OHDSI in action: Real-world evidence for clinical characterization

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Research Goal

- Generate evidence
  - Randomized trial is the gold standard
  - Observational research seen as supporting

Observational Data & Clinical Trials

- Sample size calculations
  - Do we have enough patients to carry out a trial?
- Recruitment
  - Find patients or their clinicians from EHRs
- Pragmatic trials: recruitment and data collection
  - ADAPTABLE aspirin trial

…

- Complementary causal evidence (future)
  - New methods to handle confounding and ascertain causes from retrospective observational databases

Characterization

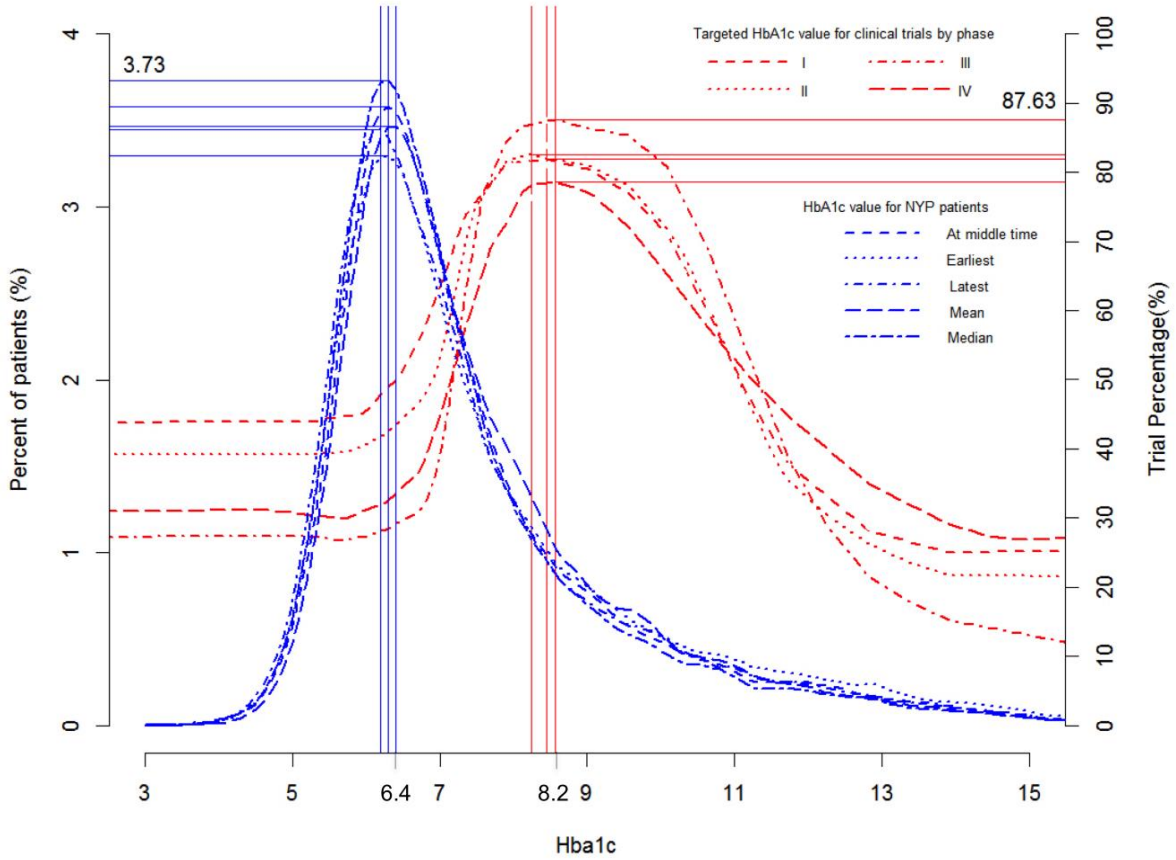
- Today we carry out RCTs without clear knowledge of actual practice
  - Compare treatments within a medical center or several medical centers without knowing what is used in the centers or outside of them

Characterization

- There will be no RCTs without an observational precursor
  - It will be required to characterize a population using large-scale observational data before designing an RCT
  - Disease burden
  - Actual treatment practice
  - Time on therapy
  - Course and complication rate
  - Done now somewhat through literature and pilot studies
- How do the proposed centers differ from the rest of the world?

