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REAL WORLD REPLICATION OF CLINICAL TRIAL FINDINGS IN ALZHEIMER'S DISEASE

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Introduction

While randomized controlled clinical trials are the gold standard for demonstrating efficacy, there is a need to facilitate comparison of trial findings with real world populations. This is evident in the 21st Century Cures Act with the FDA and large public-private initiatives, such as IMI GetReal in Europe.[1,2] In this study we propose the use of common data model transformation and standardized clinical vocabularies to facilitate replication of the study cohort from an Alzheimer's trial, publicly available in the Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM) format, in a real-world data Electronic Medical Record data source.[3] For data transformation, the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) was used.[4]

Methods

Data Sources

- This study was conducted using a publicly available Alzheimer's placebo-controlled clinical trial dataset from CDISC, of mild-to-moderate patients on experimental therapy[6,7]
- Findings were compared to a US outpatient electronic medical records (EMR) data source from the HealthVerity® Marketplace platform of data suppliers from January 1, 2014 to December 31, 2018

Data Transformation and Analysis

- Both datasets were transformed into the OMOP Common Data Model, version 5. Conversion completeness for both data sources was in excess of 99%
- Analyses were conducted using the SHYFT Quantum V6.7.0 solution

Analyses

- Inclusion/exclusion criteria for the trial were applied to the EMR data to create a comparison cohort.
  - Inclusions:
    - Patients with ≥2 diagnoses of Alzheimer's with at least 182 days in between
    - At least 1 prescription of donepezil, memantine, rivastigmine, galantamine, or Namzaric
    - Age ≥60 at index
    - Known gender at index
    - ≥180 days continuous activity pre-index
  - Exclusions:
    - exclusions for baseline MMSE, severe Alzheimer's, could not be applied due to data limitations
    - exclusions for alpha-adrenergic blockers, calcium channel blockers, anti-epileptics, neuroleptics, anti-depressants corticosteroids, sedative/hypnotics could not be applied due to impact on sample size
- Common OMOP vocabularies were used to derive equivalent clinical (concomitant medications, comorbidities), demographic (age, gender), and outcomes variables across both cohorts, and to replicate generation of descriptive statistics and Kaplan-Meier time-to-event analyses for key outcomes measurable in both datasets.
- Rates of common trial safety events were assessed (e.g., application site disorder, erythema, rash, site irritation, application site pain, edema).
- Clinical outcomes were assessed
  - For the CDISC SDTM dataset, this was assessed by change in Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-COG) from baseline (Increase or Decline). Increase in ADAS-COG score is indicative of a greater cognitive impairment.
  - ADAS-COG was not available in the EMR data. Instead, change from baseline-to-final Mini-Mental Status Exam (MMSE) was measured within patients having at least 2 observations, with patients designated as Maintained (increased or unchanged), or Declined (decreased)
  - For the EMR data, time-to-treatment-discontinuation (TTD) was also assessed, defined as >60 day gap in days' supply
  - Kaplan-Meier analyses were adjusted for age and visit frequency

Figure 1A: Electronic Health Care Dataset Attrition

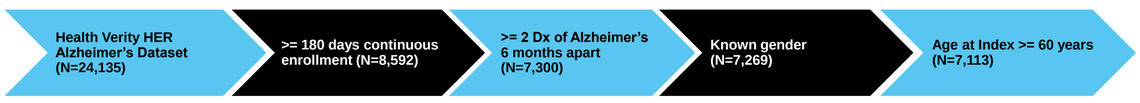


Figure 1B: CDISC Dataset Attrition

Table 1: Demographics

Variable	Result	CDISC	HealthVerity® EMR
Total Patient count included	***N***	**240**	**7,113**
Drug Reaction AEs	*FALSE, N (%)*	123 (51.2%)	6,984 (98.2%)
	TRUE, N (%)	117 (48.8%)	129 (1.8%)
Age at Index	*Mean (SD)*	76.2 (7.0)	79.3 (7.3)
	Median	77	79
Age Subgroup: 10 years bins	*60-70, N (%)*	46 (19.1%)	727 (10.2%)
	70-80, N (%)	106 (44.2%)	2,957 (41.6%)
	80-90, N (%)	88 (36.7%)	3,077 (43.3%)
	90+, N (%)	0 (0.0%)	352 (4.9%)
Gender	*FEMALE, N (%)*	135 (56.2%)	4,681 (65.8%)
	MALE, N (%)	105 (43.8%)	2,432 (34.2%)
Drug Reaction AEs	*FALSE, N (%)*	123 (51.2%)	6,984 (98.2%)
	TRUE, N (%)	117 (48.8%)	129 (1.8%)
Donepezil Exposure	*FALSE, N (%)*	235 (97.9%)	2,872 (40.4%)
	TRUE, N (%)	5 (2.1%)	4,241 (59.6%)
Baseline ADAS Score	*Mean (SD)*	23.9 (12.1)	—
	Median	21	—
ADAS Delta Score (Final – Baseline)	*Mean (SD)*	2.1 (5.2)	—
	Median	1.00	—
Baseline MMSE Score	*Mean (SD)*	—	15.4 (7.84)
	Median	—	16
MMSE Delta Score (Final – Baseline)	*Mean (SD)*	—	-1.14 (4.06)
	Median	—	0

Results

When converted to the OMOP Common Data Model, record capture for both data sources was in excess of 99% for relevant tables. Custom concepts were created for ADAS-COG and MMSE scores in the Observations table, in accordance with OHDSI recommendations.

