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Treatment Patterns, Treatment Outcomes, and Health Care Costs Before and After Humulin R U-500 Initiation or Device Change among Patients with Type 2 Diabetes in the United States

HUMULIN R U-500 (LY041001)

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Observational Study Protocol Electronically Signed and Approved by Lilly

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3. Background and Rationale

It is often more challenging to achieve desired blood glucose levels among type 2 diabetes mellitus (T2DM) patients with severe insulin resistance, using 100 units/mL (U-100) insulin.[1] Patients often require 4-8 daily injections to meet their high insulin requirements; these repeated injections may lead to a painful injection site reaction, which can adversely affect adherence to the insulin replacement therapy.[2]

U-500 regular insulin (U-500R) is a five-fold concentrated form of insulin (contains 500 units of insulin per mL) for the treatment of T2DM patients with severe insulin resistance (T2DM conditions that require >200 units of insulin per day). It was first approved in 1994 by the United States Food and Drug Administration (FDA).[3,4] To avoid dosing errors, it is currently available for administration through pens and vials with the dedicated U-500R syringe.[5] In addition, off-label continuous subcutaneous insulin infusion (CSII) administration has been employed increasingly for the administration of U-500R.[6] The high concentration of insulin in U-500R allows the administration of high doses, at 20% of the volume of a corresponding dose of U-100, which leads to improved subcutaneous depot absorption.[1,7] In addition, high doses of insulin may be achieved with twice or thrice-daily administrations of U-500, which mitigate physical discomfort and potential barriers to adherence associated with U-100.[4,8] Furthermore, the increase in insulin at subcutaneous depots increases the formation of insulin hexamers, which prolong the duration of the hypoglycemic effect of insulin therapy.

U-500R use has been shown to improve glycated hemoglobin (HbA1c) levels among T2DM patients who switched from U-100 to U-500R.[7] U-500R use has also been found to be associated with lower health care costs and better adherence than U-100 users prescribed a similar dose.[9,10] Previous research suggests that T2DM patients who initiated therapy with an insulin pen are more adherent to treatment than those using the vial/syringe method.[11] Insulin pen devices have also been shown to provide more reliable, accurate, and simplified dosing than vial/syringe administration.[11,12] However, little is known on treatment patterns, treatment outcomes and economic burden of the U-500R administration in the real-world setting. Therefore, STATinMED Research will use real-world data to evaluate treatment patterns, treatment outcomes including HbA1c and hypoglycemia, and health care costs among T2DM patients who initiated U-500R and among those who switched from U-500R syringe administration to Kwikpen.

4. Objectives

4.1 Research Objectives

Research Objective 1: Treatment Patterns

- **Primary Objective 1:** Evaluate the treatment patterns of insulin including observed total daily dose [TDD] in claims, adherence, prescription fill rate, claim gaps, persistence and concomitant medication use among T2DM patients before and after U-500R syringe initiation and U-500R Kwikpen initiation separately as well as before and after U-500R device switch from syringe to Kwikpen:
  - Characterize U-500R Kwikpen patients;
  - Determine differences between treatment patterns before and after U-500R Kwikpen initiation;
  - Determine differences between treatment patterns before and after U-500R syringe initiation; and
  - Determine differences between treatment patterns before and after U-500R device switch from syringe to Kwikpen.

Research Objective 2: Treatment Outcomes

- **Primary Objective 2:** Evaluate the HbA1c level among T2DM patients before and after U-500R syringe initiation and U-500R Kwikpen initiation separately, as well as before and after U-500R device switch from syringe to Kwikpen:
  - Determine differences between HbA1c level before and after U-500R Kwikpen initiation;
  - Determine differences between HbA1c level before and after U-500R syringe initiation;
  - Determine differences between HbA1c level before and after U-500R device switch from syringe to Kwikpen; and
  - Determine whether observed TDD in claims or insulin adherence played a role in HbA1c changes among U-500R syringe initiators, U-500R Kwikpen initiators, and device switchers from syringe to Kwikpen.
- **Secondary Objective 2a:** Evaluate the hypoglycemic events among T2DM patients before and after U-500R syringe initiation and U-500R Kwikpen initiation separately, as well as before and after U-500R device switch from syringe to Kwikpen:
  - Determine differences between hypoglycemia events before and after U-500R Kwikpen initiation;
  - Determine differences between hypoglycemia events before and after U-500R syringe initiation;

- Determine differences between hypoglycemia events before and after U-500R device switch from syringe to Kwikpen; and
- Determine whether observed TDD in claims or insulin adherence played a role in hypoglycemic events among U-500R syringe initiators, U-500R Kwikpen initiators, and device switchers from syringe to Kwikpen.

❖ **Secondary Objective 2b:** Evaluate the treatment outcomes (HbA1c and hypoglycemic events) and prescriber behavior (observed TDD in claims and prescribed TDD from the physician) among T2DM patients before and after U-500R syringe initiation and U-500R Kwikpen initiation separately, as well as before and after U-500R device switch from syringe to Kwikpen in a subset of T2DM patients who had information on HbA1c, prescribed TDD by a physician, and had observed TDD information available in the claim:

- Determine how, in each cohort, the observed TDD in claims differs from the physician-prescribed TDD.
- Determine, in each cohort, the dynamics between observed TDD in claims, physician-prescribed TDD, and treatment outcomes (HbA1c and hypoglycemic events).

Research Objective 3: Health Care Costs

❖ **Primary Objective 3:** Evaluate out-of-pocket costs and total health care costs among T2DM patients before and after U-500R syringe initiation and U-500R Kwikpen initiation separately:

- Evaluate and characterize the dynamic relationship between observed TDD in claims, insulin adherence, and out-of-pocket costs.
- Evaluate and characterize the dynamic relationship between observed TDD in claims, insulin adherence, and total health care costs.

5. Research Design

5.1 Summary of Research Design

This will be a retrospective cohort study using the Veterans Health Administration (VHA) database, linked Truven MarketScan Claims and Electronic Medical Records [EMR] Data (LCED), as well as the Truven MarketScan claims databases (Table 1).

Multiple datasets will be used due to unavailability of the certain study outcomes in one single dataset. (e.g. out-of-pocket costs are not available in VHA dataset; HbA1c not available in Truven claims dataset). Additionally, using multiple datasets will improve the generalizability of the study, and since U-500R Kwikpen is recently available in the market, linking two databases would ensure that the study has adequate sample size. Furthermore, the patient population in the VHA primarily consists of veterans across the country (non-commercial database), whereas Truven is an employment-based health insurance (commercial database). Therefore, conducting the analysis separately in each of these databases as well as in the pooled dataset would give a more comprehensive and complete picture of the treatment patterns and outcomes in the real-world in this patient population.

To meet the analytical requirement of multiple research objectives, the following criteria will be used:

- The first prescription claim date for U-500R syringe or U-500R Kwikpen administration will be considered U-500R initiation and designated as Index Event 1 (syringe: Index Event 1a; Kwikpen: Index Event 1b).
- The date for U-500R device switch from syringe to Kwikpen will be designated as Index Event 2.
- The study period will range from 01APR2013-31MAR2018 for VHA and LCED; and 01JUL2013-30JUN2018 for Truven MarketScan claims.
- The identification period will be 01JAN2014-30JUN2017 for VHA and LCED; and 01APR2014-30SEP2017 for Truven MarketScan claims; the baseline and follow-up periods will be 9 months pre- and 9 months post-index date, respectively (Figures 1-3).

