PharmaSUG 2018 - Paper RW-06

Improved Transparency in Key Operational Decisions in Real World Evidence

Rebecca Levin, Irene Cosmatos, Jamie Reifsnyder

United BioSource Corp.

ABSTRACT

The joint International Society for Pharmacoepidemiology and the International Society for Pharmacoepidemiology and Outcomes Research (ISPE-ISPOR) Special Task Force on *Real World Evidence in Health Care Decision Making* recently published a paper that emphasized the need to improve the reporting of study details in research conducted using longitudinal healthcare databases.[1] Lack of transparency in the operational details of published studies has led to "controversies over apparent discrepancies in results, and reduced confidence in evidence generated from healthcare databases."

Transparency in large healthcare databases is dependent on several factors, including clarity regarding (1) pre-processing of source data, (2) operational decisions to create an analytic dataset, and (3) analytic choices. If independent investigators apply identical operational choices to the *identical* source data as the original researchers, similar if not identical results should be reproduced.

This presentation uses integrated pharmacy and medical claims data from a large US pharmacy benefits plan to consider issues in defining drug exposures using pharmacy claims data and the subsequent effect on the identification of health outcomes. The example presented is a cohort of patients exposed to opioid-induced constipation (OIC) medications and the subset that experience major adverse cardiovascular events (MACE) of interest. The algorithms used to define medication exposures, including details regarding the "allowable gap" between pharmacy dispensings (i.e., the specified gap, above which indicates treatment episode has ended) are explored and various scenarios for defining exposures are presented. The effect of methodologic decisions regarding the identification of outcomes of interest are also described and the results of sensitivity testing of various follow-up windows are shared. The implication of the methodologic details articulated in this exercise is to inform researchers using algorithms for defining drug exposures and related outcomes using claims data.

INTRODUCTION

To address the growing demand for the use of real world evidence for decision making by drug safety regulators, effectiveness researchers and health technology assessments, the joint ISPE-ISPOR Special Task Force on *Real World Evidence in Health Care Decision Making* recently published a paper that emphasized the need to improve the reporting of study details in research conducted using longitudinal healthcare databases.[1] Lack of transparency in the operational details of these studies has led to "controversies over apparent discrepancies in results, and reduced confidence in evidence generated from healthcare databases."

Transparency in decision-making in studies using large healthcare databases is dependent on several factors, including clarity regarding (1) pre-processing of source data, (2) operational decisions used in created variables and metrics included analytic dataset, and (3) methodological decisions regarding temporal relationships for population and outcome identification. The operational decisions made by researchers and programmers in working with healthcare data can have important impacts on study results. Clear documentation and communication of these decisions is important for future independent investigators who need to interpret and apply similar methods to their studies, and is critical for those attempting to replicate findings on the same data source.

This presentation describes the complexities involved with the development of algorithms for a study of adverse event risks related to exposure to opioid-induced constipation (OIC) medications. The study evaluated risk of major adverse cardiac events (MACE) among identified chronic opioid users who were using constipation medications. The use of a 21 CFR Part 11-compliant analytic software package to identify the study cohort and generate study results is described, highlighting the benefit of using validated and well-documented analytic software, when appropriate, to perform rapid and thorough investigations of issues related to implementing study definitions. Concrete examples of analytic decisions and data processing issues are provided and presentation of sensitivity testing performed to explore the issues related to these decisions provides clarity supporting these decisions.

IMPORTANT METHODOLOGIC DECISIONS

There were a number of methodologic decisions to make, such as:

1. The algorithm to identify *chronic opioid exposures*;
2. The appropriate temporal relationship between the constipation medication of interest and chronic opioid exposure;
3. The appropriate temporal relationship between the constipation medication exposure and the adverse events of interest.

Ultimately, one must consider the impact of these decisions on the risk of misclassification of a subject's exposure status and/or the association of events with the exposure. In this study, the definition of "chronic opioid users" affects the patient base from which users of constipation drugs are identified. Also, the timeframe used to identify constipation medication users who also are on chronic opioid therapy will affect how many constipation medication users are included. Finally, the timeframe designated for identifying outcomes of interest has an impact on which outcomes will be identified.

All of these issues and assumptions can affect the identification of enough subjects for the study in relation to pre-specified sample size calculations based on population rates from the literature or other studies. If sample size requirements are based off event rates calculated under very different circumstances or with very different underlying algorithms for population and event identification, sample size calculations and statistical power assumptions could be off.

