An Automated Model to Estimate the Probability of a Use Error Related Adverse Event for In Vitro Diagnostic Medical Devices

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Dedication

This praxis is dedicated to my family, who form the root of my motivation. A special dedication to my children, Aiden and Kai whose bright fire and flowing ocean inspire me, and with this praxis, I hope I have inspired them and they know that their dreams are achievable.

In memory of Sidney A. Jengelley, 1951-2010

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Praises to the almighty for blessing me with talents, and endurance to persevere through this journey.

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Finally, to the committee for the opportunity to present the results from my journey.

Eternally Grateful

Abstract of Praxis

An Automated Model to Estimate the Probability of a Use Error Related Adverse Event for In Vitro Diagnostic Medical Devices

The FDA, the MHRA, and other regulatory authorities recommend that during the development process of a device, manufacturers should aim to understand the use errors of comparable devices to the ones of interest. Knowing the probability and severity of use errors for similar products, they can be eliminated or reduced by implementing HFE/UE principles related to them. In this study, the MAUDE database was used as the data source to create an automated model that is able to estimate the probability of use related errors associated with IVD devices. Several characteristics related to the device, operator, error type and location were found to be important in identifying the probabilities of a use error related adverse event that are readily available to a user of the proposed model and do not require a burdensome number of characteristics to generate accurate probability results. The final model provides an objective and time saving approach using the Bootstrap Forest algorithm with these characteristics. It is shown to accurately characterize use error related adverse events with a generalized R-squared value of 0.8587 and provides a highly accurate method with a low misclassification rate of 6.95% and is an effective model for distinguishing if an event is an adverse event with a high AUC of 97.5%. In addition, a knowledge model for use errors is utilized that provides an understanding from a human factor and usability perspective and allows the design team to address the design based on the cognitive areas that are impacted for the new device rather than a specific design issue. The long term goal is to facilitate device design improvements to ensure safety and prevent patient injury and death caused by use errors adverse events associated with IVD medical devices.

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List of Acronyms

AAMI	*Association for the Advancement of Medical Instrumentation*
AI	*Artificial Intelligence*
AMDE	*Adverse Medical Device Event*
ANSI	*American National Standards Institute*
AUC	*Area Under the Curve*
CDRH	*Center for Devices and Radiological Health*
EMR	*Electronic Medical Records*
FDA	*The Food and Drug Administration*
HFE	*Human Factors Engineering*
HFE/UE	*Human Factors Engineering/ Usability Engineering*
IRR	*Interrater Reliability*
IVD	*In Vitro Diagnostics*
MAUDE	*Manufacturer and User Facility Device Experience*
MDDD	*Medical Device Design and Development*
MHRA	*Medicines and Healthcare Products Regulatory Agency*
ML	*Machine Learning*
PMA	*Premarket Approval*
RMSE	*Root Mean Square Error*
SRS	*Spontaneous Reporting Systems*
UCD	*User-centered Design*
UE	*Usability Engineering*
UEM	*Usability Evaluation Methods*

UK	*United Kingdom*
US	*United States*

Chapter 1—Introduction

1.1 Background

Medical Devices including In vitro Diagnostic (IVD) medical devices are intended primarily to promote and maintain patient health. However, they can also be the cause of significant harm or adverse events, due to preventable use and misuse errors (Chai J. Y., 2000). Devices 'fail' when they are not able to perform the functions they were designed for or originally intended to be capable of performing. In 2008, medical errors were estimated to cost the United States (US) $17.1 billion annually, and device-associated errors were among the top 10 contributors. Furthermore, device use-errors are observed to be more frequent and cause more harm than failures of devices (Van Den Bos, et al., 2011).Across the approximately 100,000 reports to the Center for Devices and Radiological Health (CDRH) related to device issues, one-third are associated with errors due to the device users (Kaye, North, & Peterson, 2003). In fact, for IVD medical devices, which accounts for 12% of the total adverse events reported, over half are related to use errors (Food and Drug Administration, 2011). The Food and Drug Administration (FDA) suggests that device design is a key factor in the cause of many errors: '. . .most use errors with medical devices are not ''inevitable human error.'' Rather, they are largely influenced by device design and device labeling' (Ward & Clarkson, 2003). Furthermore, use errors and can occur even if the user is aptly trained and possess the ability to use the device if the device is not designed well (Zhang, Patel, Johnson, Chung, & Turley, 2005).

Given the astounding numbers and the high impact, ensuring patient safety and device effectiveness during their use has been the forefront of regulatory authorities and

device manufactures in recent years (Chai J. Y., 2000). Regulatory requirements have been devised in most developed countries to ensure safety and in some cases ensure performance and efficacy (Chai J. Y., 2000). The FDA in the US is a highly regarded regulatory authority but is also seen to be the most stringent and often cited by innovators to be the reason for earlier and rapid growth in Europe (Maak & Wylie, 2016). Nevertheless, with several high profile device failures, the European Union is set to impart reformations that may confer similar restrictions as the FDA. (Maak & Wylie, 2016). Though there are several differences, regulatory authorities recommend that during the development process of a device, manufacturers should aim to understand the use errors of comparable devices to the ones of interest (Gupta & Pidgeon, 2016). Successful usability of a device can be measured by the number and type of errors associated with it and therefore actions that result in unintentional errors can provide insight into areas of challenge or concern (Barg-Walkow, Walsh, & Rogers, 2012). Using the knowledge and understanding of potential use errors, can help to focus efforts and eliminate or reduced them by implementing Human Factors Engineering/ Usability Engineering (HFE/UE) principles related to them to improve the safety, efficiency, and usability of a device (Gupta & Pidgeon, 2016). Hazards that are identified can then be incorporated into the Risk Management process during device design evaluation, see Figure 1 (Ward & Clarkson, 2003).