Table 1 Study Design by Objectives

Research Objectives	Database (study period)	Study Cohorts
Research Objective 1		
Primary Objective 1	• VHA (01APR2013-31MAR2018) • Pooled VHA and LCED (01APR2013-31MAR2018) • Truven MarketScan Claims Database (01JUL2013-30JUN2018)	U-500R syringe initiators U-500R Kwikpen initiators U-500R device switchers
Research Objective 2		
Primary Objective 2	• VHA (01APR2013-31MAR2018) • Pooled VHA and LCED (01APR2013-31MAR2018) • LCED (01APR2013-31MAR2018)	U-500R syringe initiators U-500R Kwikpen initiators U-500R device switchers
Secondary Objective 2a	• VHA (01APR2013-31MAR2018) • Pooled VHA and LCED (01APR2013-31MAR2018) • LCED (01APR2013-31MAR2018)	U-500R syringe initiators U-500R Kwikpen initiators U-500R device switchers
Secondary Objective 2b	• LCED (01APR2013-31MAR2018)	U-500R syringe initiators U-500R Kwikpen initiators U-500R device switchers
Research Objective 3		
Primary Objective 3	• Truven MarketScan Claims Database (01JUL2013-30JUN2018)	U-500R syringe initiators U-500R Kwikpen initiators

Figure 1 Study Design for U-500R Syringe Initiation (Index Event 1a)

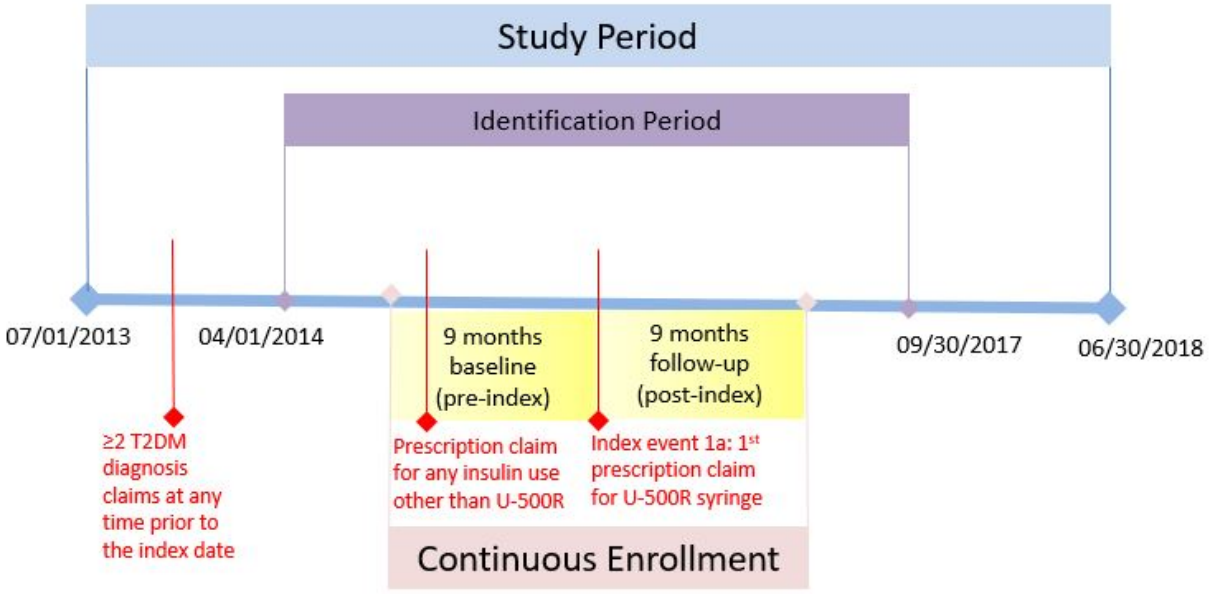


Figure 2 Study Design for U-500R Kwikpen Initiation (Index Event 1b)

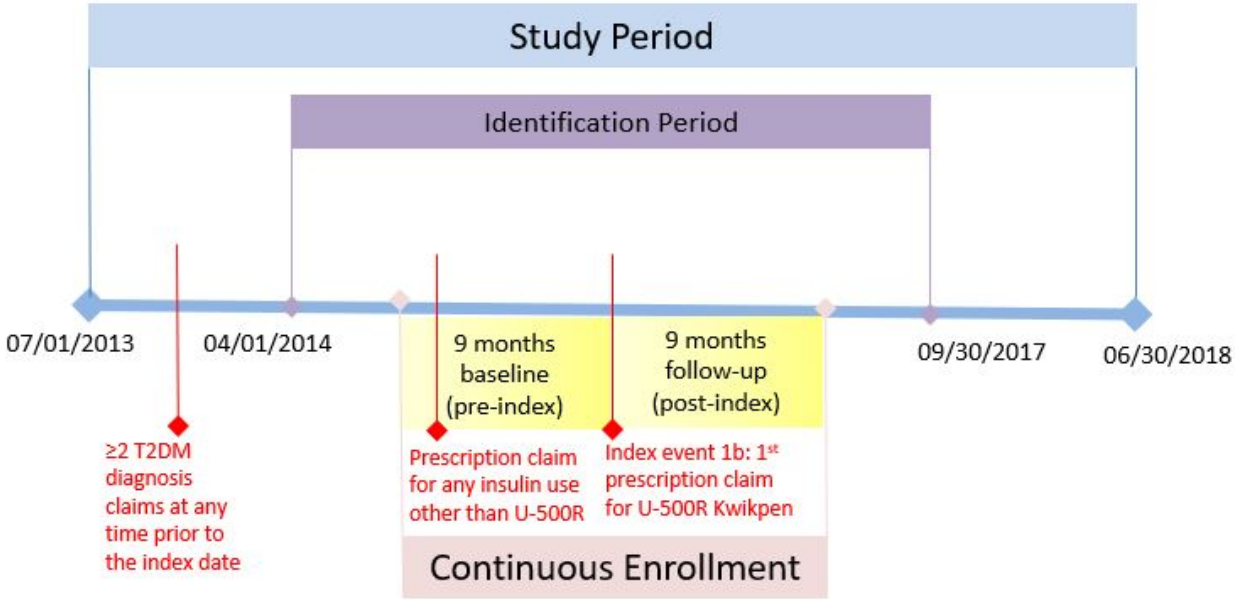
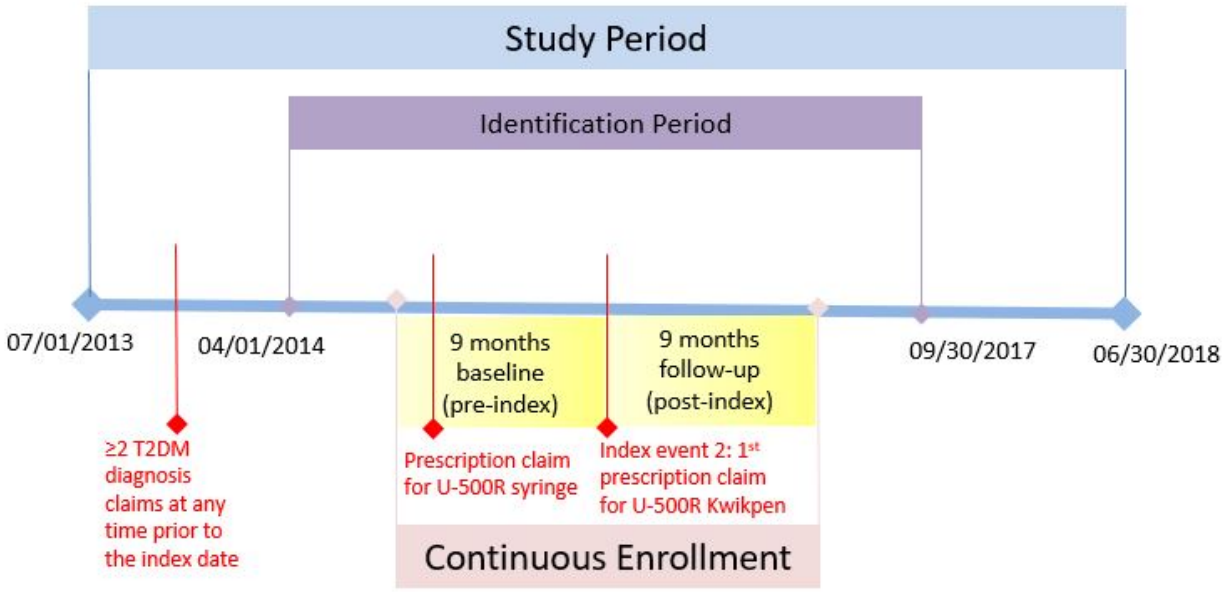


Figure 3 Study Design for U-500R Device Switch (Index Event 2)



The figures above depict a schematic representation of the study design using the study periods for the Truven MarketScan claims database.

