The National Evaluation System for health Technology Coordinating Center (NESTcc): Validating NESTcc's Active Surveillance Approaches Using Blinded, Synthetic Medical Device Performance Datasets

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Background

NESTcc Mission

The NEST community is passionately committed to transforming the way medical device technologies are tested, approved and monitored.

Active Surveillance

Helping to fulfill NESTcc's Mission & Vision through the continuous monitoring of large, real-world data sets for medical devices in routine use.

NESTcc Vision

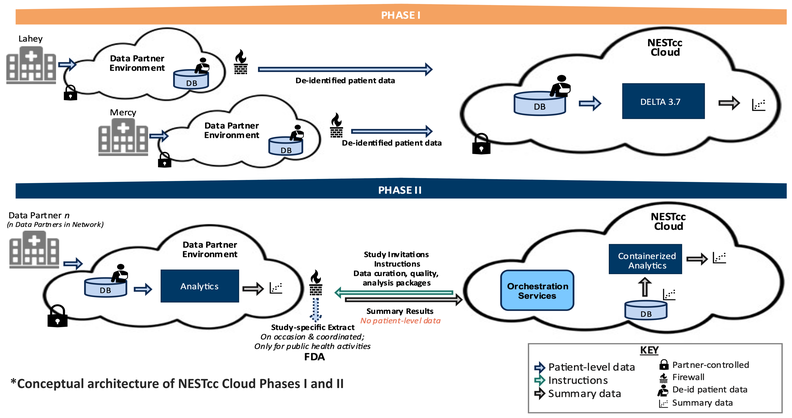
We envision a world in which people are empowered to make informed medical choices that enable patients to live their lives to the fullest extent possible.

In 2018, FDA tasked NESTcc with establishing **postmarket active surveillance capabilities** to more quickly detect emerging signals for patient safety by "continuously generating, accessing and evaluating large data sets on device performance and clinical outcomes associated with device use in routine clinical practice" and "improv[ing] the FDA's ability to link adverse events with specific devices." (Gottlieb & Shuren, 2018)[1]. The capability to continuously monitor and evaluate large Real-World Data (RWD) generated during routine clinical device usage has the potential to enable stakeholders to make timelier, evidence-based decisions for patient safety (Gottlieb & Shuren, 2018)[1]. This capability can transform how medical device benefit-safety profiles are monitored using RWD.

NESTcc is building a **cloud-based, federated learning environment** to facilitate the collection and analysis of RWD for performing **safety signal refinement and signal detection** for active surveillance of medical devices. Signal refinement studies are expected to be the initial focus of the NESTcc Cloud, and NESTcc expects to support signal detection studies in time. Across both signal refinement and signal detection studies, **Data Partners retain full ownership and control of patient-level records, without the risk exposure that accompanies data sharing.**

Phase I of Active Surveillance delivered a basic cloud infrastructure with capabilities of data ingestion, processing, analysis and reporting for a single cloud instance. Phase I's synthetic data use cases validated the Data Extraction and Longitudinal Analysis (DELTA) open-source statistical analysis tool, developed by Lahey Health, and deployed to the NESTcc Cloud by identifying hidden signals in synthetic datasets.

Phase II of Active Surveillance will begin in Q4 of 2021. A Request for Information is currently open to seek Active Surveillance Data Partners and use case ideas.



*Conceptual architecture of NESTcc Cloud Phases I and II

Introduction

- The objective of this research was primarily to provide Phase I NESTcc Cloud system and DELTA methods validation.
- NESTcc obtained synthetic datasets from Vanderbilt University Medical Center, which contained hidden signals.
- NESTcc used Lahey's DELTA tool, containerized and deployed in the NESTcc Cloud and compared to an existing local deployment, to confirm basic operations of the NESTcc Cloud system and equivalent functionality of the DELTA methods.
- NESTcc also validated the DELTA methods by correctly identifying hidden signals within the synthetic datasets.

Synthetic Datasets

- 10 datasets (five unique datasets from two different data submitters)
- Each dataset contained approximately 10,000 records.
- The datasets contained 24 clinical covariates as well as three clinical outcomes.
- Distributions of covariates and outcomes were based on percutaneous coronary intervention covariates from a national registry.
- Within the datasets, two hidden "device" exposures were included (each with differing risk outcomes).

