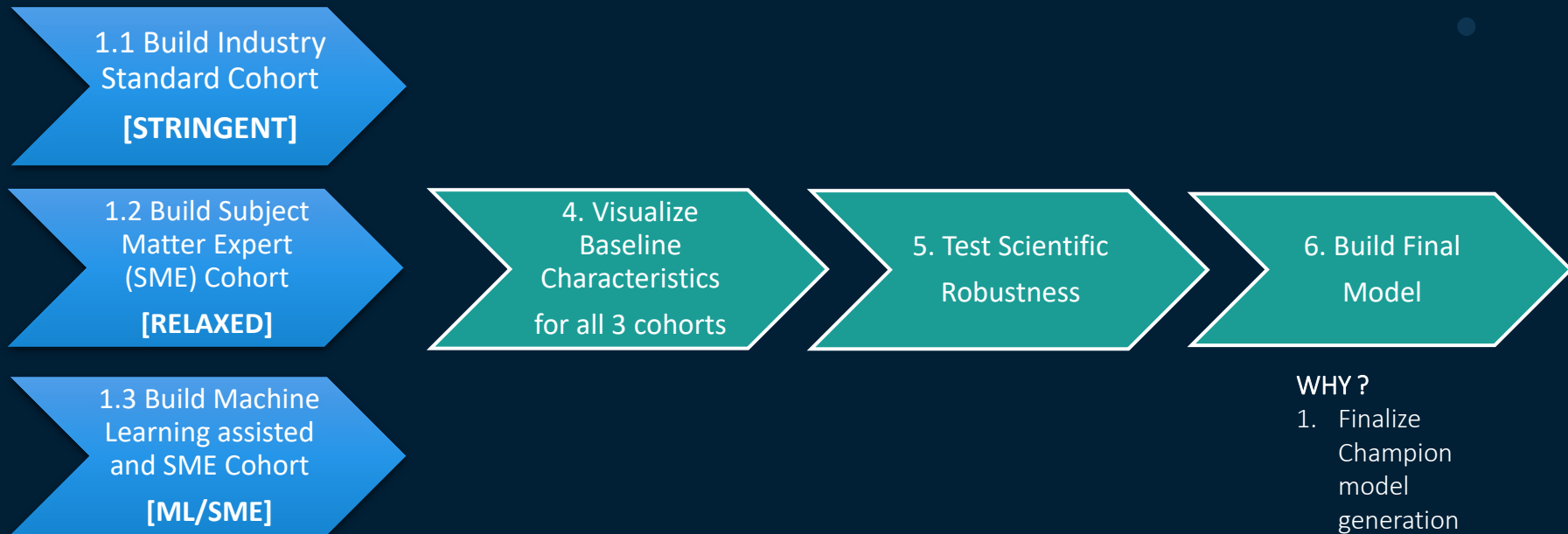
Process Flow



WHY ?

1. Explore relationships between variables
2. Explore different models on all cohorts
3. Test impact of eligibility criteria on the statistics