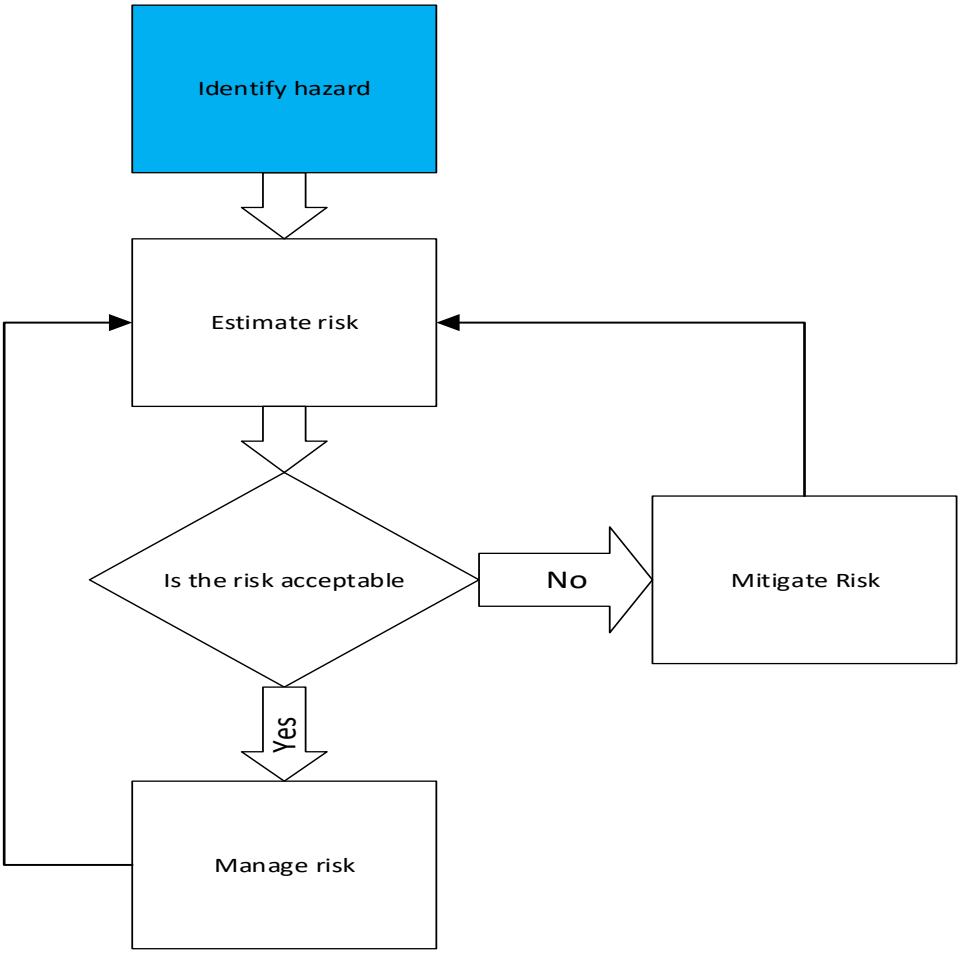


Figure 1 Risk identification flow diagram (Ward & Clarkson, 2003).

In general, the information and understanding of device use issues initially in the design process of a new medical device can be applied in several areas including design, risk management, regulatory and innovation, as detailed in Figure 2 (Gupta & Pidgeon, 2016).

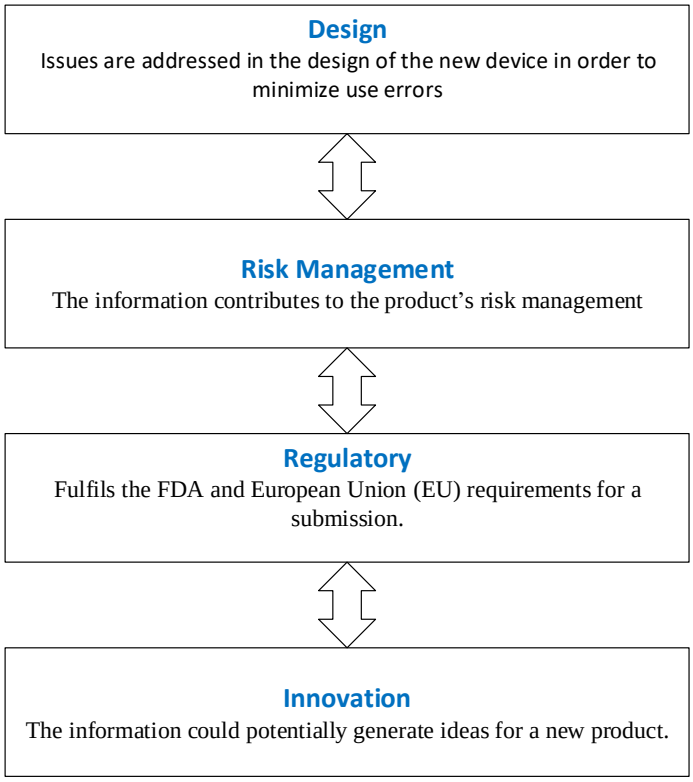


Figure 2 Application areas of prior use-error related knowledge.

Reduction of an adverse event can be approached in two ways; from a person perspective or a system perspective. The former concept is based on blaming the individuals and focuses on their errors, including poor memory, inattentiveness, or moral weakness (Reason, 2000). The latter focuses on the circumstances in which the process are carried out and identifies measures to reduce the effects or prevent the associated errors (Reason, 2000).

HFE/UE provides a systems approach to reducing use related errors through understanding of the interactions between the user and the device and the associated errors and determines measures to address identified issues. Both the US and the European Union regulatory bodies have provided very similar guidance and standards on the suggested approaches for incorporating HFE/UE into medical device design (Gupta & Pidgeon, 2016). One key aspect regarding implementation is the importance in applying

HFE/UE throughout the entire design process (Chagpar & Cafazzo, 2010). Incorporation into the model design process confers several advantages across the life cycle of the device, several of which are depicted in Figure 3 (AAMI, 2001).