CHRONIC OPIOID EXPOSURE CONSIDERATIONS

In this study, algorithms hinge on relationships between dispensing dates and days of supply represented for each dispensing. Each dispensing has a designated length, which is usually represented in pharmacy claims data by a "days supply" field. For research involving length of exposures to particular medications of interest, a series of prescription, each with their specified length, may contribute to an exposure episode. Gaps may exist between refills if patients refill late, or overlapping supply from two separate prescriptions can occur if patients refill early. Decisions have to be made regarding how to handle situations such as a medication of the same class, type, or ingredient being dispensed before the last day of supply of the prior prescription, or when multiple medications are filled on the same day. Does this mean each medication prescribed on the same day is taken daily starting on the dispensing date? Or, does one of these prescriptions signify an early refill that would not be started until the days of medication of the associated prescription is depleted?

Often, dispensing patterns are indicative of medication-specific prescribing issues, so proposed assumptions should be explored with clinical experts. For example, opioids may be used for acute pain for short periods of time, or for longer, ongoing situations of chronic pain. Understanding the average days of supply for opioid medications prescribed under different circumstances would also be good helpful. Additionally, it is important to consider how similar these medications should be when considered for exposure. Can we assume a similar exposure across various medications within a class of medications (any opioid), should we make the assumption at the ingredient level, or should we only make this assumption if two drugs of the exact same formulations (identified with the same National Drug Code (NDC)) are dispensed on the same day?

CONTINUOUS OPIOID EXPOSURE EPISODES

In this analysis, dispensed opioid prescriptions in a subject's pharmacy claim data are summarized to create *continuous opioid exposure episodes*, as follows:

- The *end of supply* of each prescription claim was calculated as the prescription fill date + the days of supply obtained;
- *Early refills* (i.e., dispensing date is prior to the calculated end of supply date of a prior dispensing) lead to overlapping days of supply from each opioid dispensing. Under these conditions, exposures were adjusted such that the days of supply of the overlapping prescription are accumulated and added to the end of supply date of the prior prescription;
- Opioid *prescriptions filled on the same day* same day are assumed to be being taken concomitantly. Accordingly, the prescriptions are combined and the latest of the end of supply dates is retained.
- When gaps are not longer than the allowable gap, exposures are '*persisted'* (continuous exposure is assumed) and combined into *continuous opioid exposure episodes*.

Continuous opioid exposure episodes are created by assessing all gaps between the end of supply of a prior prescription and the beginning of supply of the subsequent prescription toward identifying which gaps are greater than the allowable gap (the tolerable days between prescriptions over which continuous therapy can be assumed). Sensitivity testing compared the impact of various allowable gap thresholds on patient identification. The details regarding how claim level data are summarized into continuous exposure episodes are demonstrated below (Figure 1). They are based on three different assumptions:

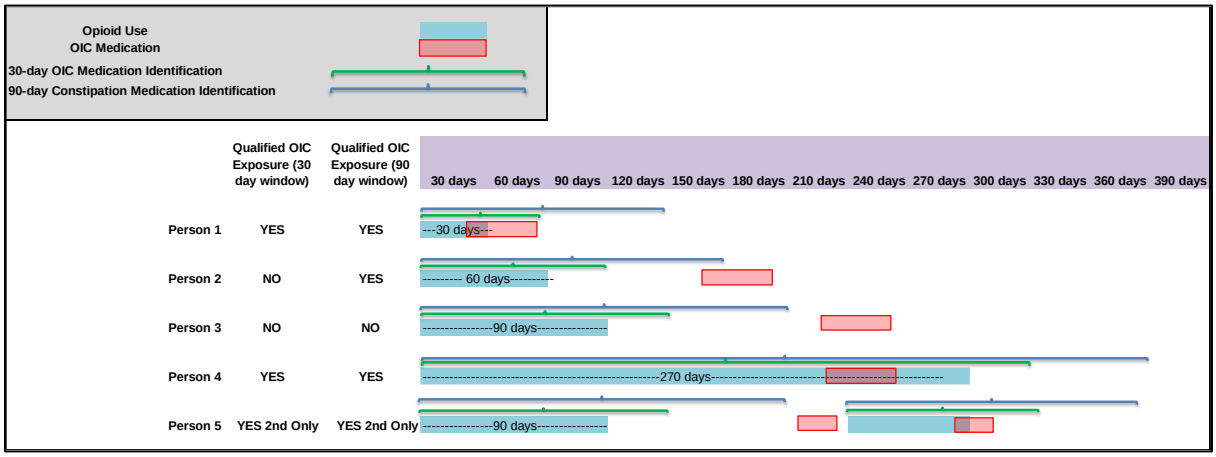
1. No allowable gap (claims-level data, no persistence applied);
2. A 30-day allowable gap;
3. A 90-day allowable gap.

