Methodologic considerations for data source selection and study design of non-interventional studies comparing the safety and effectiveness of biosimilars and reference biologics: insulin glargine products as a case example

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This work was funded by a research contract between Optum Epidemiology and BBCIC. NDL and JDS are employees of Optum Epidemiology. JLFB is an employee of IQVIA. CHH is an employee of Abbvie. CML is an employee of BBCIC.

Background

The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) is a multi-stakeholder consortium established to support transparent, methodologically rigorous research to generate real world evidence on the use, safety, and effectiveness of novel biologics and biosimilars.

Careful consideration of the fit among (1) informational needs for a research question of interest, (2) study design, and (3) real world data (RWD) sources is crucial for unbiased assessment of biosimilars and their reference biologics.

Objective

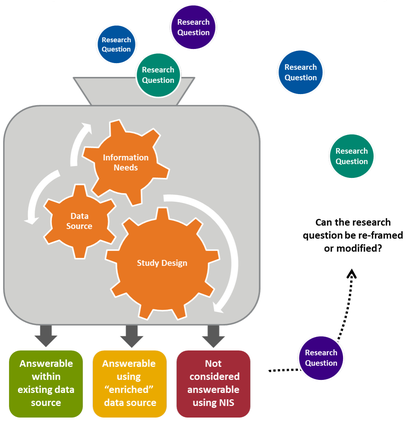
To establish a data source and study design framework and recommendations to aid BBCIC in planning and evaluating comparative safety and/or effectiveness research (CSR/CER) studies of biosimilars and reference biologics

Methods

Workgroup of research scientists and clinicians from payers, industry, and academia met remotely 5 times between June-November 2018 to develop a conceptual framework (Figure 1) and recommendations.

Insulin glargine products were selected as a use case to illustrate selected aspects of the framework.

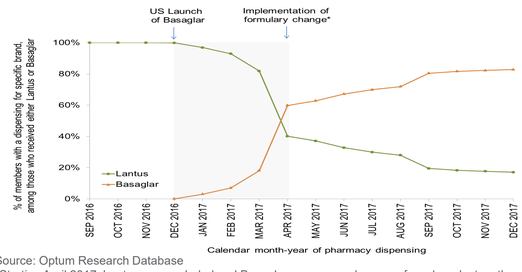
Figure 1. Conceptual framework
Can the question be answered by observational study?



Use case: utility of the BBCIC distributed research network (DRN) to support insulin glargines CSR/CER

- Historically regulated by the US FDA as drugs, insulins will be regulated as biologic medicines starting in March 2020
  - Lantus ("reference"): US FDA approval in 2000
  - Basaglar ("follow on"): US FDA approval in 2015; launch in 2016
- Utilization trends within a single RWD source suggest changes in formulary policy may affect treatment selection (Figure 2)
- Variation in formulary/reimbursement policies across payers presents a potential opportunity to use quasi-experimental study designs (e.g., instrumental variables [IV], interrupted time series [ITS] with segmented regression)
- BBCIC DRN leverages FDA Sentinel infrastructure
  - Access to administrative claims data via 5 research partners
  - Linkage to laboratory results and/or structured electronic health record (EHR) data available for population subsets

Figure 2. Illustrative example: shift in relative share of pharmacy dispensings for insulin glargines among commercially insured members affiliated with a national US insurer



Source: Optum Research Database
*Starting April 2017, Lantus was excluded and Basaglar was covered as a preferred product on the formulary.

Use case results: workgroup assessment and recommendations

Table A. Assessment of selected information needs and features of RWD types in the BBCIC DRN

