A Framework for Evaluating the Impact of Prescription Drug Postmarketing Safety Labeling Changes

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WHITE PAPER

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INTRODUCTION

One of the U.S. Food and Drug Administration's (FDA) key functions is communicating the most up-to-date information on a product's safety to ensure that health care providers and patients are making the most informed decisions about their treatment choices. When FDA identifies potential safety concerns with a medical product already on the market, it can take a range of actions to communicate that information, including requiring a change to the product labeling. However, the impact of a safety-related labeling change on key outcomes such as prescriber and patient behavior, utilization patterns, and incidence of adverse events, is often not clear. In order to achieve its public health goals, FDA needs objective and actionable information about the impacts of its postmarketing safety activities.

Under a cooperative agreement with FDA, the Duke-Margolis Center for Health Policy has been working with the Agency to gain a better understanding of the existing literature on postmarketing safety labeling changes and develop a research agenda that can help spur the generation of additional evidence on this topic. As a first step, the Center conducted a review of the existing literature on the impact of safety labeling changes for a variety of drugs.[1]

On February 8, 2018, the Center convened an expert workshop entitled, "Assessing the Public Health Impact of Prescription Drug Postmarketing Safety Labeling Changes." This meeting provided an opportunity for stakeholders to further explore the gaps and limitations in previous research and to identify the research questions, data sources, methods, and outcome measures that could be used to address these gaps. The workshop discussion highlighted the need for additional studies on postmarketing safety labeling changes as well as a potential framework to facilitate this research.

This paper represents both a summary of the discussion at the meeting as well as additional input from a working group of experts from FDA, academia, and industry to develop and implement a collaborative research agenda and a set of best practices for carrying out this research. This document also provides key recommendations and outlines next steps to help FDA advance its understanding of the impact of its postmarketing safety activities.

BACKGROUND

When determining whether to prescribe a drug, health care providers must consider both its benefits and risks. These benefits and risks are described in the drug's labeling (e.g. prescribing information), which is the primary source of information about a drug's established safety and efficacy and is aimed at health care providers.[2] Prescribing information may also include patient package inserts or Medication Guides which are intended for patients. All FDA-approved labeling must be informative and accurate, it must not be promotional in tone, false or misleading, and may need to be updated when new safety information becomes available.[3] Both sponsors and the FDA are responsible for monitoring the safety of drugs after approval and ensuring that the labeling reflects the most up-to-date and accurate information about the safety and effectiveness of a drug.

During drug development, FDA learns about the most common adverse events associated with a drug. The Agency may also become aware of safety signals that merit additional evaluation and scrutiny, which can include pharmacovigilance planning, a Risk Evaluation and Mitigation Strategy (REMS) or postmarketing studies. After approval, FDA may learn about new adverse events as postmarketing experience with the drug, including use among individuals who are unlike those studied in clinical trials, accrues.

When a sponsor or FDA learns of information related to a potential adverse drug reaction or other safety issue, FDA and the sponsor in parallel review the data and evaluate whether there is an emerging safety concern. Once FDA determines the need to address an emerging safety issue, it can take a range of actions to communicate this information to the public. These actions can include issuing Drug Safety Communications (DSC) and Dear Health Care Provider letters, which can be disseminated through a variety of communication channels depending on the audience.[4] FDA may also determine that regulatory action is needed and revisions to key safety sections of the labeling are warranted. The decision to revise the labeling depends on a number of factors including the seriousness of the event relative to the benefits of treatment, the magnitude of the risk, the strength of causality or biological mechanism between the drug and the adverse event, how broadly the drug is used, and the availability of alternative therapies.[5]

Sections of the labeling that may be amended include *Dosage and Administration, Contraindications*, *Warnings and Precautions*, *Adverse Reactions,* and *Drug Interactions*, among others. Each section has its own set of standards that determine which adverse reactions or other potential safety hazards warrant inclusion.[6] A boxed warning may also be added to call attention to the most serious adverse reactions, such as the potential for a fatal, life-threatening or permanently disabling adverse reaction.[7] FDA may also implement additional risk management strategies, require additional postmarketing studies, or issue additional communications.

THE CURRENT LANDSCAPE OF POSTMARKETING SAFETY LABELING CHANGES AND THE NEED FOR IMPROVING THE STATE OF RESEARCH

Changes to prescription drug labeling after approval are common. According to one recent analysis, of the 278 prescription New Molecular Entity (NME) drugs that were approved by FDA between October 1, 2002 and December 31, 2014, at least one safety-related labeling update was added to the labeling of 70% of the drugs studied.[8] The frequency of these changes reinforces the need to better understand their impact in order to protect patient safety as well as provide the best information to patients, providers, and the public. However, there are gaps in existing evidence as well as barriers to conducting research, and it will take a collaborative effort by stakeholders to address these challenges.

Gaps in Existing Evidence on Postmarketing Safety Labeling Changes

A small number of literature reviews have been conducted to evaluate the evidence related to the impact of postmarketing safety labeling changes (including FDA safety communications) on prescription drug use and other health outcomes.[9,10,11] The results of these reviews varied, with some studies observing significant associations between the labeling change and the outcome of interest, and others finding no significant associations. These reviews have also noted several important gaps in the literature.

Few studies assessed outcomes beyond use of a targeted drug or drug class. For example, few studies examined treatment outcomes or the effects of labeling changes on medication switching.[12]
Few studies evaluated how FDA safety issues are communicated and how this impacts patient-provider communication.[13] There is also a lack of studies examining how new safety issues are disseminated to patients and health care providers, and how these and other stakeholders use this information.

A majority of studies that assessed labeling updates focused on the additions of boxed warnings; however, only approximately 9% of labeling changes relate to boxed warnings.[14, 15, 16] There are few studies examining other sections of the labeling such as the *Warnings and Precautions* and *Adverse Reactions* sections, though these sections are the most frequently updated.[17] Other changes to the labeling, such as the effects of monitoring recommendations, are often not well characterized. Most studies have been limited to a narrow range of drugs, such as antidepressants and antipsychotics.[18,19,20]

There have not been many studies employing rigorous research designs and analytical methods to evaluate FDA's actions on postmarketing safety labeling changes. Most studies to date have not relied on the standard designs used in policy analysis or economic evaluation. Instead, these studies have relied on descriptive statistics or regression models that did not have adequate controls.[21] However, there has been a shift to employing more rigorous approaches, as evidenced by recent studies.[22,23]

Finally, few studies have evaluated the unintended consequences and spillover effects associated with FDA labeling changes. Some studies have detected the potential for unintended consequences such as decreased use of the drug in a non-indicated population, substitute prescribing, and negative health outcomes. [24,25] However, these examples are limited, and the potential for unintended consequences is of great interest to FDA, public health experts, and the research community. The potential impact of unintended consequences is illustrated in the case example relating to labeling changes made to the drug Chantix (see sidebar).