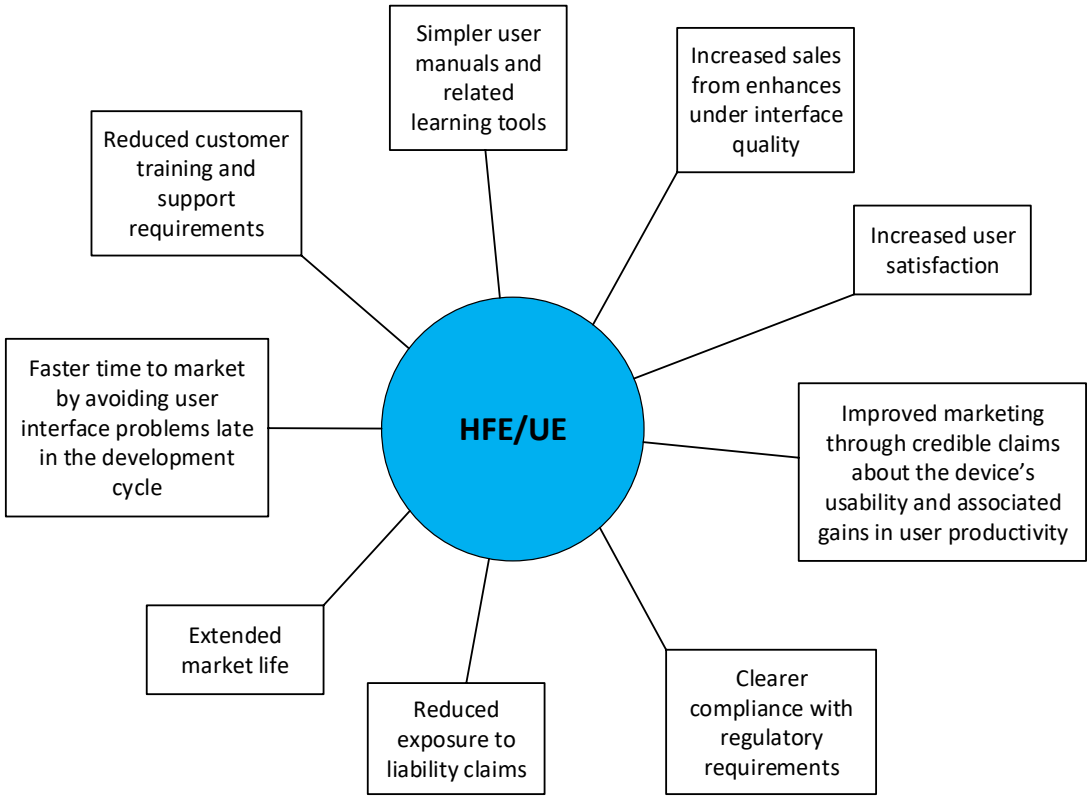


Figure 3 Potential advantages of following good HFE/UE during product life cycle (AAMI, 2001).

1.2 Research Motivation

To gain an understanding of use related errors, it is important that the data source provides adequate information to ensure that key design related issues are addressed during the medical device design and development (MDDD) process, a high risk and complex activity, due to the regulatory oversight (Money, et al., 2011). The FDA's Manufacturer and User Facility Device Experience (MAUDE) database is a collection of adverse events reported by manufacturers, importers and device user facilities (Food and Drug Administration, 2018a) and provides a valuable resource for product-related

adverse events that can reveal information about fundamental issues with medical devices (Barg-Walkow, Walsh, & Rogers, 2012) (Duggirala, et al., n.d.). The praxis proposes the utility of the MAUDE database as a data source to understand use related errors for incorporation into the MDDD process, and given the contents, ensures usability and relevance.

As with most Spontaneous Reporting Systems (SRS) the database contains a large amount of data, that although may be insightful, may be prohibitive to manual review (Duggirala, et al., n.d.). Furthermore, the inherent nature of the manual reviewing process confers challenges related to subjectivity, reproducibility, accuracy and interpretation of the data. An automated method, provides a quantitative and data driven approach that uses systematic methods based on statistics and objective criteria (specific codes and categories) leading to a standardized identification processes and should eliminate reviewer subjectivity and error (Alemayehu, Alvir, Levenstein, & Nickerson, 2013) (Duggirala, et al., n.d.). The praxis presents an automated statistics based approach to reduce the subjectivity and burden (time) when identifying related use errors for devices in development.

Incorporating HFE fosters approaches that uses fundamental device design procedures which in effect evaluate the array of device interfaces and differences among users such as their cognitive skills (Ward & Clarkson, 2003). Understanding the use-error probabilities from a cognitive perspective to form a knowledge model of errors directly connects the issues associated with the user with the corresponding design deficiencies (Barg-Walkow, Walsh, & Rogers, 2012) (Reason, 2000). The praxis therefore presents a tasked based approach for identifying the specific design areas that should be addressed,

improving the efficiency of the identification process and the impact to the design process.

In culmination of the previously identified areas, the approach presented in the praxis provides an automated method to classify use error related adverse events for IVD devices and therefore an estimation of the use error probabilities. The use errors are based on the rich source of information in the MAUDE database and are classified into actionable types to enable better determination of design gaps. These probabilities can then be used to determine focus areas to inform the risk management efforts and protocol development for human factors validation testing. The long term goal is to facilitate device design improvements to ensure safety and prevent patient injury and death caused by adverse events associated with use errors with IVD Medical devices. Figure 4 provides and overview of the significant aspects of the research in the praxis and the benefits expected.