5.2 Data Source

Truven MarketScan Claims Database (01JUL2013-30JUN2018)

The MarketScan® claims databases offer the largest convenience sample available in proprietary databases, with 69 million unique patients since 1996. In the most recent data year, MarketScan® claims databases contain data on 29 million covered lives. The stability of MarketScan® data sources allows superior continuity of patients over multiple years, which is generally longer than other claims databases. This is due to the fact that the majority of MarketScan® data is sourced from large employers. Employer-provided data also allow tracking of patients across health plans. This tracking ability is useful because people change health plans more often than they change jobs, and these data are able to capture patients who are "lost" in plan-based data sources - upward of 17% of patients in those databases. In the most recent 5 years of MarketScan® data, nearly 29 million patients (73%) have at least 12 months of continuous enrollment.

The MarketScan® claims databases contain complete information on outpatient prescriptions. These databases afford distinct advantages over others that track only prescription fills. MarketScan® data allow for disease type identification (from medical claims) and can be used to determine whether clinical, demographic, and provider characteristics influence prescribing patterns. Because individual patients' prescription fills are recorded, therapies prescribed

concurrently (and presumably used in combination) can also be identified. This provides vital information about actual drug use patterns, as opposed to individual drug prescription trends.

LCED (01APR2013-31MAR2018))

The Truven MarketScan administrative claims can be linked to the IBM Explorys EMR data, which allows access to complete longitudinal patient records from all patient's health care providers. Therefore, the integrated dataset provides comprehensive patient data to allow for a complete understanding of the research questions related to health care. For example, the powerful dataset provides licensed access to the following key information, including:

- Complete payment/charge information
- Outpatient prescription for drugs
- Claims and eligibility data from multiple U.S. payers
- Vitals and biometrics
- Patient reported outcomes (PHQ 9, pain scores etc)
- Laboratory results

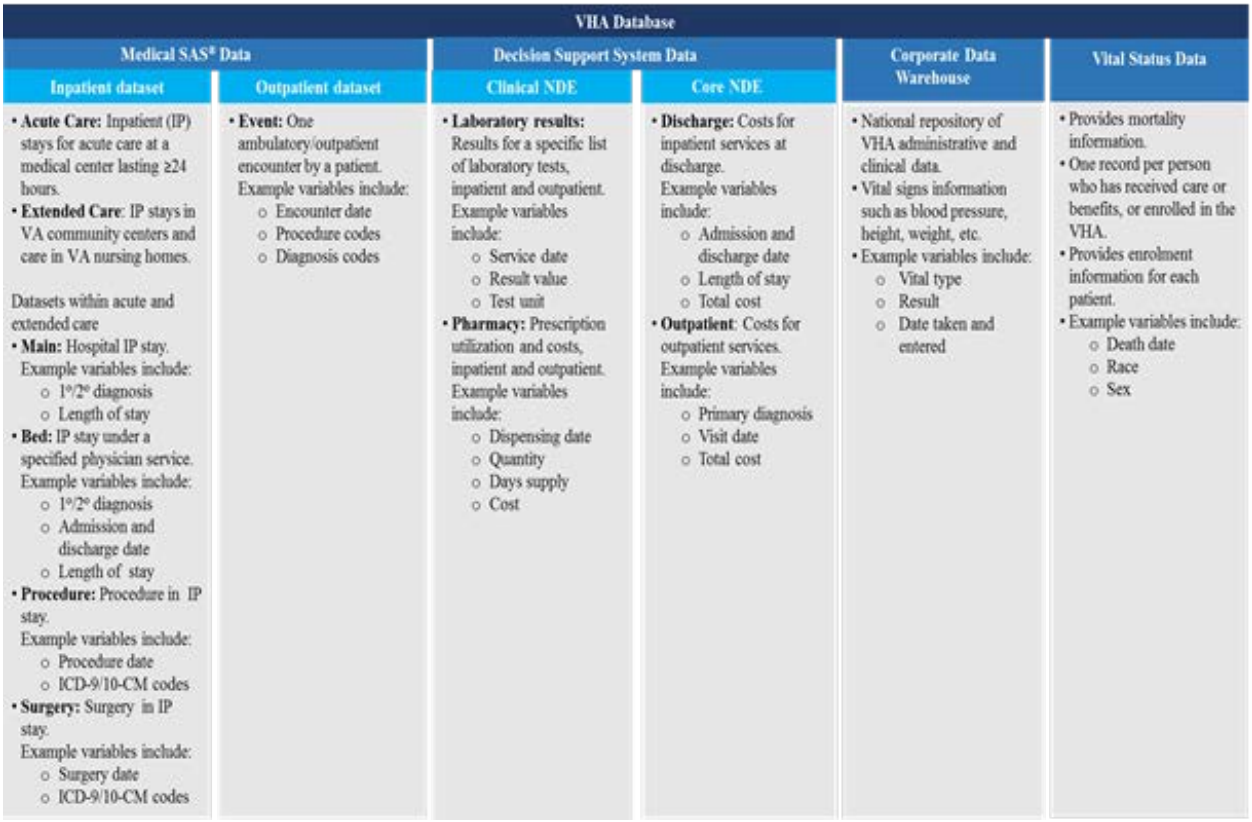
VHA Database (01APR2013-31MAR2018)

The VHA is the largest integrated health care system in the US, providing quality care at efficient prices for >5 million veterans across the country. According to VA estimates, there were about 22 million living US veterans in 2014.[13]

The size and structure of the VHA system differs from most private care organizations. The system includes:

- 153 medical centers;
- 136 nursing homes;
- 207 Vet Centers;
- 882 ambulatory care and community-based outpatient clinics;
- 45 residential rehabilitation treatment programs;
- 92 comprehensive home-based care programs;
- 13,000 physicians;
- nearly 55,000 nurses; and
- 9 million veterans.[14,15]

Figure 4 **VHA Data Elements**



IP: inpatient stays; NDE: National Data Extracts; VA: Veterans Administration; 1°/2°: primary/secondary.

The VHA Medical SAS® datasets are national administrative data for VHA-provided health care used by veterans. The datasets are provided in SAS format by fiscal year (01OCT-30SEP). These data are extracted from the National Patient Care Database and maintained by the VHA Office of Information at the Austin Information Technology Center (the central repository for VA data).

VHA Medical SAS Inpatient Datasets

The Medical SAS Inpatient datasets cover the care received in acute, extended care settings. Within these categories, there are four datasets:

- main—a patient's inpatient stay (episode of care);
- bed section—a patient's inpatient stay under a specified physician treating for a specialty service;
- procedure—1 day's procedure during an inpatient stay; and
- surgery—1 day's surgery during an inpatient stay.

Inpatient variables describing each hospital admission include date, time, facility, and the primary diagnosis at admission. Discharge data include date, time, destination (eg, home, hospice,

community nursing home), type of discharge (eg, regular, transfer to another hospital, death), and length of stay (LOS).

VHA Medical SAS Outpatient Datasets

Each outpatient data record represents 1 date of service for 1 outpatient and includes the facility identifier, date, and time of visit. Visits on a single day to multiple clinics, laboratories, and treatment programs are reported.

Outpatient care is reported by diagnoses (ICD-9-CM and ICD-10-CM codes) and procedures (CPT codes), including dates and times.

Currently, there is 1 Medical SAS® dataset for outpatient care:

- Event: 1 ambulatory encounter (coded as Decision Support System [DSS] Identifier).

VHA Decision Support System

The VHA DSS is a managerial cost accounting system based on the commercial software Eclipsys©. The VHA must populate data elements required to allocate VHA costs to VHA products (goods and services provided during patient care). Towards that end, the VHA has modified Eclipsys to interact with VistA and other VA national databases. The VHA DSS was introduced in 1994 and fully implemented in all facilities by 1999.

The VHA DSS data files comprise a longitudinal, secondary relational database combining selected clinical and cost data. The DSS provides a mechanism for integrating expenses, workload, and patient utilization. DSS information supports process and performance improvements by measuring quality of care, clinical outcomes, and financial impact. Within a fiscal year, periodic rollups of production data are performed to produce year-to-date, non-destructive examinations.

DSS Clinical National Data Extract

- Laboratory Results: laboratory test results for a specific list of tests (inpatient and outpatient)
- Pharmacy: pharmacy prescription utilization and costs (inpatient and outpatient)

VA Vital Status Files

The VHA Vital Status File (VSF) contains the date of death for veterans who have received care from the VHA since 1992, have enrolled in the VHA, or have received compensation or pension benefits from the VHA since 2002. The VHA VSF file is updated quarterly.

