

TITLE PAGE

Title of project: “An analytic retrospective pretest-posttest design with interventions, used to evaluate the time taken to document drug adverse events at Banner Health Specialty Pharmacy, as well as identifying the top five medications that lead to adverse events to help increase medication awareness.”

Course title: PHPR 898B: Writing a Proposal for a Scientific Study

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ABSTRACT

Specific Aims: (1) Decrease in the amount of time taken to report adverse events (ADE) at Banner Specialty Pharmacy-Chandler. (2) Identify the top five medications that cause ADE's in the pharmacy and determine based on reaction type, frequency, and event severity, important drug information that can be given to future and existing patients. Subjects: Adverse events and medications only.

Methods: A data document was used to analyze ADE's taken from Oct 2018 thru May 2020 to identify the top five medications that cause the most ADE's. Intervention tools, pharmacist template and use of pharmacy techs, were started on Nov. 11th 2020 till March 1st 2021. Pre-intervention period was from July 2020 to October 2020. ADE pre and post intervention groups were compared to note difference in documentation time.

Main Results: The total average documentation time for the pre-intervention period was 12.22 min per event (SD=0.83), while the total average documentation time for the post-intervention period was significantly faster at 10.00 min per event (SD=2.68) (p-value=0.032). Humira, Enbrel, Capecitabine, Imbruvica and Sutent were identified at the top 5 medications to cause ADE's, and no significant difference was noted in severity between groups (p-value= 0.843).

Conclusions: Intervention strategies appeared to decrease the documentation time of ADE's at Banner Specialty Pharmacy-Chandler. Other variables during the intervention period cannot be ruled out. The information regarding the top five medication that cause adverse events at Banner Specialty Pharmacy-Chandler should only be used as a tool to highlight important counseling points for each of these medications

INTRODUCTION

Adverse Drug Events (ADEs), although known for their negative effect on patient quality of life, can be used to improve safety and monitoring of patients through the mitigation strategies equipped by Specialty Pharmacies¹. ADEs are common in most clinical settings including adult inpatients with a reported incidence of 6.5%, adult outpatients with an incidence of 27.4%, and pediatric inpatients with a reported incidence of 2.3%². Specialty pharmacies, due to their unique setting and qualities, provide additional value-added services compared to the adverse events reported by different inpatient or outpatient settings, in addition to the usual reporting requirements of notifying the drug manufacturer and the FDA³. By utilizing these services fully, Specialty Pharmacies can improve current adverse event reporting processes and use them to provide new drug information/ warnings to their patients, overall improving outcomes in these areas.

Adverse Drug Events (ADE) can lead to morbidity, hospitalization, increased healthcare costs by the patient inflicted and, in some cases, can lead to death⁴. Each year more than 770,000 people are injured or die from ADE's and from 2006-2014, 38 drugs had more than 1,000 reports of serious ADEs in a given year: two drugs currently withdrawn from the market (rofecoxib and parecoxib), 10 drugs with an FDA risk evaluation and mitigation strategies (REMS) program, 13 biologic or specialty drugs, and 14 others⁵. Specialty medications have a large impact on the number of drug adverse events reported overall. Specialty Pharmacies have the ability to improve the severity and number of adverse events through utilization of their mitigation and management strategies³. Using these strategies, they are able to help patients tackle adverse events properly and be advised on what to do if one should occur. Clinical pharmacists practicing in specialty pharmacies have the ability to educate patients on their specific disease state and the role of their specialty medication³. Identification and documentation of these specialty adverse events can expose previously undiscovered adverse events, leading to

improvements in the safety and monitoring profiles of specialty products and reveal positive effects that were not originally listed as a medication's known benefit³. This can change how specialty medications are counseled in the future and identify new promising indications³. These aspects can be used to enlighten change and make interventions in current Specialty Pharmacy ADE reporting processes to overall improve patient adverse event outcomes and decrease the severity of their events.