Potential Unintended Consequences of FDA Risk Communications: Chantix

Smoking is the leading cause of preventable death and disease in the United States. In 2006, the drug Chantix (varenicline) was approved to treat nicotine addiction. However, in 2008, there were reports of an increased risk of serious neuropsychiatric side effects.[1] These safety data led FDA to issue a boxed warning in 2009, noting changes in behavior and suicidal thoughts when using the drug.[2] In the years following the boxed warning, researchers observed a considerable decline in Chantix utilization.[3]

While the drop in utilization may have been an intended goal of the boxed warning, how the drop in utilization impacted public health is unknown. After the introduction of Chantix, there was a corresponding increase in quit attempts and use of Nicotine Replacement Therapies (NRTs). After the introduction of the boxed warning, the use of Chantix declined, while the use of other NRTs remained the same, indicating that those smokers who were using Chantix may not have switched to other therapies.[4] This warning may also have resulted in unintended consequences. Studies have shown that Chantix has better long-term cessation rates compared to other NRT monotherapies.[3] However, doctors were less likely to prescribe this therapy following the warning, meaning that some smokers may not have been using a therapy that could have been most effective for them.[3] These outcomes highlight the need to better understand how labeling changes can impact heath care choices and decision-making.

[1]http://wayback.archive-it.org/7993/20161022204614/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051136.htm

[2]http://wayback.archive-it.org/7993/20161022204520/http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm169988.htm

[3]Shah et al., Trends in utilization of smoking cessation agents before and after the passage of FDA boxed warning in the United States. Drug and Alcohol Dependence. 2017. 177: p.187-193.

[4]Kasza et al., Use of stop-smoking medications in the United States before and after the introduction of varencline. 2014. Addiction 110: p.346–355.

Barriers to Conducting Research on Postmarketing Safety Labeling Changes

The gaps in the existing evidence on postmarketing safety labeling changes are compounded by the challenges to conducting research on this topic. It can be difficult for researchers to access and aggregate the necessary data to perform these analyses. Researchers cannot always gain access to certain databases because they are often proprietary and/or cost-prohibitive to utilize. Depending on the research question, the data required for an analysis may be located across several databases and systems, which may be challenging to externally link.[26]

Most postmarketing studies to date rely on pharmacy, medical, and insurance claims data due to their ready availability, large size, and representativeness of routine clinical care.[27] However, there are limitations with these datasets. For example, when evaluating changes in the use of prescription drugs, most databases only provide information on filled drugs. Therefore, researchers are unable to tease apart prescriber behavior (a reduction in the writing of prescriptions for a drug) and patient behavior (the patient received a prescription, but chose not to fill it due to safety or cost concerns). Furthermore, claims data may not allow researchers to grasp all the possible effects of a labeling change. In order for a record to be generated, there must be an encounter with the health care system that is accompanied by a diagnosis, procedure, or prescribing of medicines.[28]

There are also issues surrounding the use of patient-level data. There are ongoing data privacy concerns, including difficulties navigating HIPAA as well as pre-identification risks, which will continue to make the use of patient-level data challenging. However, patient-level data is not always necessary and researchers can focus instead on population-level effects.

To capture the full spectrum of outcomes associated with a labeling change, it may require linking multiple data sources. For example, linking claims data to other data sources, such as registries, electronic health records, and other relevant sources. These might be achieved through big data-sharing networks like FDA's Sentinel System, the National Patient-Centered Outcomes Research Network (PCORnet), the Observational Health Sciences and Informatics (OHDSI) program, the National Institutes of Health's Collaboratory Distributed Research Network (DRN), and the Health Care Systems Research Network (HCSRN).

Research on this topic is further complicated by the fact that FDA risk communications do not exist in a vacuum. Before issuing a labeling change, FDA reviews the safety issues and communicates the potential risks through different mechanisms, including DSCs, press releases, Dear Health Care Provider Letters, and via other media channels. Therefore, it is difficult to isolate the direct impact of a labeling change from other sources of information that can influence prescribing behavior—such as drug safety related publications, various FDA's post-market safety communications, and media coverage—as described in the case study of Ambien (see sidebar).

For practical and ethical reasons, FDA cannot randomize patients and providers into different groups, in which one receives communication on labeling changes while the other group does not. Therefore, the use of treatment and control groups to study labeling changes is precluded in most situations. The inability to use this type of experimental design makes it difficult to understand if an intervention, in this case the labeling change, causally relates to outcomes. However, there are some promising methods that can be applied in real-world settings, which are discussed in further detail in the Research Design Considerations and Selecting Appropriate Methods sections.

How Information Channels Can Mediate the Effects of Labeling Changes: Ambien

In 2013, FDA issued two DSCs regarding drugs containing the sleep aid Ambien (zolpidem) because of concerns about dangerous next-day drowsiness. The first DSC, issued in January 2013, was followed by a great deal of media coverage.[1] In May 2013, FDA issued a second DSC, which confirmed the content included in the first DSC and added formal changes to the drug's labeling that included an additional warning about next-day driving impairment for the extended-release version of the drug.[2] However, there was significantly less traditional media[1] and social media coverage[3] following the second DSC.

The surrounding media coverage and the way it was transmitted to the public illustrates that communications can have varying impacts on patients and prescribers. More media coverage was followed by a greater response from stakeholders. For example, after the first DSC, there was a decline in high dose prescriptions and an increase in low dose prescriptions, consistent with the content of the first DSC,[4] while there were no additional dispensing changes observed after the second DSC.[4] However, recommendations concerning next-day driving impairment were not reported widely[1], and extended-release dispensings did not change after the second DSC/labeling change.[4] This demonstrates that FDA's press release, DSC, and media coverage can have a stronger effect on patient and prescriber behavior than the labeling change itself. However, because the labeling recommendations were mediated through a variety of channels and sources, it makes it difficult to tease out which elements were having the greatest impact.

[1] Woloshin, S., et al., Media Coverage of FDA Drug Safety Communications about Zolpidem: A Quantitative and Qualitative Analysis. Journal of Health Communication, 2017. 22(5): p. 365–372.

[2] FDA Drug Safety Communication: FDA approves new labeling changes and dosing for zolpidem products and a recommendation to avoid driving the day after using Ambien CR. May 14, 2013.

