Society for Clinical Data Management
DATA DRIVEN

Theme:
Capabilities | Collaboration |
Change on the way to Clinical Data Science

SCDM Live

India conference

2nd - 3rd December 2022
Radisson Blu Hotel, Bengaluru

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IDEATANK

- Ram Mudaliar, Sr Dir, Clinical Data & Insights, AstraZeneca
- 13+ years DM experience
- India Head of Clinical Data & Insights group
- Strategic accountability for Data Management, Programming, Centralized Monitoring, Patient Safety and Data Standards, Automation in India
- Established effective DM teams in EU and North America
- Previous experience in Oncology Data Management and partnered on COVID trials with Oxford

Sowmyanarayan Srinivasan

- *Sowmya has over 22 years of experience in Life Sciences working at the intersection of business and technology.*
- *He has worked in start ups to large consulting firms with a focus on technology transformation and innovation.*
- *He has set up and grown R&D technology teams and has played roles ranging from product management, business development, capability development & leading innovation*
- *Currently working with Novartis as the Head of Technology Innovation & Strategic Partnerships*

Dr. Nirali Mehta

- *Dr. Nirali Mehta is CEO & Founder at Pharma-Stats, India*
- *Trainer for Pharmaceutical Statistics across 7 countries*
- *Biostatistical consultant for pharmaceutical regulatory issues.*
- *DSMB member for vaccine trials & IDMC member for PK studies*
- *Consultant SME – Health intelligence, New Jersey, USA*
- *Regulatory consultant at Trident Biopharm Solutions UK*
- *Strategic Advisor for Pharmaceuticals and Medical devices at Sicrum, Pune and South Korea*

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Deepu Joseph

- *Deepu Joseph is currently the Vice President and Country Head of Excelya India, the Indian entity of French CRO Excelya.*
- *With 18 years of experience in clinical research focused on Data Management and Biometrics, Deepu has worked with major CROs like Quintiles, ICON and Quanticate and has held global positions handling big and small team across the globe and different locations in India.*
- *Active member of SCDM India Steering committee for the last 4 years and has been contributor, speaker, and co-chair for conferences in the past*

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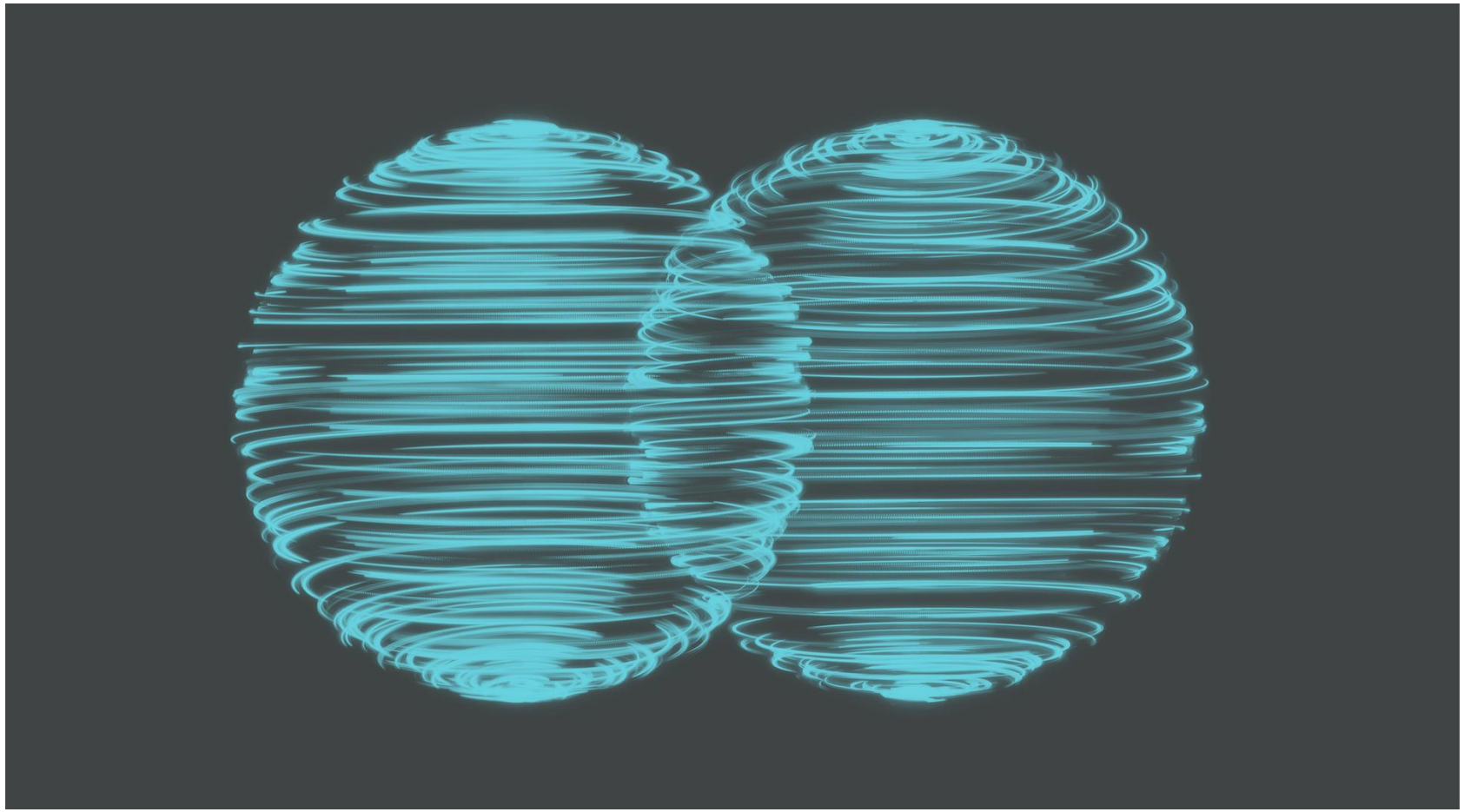
“Agile Methodology in Clinical Data Sciences”