Banner Health Specialty Pharmacy is a specialty pharmacy setting that utilizes its own adverse event reporting process by documenting the event in their therapy management system (Therigy) and then forwarding the report to the patient provider, drug manufacturer, FDA, and the company's own ADE database (Verge). However, despite this process, the specialty pharmacy has the ability to identify new common adverse events by analyzing the drugs and type of reactions responsible for most of the medication ADE's reported. Therefore, the purpose of this study is to improve the average time taken to document adverse events before and after new strategies are implemented. In addition to this, severity and frequency of adverse event type will be analyzed amongst the top five specialty medications that cause these events in order to highlight important drug information for future and existing patients.

METHODS

Design: This is an analytic project design using retrospective pretest-posttest with interventions. This study was approved by the University of Arizona Human Subjects Protection Program and also approved by the Banner Health NRDUC committee.

Subjects: The study does not focus on human subjects or human demographics but more so on the adverse events and top five medications that cause them at Banner Health Specialty Pharmacy-Chandler. In terms of inclusion criteria, all adverse event data was required to be reported by Banner Health Specialty Pharmacy-Chandler and had to be related to medications sold specifically by this

facility. The adverse event data used to improve event documentation times were specifically taken from July 2020 through October 2020 to ensure enough data for data collection⁶. After documentation strategies were implemented in November 2020, post-intervention adverse event data was collected from November 2020 to February 2021. Data that was used towards identifying the top five medications were taken from October 2018 through May 2020. Adverse events excluded were those that were due to prescribing errors, medication dispensing errors, wrong name/wrong drug, and injectable drug errors. The study only focused on side-effect related adverse events that came directly from taking/using the medication that was prescribed.

Treatment [or Intervention]: The first objective of the study was to make the adverse event reporting process more efficient by implementing an intervention to decrease the average time spent documenting events. The intervention involved requiring the help of pharmacy technicians and a pharmacist documentation tool to minimize the time pharmacists spent completing adverse events (Appendix A). The intervention was implemented on November 11th, 2020 using an email that was sent out to all employees at Banner Specialty Pharmacy-Chandler. The email carried instructions for the intervention asking pharmacy technicians to transfer any patient with an adverse event to an available pharmacist so they could collect additional information on the reaction. If not available, the technician would then send a mass email to all clinical pharmacists at the site with specific patient information and have them call the patient back within 24 hours (Appendix A). Pharmacists who counseled on adverse events were also encouraged to use the provided documentation tool to help streamline their questioning when collecting more information. The instructions for technicians and pharmacists were stored in the Banner OneNote for them to reference off of throughout the intervention period which lasted from November 11th, 2020 to March 1st, 2021. The second objective of the study was to highlight important drug information by analyzing the top five drugs that caused the most adverse events in the

past. A data collection tool was designed to collect statistics on the drugs that caused the most adverse events (i.e. frequency, severity, etc.) from October 2018 through May 2020 (Appendix A).

Measures: Data for the first and second objectives were both collected using the same data collection tool, given that all data was analyzed at once (Appendix A). The data collection document was modeled off of the intervention made in the study by *Lopez-Gonzalez et al.*⁶. Adverse events for the second objective, were broken down and examined based on medication name, date of adverse event, adverse event reaction, and severity. Severity was classified as either mild (medication discontinuation), moderate (close monitoring), severe (hospitalization), death, or other based on what was selected in Verge. Adverse events used to examine the first objective (time to document), were broken down and analyzed based on date of adverse event and subjective time (minutes) that had been documented in Therigy. Other aspects included on the data collection tool such as adverse event type were used to help identify if the adverse events were related to medications or another type of error, that way they could potentially be excluded from the study. Information regarding sex, indication, prior health status, and comorbidities were collected for future analysis but was not examined or included in the study.

Data Collection: Adverse event data between October 2018 and March 2021 were downloaded from the Banner Health Verge database, deidentified, and stored in a secure Google Drive for analysis off-site. Time to document data from July 2020 to March 2021 was also downloaded from the Banner Health Therigy database, deidentified, and stored in the same secure Google Drive. Members of the research team used the data collection tool to analyze each event and perform statistical tests for the study. Data analysis started December 2020 and ended March 2021.