[3] Sinha, M.S., et al., Social Media Impact of the Food and Drug Administration's Drug Safety Communication Messaging About Zolpidem: Mixed-Methods Analysis. JMIR Public Health Surveill, 2018. 4(1).

[4] Kesselhim, A.S., et al. Changes in prescribing and healthcare resource utilization after FDA Drug Safety Communications involving zolpidem-containing medications. Pharmacoepidemiology and Drug Safety, 2017. 26: p. 712–721.

Finally, securing funding can also be an issue for this research, which is perceived to be of interest to FDA or industry, rather than NIH and other government agencies that typically fund health services research. In addition to the funding needed to access certain databases, there must be adequate funding to cover researchers' time when performing these analyses.

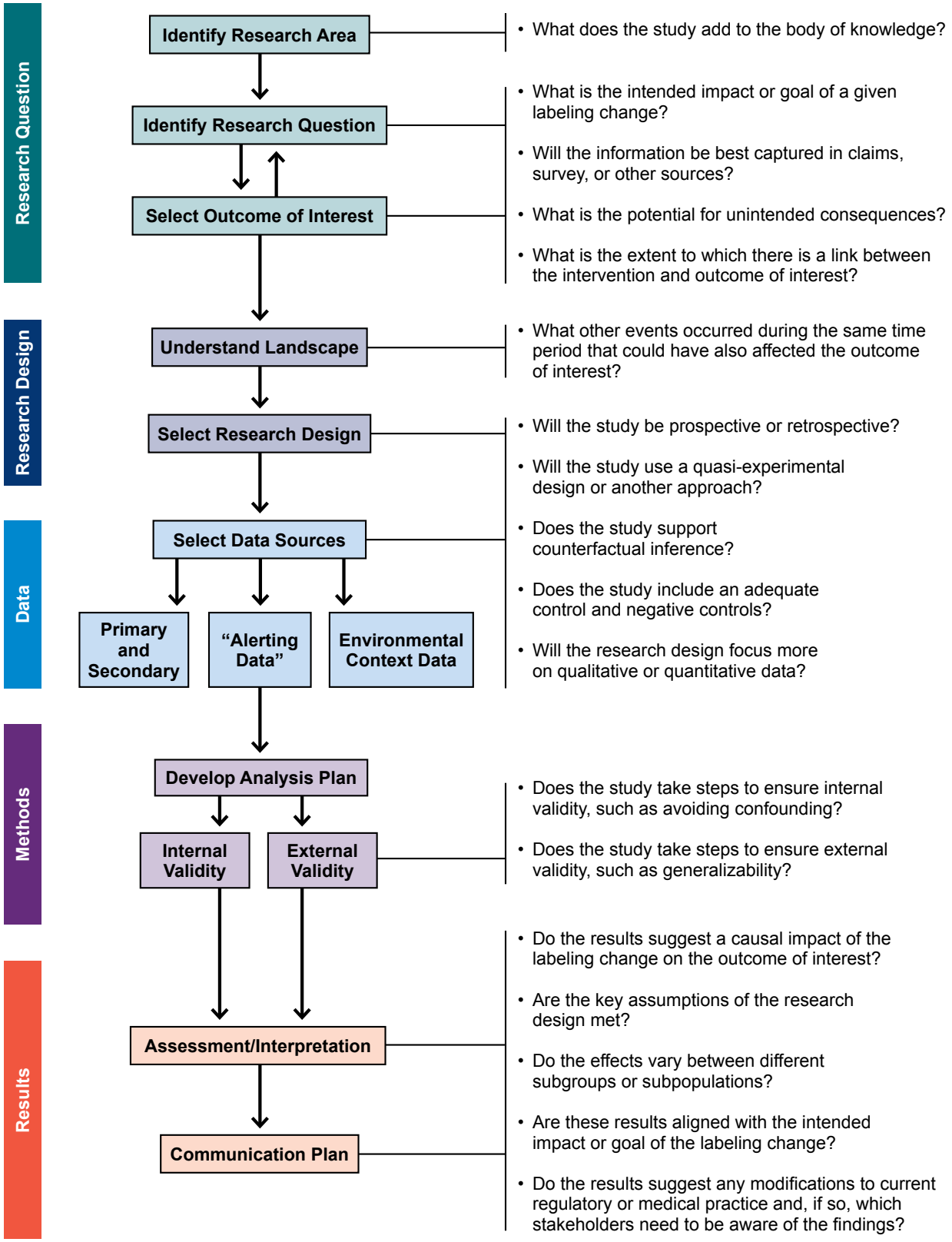
IMPLEMENTING A COLLABORATIVE RESEARCH AGENDA TO EVALUATE THE IMPACT OF POSTMARKETING SAFETY LABELING CHANGES

For many of the reasons highlighted above, there is a clear need for more high-quality research on the impact of postmarketing safety labeling changes. It will be important for stakeholders to coordinate on a broader research agenda and the related research questions, data, and methods, which will drive research in this field forward.

Best Practices: A Framework for Evaluating Postmarketing Safety Labeling Changes

The development of this research agenda is a first step in guiding researchers to undertake a variety of individual studies. **Figure 1** outlines best practices in study design and demonstrates the process from identifying the research area to the final step of communicating results. It is important to note that this is an iterative process and no factor should be considered in isolation. Each step in the process is described in further detail on page 8.

Figure 1: Framework for Evaluating Postmarketing Safety Communication and Labeling Changes



Identifying a Research Area

One of the primary tasks to obtain better information about the impact of a safety labeling change is to determine where there is the greatest research need. While the list in **Table 1** is not exhaustive, it highlights clear gaps in existing evidence and how new research would add to the body of knowledge on labeling studies.

Table 1: Research Areas that Warrant Further Exploration

RESEARCH AREAS OF INTEREST	RATIONALE FOR STUDY
Expanding the class and type of drugs under examination	Impact of safety messages may vary by clinical/therapeutic area or type of risk.
Expanding the types of labeling changes evaluated beyond boxed warnings	Boxed warnings are commonly studied but not the most common form of changes to labeling.
Understanding the impact of descriptions within labeling sections (both on patients and on physicians), such as monitoring recommendations	There is often low compliance with monitoring recommendations, which may not lead to the intended health outcome set out by the labeling change.
Evaluating the unintended consequences of a labeling change	Unintended consequences have been observed in some studies,[29,30] but the effects on health outcomes and how best to mitigate these effects are not well understood.
Understanding the extent to which labeling changes affect formularies and payer coverage policies	Potential effects on formularies and payer coverage policies have not been frequently studied and it is unclear what the downstream impacts of these changes may be on other outcomes, such as utilization.
Understanding whether and how labeling information is used by patients as part of decision-making and whether this varies with patient characteristics	How different types of patients respond to labeling changes has not been well-characterized and discrepancies may lead to unintended consequences.
Understanding the impact of how channels of communication impact patient, provider, and payer decision-making	Different communication channels may shape the messaging around postmarketing safety labeling changes and result in varying stakeholder responses.