Figure 1. Creating Continuous Opioid Exposures with Various Allowable Gaps (None, 30 Days, 90 Days).

IDENTIFICATION OF OIC AND CHRONIC OPIOID MEDICATION USERS

The use of constipation medications during or after a recent exposure to an opioid was key to identifying the opioid-induced constipation population for this study. Subsequently, decisions were required regarding the appropriate temporal relationship between the filling of a constipation medication of interest and chronic opioid exposure. Two OIC identification periods were considered: 1) OIC identification during and 30 days after a chronic opioid exposure period ends; 2) OIC during and 90 days after the end of a chronic opioid exposure (see Figure 2, below).

Figure 2. Identifying Opioid-Induced Constipation Medication Users with Chronic Opioid Use

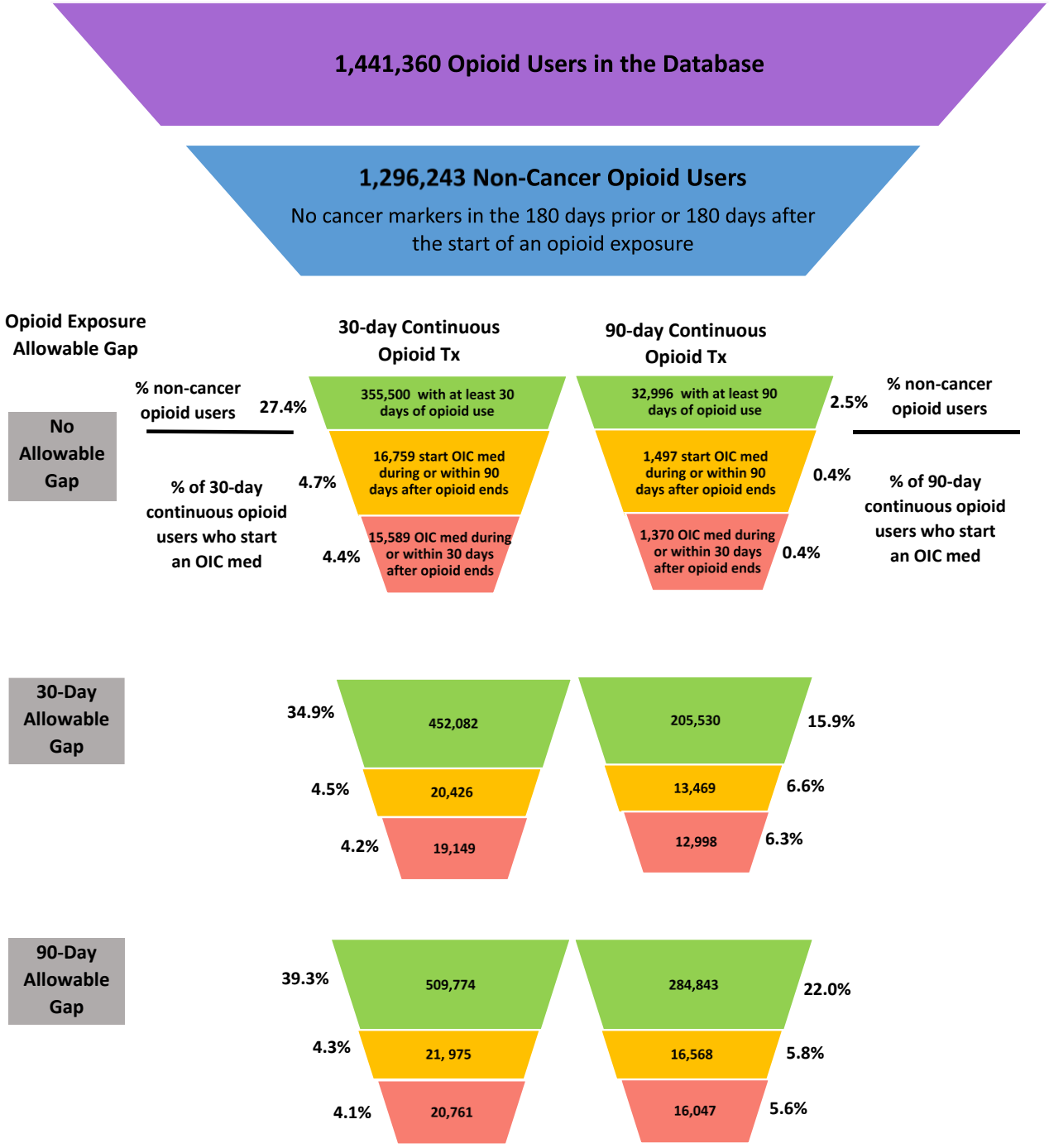


An automated tool was used to rapidly perform sensitivity testing to inform decision-making surrounding the issues affecting identification of chronic opioid users who also use drugs for opioid-induced constipation. Sensitivity testing included analysis of:

1. The appropriate *allowable gap* to create *continuous opioid exposures* (no persistence, 30-day allowable gap, 90-day allowable gap);
2. The required days of continuous therapy to be considered a *chronic opioid exposure* (30 versus 90 days);
3. The maximum length of time after the end of an opioid exposure that an opioid-induced constipation drug user could be identified (30 vs. 90 days).

Results of these sensitivity tests are in presented below (Figure 3).

Figure 3. Chronic Opioid User Identification Scenarios



These scenarios reveal important differences in the number of potential chronic opioid users that would qualify for the evaluation of MACE risk following OIC medication exposure under different methodologic assumptions. The importance of assigning a minimum allowable gap between opioid dispensings is clear given the differences seen in the ability to identify users with 30 days or 90 days of continuous opioid use (See Table 1, below).

Table 1. Population Identification Given Various Opioid Continuous Exposure Allowable Gaps

	Total Opioid Users with No Cancer Markers:		1,296,243	
	Users with 30 days continuous use		Users with 90 days continuous use	
	N	**%**	**N**	**%**
No allowable gap	355,500	27.4%	32,996	2.5%
30-day allowable gap	452,082	34.9%	205,530	15.9%
90-day allowable gap	509,774	39.3%	284,843	22.0%