Sources for vital status available to the VA include the VA Beneficiary Identification and Record Locator System, the Death Master File from the Social Security Administration (SSA), patient treatment file, and Medicare vital status. The primary source for dates of death in the Vital Status file is the SSA Death Master File. The impetus for the development of the VHA VSF was the VA Information Resource Center's (VIReC) Veterans Administration National Death Index (NDI) Data Merge Project. This work was supported by funding from the Health Services Research and Development Service (SDR 03-157) and VIReC (SDR 98-004). The project compared the dates

of death from sources available within the VA to those obtained from the NDI, a repository of data from death certificates that is considered the gold standard for mortality data in the US. The study found that using a combination of the available death data sources in the VA resulted in death ascertainment nearly as complete as using the NDI.

The stability of VHA data sources allows for superior analysis of the continuity of care of patients over multiple years.

Data Limitations

While claims data are extremely valuable for the efficient and effective examination of health care outcomes, they are collected for payment and not research. Therefore, the use of claims data has certain limitations. First, the presence of a claim for a filled prescription does not indicate that the medication was consumed or taken as prescribed. Second, medications filled over-the-counter or provided as samples by the physician will not be observed in the claims data. Third, the presence of a diagnosis code on a medical claim does not necessarily indicate a positive presence of disease, as the diagnosis code may be incorrect or included as rule-out criteria rather than actual disease. Finally, certain information is not readily available in claims data that could influence study outcomes, such as clinical and disease-specific parameters.

5.3. Study Population

5.3.1 Selection Criteria

Patient selection criteria for the U-500R Syringe Initiators [Index Event 1a]:

- Include patients who had ≥1 prescription claim for U-500R vial during the identification period (VHA and LCED: 01JAN2014-30JUN2017; Truven: 01APR2014-30SEP2017)—the first prescription claim for U-500R vial will be designated as index Event 1a (U-500R syringe initiation), and the date will be designated as the index date;
- Include patients who had ≥2 claims with an ICD-9/10-CM code (Appendix 1) for T2DM in any position (primary/secondary) at any time prior to the index date;
- Exclude patients who had both T1DM and T2DM, had no oral anti-diabetic drug (OADs; Appendix 1) other than metformin, and the ratio between the number of T1DM and T2DM claims >0.5 at any time in the study period (VHA and LCED: 01APR2013-31MAR2018; Truven: 01JUL2013-30JUN2018);
- Include patients who were aged ≥18 years on the index date;
- Include patients who had continuous health plan enrollment with medical and pharmacy benefits for ≥9 months pre- and post-index event;
- Exclude patients with no evidence of insulin including U-500R (any type; Table 2) in the 9 months pre-index period (baseline);

- Exclude patients with ≥1 prescription claim for U-500R use in the 9 months pre-index period;
- Include patients who had ≥1 prescription claim for any insulin other than U-500R in the 9-month pre-index period;
- Include patients who had ≥1 HbA1c measurement within 90-day pre-index or 30-day post-index event;
- Include patients who had ≥1 HbA1c measurement after the 30-day post-index period at any time in the 9-months follow-up period;
    - Patients with ≥1 HbA1c measurement after the 30-day post-index and within 30 days prior to the end of the 9-months follow-up period will be flagged; and
    - Patients with ≥1 HbA1c measurement after the 30-day post-index and within 2 months prior to the end of the 9-months follow-up period will be flagged;
- Exclude patients who had ≥1 claim with a ICD-9/10-CM code (Appendix 1) for secondary diabetes, gestational diabetes, diabetes complicating pregnancy, childbirth, or puerperium, or non-clinical diabetes at any time during the 9-month baseline period;
- Exclude patients who had claims indicating pump use (Appendix 2) in the 9-month post-index (follow-up) period;
- Exclude patients who had claims indicating TDD above 2000 units/day at any time in the pre-index or post-index periods.

<u>Sample selection criteria for U-500R Kwikpen Initiators [Index Event 1b]</u>

- Include patients who had ≥1 prescription claim for U-500R Kwikpen administration during the identification period (VHA and LCED: 01JAN2014-30JUN2017; Truven: 01APR2014-30SEP2017)–the first prescription claim for U-500R Kwikpen administration will be designated as Index Event 1b, and the date will be designated as the index date;
- Include patients who had ≥2 claim with an ICD-9/10-CM code (Appendix 1) for T2DM in any position (primary/secondary) at any timeprior to the index date;
- Exclude patients who had both T1DM and T2DM, had no OADs (Appendix 1) other than metformin, and the ratio between the number of T1DM and T2DM claims >0.5 at any time in the study period (VHA and LCED: 01APR2013-31MAR2018; Truven: 01JUL2013-30JUN2018);
- Include patients who were aged ≥18 years on the index date;
- Include patients who had continuous health plan enrollment with medical and pharmacy benefits for ≥9 months pre- and post-index event;

- Exclude patients with no evidence of insulin including U-500R (any type; Table 2) in the 9 months pre-index period (baseline);
- Exclude patients with ≥1 prescription claim for U-500 use in the 9 months pre-index period;
- Include patients who had ≥1 prescription claim for any insulin other than U-500R (Table 2) in the 9-month pre-index period;
- Include patients who had ≥1 HbA1c measurement within 90-day pre-index or 30-day post-index event;
- Include patients who had ≥1 HbA1c measurement after the 30-day post-index period at any time in the 9-months follow-up period;
    - Patients with ≥1 HbA1c measurement after the 30-day post-index and within 30 days prior to the end of the 9-months follow-up period will be flagged; and
    - Patients with ≥1 HbA1c measurement after the 30-day post-index and within 2 months prior to the end of the 9-months follow-up period will be flagged;
- Exclude patients who had ≥1 claim with a ICD-9/10-CM code (Appendix 1) for secondary diabetes, gestational diabetes, diabetes complicating pregnancy, childbirth, or puerperium, or non-clinical diabetes at any time during the 9-month baseline period;
- Exclude patients who had evidence of pump use (Appendix 2) in the 9-month follow-up period;
- Exclude patients who had claims indicating TDD above 2000 units/day at any time in the pre-index or post-index periods.

<u>Sample Selection Criteria for U-500R Device Switchers from Syringe to Kwikpen [Index Event 2]</u>

- Include patients who had ≥1 claim for U-500R Kwikpen administration in the identification period (VHA and LCED: 01JAN2014-30JUN2017; Truven: 01APR2014-30SEP2017)–the first prescription claim for U-500R Kwikpen administration will be designated as the Index Event 2, and the date will be designated as the index date;
- Include patients who had ≥2 claim with an ICD-9/10-CM code (Appendix 1) for T2DM in any position (primary/secondary) at any timeprior to the index date;
- Exclude patients who had both T1DM and T2DM, had no OADs (Appendix 1) other than metformin, and the ratio between the number of T1DM and T2DM claims >0.5 at any time in the study period (VHA and LCED: 01APR2013-31MAR2018; Truven: 01JUL2013-30JUN2018);
- Include patients who were aged ≥18 years on the index date;
- Include patients who had continuous health plan enrollment with medical and pharmacy benefits for ≥9 months pre- and post-index event;
- Include patients who had ≥1 prescription claim for U-500R vial use in the 9-month baseline period;

- Include patients who had ≥1 HbA1c measurement within 90-day pre-index event or 30-day post-index event; and
- Include patients who had ≥1 HbA1c measurement after the 30-day post-index period;
    - Patients with ≥1 HbA1c measurement after the 30-day post-index and within 30 days prior to the end of the 9-months follow-up period will be flagged; and
    - Patients with ≥1 HbA1c measurement after the 30-day post-index and within 2 months prior to the end of the 9-months follow-up period will be flagged;
- Exclude patients who had ≥1 claim for U-500R Kwikpen administration in the 9-month baseline period;
- Exclude patients who had ≥1 claim with a ICD-9/10-CM code (Appendix 1) for secondary diabetes, gestational diabetes, diabetes complicating pregnancy, childbirth, or puerperium, or non-clinical diabetes at any time during the 9-month baseline period;
- Exclude patients who had claims indicating pump use (Appendix 2) in the identification period;
- Exclude patients who had claims indicating TDD exceeding 2000 units/day at any time in the pre-index or post-index periods.