Defining Research Questions and Outcomes of Interest

There are some key considerations researchers should keep in mind when selecting research questions and relevant outcomes. Principally, researchers should select the outcome based on the goals or intended impact of a given labeling change. We recommend below that FDA make more explicit the intended impact of a labeling change or related risk communications going forward. This outcome can then be refined later (if needed) based on the availability of data and any funding limitations. Another primary consideration is the extent to which there is a link between the intervention and outcome of interest. Importantly, researchers should consider the potential for unintended consequences. Detecting unintended consequences will illuminate whether the labeling change is having an unintended or spillover effect, which may have implications for the wider health care system and public health overall. **Table 2** delineates potential outcomes of interest depending on the impact area as well as the sources

of data that can be used to assess those outcomes. While this table is not exhaustive, it showcases the range of outcomes that could be studied by stakeholders.

Table 2: Potential Outcomes When Assessing the Impact of a Labeling Change

IMPACT AREAS	OUTCOME EXAMPLES	DATA SOURCE EXAMPLES
Utilization Patterns	• Prescription filled • Treatment switching or substitution • Discontinuation • Adherence	• Claims • EHRs • Pharmacy Only Data • Wearables or mHealth Devices • Registries (e.g. patient, disease state, drug) • Qualitative Interviews • Survey Data (targeted)
Prescriber Behavior	• Awareness of FDA labeling change or related communications • Prescribing in targeted population • Prescribing in non-targeted population • Perceptions of benefits and risks • Substitute prescribing • Compliance with clinical/laboratory monitoring recommendations	• Claims • Pharmacy Only Data • EHRs • Clinical Lab Data • Diagnostic Data • Qualitative Interviews • Survey Data (targeted)
Patient Behavior	• Awareness of FDA labeling change or related communications • New starts versus prevalent users • Perceptions of benefits and risks • Characteristics of patients using the drug (e.g. health or socioeconomic status)	• Claims • Pharmacy Only Data • EHRs • Clinical Lab Data • Diagnostic Data • Qualitative Interviews • Survey Data (targeted)
Treatment and Health Outcomes	• Disparities in treatment • Adverse event incidence • Adverse event reporting • Decrease in detection	• Claims • EHRs • Registries (e.g. patient, disease state, drug) • Adverse Event Reporting System Data • Wearables or mHealth Devices • Clinical Lab Data
Organization Behavior	• Changes to formularies • Changes to coverage • Communication with providers • Communication with patients • Changes in prescribing rules • Decisions about formulary placement, prior authorization, step therapy • Policy changes • Cost of care	• Insurance Plan • Formulary Files • Qualitative Interviews • Survey Data
Unintended Consequences and Spillover Effects*	• Prescribing in non-targeted populations • Prescribing less effective or less safe alternative therapies • Changes in other health outcomes besides the one targeted as a result of changes in prescribing • Discontinuation of treatment (non-targeted therapies and populations) • Impact on health outcomes (rise or decline in disease rates)	• Claims • EHRs • Pharmacy Only Data • Qualitative Interviews • Survey Data

Understanding the Landscape of the Labeling Change

After identifying the potential research question(s) and outcome(s) of interest, a key next step is understanding the context in which the labeling change occurred. Specifically, it is important to determine what other events were occurring during the same time period that could have also affected the outcome of interest. For example, drug shortages, updates to insurance plan formularies, updates to clinical practice guidelines, the availability of treatment alternatives, and other regulatory changes may be driving the response rather than the change to the labeling; this is especially true as more time passes since the change.

It is also essential to have a clear sense of the flow of information around safety communications and who was targeted by this information. For example, if two DSCs were issued, the second of which communicated changes to the labeling, it is necessary to ascertain at which time points the information was communicated, the content included in each communication and how it may have differed, and whether patients, providers, or other stakeholders were the target of those communications. Understanding all the aspects at play is a necessary first step in ensuring that the study is taking into account all potential confounding factors.

Research Design Considerations

Once the research question has been chosen and the landscape in which the labeling change occurred is clarified, a robust research design will help guide the rest of the components of the study. A key research design consideration is whether the study will be prospective or retrospective. In general, these types of evaluations use retrospective study designs. FDA enacts a labeling change and communicates this information to the public; subsequently, researchers evaluate how that labeling change impacted a specific outcome of interest. However, some researchers have suggested increasing the frequency of prospective studies, where researchers are evaluating the impact of a labeling change in close to real time. This may be an opportunity for FDA to understand how the public is reacting following the labeling change, and make adjustments if there are unintended consequences resulting from the labeling change.

Another important consideration for researchers during the design stage is whether they will evaluate the impact of a labeling change by examining health system behavior or patient-generated or provider-generated outcomes. For example, if the goal of a potential study is to examine whether new recommendations in the *Dosage and Administration* section of a labeling led to changes in prescribing, this information will be evident in data generated by health systems, such as claims or EHRs. However, if the goal is to understand *why* prescribers altered their prescribing, such as to understand their perceptions of risk following this change, a patient-or-provider approach may be needed, which may necessitate primary data collection from surveys or interviews. Both of these approaches are retrospective (i.e., after the occurrence of the outcome of interest), but the time frame for analysis may

be shorter for the patient-or-provider approach as primary data collection can happen relatively quickly and should be carried out quickly as memories fade and the reliability of recall declines. Data generated by health systems will take longer to analyze as there is a time lag before it is populated in databases. There is also the possibility for incorporating multimodal approaches, utilizing both primary and secondary data, also known as hybrid study design.

Definitions

Quasi-experimental design: Study design used to evaluate the impact of an intervention on a target population by taking advantage of real-world conditions that approximate random assignment.

Counterfactual inference: A modeling approach which also estimates what would have happened in the absence of an intervention. Counterfactuals are used for understanding whether an effect is causal rather than correlational.