The effect of requiring 90 days of continuous exposure is also important to note, given the big decreases in the opioid population with continuous use available for the identification of OIC medication users. With no allowable gap, there is a substantial drop from 27.4% of the total non-cancer opioid users with continuous opioid exposure for 30-days, versus 2.5% with 90-days of continuous opioid exposure. The scenarios also show how varying the number of days after an opioid exposure ends that an OIC medication can be identified had only a small impact on study population size, when considering 30- and 90-days post-opioid OIC identification periods. (See Table 2, below). For example, given a 30-day allowable gap, the difference between OIC medication use starting within 30 days vs. 90 days is 4.5% and 4.2% respectively, among the users with 30 days of continuous opioid exposure.

Table 2. Varying the Days Post-Opioid Exposure for Identifying OIC Medication Use

Allowable Gap	**Opioid Users Starting OIC Medication in X Days**	**Users with 30 Days Continuous Use**		**Users with 90 Days Continuous Use**	
		N	**%**	**N**	**%**
No allowable gap	Within 90 days	16,759	4.7%	1,497	0.4%
	Within 30 days	15,589	4.4%	1,370	0.4%
30-day allowable gap	Within 90 days	20,426	4.5%	13,469	6.6%
	Within 30 days	19,149	4.2%	12,998	6.3%
90-day allowable gap	Within 90 days	21,975	4.3%	16,568	5.8%
	Within 30 days	20,761	4.1%	16,047	5.6%

MACE OUTCOMES IDENTIFICATION

Once the study population has been defined using the operational decisions described above, the next key analytic decision is the appropriate temporal relationship between the constipation medication exposure and the timing of the adverse events of interest (MACE outcomes). The outcomes observation period for this study was specified as the duration of OIC treatment plus a 30-day period after the end OIC treatment (i.e., an additional 30-day 'at risk' period following exposure ending, recommended by clinical experts to account for the drug half-life and patients stretching medication use).

Sensitivity testing around acute myocardial infarction (MI) and acute ischemic stroke (both components of MACE outcomes) were performed a number of ways:

1. **Longer or Shorter Window After Exposure Ends.** Outcomes were assessed over the exposure period plus a 15-day period and 90-day period after constipation medication exposure ends.
2. **Acute Exposure to OIC**. Outcomes were only assessed over the first 90 days of treatment, or if they dropped off therapy after the length of exposure + 30 days.
3. **Longer Versus Shorter Exposure to Opioids**. Outcome prevalence was compared among longer term chronic opioid users (90 days of continuous use) and shorter continuous opioid users (30 days of continuous use).