Research on generalizability

- Set of all RCTs (ClinTrial.gov) as a distribution



(Weng ACI 2014)

Causation

Similar leaps:

- Observational associations -> Causes
- RCT-based causes -> Individual treatment
  1. Study population -> Local population
     - Characterization
  2. Local population -> Individual
     - Precision medicine
  - Are the same causes operative, confounders, etc.
  - That is, if deriving causes from observational data is futuristic, then so is using RCT results

(Fuller 2015)

Characterization

- What do we need to study?
  - Disease burden, current practice, complication rate
- Interactive design (cost of adding exclusions)
  - Fine details in designing my study (age 62 or 65)
- Effect size and variance
  - How many study subjects do we need?
- Will the result generalize
  - Do patients here look like patients at study site?
  - Do observational results on the study population match observational results on the local population

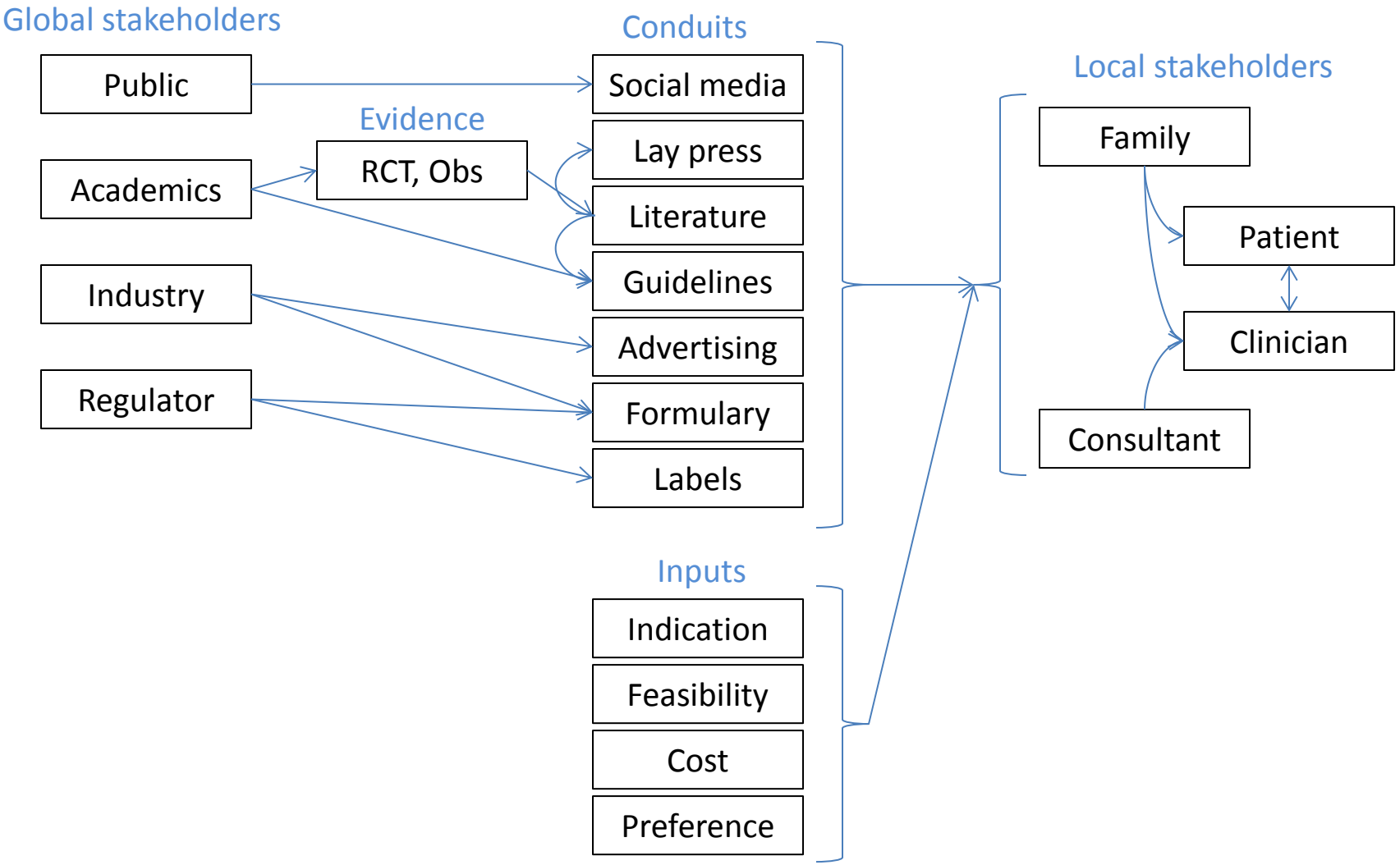
Treatment Pathways

- In literature
  - Recommended sequence of treatments
- How are patients actually treated?
  - Sequence of medications each patient took

Treatment Pathways

- Stakeholders
  - Clinician
  - Patient
  - Family
  - Public
  - Consultants
  - Field
  - Industry
  - Regulator
- Conduits
  - Literature
  - Lay press
  - Social media
  - Formulary
  - Guidelines
  - Drug product label
  - Advertising
  - Electronic health record
  - Direct interaction
- Evidence
  - Randomized trials
  - Observational studies
  - Experience
- Decision inputs
  - Clinical course
  - Feasibility of administration
  - Cost
  - Preference

Treatment Pathways