For labeling changes, the use of experimental designs and randomization is usually not possible. In the absence of randomization, quasi-experimental designs are most applicable. Quasi-experimental designs that have strong internal validity and support counterfactual inference about what would have happened in the absence of FDA regulatory action may be the best approach to evaluate the impact of a labeling change.[31] Some examples of these designs include interrupted-time series, segmented regression, and difference-in-differences, which can be particularly useful for analyzing utilization patterns. However, there are a range of quasi-experimental designs, and some of these, such as pre- and post- designs, do not have control groups. Incorporating experimental design elements such as control groups and comparison groups can strengthen the research if there is a pre-existing evidence base. However, identification of appropriate controls in pharmacoepidemiologic studies of drug safety communications can be complex. Researchers should include control exposures and/or control outcomes (both positive and negative) to the extent possible to ensure their findings are robust.[32] For some labeling changes, if there are untargeted populations, these may be used as a control or comparison group (although the potential for spillover effects should be carefully considered).

Data Sources, Accessibility, and Use

Identifying the appropriate data required for an analysis will depend on the outcome of interest and research design, but some general principles apply. There are three types of data: 1) “alerting data” which captures how a stakeholder became aware of a labeling change (e.g. traditional media/press, social and online networks, professional societies, payer and provider information about coverage and use, and manufacturer marketing and promotional activities); 2) data that capture the environmental context – specifically, what other events could be happening at the same time that could be impacting outcomes; and 3) data that reflect how the stakeholder reacts to the labeling change (e.g. changes in prescribing behavior, utilization, and reimbursement). This type of data is often captured in large administrative datasets and is typically the primary source for most labeling change analyses, while alerting data and environmental context data are often not included.

Alerting data is a key and necessary element of any analysis as it corresponds to understanding the landscape of the labeling change mentioned above. Where and how stakeholders learn of a labeling change may impact their understanding and actions in response to the labeling change. Alerting data can be used to identify when and how a communication, including a labeling change, was disseminated, as well as specific details of the communication or labeling change itself. Selection of alerting data may also be used to consider who might be impacted by a communication. For example, if FDA issued Dear Health Care Provider Letters to specialists treating patients who would likely be impacted by a labeling change, one approach may be to survey specialists about their response to the communication to understand the effect of the labeling change. Alerting data should be considered in the design of any study, though it may not be available for inclusion as part of the evaluation.

Data that capture the environmental context also relate to understanding the landscape of the labeling change. These data account for other events that might be happening concurrently and could influence the outcome of interest. Therefore, these data can be used to minimize confounding later in the analysis. For example, they may help to explain unusual patterns in secondary data, such as what led to unexpected changes in utilization that are not clear solely by examining the secondary data. Events such as a drug shortage could be driving utilization of another drug, which would only be made evident by evaluating the environmental context.

Finally, stakeholder response data are the most common type of data used in labeling change studies and often come from secondary data sources (e.g. claims, EHRs, registries). Data that is used to evaluate labeling changes may also be obtained through primary data collection methods such as surveys, interviews, and Patient Reported Outcomes (PROs). Furthermore, patient supported networks, such as PatientsLikeMe and Patient-Powered Research Networks (PPRNs) that are part of PCORnet, have data that is mostly derived from patient self-reports and could provide additional context on the impact of a labeling change.

Regardless of data type, some key factors to consider when determining whether to employ a dataset are potential anomalies in the data, whether it includes a representative patient population, and whether the proposed outcomes are captured in the dataset. Furthermore, researchers may also perform exploratory data analysis on the dataset, which may include plotting out trends or examining distributions over time in key variables. This exercise may ultimately influence the research design. For example, it may help illuminate what time period to use when dividing the analysis into pre- and post-periods. **Table 3** outlines various types of data available and provides examples of some sources where these data can be accessed, though these examples are not exhaustive.

In addition to the sources mentioned above, there are opportunities to better leverage the existing data infrastructure. FDA's Sentinel System, the Observational Health Sciences and Informatics (OHDSI) program, and other tools are now more readily available for proactive monitoring and close to real-time assessments, rather than just retrospective analysis.

Table 3: Data for Evaluating Labeling Changes	
DATA TYPES	**DATA SOURCE EXAMPLES**
Clinical Data (Secondary)	• Claims • EHRs • Pharmacy • Registries (e.g. patient, disease state, drug) • Patient-generated Data • Wearables or mHealth Devices • Clinical Lab Data • Diagnostic Data
Individual Data (Primary)	• Surveys (patient and prescriber targeted) • In-Depth Individual or Focus Group Interviews • PROs
Other Data (Secondary)	• Poison Control (National Poison Data System) • Department of Motor Vehicles (DMV) • Accident Data (National Highway Traffic Safety Administration)
Alerting Data	• Social Media • Traditional Media • Medical Journals and Websites • Professional Societies
Environmental Context Data	• FDA or ASHP Drug Shortage Website • Medwatch • Insurance Policy Data • Professional and Advocacy Organization Recommendations • Therapeutic Area/Treatment Guidelines

Selecting Appropriate Methods

The methods selected will be driven in large part by the research design, but nevertheless, there are a number of challenges and analytical considerations that must be addressed when selecting a method for any study. One of the key components of the design is identifying the counterfactual. If possible, researchers should be able to describe what would have been the outcome had the labeling change not occurred, as this is an important aspect of conducting causal inference. However, because experimental design and randomization is typically not possible, a number of problems may arise in measuring the counterfactual, including the potential for confounding factors.

There are two types of confounding factors – measured and unmeasured. Confounding occurs when characteristics or events that may be affecting the outcome are not properly controlled for, leading to biased or skewed results. Importantly, these excluded factors must be correlated with the event that is being studied. Measured factors typically include patient characteristics (e.g. age, sex), demographic characteristics (e.g. income, education) and health status (e.g. disease progression, comorbidities). Measured factors can also include other elements that may have impacted the control and treatment groups differentially, such as media coverage of safety concerns for the drug or change in the practice of medicine for a disease area. For example, if the use of a drug declines after a warning is added to a

labeling, it can be difficult to determine if a decline in patient use is directly related to the warning or if some other event might be driving outcomes, such as decreases in prescribing for other non-targeted indications or recent approval of an alternative treatment. Understanding whether these or other events may be driving outcomes may require engaging appropriate clinical partners to determine which outcomes are the most important to consider.

When confounding variables are not adequately adjusted for during either the design or analysis phases of a study, unmeasured confounding can arise.[33] This may occur when researchers are unaware of the existence of the confounding variable or the data for this variable were unavailable during the data collection phase of the investigation. These issues can be implicitly controlled by methods such as instrumental variable analysis, pre- and post- comparison of outcomes between individuals within the same groups, propensity score matching, fixed effects, as well as by having a strong control group.