Figure 4. Rates of Outcomes (Either MI or Stroke) Using Proposed Definition

	Persons	Person Eras	Person Eras with Outcome Occurrence	Prevalence[1] (%)
All Persons	19,149	19,149	734	3.83%
Female	13,017	13,017	494	3.8%
Male	6,128	6,128	240	3.92%
Unknown	4	4	0	0%

1. ***Prevalence:*** *Percent of total Person Eras within the cohort with at least one occurrence of the outcome. For analyses where only one Era is analyzed per Person, the Person Era count is the same as the Persons count.*

- 30-day allowable gap
- 30 days of continuous opioid exposure
- OIC medication use identified during or within 30 days after continuous opioid exposure
- MACE Outcomes Observation Period = During OIC medication exposure + 30 days after OIC medication exposure ends

Figure 5. Outcome Rates Given 90 Days Continuous Opioid Use

	Persons	Person Eras	Person Eras with Outcome Occurrence	Prevalence[1] (%)
All Persons	12,998	12,998	653	5.02%
Female	8,906	8,906	437	4.91%
Male	4,089	4,089	216	5.28%
Unknown	3	3	0	0%

- 30-day allowable gap
- 90 days of continuous opioid exposure
- OIC medication use identified during or within 30 days after continuous opioid exposure
- MACE Outcomes Observation Period = During OIC medication exposure + 30 days after OIC medication exposure ends.

Figure 6. Outcome Rate Given Longer Outcome ID Window (90 Days) after Discontinuation of OIC Medication

	Persons	Person Eras	Person Eras with Outcome Occurrence	Prevalence[1] (%)
All Persons	19,149	19,149	795	4.15%
Female	13,017	13,017	532	4.09%
Male	6,128	6,128	263	4.29%
Unknown	4	4	0	0%

- 30-day allowable gap
- 30 days of continuous opioid exposure
- OIC medication exposure identified during or within 30 days after continuous opioid exposure
- MACE Outcomes Observation Period = During OIC medication exposure + 90 days after OIC medication exposure ends

Figure 7. Outcome Rate Given Shorter Outcome ID Window (15 Days) after Discontinuation of OIC Medication

	Persons	Person Eras	Person Eras with Outcome Occurrence	Prevalence[1](%)
All Persons	19,149	19,149	711	3.71%
Female	13,017	13,017	478	3.67%
Male	6,128	6,128	233	3.8%
Unknown	4	4	0	0%

- 30 day allowable gap
- 30 days of continuous exposure
- OIC identification during or within 30 days after continuous opioid exposure
- MACE Outcomes Observation Period = During OIC medication exposure + 15 days after OIC medication exposure ends.

Figure 8. Acute OIC Medication Exposure (First 90 days of OIC Medication Exposure Only) for Outcomes Identification

	Persons	Person Eras	Person Eras with Outcome Occurrence	Prevalence[1](%)
All Persons	19,149	19,149	274	1.43%
Female	13,017	13,017	186	1.43%
Male	6,128	6,128	88	1.44%
Unknown	4	4	0	0%

- 30-day allowable gap
- 30 days of continuous opioid exposure
- OIC medication exposure identified during or within 30 days after continuous opioid exposure
- MACE Outcomes Observation Period = During the first 90 days of OIC medication exposure only

Considering the results of the sensitivity testing regarding outcomes identification windows, it was clear that there was only a small, incremental impact that occurred when varying the length of the timeframe after the end of an OIC medication exposure for outcomes identification. A 15-day post OIC medication exposure period led to 711 (3.71%) OIC patients with MACE outcomes, a 30-day period led to 734 (3.83%) patients and a 90-day period post OIC exposure led to 795 (4.15%) with MACE outcomes. It was important to note that those who used opioids for at least 90 days had a substantially higher proportion of MACE outcomes, 998 (6.02%) compared with patients who only used opioids for at least 30 days (734 patients, 3.83%). Finally, considering outcome rates over just the first 3 months of use answers questions about risk upon initiating OIC medications (Figure 8).

OTHER ISSUES IMPORTANT FOR TRANSPARENCY OF METHODS

Data Censoring

It is also important to provide detailed documentation regarding all censoring applied to the data. For composite MACE outcomes, subjects were censored at their first qualifying MACE. Subjects without an event would be censored at whichever comes first:

1. 30 days after the end of the observation period;
2. After the end of the final observation period, if multiple treatment episodes exist;
3. The date they leave the health system, as indicated by enrollment data;
4. The date of a switch to a different OIC medication (as it was decided that for the primary analysis, treatment switches will not be considered).

