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

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)

Data inputs

Data Ingestion (Historical Trial Data + Protocol + External Data Sources)

Configuration and Data Engineering

Configuration will include specification of input/output variables, join specifications etc.

Hypothesis Generation and Prioritization

Hypothesis Generation and Prioritization

Synthesis and Feedback

Synthesis/Summarization (for Prioritized Hypothesis)

Human in the loop / expert review

Feedback to Hypothesis Generation and Prioritization Module

Validation by Clinical SMEs

Insights for Future Studies

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

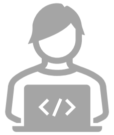
Synthesis/Summarization

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

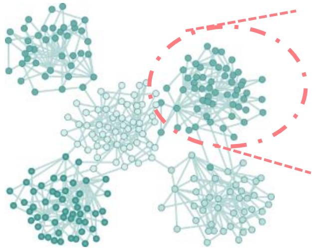
Outcomes

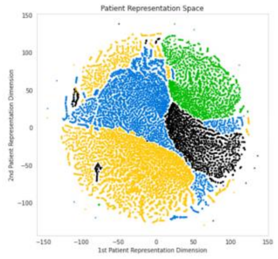
- Was able to identify patients with high/low response early in the trial (utilizing data available in the first snapshot), along with drivers; subsequent data improved the accuracy
- Uncovered clinically meaningful trends or patterns during study conduct, such as (but not limited to) -
  - High response 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

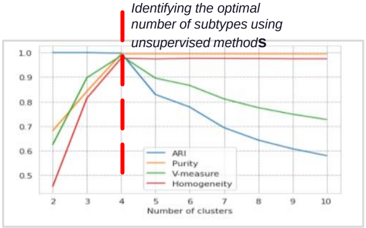




Illustration

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



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

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)

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

Insight Engine

Master Database

Master dataset generated by combining identifiers, patient demographics, eCOA responses, safety and efficacy indicators, at a patient-time level

Relationship Extractor

Enumerate possible data aggregations and corresponding operations, applicable for aggregated subgroups

Knowledge Extractor

Compute possible relationships from the data

Optimization to reduce search space

Insight Generator

Generate insights based on aggregated data and ranks them based on ***Domain Knowledge*** and ***Statistical Analysis***

Signals

Top-K insights for Clinical SME review

Configurable taxonomy for aggregations and operators

Configurable statistical tests and domain related scoring functions

Configuration

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