Note:

- Since the Truven claims database does not have the lab data, the criteria to have at least 1 HbA1c will be removed from the inclusion criteria while using this database.
- The corresponding ICD-9/10 codes for all the diagnoses and the NDC codes for the insulins are provided in Appendix 1.

Table 2. Classification of Insulin Products

Insulin Class	Generic Name	Product Name
Inhaled Insulin	Insulin Human Inhaled	AFREZZA
		EXUBERA
		EXUBERA COMBINATION PACK 12
		EXUBERA COMBINATION PACK 15
		EXUBERA KIT
Intermediate-Acting Insulin	Insulin Human Zinc (lente)	HUMULIN L
	Insulin Human Isophane (nph)	HUMULIN N (NPH)
		HUMULIN N (NPH) KWIKPEN
		HUMULIN N PEN
		INSULATARD HUMAN INSULIN
		MIXTARD HUMAN INSULIN 70/30
		NOVOLIN N
		NOVOLIN N (NPH)

		NOVOLIN N INNOLET
		NOVOLIN N PENFILL
		RELION HUMULIN N
		RELION NOVOLIN N INNOLET
Long-Acting Insulin	Insulin Glargine Soln Pen-Injector	Basaglar KwikPen
	Insulin Glargine, Recombinant	LANTUS
		LANTUS SOLOSTAR
	Insulin Detemir	LEVEMIR
		LEVEMIR FLEXPEN
		LEVEMIR FLEXTOUCH
	Insulin Glargine, Recombinant	TOUJEO
	Insulin Degludec	TRESIBA
Pre-Mixed Insulin	Insulin Lispro Protamine/insulin Lispro	HUMALOG MIX 50/50
		HUMALOG MIX 75/25
		HUMALOG MIX 75/25 PEN
	Insulin Human Isophane (nph)/insulin Human Regular	HUMULIN
		HUMULIN 50/50
		HUMULIN 70/30
		HUMULIN 70/30 KWIKPEN
		HUMULIN 70/30 PEN
	Insulin Beef Regular/insulin Pork Isophane (nph)	ILETIN NPH I
	Insulin Human Isophane (nph)/insulin Human Regular	NOVOLIN 70/30
		NOVOLIN 70/30 INNOLET
		NOVOLIN 70/30 PENFILL
	Insulin Aspart Protamine/insulin Aspart	NOVOLOG MIX 70/30
		NOVOLOG MIX 70/30 FLEXPEN
	Insulin Human Isophane (nph)/insulin Human Regular	RELION HUMULIN 70/30
		RELION NOVOLIN 70/30
		RELION NOVOLIN 70/30 INNOLET
Rapid-Acting Insulin	Insulin Glulisine	APIDRA
		APIDRA SOLOSTAR
	Insulin Lispro, Recombinant	HUMALOG
		HUMALOG KWIKPEN
		HUMALOG PEN
		LISPRO-PFC
	Insulin Aspart, Recombinant	NOVOLOG
		NOVOLOG FLEXPEN
		NOVOLOG PENFILL
Short-Acting Insulin	Insulin Human Regular, Buffered	HUMULIN BR
	Insulin Human Regular	HUMULIN R

		INSULIN HUMAN REGULAR
		NOVOLIN 70/30 PENFILL
		NOVOLIN N PENFILL
		NOVOLIN R
		NOVOLIN R INNOLET
		NOVOLIN R PENFILL
		RELION HUMULIN R
		RELION NOVOLIN R
	Insulin Human Regular, Buffered	VELOSULIN BR
U-500R	Insulin Human Regular	HUMULIN R CONCENTRATED U-500
		HUMULIN R CONCENTRATED U-500 KWIKPEN
	INSULIN REGULAR (HUMAN)	HUMULIN R U-500 KWIKPEN

5.3.2 Subject Groups

After applying the inclusion and exclusion criteria, our analysis will focus on the following cohorts.

Index Event 1a

- U-500R Syringe Initiators Cohort: Patients who initiated U-500R syringe administration (index event 1a) on their index date.

Index Event 1b

- U-500R Kwikpen Initiators Cohort: Patients who initiated U-500R Kwikpen administration (index event 1b) on their index date.

Index Event 2

- U-500R Device Switchers Cohort: Patients who switched from U-500R syringe to Kwikpen will be included in this cohort.

Note: U-500R syringe/ Kwikpen initiators cohorts who were identified based on the index event 1a or 1b were U-500R naïve patients who did not have any evidence of U-500R use prior to the index date; whereas patients in U-500R device switchers cohort identified from index event 2 had been exposed to U-500R prior to the index date due to U-500R syringe use.

5.4 Time Periods

The study period will range from 01APR2013-31MAR2018 for VHA and LCED; and 01JUL2013-30JUN2018 for Truven MarketScan claims. The identification period will be 01JAN2014-30JUN2017 for VHA and LCED; and 01APR2014-30SEP2017 for Truven MarketScan claims; the baseline and follow-up periods will be 9 months pre- and 9 months post-index date, respectively (Figures 1-3).

5.5 Variables/Measures

Table 3 presents the study variables and operational definitions.

Table 3 Variables and Definitions

Variable	Source	Definition
Exposure		
Insulin use	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	Index Event 1a: any insulin use other than U-500R in the pre-index and U-500R syringe use in the post-index period; Index Event 1b: any insulin use other than U-500R in the pre-index and U-500R Kwikpen use in the post-index period; and Index Event 2: U-500R syringe use in the pre-index and U-500R Kwikpen use in the post-index period.
Baseline Characteristics*		
Age	Truven: Inpatient service table, outpatient service table, outpatient pharmacy claims table VHA: Enrollment file	Age will be retained in the dataset as a continuous variable for groups aged 18-25, 26-35, 36-45, 46-55, 56-64, and ≥65 years.
Sex	Truven: Inpatient service table, outpatient service table, outpatient pharmacy claims table VHA: Enrollment file	A flag will be created for male and female patients.
Race (only VHA)	VHA: Enrollment file	A flag will be created for White, Black, and other race patients.
U.S Region (only Truven)	Truven: Inpatient service table, outpatient service table, outpatient pharmacy claims table	A flag will be created for patients belonging to Northeast, Northcentral, South and West regions
Medicare eligibility (Only Truven)	From Truven	A flag will be created for patients who are enrolled in Truven Medicare
Body mass index (BMI)	VHA: Vital Status file	BMI on the index date will be calculated and reported as a continuous variable.
Quan-Charlson comorbidity index (CCI) Score[16]	Truven: Inpatient service table, outpatient service table VHA: Inpatient and outpatient files	Quan-CCI score will be constructed using enhanced ICD-9/10-CM codes for 17 different comorbid conditions.

Individual Comorbidities[17]	Truven: Inpatient service table, outpatient service table VHA: Inpatient and outpatient files	A flag will be created using ICD-9/10-CM codes (Appendix 1) for patients diagnosed in the baseline period with any of the following individual comorbidities: retinopathy, nephropathy, neuropathy, coronary artery disease, peripheral vascular disease, congestive heart failure, hypertension, depression, obesity, or malignant tumor.
Health Economics Outcomes Research (HEOR) Outcomes		
Observed TDD in claims	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	The observed insulin TDD will be calculated as the total number of insulin units/total unique days of supply as recorded in claims and will be calculated both in the pre-and post-index periods among the U-500R syringe initiators, U-500R Kwikpen initiators, and the U-500R device switchers. TDD will be reported both as continuous and categorical variable. For U-500R syringe initiators (index event 1a): Total insulin units correspond to all the insulin units in pre-index and post-index periods respectively Additionally the TDD of U-500R syringe only will be reported in the post-index period For U-500R Kwikpen initiators (index event 1b): Total insulin units correspond to all the insulin units in pre-index and post-index periods respectively Additionally the TDD of U-500R Kwikpen only will be reported in the post-index period For U-500R device switchers (index event 2): For device switchers the total insulin units correspond only to the total units of U-500R syringe use in the pre-index period and U-500R Kwikpen in the post-index period Note:

		For the unique days supply in patients with evidence of a basal-bolus regimen, or basal/bolus-pre-mixed or basal/bolus-U-500R the overlap days will be adjusted for the concomitant use of basal and bolus insulins, but will not be adjusted within basal and within bolus insulins.
Observed average daily dose (ADD) in claims	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	The observed insulin ADD will be calculated both in the pre-and post-index periods among the U-500R syringe initiators, U-500 Kwikpen initiators, and the U-500R device switchers. ADD will be reported both as continuous and categorical variable. Pre-index ADD: total number of insulin units/ the total number of days in the pre-index period. Post-index ADD: total number of insulin units/ the total number of days in the post-index period. Additionally the ADD of U-500R syringe only and the U-500R Kwikpen only will be reported in the U-500R syringe initiators and Kwikpen initiators respectively. Note: Total insulin units calculation in based on the similar approach as described in TDD.
Adherence	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	Adherence to insulin will be assessed using the proportion of days covered (PDC), and reported in categories of 0-20%, 20-40%, 40-60%, 60-80%, and 80%-100%. PDC will be calculated both in the pre-and post-index periods among the U-500R syringe initiators, U-500 Kwikpen initiators ,and the U-500R device switchers. For U-500R syringe initiators (index event 1a):

		PDC before U-500R initiation will be calculated as the number of days covered by the prescription claims of insulin (any insulin)/total days in the pre-index period; PDC after U-500R initiation will be calculated as the number of days covered by the prescription claims of insulin (any insulin)/total days in the post-index period. For U-500R Kwikpen initiators (index event 1b): PDC before U-500R initiation will be calculated as the number of days covered by the prescription claims of insulin (any insulin)/total days in the pre-index period; PDC after U-500R initiation will be calculated as the number of days covered by the prescription claims of insulin (any insulin)/total days in the post-index period. For U-500R device switchers (index event 2): PDC before switching will be defined as the number of days covered by the prescription claims of insulin (U-500R syringe)/total days in the pre-index period; PDC after switching will be defined as the number of days covered by the prescription claims of insulin (U-500R Kwikpen)/total days in the post index period Note: For the calculation of PDC in patients with evidence of a basal-bolus regimen, basal/bolus-premixed, or basal/bolus-U-500R, the overlap days will be adjusted for the concomitant use of basal and bolus insulins, but will not be adjusted within basal and within bolus insulins.

Persistence/time to discontinuation	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	Persistence will be defined as the percentage of patients continuing on the index medication in the post-index period. Patient is considered to discontinue if there is no refill of the index medication within 60 days from the run-out date (date of last prescription + days of supply) i.e, a gap of >60 days from the run out date. The run-out date will be the discontinuation date. Time to discontinuation will be defined as the total number of days from the index date to the discontinuation date during the post-index period.
Abandonment/fill rates	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	The average number of insulin prescription fills will be calculated in the pre- and post-index periods among all the study cohorts.
Claim gaps	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	The average gap between prescription fills of insulins will be calculated in the pre- and post-index periods among all the study cohorts.
Concomitant medications [18,19,20]	Truven: Outpatient pharmacy claims table VHA: Pharmacy file	A flag will be created for patients prescribed antihyperglycemic agents (AHA): thiazolidinediones, sulfonylureas, biguanides, meglitinides, alpha-glucosidase inhibitors, DPP-4 inhibitors, bile acid sequestrants, fixed-dose combinations, GLP-1 receptor agonists, and amylin agonists (Appendix 1).

HbA1c [21]	VHA: Lab file	The HbA1c value in the baseline and follow-up period for each index event will be reported. Baseline HbA1c (pre-index HbA1c) will be the HbA1c measurement -90/+30 days of the index date. For patients with multiple HbA1c measurements within this period, the measurement taken closest to the index event date will be reported as the baseline HbA1c value. The follow-up HbA1c value will be the HbA1c measurement taken furthest in the time period after the 30 day-post index event date. However, based on the sample size, HbA1c within 2 monthsprior to the end of the study follow-up will be considered as the post-index HbA1c.
Hypoglycemic events	Truven: Inpatient service table, outpatient service table VHA: Inpatient and outpatient files, Lab file and Pharmacy file	Hypoglycemia events in the pre-index and post-index period will be evaluated using the ICD-9 codes from the Ginde algorithm (Appendix 1)[22] or the presence of a cutoff of blood glucose ≤70 mg/dL, or any evidence of intramuscular glucagon administration (Appendix 1). Hypoglycemia event occurred on or after the index date will be considered as the follow-up hypoglycemia event; and hypoglycemia event occurred on or prior to - 1 day of the index date will be considered as the baseline hypoglycemia event. Number of hypoglycaemia events per patient per year (PPPY) will be reported in both the pre-index and post-index periods.
Prescribed TDD	Linked Truven claims and EMR data:	The prescribed physician TDD will be calculated, and will be reported both as continuous and categorical variable.

All-cause health care total and out-of-pocket costs	Truven: Inpatient service table, outpatient service table, outpatient pharmacy claims table	All-cause health care costs for total and out-of-pocket costs including inpatient costs, outpatient costs, pharmacy costs, total costs (inpatient + outpatient + pharmacy), out-of-pocket inpatient costs, out-of-pocket outpatient costs, out-of-pocket pharmacy costs and total out-of-pocket costs (inpatient + outpatient + pharmacy) will be computed among T2DM patients before and after U-500R syringe initiation and U-500R Kwikpen initiation. Costs will be adjusted to 2018 US dollars using the annual medical care and drug costs components of the Consumer Price Index (CPI) to reflect inflation.

Note: When comparing the TDD, ADD, adherence, fill rates and claim gaps in the pre vs post-index periods among the U-500R device switchers, only the claims corresponding to U-500R (syringe in the pre-index and Kwikpen in the post-index) will be considered. To be more specific we will be looking only at the treatment patterns of U-500R alone rather than the regimen.

However, for the U-500R initiators, the regimen use (use of different types of insulin) in the pre-index period will be compared to the regimen use (U-500R + other insulins) in the post-index period.

6. Sample Size and Statistical Methods

6.1 Determination of Sample Size

The preliminary sample sizes for the VHA databases from 2013-2018 are shown below. This study will use the most recently available 5 years of data.

Table 4. Preliminary Sample Size

Database	Counts
VHA (01APRIL2013-31MARCH2018)	
T2DM (ICD-9: 250.x0, 250.x2) + Humulin R U-500 Kwikpen (NDC: 00002882427, 00002882459	4,120
≥2 HbA1c measurements	4,066
T2DM + Humulin R U-500 Vial (NDC: 00002850101)	5,863
≥2 HbA1c measurements	5,718

6.2 Missing Data

Patients with missing information on the demographics including age, gender, race will be excluded from the study.

6.3 Significance Levels

Two-sided hypothesis testing will be applied to test the statistical significance, and multiple testing adjustment for controlling error rates will not be applied. A p-value of <0.05 will be considered statistically significant. SAS for Windows Version 9.4 will be used for all statistical analyses.

6.4 Other Analyses

6.4.1 Outcomes Analyses

All the analyses will be performed separately in VHA, linked Truven claims and EMR data, Truven claims database, and the pooled VHA and linked Truven claims and EMR data.

Pooling Multiple Databases

The VHA and linked Truven Claims with EMR databases will be pooled. To remove potential duplicate patient records from multiple data sources, probabilistic matching will be utilized. Potential duplicate patients across the databases will be identified by a STATinMED Research algorithm using age, sex, hospital admission date, hospital discharge date, and primary discharge diagnosis.[23,24] Identified patients with the same information for the variables listed above will be assumed to be the potential duplicated patient and flagged in the pooled dataset. The rate of duplicate patients is expected to be low based on references and a previous study (<1%).[23] Duplicate patients can be potentially retained in the analytic file if the rate is low. After pooling, we will check if there are any potential duplicates across datasets. If the % will be small (<3%), we will not delete any duplicates because the impact to the final outcomes are considered minimal. If the % is significant (>3%), we will remove the duplicated records from the dataset that has the

larger sample size. Analyses will be conducted on each individual database as well as the pooled dataset.

Research Objective 1: Primary Objective 1

Descriptive Analysis

All study variables including demographics, clinical characteristics, and treatment patterns of insulin (i.e., TDD, adherence, prescription fill rate, claim gaps, persistence, and concomitant medication use) will be analyzed descriptively before and after U-500R syringe initiation and U-500R Kwikpen initiation, and before and after U-500R device switch from syringe to Kwikpen.