Data analysis: Sample sizes were predicted based on the average number of adverse events reported every month (approximately 6 to 10 adverse events per month). With about 31 adverse events estimated for each group (pre- and post-intervention periods), this would give the study adequate

power to identify an 18% difference between groups. For the second objective, the sample size was predicted to be 50 to 300 adverse events taken from October 2018 to May 2020. A total of 170 adverse events were evaluated to analyze the top five medications that caused the most adverse events.

Collected data pertaining to the first objective were summarized using means, standard deviations, and total number of events, while average documentation times for the pre and post intervention groups were compared using a student's paired t-test. Frequencies and percentages were used to summarize the adverse events used towards the study's second objective. Severity of adverse event reaction types for each medication were compared using a Chi square test. The alpha priori p-value was 0.05.

RESULTS

Average time taken to report adverse events for the pre- and post- intervention periods were listed in Table 1. Total number of adverse events prior to the intervention from July to October 2020 were similar to the number of adverse events identified after the intervention from November 11th, 2020 to March 1st, 2021 (33 and 31 events respectively). The total average documentation time for the pre-intervention period was 12.22 minutes per event (SD=0.83), while the total average documentation time for the post-intervention period was 10.00 minutes per event (SD=2.68). This result shows a significant difference in documentation times after new intervention strategies were implemented (p-value= 0.032). This shortened the documentations process by a little over 2 minutes (p-value= 0.032).

The top five medications at Banner Specialty Pharmacy-Chandler that cause the most adverse events were listed in Table 2. Humira (18 events), Enbrel (13 events), Capecitabine (9 events), Imbruvica (5 events), and Sutent (5 events) ended up being the top five medications that caused the most adverse events from October 2018 to May 2020. A total of 170 adverse events were used as the sample size for this period of time. For Humira, the most common reaction types reported were skin-related allergic reactions (6 events), infections (3 events), and neurologic events (2 events)—all of which reported mild

to moderate events in patients from October 2018 to May 2020. In regard to Enbrel, injection site reactions (3 events), neurologic events (3 events), and musculoskeletal reactions (2 events) were the most common reaction types with gastrointestinal events being the only reaction to be moderate in severity. Capecitabine had gastrointestinal events (3 events) and skin-related allergic reactions (3 events) as the most frequent adverse event type, with gastrointestinal events and low ANC counts both moderate in severity. Imbruvica reported to have mainly moderate reactions related to gastrointestinal and cardiac events while most of Sutent's reactions were gastrointestinal related (2 events) with infection being the only event moderate in severity. No reactions were indicated to be severe or worse than severe among the events reported for all five medications. Few events were labeled as 'unknown' due to there being no severity marker specified for that event among the Verge data. When comparing mild and moderate severity of reactions of the top five medications, there was found to be no significant difference (p -value=0.843)

DISCUSSION

There were two main findings to the study. The first finding showed that implementing new documentations strategies through the inclusion of pharmacy technicians and pharmacist reporting templates significantly reduced the time to document adverse events at Banner Specialty Pharmacy. These strategies shortened the original adverse event reporting time by about two minutes, while the total number of adverse events identified during the pre-and post-intervention periods remained the same. *Lopez-Gonzalez et al.*⁶ took a similar approach in documenting drug adverse events and assessed the effectiveness of an educational intervention designed to improve event reporting in a robust medication safety system. The educational intervention consisted of two approaches-one active (group sessions), the other passive (educational material, reporting form). These interventions were

implemented from November 2007 to December 2008, with a follow-up period of 8 months⁶. The study showed that the intervention increased the adverse event reporting rate/time and appeared to be greater in the four months following the intervention date⁶.