Cohort comparisons between the two data sets revealed similar demographic characteristics, with slightly higher average age and percent female patients in the EMR population (**Table 1**). While the trial population was overwhelmingly on experimental treatment or placebo, the EMR population was mostly (59.6%) donepezil. Overall, the rate of drug reaction adverse event rates was much lower in the electronic health record data, an expected result given original trial findings (**Table 1**). This was consistent with Kaplan-Meier assessment of time-to-adverse event **(Figure 2,3)**. Median time to ADAS-COG increase in the clinical trial population was approximately 176 days **(Figure 4)**. In the EMR population, comparison to ADAS-COG was not possible, but median times-to-decline for MMSE- declining patients was 580 days, with initial decline seen at around 250 days (**Figure 5**). It is worth noting that the majority of MMSE assessments were done prior to diagnosis or initiation of therapy, with frequency declining markedly after index date. Although medians were not reached, Time-to-Treatment Discontinuation trends were similar, with greater rates of discontinuation in patients with declining MMSE score **(data not shown)**. This is not surprising, given the reduced frequency of assessment in real-world populations. Consistent with this, Kaplan-Meier curves factored by age and visit frequency trended towards faster discontinuation in patients with younger age or more frequent visits **(Figure 6,7).**

Figure 2: Time to Drug Reaction Adverse Events (CDISC clinical trial data)

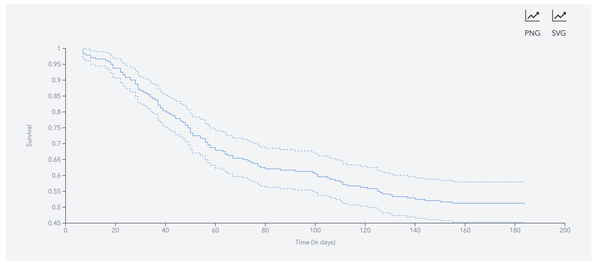


Figure 3: Time to Drug Reaction Adverse Events (HealthVerity® Real-world data)

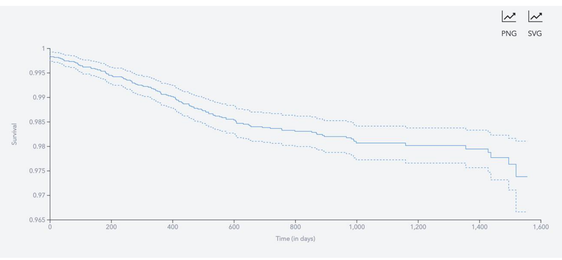


Figure 4: Time to ADAS Score Increase (CDISC clinical trial data)

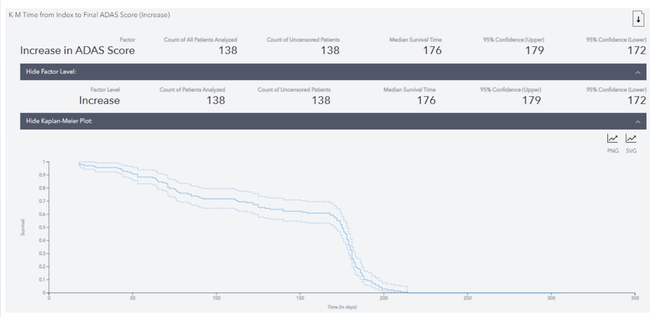


Figure 5: Time to MMSE Score Decline from index (HealthVerity® Real-world data)

Figure 6: Time to Treatment Discontinuation, factored by age at index (HealthVerity® Real-world data)

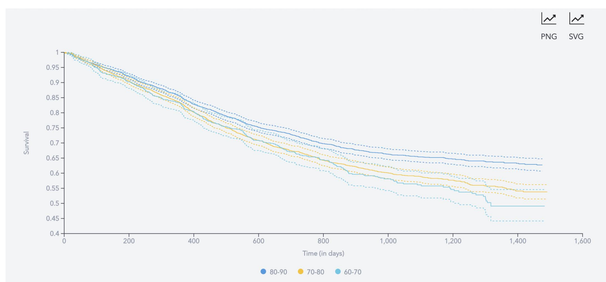
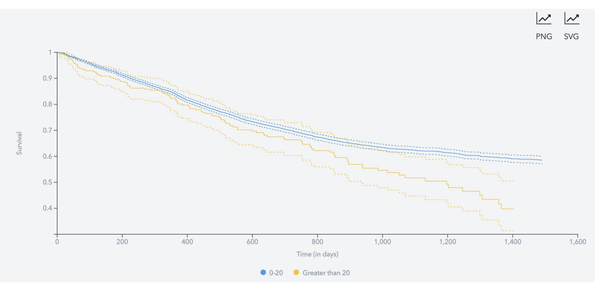


Figure 7: Time to Treatment Discontinuation, factored by count of outpatient visits (HealthVerity® Real-world data)



Conclusions

By leveraging standard OMOP vocabularies and common data modeling, cohort replication and analysis can be executed rapidly and consistently. This has potential applications for enhancing the conduct of synthetic control arms for clinical development and for extrapolation of clinical trial findings to real world treatment practices.

Within this study, we assessed the ability to measure both efficacy and safety measures between a clinical trial and real-world cohort in Alzheimer's disease. This allowed for comparison of adverse events against a population not present in the original placebo-controlled trial. While efficacy measures could not be compared directly, proxies were assessed using the same standard analytic packages, and identification of factors for future adjustment was rapid.

Potential next steps include replication in additional datasets. Expanded sample size will facilitate closer approximation of original inclusion/exclusion trial criteria, as well as other adjustment or matching techniques, if warranted.

References

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