Treatment Pathways

- Defining a pathway
  - What the clinician orders
  - What prescriptions the patient fills
  - What the patient takes

Network-based Research

- International network of researchers
  - Data holders
  - Standards developers
  - Methods developers
  - Clinical researchers
- Large-scale collaborative research
  - Larger sample sizes
  - More diverse population
  - Greater expertise

Open-source process

1. Join the collaborative
2. Propose a study to the open collaborative
3. Write protocol
   - http://www.ohdsi.org/web/wiki/doku.php?id=research:studies
4. Code it, run it locally, debug it (minimize others' work)
5. Publish it: https://github.com/ohdsi
6. Each node voluntarily executes on their CDM
7. Centrally share results
8. Collaboratively explore results and jointly publish findings

OHDSI in action:
Chronic disease treatment pathways

- Conceived at AMIA 15Nov2014
- Protocol written, code written and tested at 2 sites 30Nov2014
- Analysis submitted to OHDSI network 2Dec2014
- Results submitted for 7 databases 5Dec2014

Condition definitions

Disease	Medication classes	Diagnosis	Exclusions
Hypertension (“HTN”)	antihypertensives, diuretics, peripheral vasodilators, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system (all ATC)	hyperpiesis (SNOMED)	pregnancy observations (SNOMED)
Diabetes mellitus, Type 2 (“Diabetes”)	drugs used in diabetes (ATC), diabetic therapy (FDB)	diabetes mellitus (SNOMED)	pregnancy observations (SNOMED), type 1 diabetes mellitus (MedDRA)
Depression	antidepressants (ATC), antidepressants (FDB)	depressive disorder (SNOMED)	pregnancy observations (SNOMED), bipolar I disorder (SNOMED), schizophrenia (SNOMED)