Impact of Switching and Concomitant Therapy

Patients could have multiple types of constipation medications associated with chronic opioid exposures and thus could qualify for inclusion into multiple study cohorts (e.g., users taking peripherally-acting mu-opioid receptor antagonists (PAMORA) vs. non-PAMORA laxatives). A non-PAMORA exposure may overlap with a PAMORA exposure, or two different constipation medications may exist within the same outcomes observation window. Quantifying these situations of switching, concomitant therapy, and any potential bias caused in relation to cohort assignment and outcomes evaluations is important. Figure 9, below, displays results from a treatment patterns exercise in SÆfetyWorks used to review switching between PAMORA medications, such as Relistor (methylnaltrexone) and non-PAMORA constipation medications (polyethylene glycol). These results demonstrate that very few patients switch between these two types of medications. Only 2 of the 23,802 PAMORA and non-PAMORA users in this sub-analysis switched between these classes of medications, with the specific users switching from polyethylene glycol to Relistor.

Figure 9. Switching between Constipation Drug Groups (PAMORAs / non-PAMORAs)

Total persons in study population: 1,441,360
Persons with treatment: 81,697
Persons with qualifying first-line treatment: 23,802
Switched (Total Persons: 162)

			Time to Change of Treatment (days)				
By Treatment	N	%	Mean	Median	Std Dev	Min	Max
Non-PAMORAs to methylnaltrexone + methylnaltrexone	2	1.23	5.50	5.50	0.71	5	6
Polyethylene glycol to Relistor + Methylnaltrexone	2	1.23	5.50	5.50	0.71	5	6
Non-PAMORAs to Non-PAMORAs	160	98.77	39.13	23.00	52.12	1	323
POLYETHYLENE GLYCOL 3350 to Polyethylene glycol	83	51.23	24.04	20.00	21.69	1	110
Polyethylene glycol to POLYETHYLENE GLYCOL 3350	77	47.53	55.39	28.00	68.26	1	323

DATA PREPARATION AND PREPROCESSING STEPS

Another important factor to consider is whether any algorithms involved with pre-processing of the source data could affect study definitions. Methods for cleaning and curating data applied prior to receipt of the final dataset may need to be reviewed. For example, are there data that are imputed? One key data element for this study was the days of supply for each dispensing. It would be important to know if this field is ever imputed by the vendor, if missing. For this exercise, scrubbing methods and pre-preparation of the prescription claims for analysis were clarified with the data supplier, and it was verified that no imputation of days of therapy was conducted.

CONCLUSION

To improve the transparency of methods, important details such as those explored here must be shared at the time results are presented.

Examples of such details include:

1. Pre-processing of source data;
2. How database row-level detail is processed to create healthcare episodes or, for drugs, days of continuous therapy episodes (calculation of length of stay, or duration of therapy);
3. Use of enrollment data toward confirmation of coverage and data completeness;
4. Assumptions and decisions regarding temporal relationship between healthcare events;
5. Conditions for censoring from study observations.

Analytic software tools with their detailed but flexible and well-documented algorithms are valuable tools for finalizing study algorithms as they allow for rapid testing of various scenarios like those described here. The analyses described in this paper used a 21 CFR Part 11-compliant analytic software called SÆfetyWorks, which allows for complex cohort definitions using a point-and-click user interface, for this study. A well-tested, validated library of SAS macros or other validated, automated or semi-automated tools can also allow for rapid, repeatable algorithm testing.

This methods exercise illustrates the detailed decisions that must be made when operationalizing study criteria. The examples presented in this paper demonstrate how the assumptions and the allowable gap used in creating subject's treatment episodes, as well as the temporal relationships between health events required for subject and outcome identification, may have a big impact on the ultimate patient base used for a study, and therefore can potentially influence the study results.

REFERENCES

1. Joint ESPE-ISPOR Special Task Force on RWE in Healthcare Decision-making. "Joint ISPE/ISPOR Task Force Reports." Accessed March 14, 2018. https://www.ispor.org/RWEInHealthcareDecisions/JointISPEISPORSpecialTF

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Rebecca Levin, MPH
United BioSource Corporation
917-533-4509
rebecca.levin@ubc.com

Irene Cosmatos, MS
United BioSource Corporation
484-639-1421
irene.cosmatos@ubc.com