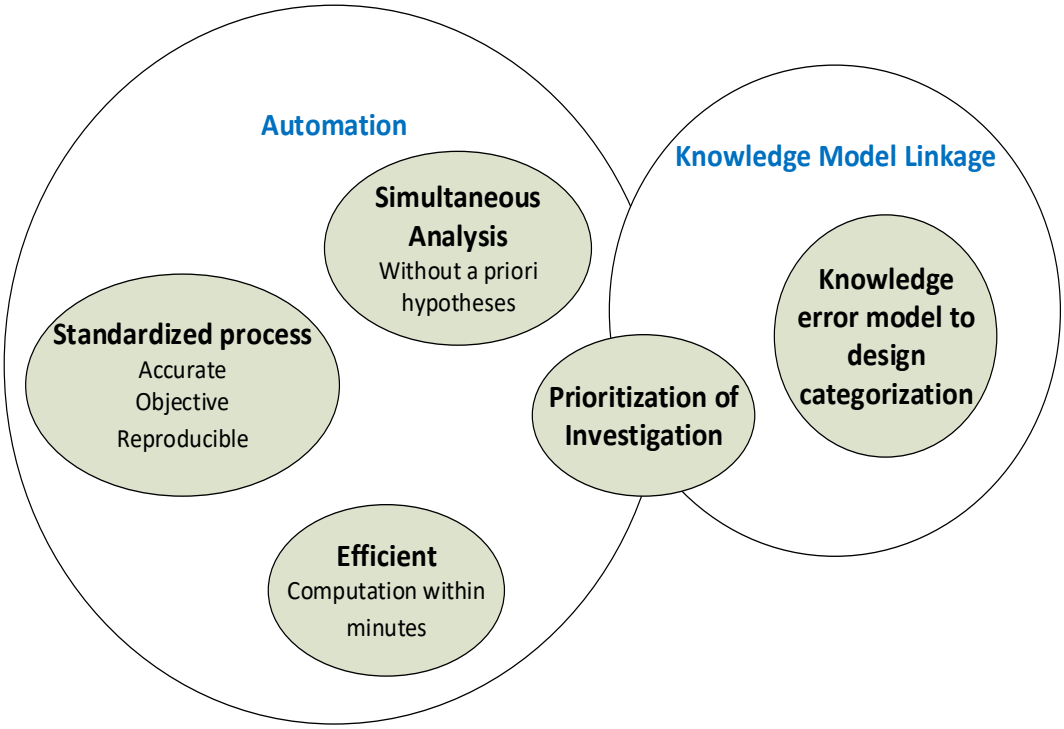


Figure 4 Overview of the key aspects and benefits of the proposed model

1.3 Problem Statement

Manual searches of the MAUDE database to identify use errors during the design process of related In Vitro Diagnostic (IVD) medical devices can be confounding, unproductive and provide irreproducible and subjective results (Duggirala, et al., n.d.) (Gupta & Pidgeon, 2016).

1.4 Thesis Statement

An automated method to classify use error related adverse events for IVD medical devices using the MAUDE database will provide statistically objective probabilities (Chen, 2018) (Orme & Buehler, 2001) *to determine focus areas for human factors design incorporation* (Zippel & Bohnet-Joschko, 2017) (CDRH, 2016).

1.5 Research Objectives

The objectives of this praxis are:

1. To develop an estimation tool that automates the determination of the relative probabilities of adverse event related use error issues which can be used in the decision making process for focus areas in HFE/UE validation testing.
2. To identify a method that improves speed, consistency and objectivity with which focus areas related to use errors for IVD medical devices are determined.
3. To develop a model that aligns use error related cognitive knowledge models with device design improvement areas to improve identification of focus areas.
4. To show that a relationship between the product characteristics and therapeutic areas within the MAUDE database are useful in predicting use related adverse events and to show that they are important factors in the classification of adverse events experienced due to use related errors.

1.6 Research Questions and Hypotheses

This praxis proposes an automated data-driven approach utilizing the MAUDE database maintained by the FDA to identify use error related adverse event probabilities given specific product characteristics and therapeutic area application. In order to determine the viability of this approach, the praxis will aim to answer the following four questions:

RQ1: How is the classification of an adverse event due to use error related to device characteristics and therapeutic area using the MAUDE Database?

RQ2: Can an automated model be created that can classify adverse events related to use error based on device characteristics and therapeutic area?

RQ3: Is the proposed automated model faster than using a manual approach?

RQ4: Is the proposed automated model more accurate in the interpretation of the MAUDE database for use related adverse events?

Given these research questions, the following four hypotheses were proposed to be tested through the praxis:

H1: The device characteristics and therapeutic area are significant contributors to the classification of an adverse event due to use error using the MAUDE Database.

H2: Supervised machine learning methods can be used to automate detection of use error related adverse events given the device characteristics and therapeutic area.

H3: There is a statistically significant difference between the time it takes to review the data between the proposed automated model and a manual approach.

H4: There is an improved reliability score when reviewing the database using the proposed automated model than a manual approach.

1.7 Scope of Research

The praxis will only focus on "use error" related errors for the IVD category of medical devices. Other types of errors and medical device types are not in focus, although the applications and methods studied can be applied to other medical devices and error of interest and are therefore proposed in the future research section of the praxis. The automated classification of an adverse event based on IVD product characteristics and therapeutic area will be used to provide probabilities of associated use errors to determine focus areas for product design during HFE/UE validation testing. The study will utilize the MAUDE database and therefore the associated probabilities are based only on regulated products that are within the scope of the FDA as well as the reported issues that are captured in the database. Additionally, the methods used are machine learning (ML)

based and therefore provides an estimation within the limitations of the methods applied. Consequently, issues with missing data and unbalanced data are compensated for to ensure optimal performance of the algorithms used.