The key analytical considerations mentioned thus far mainly assume that secondary data will be used. These do not account for primary data sources, such as surveys and interviews. Surveys and interviews can be particularly useful to gain insight into stakeholders' perceptions of labeling changes and motivations behind certain kinds of behavior.[34] However, like secondary analysis, there are potential threats to validity that must be addressed, such as self-reporting bias, which includes both recall and social desirability bias, as well as interviewer bias.[35,36]

Best practices for research design and the key design principles that must be addressed in the model are summarized in **Table 4**. (Note that approaches suggested for each modeling principle are not mutually exclusive.)

Table 4: Best Practices for Research Design

MODELING PRINCIPLES	HOW TO ACCOUNT FOR FACTORS IN THE MODEL
Ensuring Internal Validity	
Minimizing risk of time-varying and baseline confounding	• Approximating the counterfactual using robust research designs • Incorporating a control group • Using multivariate analysis to adjust for additional factors • Sensitivity analyses
Minimizing selection and channeling bias	• Sample selection correction • Incorporating additional controls • Propensity score matching
Minimizing information and self-reporting bias • Recall bias • Social desirability bias	• Conduct interview or survey close to real time • Interview a subsample prior to initiating the study (validated subsample) • Validation of self-reporting instrument
Minimizing interviewer bias	• Blind interviewer to group assignment
Ensuring External Validity	
Minimizing selection bias	• Using a representative patient population to ensure generalizability

In addition to traditional survey and interview methods, evaluations to understand how people respond to and interpret different types of information could be helpful as FDA continues to assess the most impactful ways to accurately convey and communicate labeling changes to achieve their public health goals. For example, conjoint analysis (or other stated preference methods) can be used to assess how people respond to specific labeling changes, and how language or the way information is displayed affects people's choices.[37] Like other approaches, these methods have limitations that should be considered when carrying out a study.[38,39]

Researchers may also want to consider employing multiple methods wherever possible to ensure that results are robust. Studies that use an integrated multimodal approach may offer greater insight to regulators and a more complete view of FDA advisory impacts. These include combining the following: quantitative and qualitative traditional and social media analyses; direct interviews with patients and physicians; national surveys of patients; and analysis of utilization patterns and related health outcome trends.[40] Combining these approaches with a comparative analysis of a similar drug that was not impacted by the labeling change would provide a more complete picture of the impacts of a labeling change.

Assessment and Communication Plan

The assessment and interpretation of results is an opportunity to reflect on the strength of the study. In the discussion, researchers should explore any inferences about a causal effect of the labeling change on the outcome of interest. This inference should be based on a variety of factors including the strength of the relationship, temporal relationship, plausibility of alternative theories, as well as potential biases and confounding.[41] Another important element to evaluate in the assessment is whether the key assumptions of the research design were met and if not, how that might impact the results. Researchers should also assess whether the results were aligned with the intended impact or goal of the labeling change. If not, then it is important to consider how they differ and what the effect of that difference might be on health outcomes and public health.

The answers to these and other questions must be part of a communication plan to ensure the results are imparted to relevant stakeholders. For example, if the impacts of a labeling change have resulted in unintended consequences, FDA should be informed of those results so that this evidence can inform FDA's continued assessment of the product's risks and benefits and further development of risk management strategies. To facilitate information sharing, FDA could consider amending the "Contact FDA" section for future DSCs, or another part of the FDA website, to create a mechanism, for example a monitored email inbox, for obtaining input from researchers and clinicians about the potential or actual safety impact of a labeling change. If the results suggest any modification to current medical practice, then other stakeholders should be made aware of these findings, such as clinicians, professional societies, health care institutions and payers as they may use this information as part of their decision-making. Similarly, if the results have implications for current policy, lawmakers or agencies such as CMS

may need to be made aware of the findings to evaluate whether there are potential downstream effects.

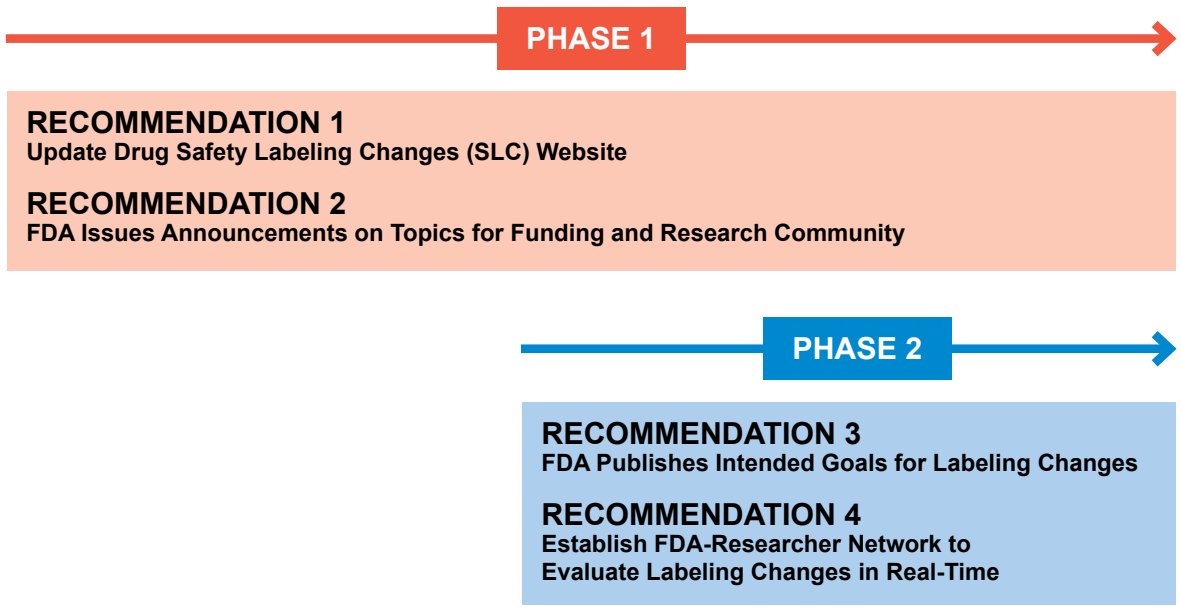
OUTLINING ROLES AND NEXT STEPS FOR STAKEHOLDERS

The process outlined in **Figure 1** clarifies and explains best practices when performing research on the impact of postmarketing safety labeling changes. However, to further improve the state of research, FDA and other stakeholders will need to take additional steps to move this field forward.

Figure 2 provides a roadmap for next steps and each recommendation is outlined in more detail in the following section. Acknowledging that some of these steps would need to take place before others, the roadmap takes a phased approach. Phase 1 recommendations could commence almost immediately and could be introduced within one to two years. Phase 2 recommendations will likely require more investment and time to initiate and may take at least three to five years to get underway. Importantly, this roadmap does not indicate that the work is complete once a recommendation has been launched. The steps laid out in the recommendations are ongoing, and will need to be consistently re-evaluated and refined to ensure that they are serving the needs of all stakeholders.