ACP Clinical Practice®
American College of Physicians
GUIDELINES

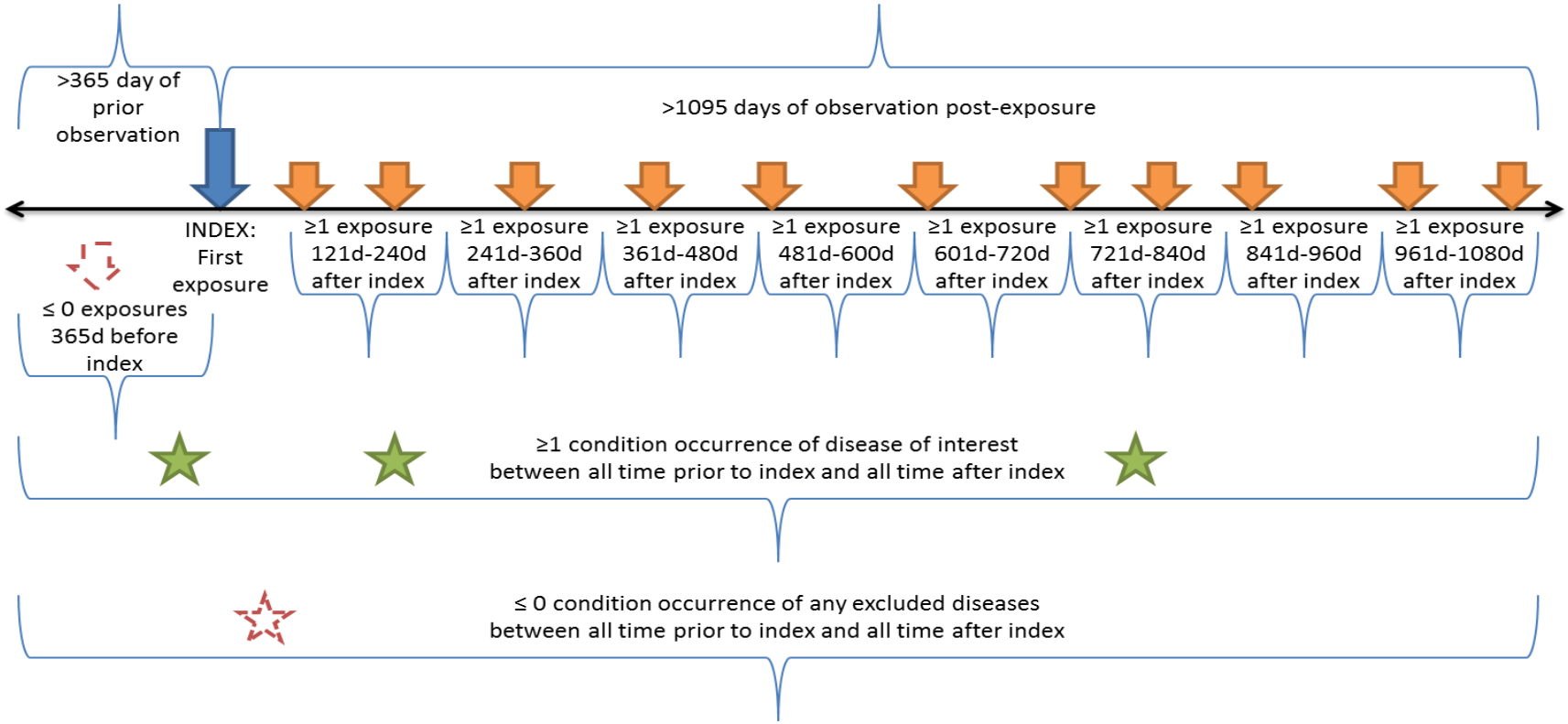
The American College of Physicians Guideline on Oral Medications for Type 2 Diabetes

Disease or condition	Type 2 diabetes
Target audience	Internists, family physicians, other clinicians
Target patient population	Adults with type 2 diabetes
Interventions	Oral pharmacologic treatment for hyperglycemia in type 2 diabetes
Outcomes	All-cause mortality Cardiovascular morbidity and mortality Cerebrovascular morbidity Neuropathy, nephropathy, retinopathy Hemoglobin A_{1c} levels Weight Plasma lipid levels Adverse effects
Recommendations	*Recommendation 1: ACP recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia (Grade: strong recommendation; high-quality evidence).* *Recommendation 2: ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes (Grade: strong recommendation; high-quality evidence).* *Recommendation 3: ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia (Grade: strong recommendation; high-quality evidence).*
Clinical Considerations	• Good management of type 2 diabetes with pharmacologic and nonpharmacologic therapies is important and includes patient education, evaluation, and self-management, for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors. • Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss. • Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss and/or lifestyle modification fails. • Metformin monotherapy was more effective in decreasing glycemic levels than other monotherapies, as well as in combination therapy with a second agent. In addition, metformin has the advantage of reducing body weight and improving plasma lipid profiles (in most cases). • Although combination therapy more effectively reduces hemoglobin A_{1c} levels, it is also associated with more adverse events.