Site Exposure Program (SEP)

Dr Venkateswarlu Tummalapenta
Associate Director, AstraZeneca

Nimisha Nigam
Associate Director, AstraZeneca

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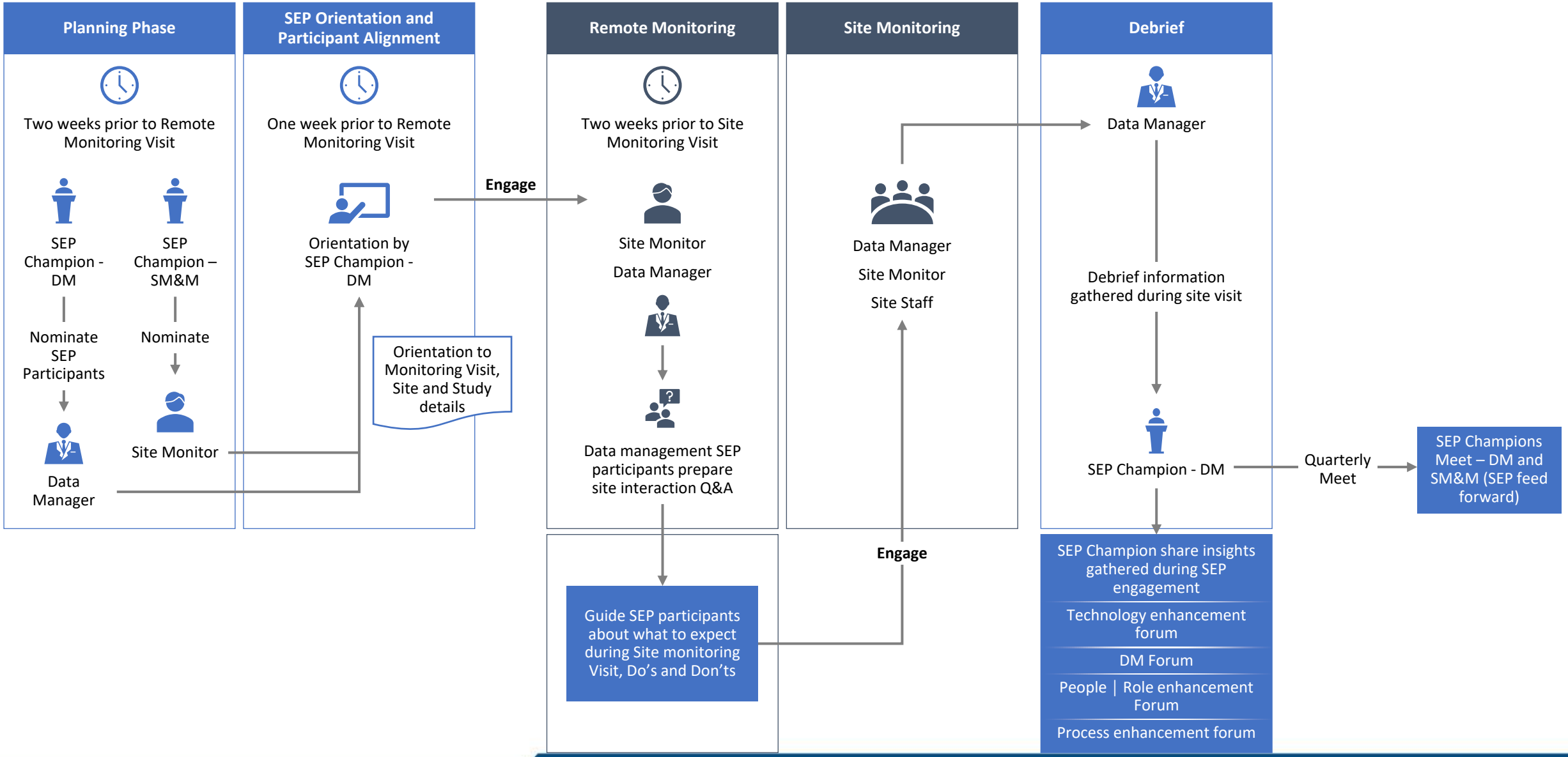
Overall Process