Stakeholders that have a role in this effort include regulatory experts, including FDA and other agencies, public health experts, funders, clinicians, payers, patient advocates, academic researchers, and industry members. While FDA does serve an important function in many of these recommendations, it is incumbent upon the rest of the stakeholder community to assist the FDA in advancing these recommendations.

Figure 2: Roadmap for Next Steps on Evaluating the Impact of Postmarketing Safety Labeling Changes



Recommendation 1: Update Drug Safety Labeling Changes (SLC) Website

Improvements to FDA's Drug Safety Labeling Changes (SLC) website will facilitate and encourage more research on safety labeling changes. Stakeholders have expressed difficulty finding all the information relating to the history of labeling changes for any particular drug. The current system is not easily navigable, especially since much of this information is archived on the MedWatch website. Potential enhancements to the website may include—

- A revision of the current system to include all the basic information about labeling changes for a drug application in one place. This would include a list of all labeling changes for a drug, the cause, source, and contents of the labeling changes, the dates those changes were issued, and if FDA is planning a re-evaluation of the changes in the future.
- The provision of information on how the labeling changes were communicated to stakeholders. This would include where and how the safety labeling message was disseminated (e.g. DSCs, Dear Health Care Provider Letters, etc.), when it was disseminated, through what channels (e.g. social media, trade press, etc.), and who was the intended audience of the communication. Having links to or copies of the correspondence would be useful as well.
- The provision of information in a downloadable format that can be integrated into an analysis database. Drug-specific information would ideally be available in a linkable format such as by National Drug Classification (NDC) code and with product names.

Recommendation 2: FDA Issues Announcements on Topics for Research Community

As there are limited resources for research, stakeholders should work together to establish which research questions pertaining to drug safety labeling changes are most important to FDA or what information the Agency would find most useful. FDA could hold a public meeting to bring together external stakeholders, including researchers, clinicians, industry representatives, payers, and patients to determine in which topic areas research is most needed. These might include certain classes of drugs, specific kinds of labeling changes, or responses by various stakeholder groups to the labeling changes, among others.

Subsequently, FDA could release public announcements on topics that potential funders and the research community should prioritize for research. This information could be disseminated through the Broad Agency Announcement (BAA) process. FDA may use BAAs to list opportunities for research and solicit proposals to carry out this research. This mechanism would encourage research in particular areas of interest and provide funding to researchers.

Recommendation 3: FDA Publishes Intended Goals for Labeling Changes

Researchers have expressed interest in wanting more clarity on FDA's goals when it enacts labeling changes or issues safety advisories. Researchers could work with FDA in order to better understand the intended goal or impact of a labeling change. At the time of a labeling change or a communication, FDA could consider stating the goals or expected outcomes from a particular advisory. This would enable researchers to directly evaluate research questions about the impact of labeling against the goals set by the Agency and assess whether those goals were met. Moreover, this would provide FDA with more actionable information on how to improve labeling changes going forward.

FDA could also provide additional information that may be of use to researchers. For example, insight about the threshold of substantial evidence supporting the decision to recommend a labeling change, particularly as different studies and data sources will have been utilized by FDA to make the regulatory decision.

Recommendation 4: Establish FDA-Researcher Network to Evaluate Labeling Changes in Real-Time

The most ambitious part of this framework is to set up a network or consortium of experts that could work with the Agency to study and evaluate labeling changes in as close to real time as possible. For example, if the Agency is seeking to understand the impact of a specific boxed warning, it can reach out to this group once the labeling change has been released to ensure that members of the group will track stakeholder response to the boxed warning. If the boxed warning is not having its intended effect or if there are spillover effects, the Agency can more swiftly take steps to remedy the situation.

This group would serve three important functions. After a labeling change has been released, 1) it would provide real-time feedback on the outcome of a labeling change and would determine if it aligns with FDA's intended goal; 2) it would help FDA systematically understand how labeling changes affect the health system and whether there are best practices that can lead to the desired impact of a labeling change; and 3) it would communicate the results and information back to FDA to ensure that the Agency takes steps to improve its messaging going forward. In order to fulfill these functions and provide actionable feedback quickly, consortium members will likely need to utilize a mix of primary data, which can be obtained fairly quickly, and secondary data that is available in near real-time, such as EHRs. Secondary data such as claims could be used for follow-up after the initial primary data collection is complete.

This consortium of experts could be comprised of different organizations or individuals who have particular expertise in the field and who have a history of performing these types of analyses. This consortium may consist of an entirely new network or could potentially be a subgroup of an existing consortium. For example, FDA may be able to leverage established relationships with Sentinel Collaborating Institutions to measure the impacts of safety-related labeling changes on key outcomes.

These academic partnerships, maintained through the Agency's Sentinel Initiative, can enable FDA to capture and analyze near real-time safety data on medical products and use these data to improve decision-making. This arrangement would require resources from FDA to allocate staff time for being a part of this consortium. Moreover, the Agency would have to take steps internally to decide what types of labeling changes or messaging warrant this kind of analysis. It is unlikely that every labeling change would merit such an analysis, nor would there be the resources to execute such an undertaking.

Funding and Resources

An important issue that will need to be addressed early on is securing funding and resources to move each recommendation forward. For the first three recommendations, it will likely be possible to leverage existing FDA resources. However, for *Recommendation 4* in particular, new funding and resources will be required. FDA may consider putting forward requests for proposals (RFPs) to study specific advisories or topics. They may also consider having committed funds that can be provided to the consortium for rapid investigations proposed as part of *Recommendation 4*, given the importance of collecting data in near real-time for such evaluations.

CONCLUSION

Postmarketing safety labeling changes are an important mechanism for promoting the safer use of drugs and biologics and providing the most up-to-date information to patients and health care providers about a product's risks. However, given the inherent uncertainty surrounding emerging safety concerns that may prompt labeling changes, more research is needed to understand fully the effects of these labeling changes on patients, practitioners, and the health care system. The framework and best practices outlined in this document provide an opportunity to improve the state of research and encourage stakeholder collaboration on this topic. Implementation of the recommendations in this paper will help FDA better understand the impact of its postmarketing safety labeling activities and, ultimately, support the effective delivery of safety information to patients and providers.

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[1] Unpublished Duke-Margolis Center for Health Policy Literature Review: *FDA Postmarketing Safety Labeling Changes: What Have We Learned Since 2010 About Impacts on Drug Utilization and Treatment Outcomes?*

[2] U.S. Food and Drug Administration, *Guidance: Drug Safety Information – FDA's Communication to the Public* 2007.