Numbers and percentages will be provided for dichotomous and polychotomous variables. Means and standard deviations (SDs) will be provided for continuous variables. McNemar's test will be used to determine statistical significance of before and after values for categorical variables, and the paired t-test will be used to assess the statistical significance of before and after values in continuous variables.

Multivariate Analysis

Mixed linear model will be used to evaluate factors associated with insulin adherence in the pre- and post-index periods among U-500R syringe initiators, U-500R Kwikpen initiators, and U-500R device switchers. Mixed linear model is used for studies with a longitudinal feature in which an continuous outcome variable is measured for the same subject repeatedly over the time period. Based on the distribution of the data, observations measured for the same subject are likely to be correlated over the study perod and these data are considered as "multilevel" data. In addition, mixed linear model has a mixed effect consisting both fixed and random effects. Time-varying and time invariant variables such as demographic characteristics can be both included in the model. In the current model, adherence which is measured at two time intervals (before and after the index event; U-500R initiation/device switch), will be considered the dependent variable. Observed TDD will be considered as the time varying covariate (measured both before and after the index event) in the model, and the time independent covariates include the demographic and clinical characteristics.

The complete list of time varying and time-independent covariates will include:

- age
- sex
- race
- BMI
- baseline CCI score
- observed TDD from claims
- time (pre/post)

Note: Age, sex, race, BMI, and CCI score will be assessed during pre-index period. Adherence (PDC) and observed TDD will be calculated during the entire pre-index and post-index periods, respectively.

Research Objective 2: Primary Objective 2

Descriptive Analysis

HbA1c will be analyzed descriptively before and after U-500R syringe initiation and U-500R Kwikpen initiation, and before and after U-500R device switch from syringe to Kwikpen.

Numbers and percentages will be provided for dichotomous and polychotomous variables. Means and standard deviations (SDs) will be provided for continuous variables. McNemar's test will be used to determine statistical significance of before and after values for categorical variables, and the paired t-test will be used to assess the statistical significance of before and after values in continuous variables.

Multivariate Analysis: HbA1c

Mixed linear model will be used to evaluate factors associated with HbA1c level in the pre- and post-index periods among U-500R syringe initiators, U-500R Kwikpen initiators, and U-500R device switchers. Mixed linear model is used for studies with a longitudinal feature in which an continuous outcome variable is measured for the same subject repeatedly over the time period. Based on the distribution of the data, observations measured for the same subject are likely to be correlated over the study period and these data are considered as "multilevel" data. In addition, mixed linear model has a mixed effect consisting both fixed and random effects. For this objective, mixed linear model helps to evaluate the effect of both time varying and time-independent variables on the HbA1c, while taking into account for correlation due to multiple assessments from the same individual. In the current model, HbA1c level which is measured at two time intervals (before and after the index event; U-500R initiation/device switch), will be considered the dependent variable. Observed TDD will be considered as the time varying covariate in the model (measured both before and after the index event), and the time independent covariates include the demographic and clinical characteristics.
The complete list of covariates will include:

- age
- sex
- race
- BMI
- baseline CCI score
- observed TDD from claims
- time (pre/post)

Note: Age, sex, race, BMI, and CCI score will be assessed during pre-index period. Observed TDD will be calculated during the entire pre-index and post-index periods, respectively. Pre-index

HbA1c will be defined as the HbA1c measurement -90/+30 days of the index date. For patients with multiple HbA1c measurements within this period, the measurement taken closest to the index event date will be reported as the pre-index HbA1c value. Post-index HbA1c will be defined as the HbA1c within 2 months of the end of the follow-up period.

Adherence will not be included as one of the covariates here due to the high collinearity between time and adherence. Hence, further mediation analysis will be performed to determine the mediator effect of adherence on HbA1c.

Mediation Analysis:

Mediation analysis following the Baron and Kenny's steps will be considered to understand the impact of index event (time: pre-index indicates use of othe insulin and post-index indicates U-500R use) on HbA1c through potential mediators.Adherence is considered as a potential mediator between the HbA1c and time. The key steps in mediation analysis include a model of the mediator (adherence) as a function of the predictor (time) and a model of the outcome (HbA1c) as a function of both the mediator (adherence) and the predictor (time). Bootstrapping method will be used to test the effect of mediator. The detailed steps are described below:

Step 1: Effect of predictor (time) on the outcome (HbA1c):

In the first step, the effect of time on the dependent variable HbA1c will be assessed. Statistically, a significant relationship between the two variables will trigger the next step of the mediation analysis. However, it is suggested that the clinical significance and theoretical evidence should be considered in the case of failure to detect an association that is statistically significant. Since the effect of time on HbA1c is the primary interest of this analysis, we will carry out the next step regardless of the significance between time and HbA1c.

Step 2: Effect of predictor (time) on the mediator (adherence):

The effect of time (predictor) on the hypothesized mediator adherence will be assessed, and adherence will be considered as a dependent variable in the model. Potential mediation effect will be supported by a statistically significant relationship between time and adherence, which will lead to the next step of the analysis.

Step 3: Combined effect of predictor (time) and mediator (adherence) on the outcome (HbA1c):

Adherence will be included and adjusted as a covariate in the model assessing the relationship between time (predictor) and the dependent variable HbA1c. Evidence of a mediation effect will be strengthened if the relationship between time and HbA1c disappears or weakens while adjusting for adherence. If the effect of time on HbA1c became insignificant, this indicates that the relationship between time and HbA1c is fully mediated by adherence (full mediation); and if the relationship remains significant with a reduced magnitude, this indicates that adherence is partially meditating the relationship between time and HbA1c (partial mediation). If any of the mediation effect exists, the next step will be used to further test the significance of the mediation effect.

Step 4: Assess the statistical significance of the effect of the mediator (adherence):

Bootstrapping method will be applied to evaluate the statistical significance of the adherence. At least 500 bootstrapping sample will be applied. All estimates will be combined in one dataset to compute the indirect, direct and total effects. The summary of effects table along with the bootstrap estimates and p-values will be provided. If the p-value of the indirect effect is significant, this clearly indicates that the mediation effect is significant. Additionally, the direct effect of time on the outcome HbA1c, as well as the total effect, which is a sum of the indirect and direct effect and the percentage mediated will be provided.

Research Objective 2: Secondary Objective 2a

Descriptive Analysis

Number of hypoglycemia events will be analyzed descriptively before and after U-500R syringe initiation and U-500R Kwikpen initiation, and before and after U-500R device switch from syringe to Kwikpen.

Numbers and percentages will be provided for dichotomous and polychotomous variables. Means and standard deviations (SDs) will be provided for continuous variables. McNemar's test will be used to determine statistical significance of before and after values for categorical variables, and the paired t-test will be used to assess the statistical significance of before and after values in continuous variables.

Multivariate Analysis: Hypoglycemia Event

Zero-inflated negative binomial mixed model will be used to evaluate factors associated with number of hypoglycemia events PPPY in the pre- and post-index periods among U-500R syringe initiators, U-500R Kwikpen initiators, and U-500R device switchers. Zero-inflated negative binomial distribution is a mixture of a binary distribution that is degenerate at zero and an ordinary coutn distribution such as negative binomial. In cases of outcome variable being repeatedly measured from the individual subjects, zero inflated models are extended to include random effects to account for the correlation among the repeated measures within a subect. In the current model, the number of hypoglycemia events which might have more zeroes (for example not every patient might have a lab visit for glucose) and is measured at two time intervals (before and after the index event; U-500R initiation/device switch), will be considered the dependent variable. Observed TDD, and HbA1c will be considered as the time varying covariates in the model (measured both in the before and after index date), and the time-independent covariates will include the demographic and clinical characteristics.

The complete list of covariates will include:

- age
- sex
- race
- BMI
- baseline CCI score

- observed TDD from claims
- HbA1c
- time (pre/post)

Note: Age, sex, race, BMI, and CCI score will be assessed during pre-index period. Observed TDD and HbA1c will be calculated during the entire pre-index and post-index periods, respectively. Pre-index HbA1c will be defined as the HbA1c measurement -90/+30 days of the index date. For patients with multiple HbA1c measurements within this period, the measurement taken closest to the index event date will be reported as the pre-index HbA1c value. Post-index HbA1c will be defined as the HbA1c within 2 months of the end of the follow-up period.

