

Janus CTR Data and Cross Study Analysis at FDA: Five Minutes versus Five Years and Millions of Dollars

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Introduction: The FDA has limited options when faced with detecting emerging safety signals. A powerful new tool, the Janus Clinical Trials Repository (CTR) enables analysis of emerging signals in clinical trials and supports a more informed regulatory decision-making process. Specifically, the CTR is a modern data warehouse application that automatically processes and maintains a database of structured, standardized study data, and makes it available for reviewer access through a variety of analytical tools. Conceptually, the CTR will allow us to create databases easily to support meta-analyses of clinical trial data so that reviewers can focus on analysis of the data instead of spending time in preparing the datasets for analysis. The CTR is currently in development and only houses legacy diabetes data that CDER has converted under an ARRA PCOR-funded contract.

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CTR Utility

- Enables signal detection
- Enables meta-analysis with minimal effort
- Automatically transforms standardized data into tool-ready format
- Maintains high data quality with validation checks
- Could increase review efficiency
- Could support regulatory decision-making process



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CTR Proof-of-Concept Results

- Two proof-of-concept analyses
 - Bladder Cancer (increases with Pioglitazone use)
 - Fractures (increases with Pioglitazone use)
- Analysis with controlled clinical trials
- Results with data in CTR concurs with gold standard
- Results in proof-of-concept were obtained more easily, more efficiently, and with much less money
- Proof-of-concept positive

Methods: A proof-of-concept analysis was conducted by a group within CDER to demonstrate the value of the CTR's ability to integrate standardized study data so that reviewers could analyze risk and safety signals across multiple studies. This analysis assessed the risk of bladder cancer and fractures with use of pioglitazone across multiple randomized studies and protocols. The originally submitted data had been converted into a standard format and loaded into the database. Analysis datasets were then built and analyzed using both SAS and JReview. These methods are exploratory and not meant to be robust from a meta-analysis methods perspective.

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Bladder Cancer Findings in Large, Expensive Studies

- In 2011, FDA released a Drug Safety Communication Update on pioglitazone and increased risk of bladder cancer
- Based on a 5-year interim analysis of an ongoing 10-year epidemiological study
- Literature and actions of other countries persuaded sponsor to agree to 10 year study

Results: Incidence of bladder cancer and fractures associated with pioglitazone use have been investigated in other large population trials and the results published in peer-reviewed literature. Performing this analysis using the CTR enabled reviewers to obtain similar results in a matter of days and with relative ease (as opposed to several months), positively demonstrating the potential value of the CTR in the detection of emerging signals. Our results were aligned with what has been published in the literature. The figures shown here are just some of our results.

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Fractures and Pioglitazone Use

- Another emerging signal: fractures with the use of thiazolidinediones (TZDs)
- In 2007, Agency warned of fracture risk in women taking pioglitazone
- Using 3 long-term pioglitazone trials in the CTR, we analyzed the risk for fractures

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Incidence of Bladder Cancer by Treatment Arm in Multiple Pioglitazone Studies

Adverse Event Term	Placebo N = 3134	Pooled Pioglitazone N = 3102
Bladder Cancer	4 (0.13%)	12 (0.39%)
Bladder Neoplasm	2 (0.06%)	3 (0.10%)
	6 (0.19%)	15 (0.48%)

Hazard Ratio = 2.53 (95% CI [1.03, 7.10]) which shows increased risk for bladder cancer with the use of pioglitazone



Discussion: Compared to the time and expense of large-scale, epidemiological trials, we were able to approximate similar results in hours – with no additional participant burden or expense.

Conclusion: The CTR's ability to store and manipulate standardized study data offers a variety of opportunities to enhance the regulatory decision-making process.

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Incidence and Hazard Ratio for Fractures in Multiple Pioglitazone Studies

Fractures	Placebo N = 3134	Pooled Pioglitazone N = 3102
Men	38 (1.21%)	37 (1.19%)
Women	24 (0.77%)	53 (1.71%)
	62 (1.98%)	90 (2.90%)

Hazard Ratio = 1.47 (95% CI 1.07, 2.04) which shows increased risk for fractures with the use of pioglitazone