Business Benefits

People

- Skill enhancement of staff
- Art of story telling and listening
- Building site user experience on evolving and adoptive study designs and decentralized trials

Process

- Reduction in cancelled queries and re-queries
- People engagement through different types of site visits
- Edit check optimization (ECO)

Technology

- EHR and EDC data flow opportunity
- RAVE as a mobile application and/or Offline EDC system
- RPA BOT for eCCG

Apply Cross Functional Strengths

- CtQ (critical to Quality) data acquisition strategy
- Hand Shake of data cleaning with monitoring visit strategy
- Functional efficiencies through impactful data insights
- Engagement through patient stories

Dr Venkateswarlu Tummalapenta

Associate Director, Clinical Data Manangement CDI, Development Operations, R&D, AstraZeneca, Bengaluru, India

Nimisha Nigam

Associate Director, Clinical Data Manangement CDI, Development Operations, R&D, AstraZeneca, Bengaluru, India

AFFILIATIONS

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"Integration/Amalgamation of Third-Party Data"

Industry Context

Full potential of EDC has not been realized and that most implementations ended-up converting existing inefficient paper processes inside an electronic tool.

Overall changes to downstream processes and systems were not transformational enough to take advantage of faster data availability from EDC.

Additionally, despite the faster availability of data from the sites compared to paper-based processes, the cycle time from last patient last visit to database lock has been hardly reduced over the last decade. Decreasing from about nine (9) weeks in 2008 to seven (7) weeks in 2018.

The volume of data collected outside EDC has already surpassed significantly the volume of data collected on eCRF and it is growing at much faster pace every year, driven by the cries for patient centricity leading to the rapid adoption of eCOA, wearables, sensors, TPV data and other eSource solutions.

Additionally, the increasing cost of Clinical Development and the need for greater predictability of outcome requires the use of tool which helps in real time data validation, tracking and reporting of data sources specially for high-volume data collected outside EDC in order to making a positive and meaningful impact on Clinical Development.