Methods

- 10 simulated device performance datasets – generated from clinical covariate distributions and containing **hidden signals** (e.g., a percentage of missing data, non-zero adverse event rate) – were analyzed using DELTA on a local server and on the NESTcc Cloud.
- DELTA methods included: descriptive statistics, multiple logistic regression (MLR), MLR with automated variable selection (AVS), propensity score matching, propensity score weighting (inverse probability treatment weighting (IPTW) and weight by odds (WxO)), and sequential probability ratio testing (SPRT).
- Success was defined a priori as (i) less than 2% discrepancy between cloud and local results (Cloud:Local), (ii) covariate distributions within 2% of hidden signal (Cloud or Local:Truth), and (iii) calculated adjusted odds ratio within 5% of truth.

PHASE I

TEST PLAN
- Synthetic dataset was designed to test the system, including data ingestion within DELTA, user and methods verification, and DELTA results extraction

INGEST
- Standardized flat file table, delivered in separate files, to represent multiple submissions over time

PROCESSING
- Automated check and rejection of files containing PHI/PII
- Data validation pipeline on formatting, data types and valid values

ANALYSIS
- Run through containerized DELTA 3.7 analytic engine [all analyses (e.g., descriptive statistics, propensity matching)]
- Format of results output in standard format (e.g., CSV)

REPORTING
- DELTA and NESTcc Cloud Dashboards

Results

- Validation analyses were performed on two instances of DELTA: 1) DELTA on a "**Local**" server (at Lahey) and 2) DELTA on the NESTcc "**Cloud**"
- Results from both instances of DELTA were compared to the hidden signals within the synthetic data ("**Truth**") to determine DELTA's methodological validity
- Differences between Cloud:Local and Cloud:Truth ratios were acceptable (≤0.3%) for descriptive statistics, MLR, AVS, and SPRT; differences between Cloud:Local and Cloud:Truth ratios were larger than (≤0.3%) but still acceptable for propensity score match and IPTW
- Ratios were outside the defined validity criteria for WxO (≥5% adjusted odds ration of Truth)

DELTA Method	Local:Truth	Cloud:Local	Cloud:Truth	Method Validation Status
Descriptive Statistics	0.998	1.000	0.998	**Pass**
LR Non-Parsimonious	0.998	1.000	0.998	**Pass**
LR Auto Variable Select	0.997	0.999	0.998	**Pass**
Propensity Match	0.947	0.967	0.945	**Pass**
IPTW	0.962	1.000	0.962	**Pass**
Weight by Odds	0.904	1.000	0.904	**Fail**
SPRT	1.000	1.000	1.000	**Pass**

Conclusion

- All seven DELTA methods in the Cloud instance replicated results from Local instance (Cloud:Local)
- Six of seven tested DELTA methods were validated on the NESTcc Cloud (Cloud:Truth) and were successful in identifying the hidden signals
- The WxO method was not validated, and further analysis is warranted
- NESTcc is confident in the NESTcc Cloud instance of DELTA and its capability to correctly find hidden signals

Upcoming Active Surveillance Activities

- **Phase I:**
  - NESTcc, Lahey and Mercy are working on two manuscripts detailing the validation use cases (synthetic data, bare metal stents vs. drug-eluting stents)
    - **Manuscript #1**: Incorporates the two synthetic data uses cases as well as a cardiac stent use case, which uses previously published Mercy data
    - **Manuscript #2**: Prospective safety analysis using IPTW and Propensity Score Matching on new drug-eluting stent data (Everolimus vs. Zotarolimus), pooled by Lahey and Mercy
- **Phase II**: **How you can get involved! – visit NESTcc.org or email nestcc@mdic.org**
  - Open call for Active Surveillance Data Partners (submit application)
  - Open call for IT Cloud Working Group applicants (submit application & resume)
  - Expansion of A/S Methodology Working Group (submit application & resume)
  - Expansion of A/S Data Curation Working Group (submit application & resume)

[1] Gottlieb, S., & Shuren, J. E. (2018, November 20). *Statement from FDA Commissioner Scott Gottlieb, M.D. and Jeff Shuren, M.D., Director of the Center for Devices and Radiological Health, on FDA's updates to Medical Device Safety Action Plan to enhance post-market safety.* Retrieved from https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-jeff-shuren-md-director-center-devices-and-2

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