Research Objective 2: Secondary Objective 2b

Descriptive Analysis

Treatment outcomes (HbA1c and number of hypoglycemic events) and prescriber behavior (observed TDD in claims and prescribed TDD from the physician) will be analyzed descriptively and quarterly before and after U-500R syringe initiation and U-500R Kwikpen initiation, and before and after U-500R device switch from syringe to Kwikpen.

Numbers and percentages will be provided for dichotomous and polychotomous variables. Means and standard deviations (SDs) will be provided for continuous variables. McNemar's test will be used to determine statistical significance of before and after values for categorical variables, and the paired t-test will be used to assess the statistical significance of before and after values in continuous variables.

Multivariate Analysis

No multivariate analysis will be applied for Secondary Objective 2b.

Research Objective 3: Primary Objective 3

Descriptive Analysis

Health care total costs and out-of-pocket costs will be analyzed descriptively before and after U-500R syringe initiation and U-500R Kwikpen initiation. More specifically, among the U-500R initiators, all the variables will be compared before and after U-500R syringe initiators and U-500R Kwikpen initiators.

Numbers and percentages will be provided for dichotomous and polychotomous variables. Means and standard deviations (SDs), along with the median, minimum and maximum will be provided for continuous variables. McNemar's test will be used to determine statistical significance of before and after values for categorical variables, and the paired t-test will be used to assess the statistical significance of before and after values in continuous variables.

Multivariate Analysis

Generalized linear mixed model with log link will be used to evaluate factors associated with total health care costs and out-of-pocket costs in the pre- and post-index periods among U-500R syringe initiators and U-500R Kwikpen initiators. Generalized linear mixed model is used for studies with

a longitudinal feature in which an continuous outcome variable is measured for the same subject repeatedly over the time period. Based on the distribution of the data, observations measured for the same subject are likely to be correlated over the study period and these data are considered as "multilevel" data. In addition, mixed linear model has a mixed effect consisting both fixed and random effects. For this objective, mixed linear model helps to evaluate the effect of both time varying and time-independent variables on the costs, while taking into account for correlation due to multiple assessments from the same individual. In the current model, costs which are measured at two time intervals (before and after the index event; U-500R initiation), will be considered the dependent variable. Observed TDD will be considered as the time varying covariates in the model (measured both before and after the index date), and the time-independent covariates will include the demographic and clinical characteristics.

The complete list of covariates will include:

- age
- sex
- region
- baseline CCI score
- observed TDD from claims
- Medicare (yes/no)
- time (pre/post)

Note: For all the multivariate analyses the covariates will be included as per the availability in each of the VHA, Truven claims, linked Truven claims and EMR data and pooled VHA and linked Truven data. Age, sex, region, medicare (yes/no), and CCI score will be assessed during pre-index period. Observed TDD will be calculated during the entire pre-index and post-index periods, respectively.

Adherence will not be included as one of the covariates here due to the high collinearity between time and adherence. Hence, further mediation analysis will be performed to determine the mediator effect of adherence on costs.

Mediation Analysis:

Mediation analysis following the Baron and Kenny's steps will be considered to understand the impact of index event (time) on costs through potential mediators. Adherence is considered as a potential mediator between the costs and time. The key steps in mediation analysis include a model of the mediator (adherence) as a function of the predictor (time) and a model of the outcome (costs) as a function of both the mediator (adherence) and the predictor (time). Bootstrapping method will be used to test the effect of mediator. The detailed steps are described below:

Step 1: Effect of predictor (time) on the outcome (costs):
In the first, the effect of time on the dependent variable costs will be assessed. Statistically, a significant relationship between the two variables will trigger the next step of the mediation analysis. However, it is suggested that the clinical significance and theoretical evidence should be considered in the case of failure to detect an association that is statistically significant. Since the effect of time on costs is the primary interest of this analysis, we will carry out the next step regardless of the significance between time and costs.

Step 2: Effect of predictor (time) on the mediator (adherence):
The effect of time (predictor) on the hypothesized mediator adherence will be assessed, and adherence will be considered as a dependent variable in the model. Potential mediation effect will be supported by a statistically significant relationship between time and adherence, which will lead to the next step of the analysis.

Step 3: Combined effect of predictor (time) and mediator (adherence) on the outcome (costs):
Adherence will be included and adjusted as a covariate in the model assessing the relationship between time (predictor) and the dependent variable costs. Evidence of a mediation effect will be strengthened if the relationship between time and costs disappears or weakens while adjusting for adherence. If the effect of time on costs became insignificant, this indicates that the relationship between time and costs is fully mediated by adherence (full mediation); and if the relationship remains significant with a reduced magnitude, this indicates that adherence is partially meditating the relationship between time and costs (partial mediation). If any of the mediation effect exists, the next step will be used to further test the significance of the mediation effect.

Step 4: Assess the statistical significance of the effect of the mediator (adherence):
Bootstrapping method will be applied to evaluate the statistical significance of the adherence. The summary of effects table along with the bootstrap estimates and p-values will be provided. If the p-value of the indirect effect is significant, this clearly indicates that the mediation effect is significant. Additionally, the direct effect of time on the outcome costs, as well as the total effect, which is a sum of the indirect and direct effect and the percentage mediated will be provided.

7. Safety Evaluations

7.1. Adverse Events

This is a non-interventional study based on secondary data use, and therefore no ICSR reporting is required. The study protocol-defined AEs include hypoglycaemia. Hypoglycemia events in the pre-index and post-index period will be evaluated using the ICD-9 codes from the Ginde algorithm (Appendix 1). All protocol-defined adverse events collected will be summarized in the final study report. No other AEs will be collected.

8. Subject Consent to Release Information, Ethical Review, and Regulatory Considerations

8.1. Subject Consent to Release Information

As this is an observational study that uses data previously collected and does not impose any form of intervention, the data has been de-identified to protect subject privacy. Therefore, a formal Consent to Release Information form is not required.

8.2. Ethical Review and Regulatory Considerations

Observational studies will be submitted to ethical review boards (ERBs) for approval or waivers sought whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with the ethical principles of the Declaration of Helsinki and that are consistent with Good Pharmacoepidemology Practices (GPPs) and applicable laws and regulations of the country or countries where the study is being conducted, as appropriate.

9. Record Keeping, Data Reporting, Data Quality Assurance, and Publications

Subject data are recorded on data forms. Investigators are responsible for the integrity of the data reported to Lilly (accuracy, completeness, legibility, and timeliness). The investigators will follow local laws and regulations or institutional practices for document retention.

All information about this observational study and individual subject medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities and as applicable by law. Publications may result from this study.

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Attachment 1. Observational Study Protocol

Table Shells

SIMR_Eli Lilly_Protocol Table S

Appendix 1. Tables for ICD 9/10 and NDC Codes

SIMR_Eli Lilly_Protocol Appen

Appendix 2. Tables for List of Codes for Pump Use

Appendix 2_Pump and pump supple cc

Summary of Study Design

This will be a retrospective cohort study with secondary use of claims data from the VHA and Truven (Commercial and Integrated) databases. The study is designed to use real-world data to evaluate treatment patterns, treatment outcomes, and health care costs among T2DM patients who initiated U-500R, and among those who switched from U-500R syringe to Kwikpen administration. The study period will range from 01APR2013-31MAR2018 for VHA and LCED; and 01JUL2013-30JUN2018 for Truven MarketScan data. The first prescription claim date for U-500R syringe or U-500R Kwikpen administration will be considered the U-500R initiation and designated as Index Event 1 (syringe: Index Event 1a; Kwikpen:Index Event 1b); the date for U-500R device switch from syringe to Kwikpen will be designated as Index Event 2. For U-500R syringe initiation, U-500R Kwikpen initiation and U-500R device switch, the identification period will be 01JAN2014-30JUN2017 for VHA and LCED; and 01APR2014-30SEP2017 for Truven,

and the baseline and follow-up periods will be 9 months pre- and 9 months post-index date, respectively. The study outcomes will be reported in the periods before and after U-500R syringe initiation and U-500R Kwikpen initiation, and the periods before and after U-500R device switch from syringe to Kwikpen.