Source: SCDM reflection Paper

Central Data Review Tool

Queries can be pushed to EDC Real time

EDC

Third Party Data

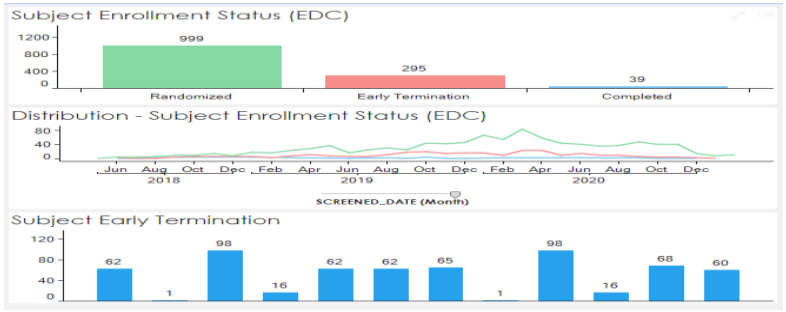
Central Data Review Tool

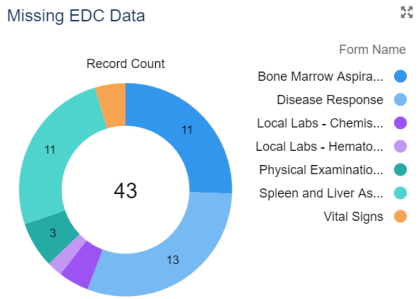
RAW DATA

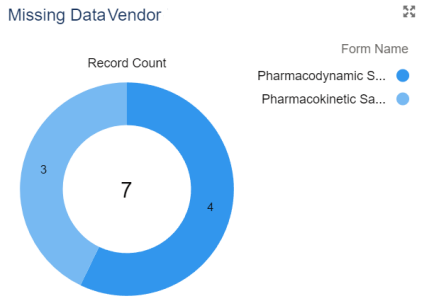
Conversion

SDTM

Clinical Database – Central Repository







Subject Name	Subject Status	Country	PI/Institution	Open EDC Queries	Answered EDC Queries	Missing Data	Pending CDR Discrepancies	Pending Vendor Queries	Pending Manual Queries	Pending SDV	Pending PI Signature	Pending SDR	Forecasted Data
12345	Early Termination	South Africa	XYZ Institute of Life Science	0	0	0	0	0	0	0	11	0	0
67893	Early Termination	United States of America	ABC Hospital	0	0	0	0	0	0	0	3	0	0
98765	Early Termination	United States of America	ABC Hospital	0	0	0	0	0	0	0	1	0	0
			TOTAL	179	42	399	55	0	9	45217	218880	799	0

Extract, Transform and Load Clinical data from all sources

Generate discrepancies through programmed edit check outside EDC

Generates meaningful Operational Analytics

Outcome and Learning

Effective Data Review

- Increase data review efficiencies
- Enables Cross functional review
- Streamlines data monitoring

Real Time Data Cleaning

- Generates data discrepancies throughout the lifecycle
- Reduce wait time
- Integrated Query management through EDC

Automation

- Semiautomated review involves less manual intervention
- Can be enhanced with AI ML capabilities
- Realtime CPT (Clean patient Tracker)

Targeted Data Review

- Enables in-scope data cleaning
- Projected metrics for upcoming milestones

Analytics

- More meaningful metrics generation and visualization to understand data trends

Cost Saving

- Operational efficiencies
- Effective Resource utilization
- Reduced LSLV to DBL TAT

CDR Tool can be 21CFR Part11 and ICH-E6-R2 compliant

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"Illuminating Clinical Trial Data with Actionable Analytics"

Situation

- Searching real-time clinical data for patterns or trends for testing clinical hypothesis is currently a manual process, requiring extensive manual intervention and prone to bias
- Early (semi or fully) automated detection of important patterns or trends in study data may help clinical teams across a broad variety of TAs to adapt study conduct and/or study oversight,