Concept	Is data available in the BBCIC DRN?		
	Administrative claims *Reimbursed services during well-defined spans of continuous health plan enrollment*	**Structured EHR** *Clinical encounter information as recorded by in-network providers, linkable to claims*	**Laboratory vendor** *Outpatient laboratory test results from contributing vendors, linkable to claims*
Exposure			
Differentiate brand	yes	generally yes, requires verification	n/a
Date of initiation	proxy, pharmacy dispensings	proxy, prescription orders	n/a
Dose	proxy, pharmacy dispensings†	proxy, prescription orders†	n/a
End of on-therapy time	proxy, pharmacy dispensings†	limited	n/a
Health outcome of interest			
Severe dysglycemia	yes‡	some	limited
Major adverse cardiovascular events (MACE)	nonfatal: yes‡; deaths: some	nonfatal: some; deaths: some	n/a
HbA1c	no	some, varies by RP	some, varies by RP
Therapeutic modification (add on, switch)	yes	some	n/a
Therapeutic modification (change in dose)	limited	limited	n/a
Covariate			
Sociodemographic (race, ethnicity, SES)	varies by RP	varies by RP	n/a
Prior use of glargine, other insulins, other antidiabetic medications	yes	some	n/a
Smoking history	limited	some	n/a
Formulary/ reimbursement benefit design	requires verification	requires verification	n/a

n/a: not applicable; SES: socioeconomic status. RP: research partner.
† Dose and on-therapy time can be calculated based on dates of dispensing, quantity dispensed and days supply information reported on pharmacy claims (or based on prescription orders for EHR structured data), but may be misclassified due to dose titration, waste, or stockpiling
‡ Claims-based algorithms based on ICD-9 codes for severe hypoglycemia and for non-fatal major adverse cardiovascular events with demonstrated good positive predictive value.

Table B. Assessment of selected health outcomes of interest and design options

Health outcome of interest	Latency between exposure and outcome	Is between-individual confounding significant?	Is within-individual confounding significant?	Design and analytic options
Severe dysglycemia	short	yes	yes	traditional matched cohort, cohort with IV analysis, ITS, case-based design
MACE	long	yes	yes	traditional matched cohort, cohort with IV analysis
HbA1c	intermediate	yes	yes	traditional matched cohort, cohort with IV analysis, ITS
Therapeutic modifications	intermediate	yes	no	traditional matched cohort, cohort with IV analysis, ITS

MACE: major adverse cardiovascular events; IV: instrumental variables; ITS: interrupted time series

Selected recommendations

Data source fitness

- Perform detailed assessment at the individual RWD source level to inform data source selection and design/analytic decisions
  - Characterization of the size of population with overlapping linked claims and HbA1c results, and patterns of missingness of HbA1c results
  - Availability of formulary/reimbursement data (e.g., timing of formulary changes, ability to link coverage/reimbursement detail at the patient level)
- Consider expansion to include new RPs or data sources with more complete claims-HbA1c linked data, if sample size in BBCIC DRN is insufficient
- Consider validation of claims-based algorithms that accommodate ICD-10 codes for severe dysglycemia and MACE outcomes

Study design and analytic approaches

- Given clinical heterogeneity of Type 1 and Type 2 diabetes, analyses should be conducted separately for these populations
- For traditional cohort and quasi-experimental (IV, ITS) designs, new user-to-new user (or switcher-to-switcher) comparisons are preferred
- Switcher-to-prevalent user comparisons may be problematic due to potential residual confounding or differences in active disease management
- Characterize temporal trends in utilization of glargines, other insulins, other antidiabetes medications – and associated population characteristics – to evaluate (1) feasibility and assumptions underlying IV and ITS approaches and (2) availability of appropriate contemporaneous or historical comparators

Discussion

- Current gaps in RWD and broader environmental factors that influence access and use pose distinct challenges and opportunities for non-interventional studies of biosimilars and their reference biologics
- This framework supports a systematic multi-dimensional approach to methodologic development to mitigate potential bias in the design and conduct of CSR/CER
- Using this approach, the Workgroup identified several specific target areas for further data infrastructure fitness assessment and/or improvement to enhance BBCIC's capability to conduct CSR/CER of insulins

We would like to acknowledge the BBCIC CER Methods Workgroup members for their collaboration and input: Kirti Batra, William Herman, Dan Kent, Katie King, Edward Li, Jim Marshall, Aaron Mendelsohn.

To download a PDF copy of the poster, please scan the QR code:

Presented at the 35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Philadelphia, PA, USA; August 24-28, 2019, Abstract #5928