[3] U.S. Food and Drug Administration, *Guidance: Drug Safety Information – FDA's Communication to the Public* 2007.

[4] U.S. Food and Drug Administration, *Guidance: Drug Safety Information FDA's Communication to the Public* 2007.

[5] U.S. Food and Drug Administration, *Guidance: Drug Safety Information – FDA's Communication to the Public* 2007.

[6] U.S. Food and Drug Administration, *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* 2011.

[7] U.S. Food and Drug Administration, *Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* 2011.

[8] Pinnow, E., el at., *Postmarket Safety Outcomes for New Molecular Entity (NME) Drugs Approved by the Food and Drug Administration Between 2002 and 2014.* Clin Pharmacol Ther, 2017.

[9] Dusetzina, S.B., et al., *Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review*. Med Care, 2012. 50(6): p. 466-78.

[10] Briesacher, B.A., et al., *A critical review of methods to evaluate the impact of FDA regulatory actions*. Pharmacoepidemiol Drug Saf, 2013. 22(9): p. 986-94.

[11] Unpublished Duke-Margolis Center for Health Policy Literature Review: *FDA Postmarketing Safety Labeling Changes: Assessing the Impact on Drug Utilization and Treatment Outcomes*

[12] Dusetzina, S.B., et al., *Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review*. Med Care, 2012. 50(6): p. 466-78.

[13] Dusetzina, S.B., et al., *Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review*. Med Care, 2012. 50(6): p. 466-78.

[14] Dusetzina, S.B., et al., *Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review*. Med Care, 2012. 50(6): p. 466-78

[15] Briesacher, B.A., et al., *A critical review of methods to evaluate the impact of FDA regulatory actions*. Pharmacoepidemiol Drug Saf, 2013. 22(9): p. 986-94.

[16] Pinnow, E., el at., *Postmarket Safety Outcomes for New Molecular Entity (NME) Drugs Approved by the Food and Drug Administration Between 2002 and 2014.* Clin Pharmacol Ther, 2017.

[17] Pinnow, E., el at., *Postmarket Safety Outcomes for New Molecular Entity (NME) Drugs Approved by the Food and Drug Administration Between 2002 and 2014.* Clin Pharmacol Ther, 2017.

[18] Dusetzina, S.B., et al., *Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review*. Med Care, 2012. 50(6): p. 466-78.

[19] Briesacher, B.A., et al., *A critical review of methods to evaluate the impact of FDA regulatory actions*. Pharmacoepidemiol Drug Saf, 2013. 22(9): p. 986-94.

[20] Unpublished Duke-Margolis Center for Health Policy Literature Review: *FDA Postmarketing Safety Labeling Changes: Assessing the Impact on Drug Utilization and Treatment Outcomes*

[21] Briesacher, B.A., et al., *A critical review of methods to evaluate the impact of FDA regulatory actions.* Pharmacoepidemiol Drug Saf, 2013. 22(9): p. 986-94.

[22] Major, J., et al. *The Effect of FDA Drug Safety Communications on Patterns of Tiotropium Dispensing: A U.S. Health Plan Claims Database Study.* J Manag Care Spec Pharm, 2018. 24(7): p. 700-09.

[23] Kesselheim, A.S., et al. *Changes in prescribing and healthcare resource utilization after FDA Drug Safety Communications involving zolpidem-containing medications*. Pharmacoepidemiol Drug Saf. June 2017. 26(6): p. 712-721.

[24] Dusetzina, S.B., et al., *Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review*. Med Care, 2012. 50(6): p. 466-78.

[25] Briesacher, B.A., et al., *A critical review of methods to evaluate the impact of FDA regulatory actions.* Pharmacoepidemiol Drug Saf, 2013**.** 22(9): p. 986-94.

[26] Schneeweiss S. and J. Avorn, A *review of uses of health care utilization databases for epidemiologic research on therapeutics.* Journal of Clinical Epidemiology, 2005. 58(4): p. 323–337.

[27] Schneeweiss S. and J. Avorn, A *review of uses of health care utilization databases for epidemiologic research on therapeutics.* Journal of Clinical Epidemiology, 2005. 58(4): p. 323–337.

[28] Schneeweiss S. and J. Avorn, A *review of uses of health care utilization databases for epidemiologic research on therapeutics.* Journal of Clinical Epidemiology, 2005. 58(4): p. 323–337.

[29] Gibbons R.D, et al. *Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents*. Am J Psychiatry. 2007;164:1356–1363.

[30] Furedi A*. The public health implications of the 1995 'pill scare'*. Hum Reprod Update, 1999;5: p. 621–626.

[31] Briesacher, B.A., et al., *A critical review of methods to evaluate the impact of FDA regulatory actions.* Pharmacoepidemiol Drug Saf, 2013**.** 22(9): p. 986-94.

[32] Duseztina, S., et al. *Control Outcomes and Exposures for Improving Internal Validity of Nonrandomized Studies.* Health Services Research, 2015. 50(5): p. 1432-1451.

[33] Vanderweele, T.J. *The Sign of the Bias of Unmeasured Confounding.* Biometrics, 2008. 64(3): p. 702-706.

[34] Kesselheim, A.S., et al., *Methodological approaches to evaluate the impact of FDA drug safety communications.* Drug Saf, 2015. 38(6): p. 565-75.

[35] Pannucci C.J. and Wilkins E.G. *Identifying and avoiding bias in research*. Plast Reconstr Surg, 2010.126(2): p.619–625

[36] Althubaiti, A. *Information bias in health research: definition, pitfalls, and adjustment methods.* Journal of Multidisciplinary Healthcare, 2016. 9: p. 211–217.

[37] Hauber, A. B., et al. *Statistical Methods for the Analysis of Discrete Choice Experiments: A Report of the ISPOR Conjoint Analysis Good Research Practices Task Force.* Value in Health, 2016. 19(4): p. 300-315.

[38] Lloyd A.J. *Threats to the estimation of benefit: are preference elicitation methods accurate?* Health Econ 2003. 12: p. 393–402.

[39] Kjaer T., et al. *Ordering effect and price sensitivity in discrete choice experiments: need we worry?* Health Econ 2006. 15: p. 1217–28.

[40] Kesselheim, A.S., et al., *Methodological approaches to evaluate the impact of FDA drug safety communications.* Drug Saf, 2015. 38(6): p. 565-75.

[41] International Society for Pharmacoepidemiology. *Guidelines for Good Pharmacoepidemiology Practices* (GPP). Available from: https://www.pharmacoepi.org/resources/policies/guidelines-08027/