1.8 Research Limitations

The objectives of the praxis are limited to use errors related to IVD devices and therefore the tool generated will only be able to estimate probabilities of products and use errors related to these devices. Furthermore, the events within the source database are those that are deemed reportable to the FDA and do not represent events that may have be reported as complaints to the manufacturer but not reportable incidence to the FDA. The probabilities are also limited to the reporting period used in training the model as the proposed model is static and does not require updating each time it is used. An understanding of the updating period is therefore proposed in the future research section. In addition, the probabilities are comparative to the total observed incidences within the MAUDE database and do not reflect the probabilities as a percentage risk for specific devices. Although the absolute number for the use of products are not tracked by the FDA, signal detection using the observed occurrences and the estimated total use can be determined using disproportionality analysis methods like the Dirichlet process (Gurtcheff, 2008) (Hu, Huang, & Tiwari, 2015). However, this is beyond the scope of the research and is also not a critical factor in determining relative probabilities for use in identifying design focus where the aim is to identify which issue occurs with the highest probability relative to all issues experienced and not if there is a signal of an issue with a specific device.

The research is also limited by the compilation of the data within the MAUDE database. The data is a collection of reported adverse events from manufactures, facilities, and users and therefore may contain replicated or incomplete information. A part of the data preprocessing steps that will be discussed in Chapter 3 is an attempt to remove duplicates based on the unique identification number used by the MAUDE database, but it cannot be guaranteed that all replicates were removed. Missing or incomplete data is identified in the data and removed depending on the extent of the missing information. However, in this praxis, methods are not applied to improve incomplete information but suggestions for handling these occurrences are provided in the recommendations for future research. Also, the information contained in the MAUDE database is from spontaneous reports and although there are some controls in place to ensure that the information is consistent, there may be some inconsistencies in the reporting of the same events as well as over-reporting and under-reporting of some events. However, given the share volume of reports in the database, the information that can be garnered from exploration can provide manufacturers with areas of focus for highly inclined use errors related to a specific type of IVD device.

1.9 Organization of Praxis

In this first chapter background information was presented about the propensity of medical devices to both help as well as cause harm during use and the need to identify use error related adverse events to determine points for improvement through the HFE/UE principles. The importance between linkage of knowledge model of errors related to use errors for users and device design was also presented. The key focus of the praxis was presented as an automated model using ML rather than a manual tool, to

determine focus areas for design improvement. Additionally, the MAUDE database was identified as an important source of information and is used to fulfill the motivation of the praxis for the proposed research questions and hypotheses that a faster more objective tool can be identified which utilizes this data source. The second chapter will present a review of the relevant literature, including a review of use errors, adverse events, cognitive knowledge model for use error descriptions, the HFE/UE process, manual reviewing time and inter-rater reliability score. Chapter 3 provides details about the MAUDE database and the process for developing a usable database, ML methods, and comparison metrics as well as analysis methods to determine the advantage of the final model. The results of the analyses based on the methods presented in Chapter 3 are presented in Chapter 4. Chapter 5 presents an interpretation of the results and evaluation against the research questions and hypotheses and impact of the results. Finally, Chapter 5 will provide recommendations for future research.

Chapter 2—Literature Review

2.1 Introduction

In order to fully understand the issues, concepts and directions taken within this praxis, this chapter will review the major components that form the foundation of the problem and give a basic understanding of medical devices and in particular IVD medical devices, their regulation and process for incorporating HFE/UE principles into device design. The chapter will also provide an overview of the MAUDE database and show the suitability for providing focus information for design improvement to meet the goals of the praxis. Additionally, knowledge model of use errors, theoretical time for manual reviewing and inter-rater reliability score are also presented which forms the foundation for some of the advantages for the proposed model.

2.2 Medical Devices

The world's approximately 100,000 different brands of medical devices are developed by about 14,000 entities (Ward & Clarkson, 2003). The US medical device industry is comprised of about 5,300 to 5,600 companies, with approximately 330,000 to 365,000 employees (MedPAC, 2017). These companies and other foreign companies contribute to the over 5,700 medical device product types regulated by the FDA and accounts for about 4 percent to 6 percent of total U.S. health care spending (MedPAC, 2017). Approximately 8,000 new medical devices are put on the US market each year (Feigal, Gardner, & McClellan, 2003) that fall into about 1,700 different classes of devices and 16 medical specialties as grouped by the FDA (Hernández-Cruz & Medina, 2017). Research has also shown that the medical device industry has grown at about the same rate as the broader health care sector while the share has remained fairly constant in

a growing sector (MedPAC, 2017).

Medical devices range from very simple to highly complex items and have a myriad of uses that can be diagnostic, which help to determine the medical issues; rehabilitative, which restore lost functions and add quality to life; and life maintaining equipment, which perform vital functions (Chai J. Y., 2000). The FDA uses the generally accepted description of a medical device as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them:

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes" (Food and Drug Administration, 2018b).

2.3 In Vitro Diagnostic Medical Devices

In Vitro Diagnostic (IVD) tests are a subset of medical devices and the focus of the praxis. The Medicines and Healthcare Products Regulatory Agency (MHRA) states that an IVD is "any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of

specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

- concerning a physiological or pathological state, or
- concerning a congenital abnormality, or
- to determine the safety and compatibility with potential recipients, or
- monitor therapeutic measures" (MHRA, 2016).

In the US, the FDA similarly describes an IVD as "those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body" (Food and Drug Administration, 2018c).

Most treatment decisions are based on IVD results thus ensuring that incorrect, ineffective or harmful treatments are not given to patients and can also aid in earlier treatment intervention (WHO, 2019). IVD test often include reagents provided in kit format or separately, as well as calibrators, and controls (WHO, 2019). These tests may be performed manually or using medical device instruments that range in size from small hand held devices to complex laboratory instruments and systems (WHO, 2019). The reagents as well as the instruments and systems they are used with are regulated together as IVD medical devices.