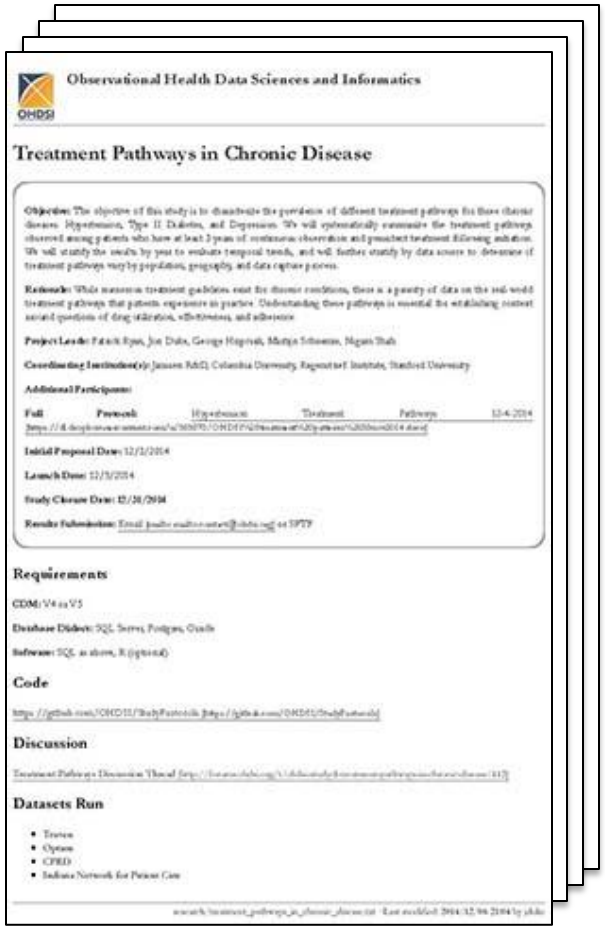
1. Metformin

2. Second agent

Treatment pathway event flow



Protocol



Observational Health Data Sciences and Informatics

OHDSI

Treatment Pathways in Chronic Disease

Objective: The objective of this study is to characterize the prevalence of different treatment pathways for three chronic diseases: Hypertension, Type II Diabetes, and Depression. We will systematically summarize the treatment pathways observed among patients who have at least 3 years of continuous observation and prescribed treatment following initiation. We will stratify the results by year to evaluate temporal trends, and will further stratify by data source to determine if treatment pathways vary by population, geography, and data capture process.

Rationale: While numerous treatment guidelines exist for chronic conditions, there is a paucity of data on the real-world treatment pathways that patients experience in practice. Understanding these pathways is essential for establishing context around questions of drug utilization, effectiveness, and adherence.

Project Leads: Patrick Ryan, Jon Duke, George Hripcsak, Mustafa Schuemie, Nigam Shah

Coordinating Institution(s): Janssen R&D, Columbia University, Regenstrief Institute, Stanford University

Additional Participants:

Full Protocol	Hypertension	Treatment Pathways	12-4-2014

Initial Proposal Date: 12/1/2014

Launch Date: 12/5/2014

Study Closure Date: 12/31/2014

Results Submissions: Email [redacted] as ZIP

Requirements

CDM: V4 to V5

Database Dialect: SQL Server, Postgres, Oracle

Software: SQL as above, R (optional)

Code

https://github.com/OHDSI/StudyProtocols [https://github.com/OHDSI/StudyProtocols]

Discussion

Treatment Pathways Discussion Thread [http://forums.ohdsi.org/t/[redacted]/[redacted]]