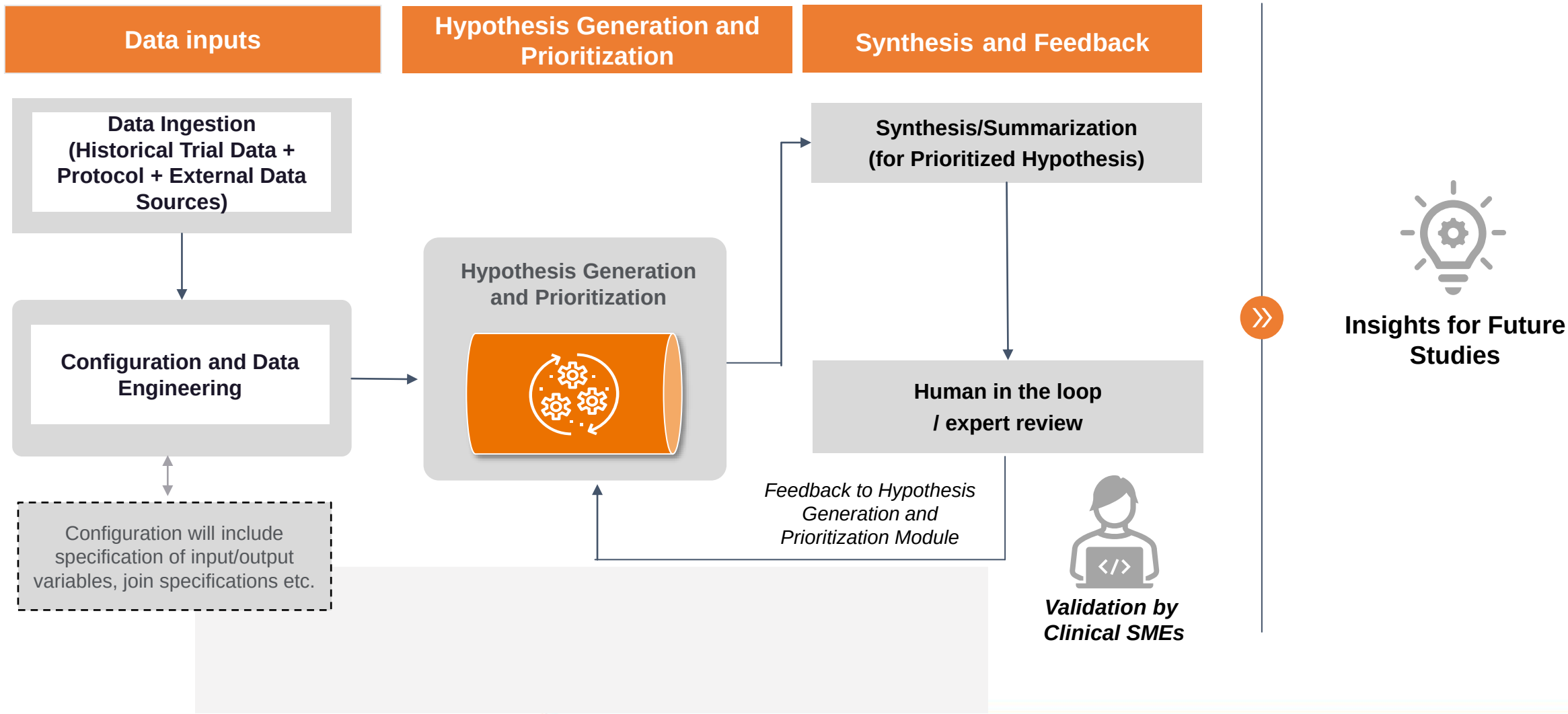
Our Approach

- A deep-learning, based hypothesis generation and prioritization module, which will leverage a range of unsupervised, deep-learning methods to identify hypothesis of potential interest, followed by synthesis and human validation

Solution Benefits

- Enable timely interventions during trial conduct - refinements to protocol document, investigator guideline updates
- Support to review large and diverse volumes of data and efficiently identify data patterns at scale

Smart Clinical Signal Detector – Solution outline for proposed proof of concept (1/2)



Smart Clinical Signal Detector – Solution outline for proposed proof of concept (2/2)

Data inputs

Data Ingestion

Primary Data Inputs
- Treatment blinded clinical trial data – **SDTM, ePRO, eCOA**
- Protocol document
- Known safety concerns

Reference Data Inputs
- Historic column mappings and **domain ontologies**

Configuration & Data Engineering

Data Configuration (Human expert inputs)
- Primary, secondary **end-points identification**
- **Column mappings** using human expert inputs/ ontologies

Data Engineering
- **Generation of multiple databases**, as needed, combining identifiers, patient demographics, eCOA responses, safety and efficacy indicators, at a patient-time or patient level as needed

Master dataset(s) with all co-variates and output variables of interest at most granular level