2.4 Premarket Regulation

Regulatory systems have been developed to ensure products are safe, effective and perform according to their intended uses. The medical device regulatory system in

comparison to those for medicines and vaccines, is newer and less developed, in Europe, beginning in the mid-1990s as a European wide initiative (MHRA, 2016). In the US, prior to 1976, the activities of the FDAs concentrated on removing fraudulent medical devices from the market (Chagpar & Cafazzo, 2010). In 1976 congressional amendment gave rise to a new medical device regulatory system and the terms pre-amendment and post-amendment; where pre-amendment devices did not need to follow the new rules and post-amendment approval of some devices was possible by only showing that they are similar to devices approved under the pre-amendment rules (MedPAC, 2017). Overall, 65% of approximately145 countries have national regulatory entities, however, regulatory implementation progress has been lagging (WHO, 2010). Nonetheless, to ensure appropriate controls for each specific device, classification systems have been developed conferring different levels of regulation (Altayyar, 2016). There are three classifications of medical devise in the US: Class I, Class II, and Class III. Class I includes devices with the lowest risk and Class III includes those with the greatest risk, though in some cases medical devices may also be unclassified (Food and Drug Administration, 2018b). These regulated devices must be registered by the manufacturers and distributors prior to being put into commercial use and also require that all related activities from these entities are provided to the FDA (Food and Drug Administration, 2018b). In some cases, either a Premarket Notification (510(k)) or Premarket Approval (PMA) submission to the FDA is required depending on the medical device use and classification (Food and Drug Administration, 2018b). A 510(k) demonstrates that a device that is substantially equivalent to a legally-marketed device which is not subject to Premarket Approval, is safe and effective (Food and Drug Administration, 2018b). A

PMA is the highest level of scrutiny and is the scientific and regulatory review process that determines the safety and effectiveness of Class III medical devices (Food and Drug Administration, 2018b) (MedPAC, 2017).

2.5 Postmarket Surveillance

It is not possible to fully assess the safety and effectiveness of a medical device before releasing it to the market, therefore postmarket surveillance activities are put in place afterwards (MedPAC, 2017). Postmarket surveillance of all medical devices including IVDs ensures the same quality, safety and performance requirements exists after initially being placed on the market and thus has the potential to capture long term product issues (WHO, 2015). Post-market surveillance is either reactive, occurring after an issue has occurred or proactive to preempt for potential product issues (WHO, 2015).

Proactive post-market surveillance activities include:

- Post Approval Studies; and
- Batch verification testing (prior and post distribution to end-users) (WHO, 2015).

According to the FDA regulatory guidelines, post approval studies are mandatory if a device requires PMA approval or for Class II and Class III products in one of the following cases:

- "failure of the device would be reasonably likely to have a serious adverse health consequence;
- expected to have significant use in pediatric populations;
- intended to be implanted in the human body for more than one year; and
- intended to be a life-sustaining or life-supporting device used outside of a user

facility" (Food and Drug Administration, 2018c).

Reactive post-market surveillance includes the following:

- "complaint reporting, including vigilance of mild, moderate and severe adverse events;
- evaluation of data from external quality assessment schemes (proficiency testing); and
- end-user quality control programs" (Food and Drug Administration, 2018c).

A key output of postmarket surveillance are SRS, which are used to monitor the safety of medical products including medical devices and IVDs. In the US, the FDA maintains the following SRS databases:

- FDA Adverse Event Reporting System (FAERS, formerly AERS) for drugs and biologics;
- Vaccine Adverse Event Reporting System (VAERS) for vaccines; and
- Manufacturer and User Facility Device Experience (MAUDE) for medical devices (Food and Drug Administration, 2018a).

This praxis utilizes the MAUDE database which contains medical device adverse events and product problems reported to the FDA from manufacturers, users and facilities.

2.6 Manufacturer and User Facility Device Experience (MAUDE) Database

Given the regulatory oversight for medical devices, the FDA has since the 1990s, maintained the MAUDE database as a repository for mandatory and voluntary reports (Barg-Walkow, Walsh, & Rogers, 2012) (Food and Drug Administration, 2019a).

Individuals, user institutions, and device manufacturers report malfunctions and adverse events (not mutually exclusive), that reflect safety issues of the associated medical devices (Food and Drug Administration, 2019a) (Barg-Walkow, Walsh, & Rogers, 2012). Although not required, manufacturers can report minor incidents at their discretion, and individuals and medical personnel can submit voluntary reports (Stern, Kramer, Ouellet, & Kesselheim, 2017). In the FDAs patient labeling guidance document for medical device, it is suggested that manufacturers encourage users to report adverse events related to design and manufacturing related issues (CDRH, 2001). The submissions contain event identification and description using both prefixed codes and narratives and includes events classified using "device problems" including those related to use errors (Food and Drug Administration, 2019a) (Barg-Walkow, Walsh, & Rogers, 2012). The intent of the database is to determine if there are actual or potential safety issues and evaluate the benefits or risks of the associated devices (Stern, Kramer, Ouellet, & Kesselheim, 2017). The FDA clearly indicates that the database should not be used to determine or compare rates of incidences including adverse events between medical devices or groups of devices (Food and Drug Administration, 2019a). Nevertheless, through evaluation of the MAUDE database there is the potential to gain an understanding of the extent, tendencies, patterns and occurrence of the adverse events related to specific products and groups of products of interest (Harris & North, 2012). Furthermore, the wealth of information in the MAUDE database provides the potential for comprehensive evaluations, and can be an asset in providing insight into use errors and associated risks related to IVD medical device usage (Barg-Walkow, Walsh, & Rogers, 2012) (Stern, Kramer, Ouellet, & Kesselheim, 2017). This information can then be used to develop

theories to incorporate into HFE/UE device design studies and evaluation (Gupta & Pidgeon, 2016).