The second finding identified the top five medications that cause the most adverse events at Banner Health Specialty Pharmacy-Chandler to be Humira, Enbrel, Capecitabine, Imbruvica, and Sutent from October 2018 to May 2020 (ordered most adverse events to least). These results were further broken up by identifying the most common reaction types and their severity. Skin-related allergic reactions, infections, and neurologic events were the most common for Humira and were all mild to moderate in terms of severity. Enbrel's adverse events consisted mainly of infections and neurologic events while gastrointestinal events appeared to be the most severe out of all of the listed reaction types. Capecitabine mainly reported skin-related allergic reactions and gastrointestinal events and Imbruvica adverse events listed gastrointestinal and cardiac related reactions as the most severe. Sutent had gastrointestinal events listed as the most recurring adverse event, while infections ended up being the most severe. However, when comparing each of the drugs and their adverse event severity (mild vs. moderate events), no significant difference in severity could be identified. Similar results were identified by a study completed by *Sonawane et al.*³ It was found that 13 biologic or specialty drugs were connected with 1,000 reports of serious adverse events in a given year, this number included oral oncolytics and medications like Humira and Enbrel³. Biologics were thoroughly examined as a source for adverse events due to their complex mechanism of action and price³.

Each finding has several implications to pursue further studies and research on these topics. For the first finding, evidence of a decrease in documentation time by implementing new strategies should encourage the ability to alter the intervention. This could be done in the hope of speeding up the documentation time even more or focusing instead on increasing the number of adverse events

identified or reported. The current pharmacist template and or strategy of utilizing pharmacy technicians can continue to be used as a baseline and later modified to fit future research or quality improvement needs. For the second finding, the goal was to identify the top specialty medications that cause the most adverse events and focus on the specific reactions or severity to focus on side effects that might require more counseling. The hope is that this data can be used to benefit patients as an informational tool. It would be interesting to identify more trends through the utilization of a larger sample size or focus on patterns that coincide with patient demographics in the future.

There were several limitations to the study. The first regarding the intervention procedures. Although there was evident improvement in the documentation time after the intervention, use of documentation strategies by technicians or pharmacists were not recorded during this period. This means it was unclear how many pharmacists relied on the actual template when speaking with adverse event patients or how many technicians successfully transferred patients to pharmacists and sent out emails. This makes it hard to identify an accurate correlation between the results and the intervention period or if other variables had an effect. Another limitation was that the current sample size of adverse events was not large enough to distinguish a difference in severity in reactions between the top five medications. Increasing the time range that data was pulled from could help increase the sample size of adverse events for future research. Discrepancies in some of the severity information pulled from Verge, for example those labeled as 'unknown', also could have had a distinct effect on the results. These results were not identified specifically as mild, moderate or even severe which could have helped with identifying a potential difference in severity when examining the top five medications.

CONCLUSIONS

Intervention strategies like the pharmacist documentation template and the utilization of pharmacy technicians appear to decrease the documentation time of adverse events at Banner Specialty Pharmacy-Chandler. Altered correlation between the intervention and a decrease in time cannot be ruled out given certain variables throughout the study were not completely controlled. However, this correlation can be investigated or changed in future studies. The information regarding the top five medication that cause adverse events at Banner Specialty Pharmacy-Chandler should only be used as a tool to highlight important counseling points for each of these medications. The hope is that it can be used to insight and act as baseline for future investigations/ quality improvement projects within specialty pharmacy settings.

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Table 1

Average Time Taken to Document Adverse Events

	<i>Pre-Intervention Period (July 2020 to October 2020)</i>	<i>Post-Intervention Period (November 11th, 2020 to March 1st, 2021)^c</i>	<i>p-value^d</i>
<i>Number of Adverse Events^a (N)</i>	33	31	
<i>Time to Document Adverse Events (min/event)^b ($\bar{x} \pm SD$)</i>	12.22±0.83	10.00±2.68	0.032

^a Total number of medication related adverse events for the pre and post intervention periods.

^b Total average time calculated for the pre and post intervention periods.

^c Intervention was started on November 11, 2020 and ended on March 1st, 2021.

^d All p-values are for a student's paired t-test.

