Individuals and Organizations Completing Research in the IMEDS Research Lab
GlaxoSmithKline

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Use of benzodiazepines and the risk of hip/femur fracture: A methodological comparison across data sources, common data model approaches, and epidemiological designs

Overview: We propose to evaluate the performance of Mini-Sentinel (MS) and Observational Medical Outcomes Partnership (OMOP) analytical tools using the example of Benzodiazepines (BZD) and Hip/Femur Fractures. Analyses will be conducted internally at GSK and within the IMEDS research lab using the US Truven MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental Beneficiaries databases (MDCR). In the longer-term, we plan to extend these evaluations to a non-US data source, using the UK Clinical Practice Research Database (CPRD).

Primary Objectives:
1. To gain experience and familiarity with the OMOP and MS Common Data Models and observational methods available within the IMEDS laboratory
2. To compare findings from MS and OMOP analyses within the IMEDS research lab
3. To assess the reproducibility of results from the OMOP 2010 experiment (http://omop.org/ResearchArchive) regarding BDZ and hip/femur fractures within the IMEDS lab

Additional Objectives: GSK authors have recently collaborated in studies evaluating Benzodiazepine (BZD) use and risk of Hip/Femur Fractures as part of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (IMI-PROTECT) project (http://www.imi-protect.eu/). In addition to the primary objectives outlined above, GSK proposes to repeat the MS analyses using a MS CDM version of UK CPRD in-house at GSK. This would address the following additional objectives:

- To assess the application of MS methods within a non-US Electronic Healthcare Records (EHR) database using CPRD
- To compare findings from analyses using the MS tools in CPRD with similar protocol driven analyses conducted within IMI PROTECT

Study Design: Descriptive, new user cohort and self controlled cases series studies

Study Population: Eligible participants will be aged 18 or older and new users of a benzodiazepine, with no record of an existing fracture at the time of study entry. Patients will be required to have a 12 month "fracture-free" period prior to the initiation of a BZD to be included in the study.

Databases: The UK Clinical Practice Research Data Link (CPRD) within GSK and the US Truven MarketScan Commercial Claims and Encounters database (CCAE) and Medicare Supplemental Beneficiaries database (MDCR) within IMEDS laboratory will be used for this research.

Exposure Measurement: For eligible patients, new use of a BZD will be defined as the date of the first BZD prescription in patients with no BZD exposure in the prior 6 months.

Outcomes of Interest: The primary outcome of this study will be the first new record of hip/femur fracture following study entry. In all data sources, outcomes will be identified using data from all available settings (primary/hospital care records).

Patients will be followed until the date a patient died, the date a patient was transferred out of the practice/end of enrollment, or the date that the practice or patient left the database.

Analysis: Descriptive analyses will be conducted first to characterize patient populations and obtain incidence rates of hip and femur fractures among new initiators of BZDs. Within the cohort analyses, Cox proportional hazards regression models will be developed to estimate adjusted hazard ratios and 95% confidence intervals comparing the risk of the events between cohorts. Conditional Poisson regression model will be used in the self-controlled case series analyses to estimate incidence rate ratios of current use compared to non-use.

Impact: This proposal meets many of the strategic objectives of the IMEDS initiative. We plan to examine the differences between MS and OMOP CDMs using the same study question within a single data source. We will demonstrate the feasibility of replicating both the MS and OMOP CDMs within the IMEDS laboratory. We will assess the application of MS methods outside of the IMEDS laboratory setting. In the longer term, we also propose to extend the work to evaluate the application and performance of MS methods within a non-US, EHR setting.

Specifically,

- Results from MS and OMOP methods from Truven (in IMEDS) will be compared. Results will provide a comparison of different analytic approaches (MS "Tools" vs. OMOP "Tools") within a common setting.
- Results from analyses within IMEDS will be compared to results generated in-house at GSK to assess the local application of available MS materials.
- Results from the application of OMOP methods by GSK will be compared with the original OMOP evaluation Madigan et al. 2013). Results will assess the ease of use and repeatability of the OMOP methods.

In the longer term,

- CPRD MS analyses will be compared with CPRD protocol defined analyses already conducted within IMI PROTECT. Results will provide a comparison of different analytic approaches (MS "Tools" vs. IMI protocol defined analyses) using the same clinical question within the same data source.
- The results of the MS analyses from CPRD and Truven will be compared. Results will provide a comparison between settings (UK vs. US, Claims vs. EHR data) using a common analytic approach.

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Investigators:

All investigators are employed by GlaxoSmithKline, specialize in the use of observational data for safety evaluations, and are qualified to conduct the proposed research. From WorldWide Epidemiology: John Logie, PhD, Hoa Le, MD, PhD, Carlyne Averell, MS, SM, Charlotte Carroll, MS; From Clinical Effectiveness & Safety: Jennifer Christian, PharmD, MPH, PhD, Ralph Horwitz, MD.

Timelines: August 1, 2014 – December 31, 2015.