2.7 Hazards, Adverse Events and Use Errors

Device problems are of two types depending on if there is harm associated (Altayyar, 2016). The first type are hazards, which are potential sources of harm that do not manifest as such, but can occur from intrinsic risks from medical treatment; or proper and improper device use; or device failure or malfunction (Altayyar, 2016). The second type are adverse medical device events (AMDEs) or adverse events as they are referred to in the praxis, and refer to events that result in harm from device usage or patient treatment application unrelated to their maladies (Samore, et al., 2004).Adverse events and hazards from medical devices are shown to be greatly due to use errors associated with device failure (Barg-Walkow, Walsh, & Rogers, 2012) (Kaye, North, & Peterson, 2003).The International Organization for Standardization (ISO) defines use error as "an act or omission [of an act] that results in a medical device response that is either not expected by the user or unintended by the manufacturer" (ISO 14971:2007, definition 2.27) (ISO 14971:2007) (Barg-Walkow, Walsh, & Rogers, 2012). The FDA further adds to the ISO definition of a use error "was not caused solely by the device and did or could result in harm" (CDRH, 2016). Use errors can therefore either result in use related hazards or adverse events during device use (Altayyar, 2016) (Barg-Walkow, Walsh, & Rogers, 2012). The reasons for use error related adverse events are varied but may include device usage not expected or unintended by the manufacturer due to unclear or poorly designed instructions or interface resulting in inconsistent results from the user's expectations; and the conditions under which the device is used including physical and

mental capacity of the user (Altayyar, 2016). However, the later does not usually relate to device design and is not the type of use error that is considered or relevant to this praxis. A review of the use errors in the MAUDE database across all devices by (Barg-Walkow, Walsh, & Rogers, 2012) found that use errors:

- occur in various medical disciplines and aspects;
- affect numerous stages during device use
- are not restricted to lay users but also occur in a professional capacity;
- have several fundamental causes;
- can occur with adverse events; and
- result in various outcomes as severe as death.

2.8 Classification of Use Errors

Unintentional (not a deliberate attempt against the rules) use errors are of three main types: slips, lapses, and mistakes (Norman D. A., 1981) (Reason, Human error, 1990).

- Slips occurs when an action is executed incorrectly but the intention or goal was correct (e.g., adding reagents in the wrong order, or pipetting too much reagent).
- Lapses occurs when someone forgets to do something, although they know how or what to do (e.g., forgetting to do daily maintenance on a device, or to recalibrate the device for each use)
- Mistakes occurs when an action is incorrectly planned for the intention or goal (e.g. heating test solution instead of thawing at room temperature to enable immediate use) (Norman D. A., 1981) (Reason, Human error, 1990)

Although, the exact mechanism of use errors is not clearly identified, one predominant explanation as quoted by (Barg-Walkow, Walsh, & Rogers, 2012) is from cognitive psychologist Donald Norman. Norman breaks down the cause into

a) Knowledge-in-the-Head (KiH),

b) concrete examples, and

c) contextual Knowledge-in-the-World (KiW) (Barg-Walkow, Walsh, & Rogers, 2012).

KiH is the use of information gained from prior interactions to make decisions (Barg-Walkow, Walsh, & Rogers, 2012). Concrete examples is the use of established rules and not based on specific circumstances to make decisions (Barg-Walkow, Walsh, & Rogers, 2012). Lastly, KiW is the use of contextual information to formulate a decision. A breakdown in these processes results in unintended consequences and unsuccessful user interactions with a medical device (Barg-Walkow, Walsh, & Rogers, 2012).

Norman proposed that by understanding the classes from which human errors occurred, systems design principles could be identified to improve the system (Norman D. A., 1983). Norman suggests that the use of a device is improved and there is a reduction in associated errors if knowledge models of errors and device design process are aligned (Norman D. A., 1983). Using Norman's descriptions (Barg-Walkow, Walsh, & Rogers, 2012) coined the following six terms for the classes of errors which align knowledge model of errors with actionable systems design tasks:

1. Judgment – identifying what is relevant to perform a task prior to and while executing the task (e.g., volume of solution required);
2. Maintenance- ensuring the device is within operating order before using the device (e.g. performing preventative maintenance according to the manufactures schedule);
3. Motor – device is incorrectly handled prior to or while operating or performing a procedure (e.g. inserting the reagents into the incorrect position);
4. Training – constraints within the learning process for how to perform a procedure (e.g., not learning the correct way to unload waste material);
5. Transfer – using knowledge from prior device usage to perform a task with another device (e.g., using the procedures of an older model with a new model);
6. Procedural – other types of errors that occur when performing a task (e.g., loading the incorrect reagent kit during testing).

These classes of use errors will be utilized in the praxis to group product problem codes into actionable device categories to better enable device design improvements. The mapping used in the classification will be discussed in the Methodology section of the praxis.

2.9 Regulation Over Device Design

The FDA offers comprehensive guidelines for incorporating HFE/UE into the design process and has published several guidelines for manufacturers (Chai J. Y., 2000) (Feigal, Gardner, & McClellan, 2003). The United Kingdom (UK) however lags behind in the available guidelines but more recently has put a lot of focus in this area (Chai J. Y., 2000). BS EN ISO 14971:2000 Medical devices is an international standard for use

throughout the life cycle of a medical device and provides an approach for identifying and managing risks including analysis, control and monitoring (ISO 14971:2007). This includes risk determination and management under normal and fault conditions (Ward & Clarkson, 2003).Another standard is the ANSI/AAMI HE48-1993, which is a joint collaboration of the Association for the Advancement of Medical Instrumentation (AAMI) and the American National Standards Institute (ANSI). This standard uses human factors engineering (HFE) principles with a focus on user interface requirements to create design guidelines for medical devices (Ward & Clarkson, 2003). Another guideline produced by the AAMI is the ANSI/AAMI HE74-2001 which uses HFE principles to determine the requirements and when to apply them to a device for it to be fit-for-purpose (Ward & Clarkson, 2003). Along with the advantages gained from incorporating HFE/UE into device design, there is also a regulatory requirement for manufactures to provide adequate evidence of evaluation and testing using the principles (AAMI, 2001) (CDRH, 2016).