Datasets Run

- Truven
- Optum
- CPRD
- Indiana Network for Patient Care

```
#####################################################################
# R script for creating SQL files (and sending the SQL   #
# commands to the server) for the treatment pattern      #
# studies for three diseases:                            #
# - Hypertension (HTN)                                   #
# - Type 2 Diabetes (T2DM)                               #
# - Depression                                           #
#                                                        #
# Requires: R and Java 1.6 or higher                     #
#####################################################################

# Install necessary packages if needed
install.packages("devtools")
library(devtools)
install_github("ohdsi/SqlRender")
install_github("ohdsi/DatabaseConnector")

# Load libraries
library(SqlRender)
library(DatabaseConnector)

#####################################################################
# Parameters: Please change these to the correct values  #
#####################################################################

folder      = "D:/Documents/OHDSI/StudyProtocols/Study 1 - Treatment Pathways/R Version" # Folder containing the
minCellCount = 1  # the smallest allowable cell count, 1 means all counts are allowed
cdmSchema   = "cdm_schema"
resultsSchema = "results_schema"
sourceName  = "source_name"
dbms        = "sql server"              # Should be "sql server", "oracle", "postgresql" or "redshift"

# If you want to use R to run the SQL and extract the results tables, please create a connectionDetails
# object. See ?createConnectionDetails for details on how to configure for your DBMS.

user <- NULL
pw <- NULL
server <- "server_name"
port <- NULL

connectionDetails <- createConnectionDetails(dbms=dbms,
                                             server=server,
                                             user=user,
                                             password=pw,
                                             schema=cdmSchema,
                                             port=port)

#####################################################################
# End of parameters. Make no changes after this          #
#####################################################################

setwd(folder)

source("HelperFunctions.R")

# Create the parameterized SQL files:
htnSqlFile <- renderStudySpecificSql("HTN",minCellCount,cdmSchema,resultsSchema,sourceName,dbms)
t2dmSqlFile <- renderStudySpecificSql("T2DM",minCellCount,cdmSchema,resultsSchema,sourceName,dbms)
depSqlFile <- renderStudySpecificSql("Depression",minCellCount,cdmSchema,resultsSchema,sourceName,dbms)

# Execute the SQL:
conn <- connect(connectionDetails)
executeSql(conn,readSql(htnSqlFile))
executeSql(conn,readSql(t2dmSqlFile))
executeSql(conn,readSql(depSqlFile))

# Extract tables to CSV files:
extractAndWriteToFile(conn, "summary", resultsSchema, sourceName, "HTN", dbms)
extractAndWriteToFile(conn, "person_cnt", resultsSchema, sourceName, "HTN", dbms)
extractAndWriteToFile(conn, "seq_cnt", resultsSchema, sourceName, "HTN", dbms)

extractAndWriteToFile(conn, "summary", resultsSchema, sourceName, "T2DM", dbms)
extractAndWriteToFile(conn, "person_cnt", resultsSchema, sourceName, "T2DM", dbms)
extractAndWriteToFile(conn, "seq_cnt", resultsSchema, sourceName, "T2DM", dbms)

extractAndWriteToFile(conn, "summary", resultsSchema, sourceName, "Depression", dbms)
extractAndWriteToFile(conn, "person_cnt", resultsSchema, sourceName, "Depression", dbms)
extractAndWriteToFile(conn, "seq_cnt", resultsSchema, sourceName, "Depression", dbms)

dbDisconnect(conn)
```

OHDSI participating data partners

Code	Name	Description	Size (M)
AUSOM	Ajou University School of Medicine	South Korea; inpatient hospital EHR	2
CCAE	MarketScan Commercial Claims and Encounters	US private-payer claims	119
CPRD	UK Clinical Practice Research Datalink	UK; EHR from general practice	11
CUMC	Columbia University Medical Center	US; inpatient EHR	4
GE	GE Centricity	US; outpatient EHR	33
INPC	Regenstrief Institute, Indiana Network for Patient Care	US; integrated health exchange	15
JMDC	Japan Medical Data Center	Japan; private-payer claims	3
MDCD	MarketScan Medicaid Multi-State	US; public-payer claims	17
MDCR	MarketScan Medicare Supplemental and Coordination of Benefits	US; private and public-payer claims	9
OPTUM	Optum ClinFormatics	US; private-payer claims	40
STRIDE	Stanford Translational Research Integrated Database Environment	US; inpatient EHR	2
HKU	Hong Kong University	Hong Kong; EHR	1

Strict criteria

- 250,000,000+ patient records to start
- 4 years continuous observation
- (first treatment for disease)
- 3 years continuous treatment
- 327,110 type 2 diabetes mellitus
- 1,182,792 hypertension
- 264,841 depression

- Sequential and simultaneous are mixed

Publication in revision

- Submitted for publication
  - Policy of open sharing pre-publication
  - Will share more details on publication

Comments

- Will see a day when funding an RCT requires an extensive observational study
  - Characterization
- Future work
  - Causal assessment
  - Foundation for interpreting trials

Collaborators

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