Poster # TH-PO840

Modeling Diversity in Diabetic Kidney Disease Clinical Trials using Real-world Data

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Introduction

- FDA places emphasis on studying clinically relevant trial populations but does not address how to define these.
- The authors have previously reported an underrepresentation of people of African descent in lupus nephritis trials[1], but this has not been investigated in more common renal disorders such as diabetic kidney disease (DKD).

Objectives

- The study aims to compare demographics of individuals with DKD from a large electronic health record (EHR) database with completed US-only DKD trials and propose statistical parameters for cohort sizes to support DKD trial planning.

Materials and methods

- We evaluated data from the TriNetX Network, which contains EHRs from >150 million individuals in the US.
- Demographics were assessed for those with an ICD-10-CM code E11.22 Type 2 Diabetes Mellitus with DKD in the last 5 years that had received healthcare services and did not also have an ICD-10-CM code N18.6 End Stage Renal Disease (ESRD).
- The gender race and ethnicity distributions were used to define statistical parameters for hypothetical study sample sizes by calculating 95% binomial Confidence Intervals (CI) for each demographic cohort.
- Data were compared to proportions of demographic cohorts in completed US-only DKD trials reported the National Institutes of Health ClinicalTrials.gov database as of.
- Differences were evaluated by calculating a z-score for each cohort for each trial using the two-proportion z-test.
- The hypothesis that the median of the z-scores is zero was tested using one-sample Wilcoxon signed-rank tests. Effect size was determined using Rosenthal correlation coefficients.
- This retrospective study used only de-identified aggregated patient data per the de-identification standard defined in Section § 164.514(a) of the HIPAA Privacy Rule and therefore was exempt from Institutional Review Board Approval.

Results

Real-world EHR Data

- 583,660 individuals met eligibility.
- The gender distribution was 50.2% Male, 45.4% Female and 4.4% Unknown.
- Race distribution was 62.8% White, 19.8% Black or African American (BAA), 4.0% Asian and 13.4% other/unknown race.
- Ethnic distribution was 19.7% Hispanic or Latino (HL), 73.5% non-HL and 6.9% unknown ethnicity (**Table 1 A**).

Clinical Trials

- 9 DKD clinical trials were evaluated (956 subjects).
- Gender was reported for 9 trials (Male 64.8%, Female 35.2%).
- Race was reported for 6 trials, 77.4.% White, 18.2% BAA, 2.0% Asian and 2.3% other/unknown.
- Ethnicity was reported for 3 trials, 35.6% HL, 64.4.% Non-HL (**Table 1B**).

Table 1. Demographic distribution of DKD patients in A) TriNetX EHR, and B) completed US-only DKD trials.

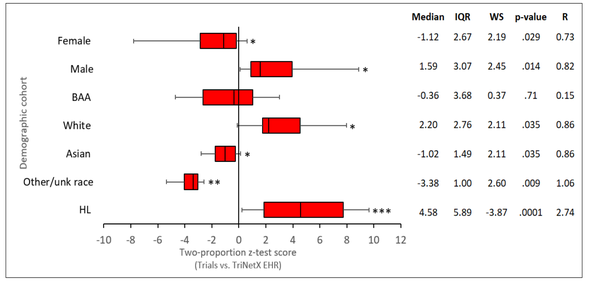
Demographic cohort	A) TriNetX EHR	B) Clinical trials
Number of patients	583,660	956
Gender (%)		**Mean (SD)**
Female	45.4	35.2 (14.1)
Male	50.2	64.8 (14.1)
Unknown	4.4	0.0 (0.0)
Race (%)		
White	62.8	77.4 (14.5)
BAA	19.8	18.2 (13.0)
Asian	4.0	2.0 (2.2)
Other/Unknown	13.4	2.3 (1.6)
Ethnicity (%)		
HL	19.7	35.6 (15.4)
Non-HL	73.5	64.4 (15.4)
Unknown	6.9	0.0 (0.0)

Abbreviations (BAA) Black or African American, (HL) Hispanic or Latino, (SD) standard deviation.

Comparative Analysis:

- A comparison of z-scores from two proportion z-tests revealed a statistically significant underrepresentation of females in US DKD trials compared to EHR (p<.05).
- White populations were significantly overrepresented (p<.05).
- Asian populations were significantly underrepresented (p<.05) as were patients of other/unknown race (p<.01).
- BAA populations were not underrepresented.
- There was a highly significant overrepresentation of HL populations in US trials compared to the TriNetX EHR-derived dataset (p<.001) (**Figure 1**).

Figure 1. Comparison of demographic cohorts from completed US-only DKD clinical trials vs DKD patients in the TriNetX EHR database.



Box and whisker plots were generated from z-scores calculated using two proportion z-tests. The lefthand boundary of the box indicates the 25th percentile, the righthand boundary of the box indicates the 75th percentile, the black line within the box marks the median z-score. Righthand and lefthand whiskers indicate the 90th and 10th percentiles respectively. Differences in z-scores from zero were tested using one-sample Wilcoxon signed-rank tests (* p < .05; ** p < .01; *** p < .001). Abbreviations (BAA) Black or African American, (HL) Hispanic or Latino, (IQR) interquartile range, (R) Rosenthal correlation coefficient, (WS) Wilcoxon standardized test statistic.

Cohort Modelling:

- Based on an analysis of binomial confidence intervals, a US DKD trial of 100 subjects would be considered statistically representative (p<.05) of the TriNetX population if it included a range of 40-60 Male, 35-55 Female, 53-72 White, 13-29 BAA, 1-9 Asian and 13-29 HL patients (**Table 2A**).
- Modelling for a larger trial of 300 patients is also provided for comparison (**Table 2B**).

Table 2. Clinical rial cohort models for A) hypothetical n=100 patient trial B) n= 300 patient trial

Demographic cohort	A) 100 patients N (range*)	B) 300 patients N (range*)
Female	45 (35-55)	136 (119-153)
Male	50 (40-60)	151 (134-168)
Other/unk gender	4 (2-11)	13 (7-22)
White	63 (53-72)	188 (171-204)
BAA	20 (13-29)	59 (46-74)
Asian	4 (1-9)	12 (6-21)
Other/unk race	13 (7-21)	40 (29-53)
HL	20 (13-29)	59 (46-74)
Non-HL	74 (64-82)	221 (205-236)
Unk ethnicity	7 (3-13)	21 (13-32)

*Ranges represent 95% binomial confidence intervals. Abbreviations (BAA) Black or African American, (HL) Hispanic or Latino, (SD) standard deviation (unk) unknown.

Conclusions

- As emphasized by the FDA, therapeutics should be investigated in trial populations that are representative of those likely to use the treatment if approved.
- Large EHR databases are one method to determine real-world demographics to support the planning of “representative” trial cohorts.
- Our data shows a statistically significant overrepresentation of white populations in completed US-only DKD clinical trials compared to an EHR-derived population.
- This is primarily at the expense of a significant underrepresentation of Asian populations and patients of other/unknown race rather than BAA populations, which were not significantly underrepresented.
- Females have been significantly underrepresented in US-only DKD clinical trials compared to EHR-derived data.

References

1. 495 Using a Large Electronic Health Record Database to Define Representative Patient Populations for Lupus Nephritis Trials. American Journal of Kidney Diseases, Volume 83, Issue 4, S153.

Learn more at https://www.ppd.com/therapeutic-expertise/nephrology-and-renal-disease

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