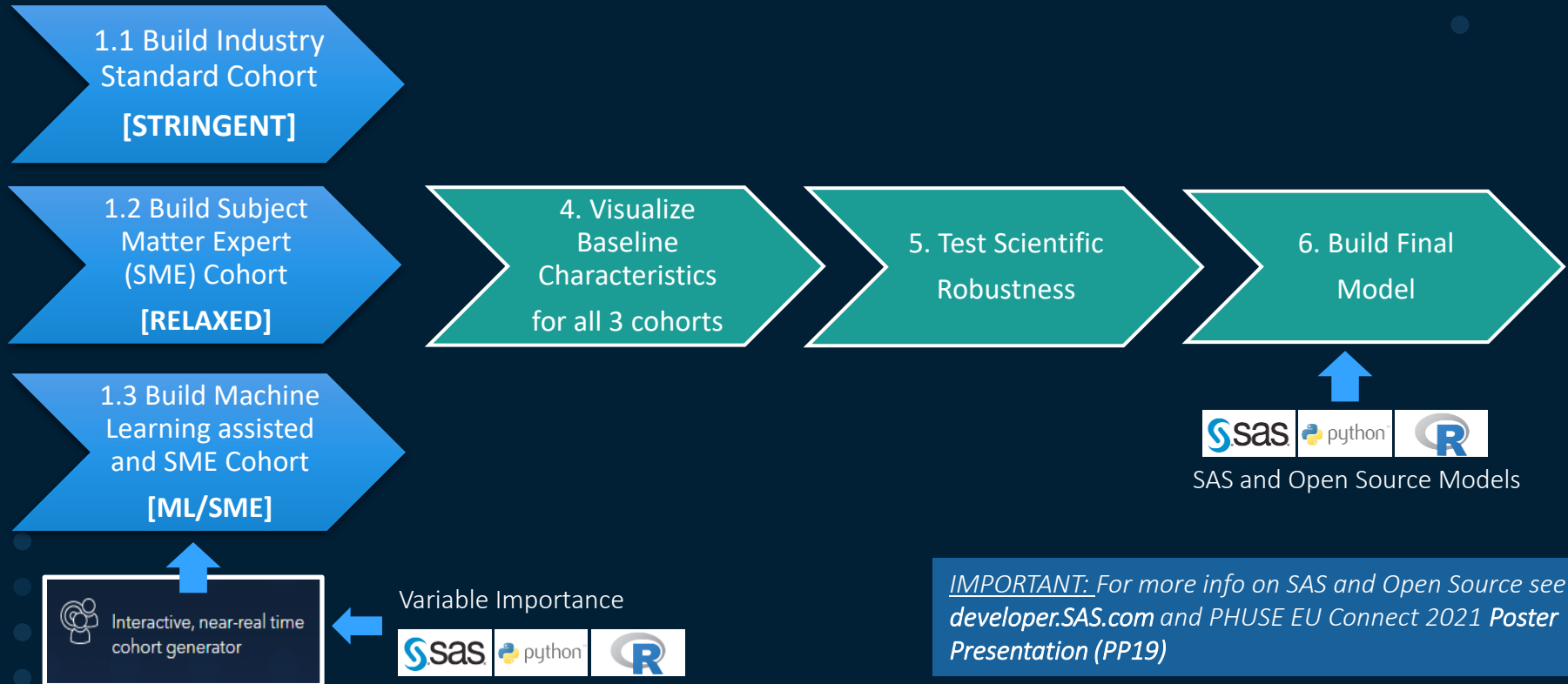
Process Flow



WHY?

1. Finalize Champion model generation
2. Generate Reports for Regulatory Submission

SAS and Open Source



What's Next ?

(1) Hands On Workshop

- ✓ You requested/received access and participated in testing beforehand.
- ✓ Please navigate to the break-out room (hands-on session).

OR

(2) Demo Time

- ✓ All other attendees will stay in main room and can follow the live demo.

For more info: See Hands-on Script (PDF)



THE
POWER
TO KNOW.



RWE WORKSHOP- FRIDAY NOV 19 HANDS-ON SCRIPT

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Podcast Series

 THE POWER TO KNOW.

ANALYTICS EXCHANGE:
PODCASTS FROM SAS



The Health Pulse

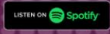


How can data, AI and advanced analytics accelerate innovation in health care? Which new technologies hold the most promise? What are the biggest roadblocks to progress? How can we solve endemic problems?

Join us for The Health Pulse podcast series as we explore fresh perspectives on digital transformation in health care and life sciences. With a special guest expert on each episode, we'll tackle the most pressing issues affecting the delivery of health care and therapies worldwide.

Quick jump to episodes 

You can access The Health Pulse podcast series on your favorite podcast platform by clicking on any of the icons below.



[The Health Pulse](#)

Hack In SAS (2021)

The screenshot displays the Hack In SAS (2021) website interface. At the top, a dark blue navigation bar contains links: Home, About, Tracks, Events, Mentors, Jury, Sponsors, and Partners. The main content area has an orange background with a wavy pattern. A section titled "Health" is centered, followed by a grid of 13 dark blue boxes, each featuring a white folder icon and a project name. The projects are: Amesto NextBridge - The Cancer Registry of Norway, AVANT - DIVA, Butterfly Data, Curve Scanning for Health, Gensenta & Dr.Regenold, Innova Tracers, ITsAmsterdam, Red Hot Chili Steppers, Scal Lab, SIRS/Sepsis, Starcore-IPB, The Positive Thinking Company SAS Hacker, and War On Cancer Analytics. Below this, a section titled "Health – Childhood Obesity" is centered, followed by a row of 6 dark blue boxes with project names: BearingPoint, Cactus, Digital Community Twin, Health Capacity, SciMinds, and Tupã Fit.

Home About Tracks Events Mentors Jury Sponsors Partners

Health

- Amesto NextBridge - The Cancer Registry of Norway
- AVANT - DIVA
- Butterfly Data
- Curve Scanning for Health
- Gensenta & Dr.Regenold
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- The Positive Thinking Company SAS Hacker
- War On Cancer Analytics

Health – Childhood Obesity

- BearingPoint
- Cactus
- Digital Community Twin
- Health Capacity
- SciMinds
- Tupã Fit

Let us know if
you are
interested to
participate in
2022 !

[Hack In SAS](#)

[Health Track - Hackers Hub \(all use cases\)](#)

A series of horizontal bars of varying lengths and colors (teal, blue, and green) are positioned on the left side of the slide, creating a decorative, layered effect.

Thank you. Questions ?

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