Hypothesis Generation and Prioritization

Generation of Candidate Insights
- Leveraging established and exploratory algorithms, such as
  - Deep learning based phenotyping methods
  - Generalized mixed effects models
  - Evolutionary Search Algorithms
  - Recursive tree-based partitioning
  - Exploratory algorithms including Deep Reinforcement Learning, Deep Learning, Frequent pattern mining etc.[1,2]

Prioritization of candidate insights
- Lift, Statistical significance tests
- Sub-group effect size estimation and comparison vs. global threshold
- Reward functions defined on the basis of interestingness, diversity and coherence

Key Trends and Patterns such as subgroups with higher/lower efficacy rates

Feedback to Hypothesis Generation and Prioritization Module

Synthesis and Feedback

Synthesis/Summarization

Synthesis
- Generation of summary insights based on subgroups and variables of interest

Summary Insights available for review

Human in the loop / expert review

Validation and Review
- Expert based qualification of signals to share back feedback

Validation by Clinical SMEs

1. Ori Bar El, Tova Milo, and Amit Somech, Automatically Generating Data Exploration Sessions Using Deep Reinforcement Learning, Tel Aviv University, Israel, DOI: https://u.cs.biu.ac.il/~somecha/pdf/atena_sigmod.pdf
2. Bo Tang, Shi Han, Man Lung Yiu, Rui Ding, and Dongmei Zhang. 2017. Extracting Top-K Insights from Multi-dimensional Data. Proceedings of the 2017 ACM International Conference on Management of DataAssociation for Computing Machinery, New York, NY, USA, 1509–1524. DOI:https://doi.org/10.1145/3035918.3035922

Case Study – an ensemble-based approach to identify historical trends or patterns in various studies and detecting safety and efficacy signals

Situation

- Client has near real-time clinical data like CRF, PRO etc. and currently rely on manual data review process which is time-consuming and laborious; wanted an AI/Machine Learning based technology platform with the ability to surface important and clinically meaningful trends or patterns during study conduct, such as
  - Cluster patients into treatment/placebo cohorts based on treatment response
  - Early prediction of treatment response
  - Identify safety signals

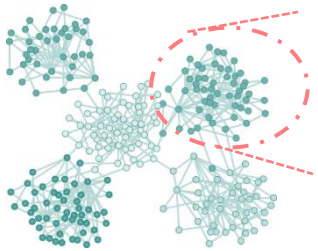
Outcomes

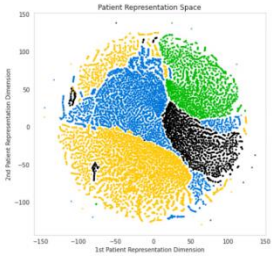
- Was able to identify patients with high/low response early in the trial (utilizing data available in the first snapshot), along with drivers; subsequent data improved the accuracy
- Uncovered clinically meaningful trends or patterns during study conduct, such as (but not limited to) -
  - High response in patients with a high dose of NSAIDs
  - High Probability of TEAE such as Arthralgia, Osteoarthritis, Back Pain, associated with ongoing medications such as ASA, Supplements, Chondroitin/Glucosamine, Levothyroxine, etc.
  - Correlation between liver adverse event, and treatment, possibly due to non-linear combination of concomitant medication and the treatment in question

Key Learnings

- Focus on explainability key as clinical SMEs are key consumers – use of effective visualizations key
- Ensemble of methods needed to capture diverse signals of interest across TAs

Approach # 1 - Computational phenotyping for identifying insights in complex, multi-dimensional temporal data

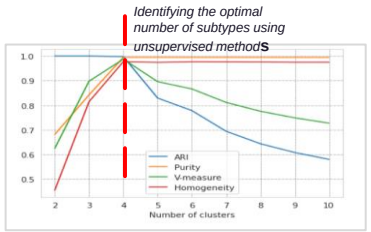




Illustration

Vector Representation

Numerical representations of individual patient/visit level data are **automatically generated** using embedding techniques to help render a **digital portrait** enabling unsupervised subtyping via graph modularity or other clustering methods



Pattern Detection

Clusters in the representations are identified, which determine why certain groups of patients lie in a tight vector space distinct from others and further what **signals are of impotance** within each of these clusters (potential trends/patterns)