Table 2

Top Five Medications at Banner Health Specialty Pharmacy that cause the most Adverse Events

Medication^a (N)	Adverse Reaction Type^b (N)	Severity^d (N;%)	p-value^e
1. Humira (18 events)	Skin allergic reaction (6)	moderate (1; 17%), mild (5; 83%)	0.843
	Infection (3)	moderate (1), mild (1), unknown ^c (1); (33%)	
	GI ^f symptoms (2)	moderate (1; 50%), mild (1; 50%)	
	Other; SOB (1)	mild (1; 100%)	
	Other; neurologic reaction (4)	mild (4; 100%)	
	Other; hematologic (1)	mild (1; 100%)	
	Other; facial swelling (1)	mild (1; 100%)	
2. Enbrel (13 events)	Injection site reactions (3)	mild (2; 67%), unknown ^c (1; 33%)	
	Infection (1)	mild (1; 100%)	
	GI ^f symptoms (1)	moderate (1; 100%)	
	Skin allergic reaction (1)	unknown (1; 100%)	
	Anaphylaxis (1)	mild (1; 100%)	
	Other; neurologic (3)	mild (1; 33%), unknown ^c (2; 67%)	
	Other; cardiac (1)	mild (1; 100%)	
	Other; musculoskeletal (2)	mild (2; 100%)	
3. Capecitabine (9 events)	Skin allergic reaction (3)	mild (3, 100%)	
	GI ^f symptoms (3)	moderate (2; 67%), mild (1; 33%)	
	Other; hepatic (1)	mild (1; 100%)	

	Other; low ANC (1)	moderate (1; 100%)
	Other; flu-like symptoms (1)	mild (1; 100%)
4. <i>Imbruvica</i> (5 events)	GI ^f symptom (1)	moderate (1; 100%)
	Other; cardiac (1)	moderate (1; 100%)
	Other; musculoskeletal (1)	mild (1; 100%)
	Other; anemia (1)	mild (1; 100%)
	Other; respiratory, neurologic, cardiac (1)	mild (1; 100%)
5. <i>Sutent</i> (5 events)	GI ^f symptoms (2)	mild (2; 100%)
	Infection (1)	moderate (1; 100%)
	Other; cardiac, hypotension (1)	mild (1; 100%)
	Other; musculoskeletal (1)	mild (1; 100%)

^a Top 5 medications identified to cause the most adverse events at Banner Health Specialty Pharmacy (170 total adverse events were identified from October 2018 to May 2020).

^b Adverse events for each medication broken down by specific reaction type and number of event.

^c Severity was classified as 'unknown' due to there being no severity that was specified in the Verge data.

^d Severity was classified as either mild (medication discontinuation), moderate (close monitoring), severe (hospitalization), death, or other based on what was selected in Verge when the event was documented.

^e p-value are for a 5X2 Chi square test, comparing the difference in severity of each medication.

^f Gastrointestinal (GI)

APPENDICES

Appendix A: Data Collection Form (Paper version)

ID: _____

1. Medication: _____

2. Sex (requirement in Verge report): Male

Female

3. Adverse Event Type if Medication Use: _____

4. Adverse Event Severity:

Mild (medication discontinuation)

Moderate (close monitoring)

Severe (hospitalization)

Death

Other, please specify _____

5. Health status before ADE (requirement in Verge report):

Poor

Average

Good

Excellent

6. Indication or Use for Medication during Adverse Event: _____

7. Adverse Event Type:

Medication Use

Data Entry Sheet:

	A	B	C	D	E	F	G	H	I	J
1	Medication (1)	Sex (2)	Type of ADEs (3)	Severity of ADEs (4)	Prior Health Status (5)	Indication (6)	Adverse event type (7)	Time taken to report event (8)	Comorbidities (9)	ID Number (10)
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										

Appendix A: Technician Callback Template

<p>Adverse Event Required Callback</p> <p>Patient Name:</p> <p>DOB:</p> <p>Medication Name:</p> <p>Date:</p> <p>Additional Info:</p>

Appendix A: Pharmacist Documentation Tool

Adverse Event Documentation Template for Pharmacists/ Interns	
Drug prescribed: _____	
Side effects or adverse event: _____	
Description of side effects	
Onset (when did it start?):	
Intensity (how severe was the reaction?):	
Duration (how long did it last?):	
Additional comments: _____	
Stopped medication d/t ADEs	Y/N
Inform doctors (is your doctor already aware of the adverse event?)	Y/N
Did event lead to hospitalization?	Y/N
Authorization to disclose PHI when reporting ADEs to manufacture	Y/N
Additional comments: _____	