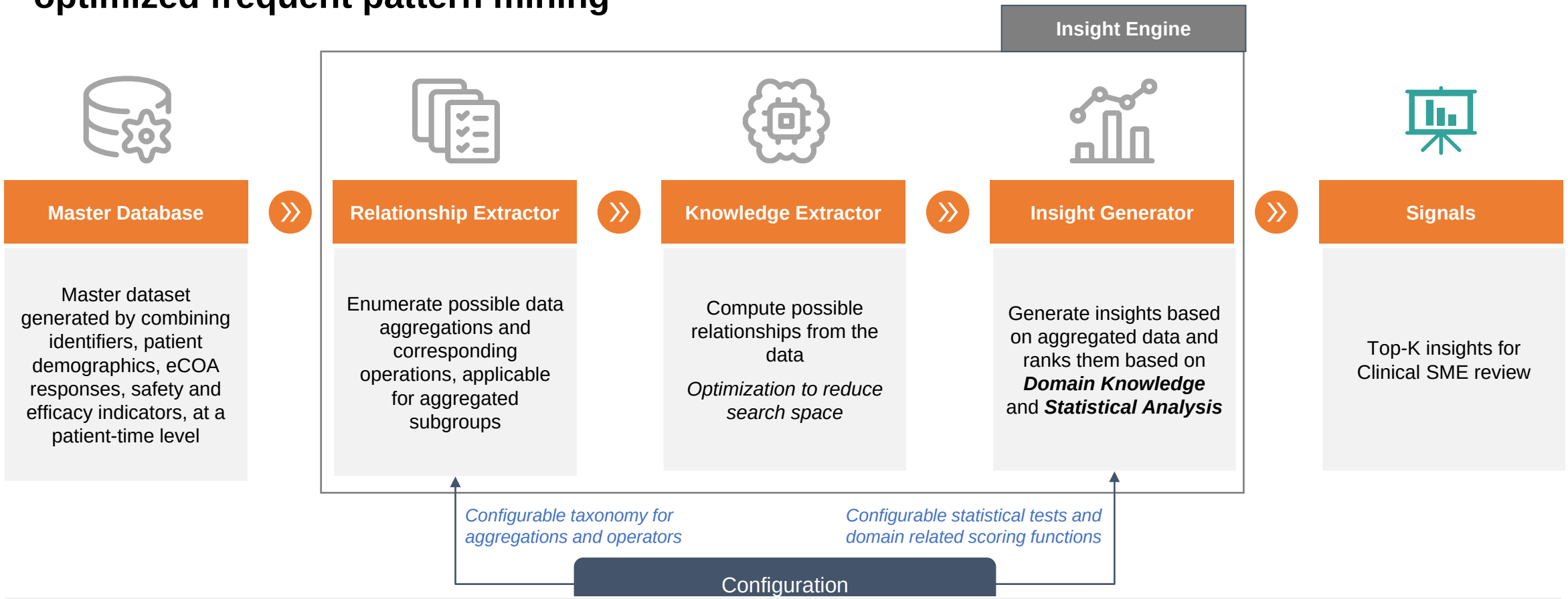
Post-profiling & Validation

Descriptive summaries to aid in hypothesis priortization

- Cohort **characteristics** to understand patterns and trends from blinded trial data

- **CNN**s to model temporal aspects coupled with **autoencoders** to enable unsupervised architectures (**ConvAE**)
- Tanh-LSTM based **encoder-decoder** architectures
- **Stacked denoising autoencoders** (DeepPatient) architecture
- **Graph-based** methods which leverage hidden structures in the data

Approach # 2 - Proposed exploratory method for an Automated Insight Engine, utilizing optimized frequent pattern mining



This proposed exploratory approach aims to extract top insights from any transactional dataset, using optimized frequent pattern mining methods – the approach requires configuration of data taxonomy, necessary operations and scoring functions to automatically traverse through potential insights and highlight top statistically significant insights.

Bo Tang, Shi Han, Man Lung Yiu, Rui Ding, and Dongmei Zhang. 2017. Extracting Top-K Insights from Multi-dimensional Data. Proceedings of the 2017 ACM International Conference on Management of DataAssociation for Computing Machinery, New York, NY, USA, 1509–1524. DOI:https://doi.org/10.1145/3035918.3035922