2.10 Human Factors Engineering and Usability Engineering

HFE uses an understanding of the characteristics of potential device users including their capabilities and restrictions in consideration of the entire design aspects and accompanying training or reference material to enhance and support a device that it is safe and fit for the task for which it is designed or intended (CDRH, 2016) (Ward & Clarkson, 2003). HFE and Usability Engineering (UE) are used interchangeable or used together when referenced (CDRH, 2016). HFE/UE experts and studies focus on the interactions users have with the device of interest to understand the impact the design has on these interactions, and how to improve the experience and reduce any risks due to

incorrect use (CDRH, 2016). Several approaches are used to achieve the goals of HFE/UE by incorporating together areas of industrial engineering, cognitive psychology, ergonomics, and systems design, which ensures a comprehensive view of the interactions and resulting enhancements (Chagpar & Cafazzo, 2010). The focus of HFE/UE on possible circumstances and user interactions that may result in unintended use and methods and ensuing issues that could result in harm, ensures that devices are designed with the user in mind, thus anticipating and reducing potential errors (Ward & Clarkson, 2003). While these are suggestions for many devices, in some cases, it is mandatory for devices considered high risk devices (FDA, 2016). Furthermore, the results from the HFE/UE studies should be provided in a PMA, 510(k) submission if during risk analysis interactions are identified that if not performed or are performed incorrectly could result in serious harm, i.e. critical tasks (CDRH, 2016). Through the praxis, use error knowledge models is utilized to create direct linkage to design inputs to further bolster the design improvements.

HFE/UE uses design principles to determine the type and method of analysis and testing which are then incorporated into the design methods applied to the device (Ward & Clarkson, 2003). The principles focus on three key areas:

1. Prevention- implement design methods to avert use errors (e.g. simple and user friendly interface or manuals);
2. Awareness- alerting users to possible dangers (e.g. warning messages); and
3. Effect- implement design methods to diminish use error consequences if they should occur (e.g. fail-safe or back up safety mechanisms (Ward & Clarkson, 2003).

HFE/UE medical device development concentrations involve three areas of the device and user interaction practice:

1. Device users- the target user or handlers of the device, including lay persons, medical professional, and maintenance personnel;
2. Device use environments - the locations conditions and areas that the device would be used in including diagnostic labs, while driving, at home;
3. Device user interfaces- all nodes and aspects of the device where there is contact between the user and the device. (Food and Drug Administration, 2017).

As will be discussed further in the methodology section, these factors are used as one of the criteria to identify the predictor variables used in building the model proposed in the praxis.

Given the value that HFE/UE principles and methods provide applying through the entire life cycle from conceptualization to risk assessment, will ensure that all aspects of the process are enhanced and benefit from the approaches (CDRH, 2016). Therefore, applying a User-centered Design (UCD) approach, HFE/UE principles should occur in each of the three phases of the design process (Chagpar & Cafazzo, 2010) (Ward & Clarkson, 2003) (AAMI, 2001). Additionally, depending on if the device is a completely new device or an update to an existing product, incorporation may be iterative over the design process.

The following describes HFE/UE essential analysis within the three phases of the design process:

1. Design requirements capture- isolate and determine modes for expected and unexpected risks associated with use, through preliminary analysis and evaluation steps;
2. Design Development- establish and implement actions and countermeasures to remove or lessen risks associated with use and application;
3. Device Design Validation- validate the finished device to show the design provides the ability to use the device without harm and with efficacy (CDRH, 2016).

The aims of the praxis focuses on the first phase, providing information for the preliminary analysis and evaluation. User functions, user interface elements and issues during use are isolated during the preliminary analysis and evaluation steps which occur at the initial stages of the design to identify known problems with similar devices or device types. This forms the foundation for the HFE/UE process and the information generated from these assessments allows focus through to the development process to ensure implementation and a final product that is without harm and fit for purpose. One of the most important outcomes of these analyses is comprehensive identification and categorization of user tasks, leading to a list of critical tasks that if not preformed correctly or at all by the user, affects the safety and effectiveness of the device causing serious harm (CDRH, 2016). The output of the proposed model in the praxis contributes to the identification of these critical tasks.

A useful point to start is to identify use-related problems (if any) associated with device use, the user interface and user interactions that have occurred with similar devices to the one of interest (CDRH, 2016). These types of problems can then be

evaluated during the development process of the new device and actions created to address potential issues (CDRH, 2016). The main aims of the praxis feeds into the most important outcome of the preliminary analysis using the MAUDE database and use error categories to determine the anticipated hazards and the relative probabilities based on the characteristics of the device of interest to isolate and classify tasks and determination of those tasks that are critical (CDRH, 2016).To further enhance the design improvements, the approach in the praxis uses cognitive knowledge models of use errors to align with design goals (Ward & Clarkson, 2003). The outcomes of this process could then feed into the risk analysis and requirements for the validation testing process (CDRH, 2016).

2.11 Methods for Evaluating Use Errors

There are several methods that can be used in the preliminary analysis and evaluation identification process. The first relates to identification of known use-related problems (the focus of this research) and two complementary categories: analytical and empirical methods (CDRH, 2016).

1. Identification of known use-related problems- This involves identification of issues that occur during interaction and use of similar devices to the device of interest (CDRH, 2016). The use-related problems can be identified from several sources including customer complaint files, previous HFE/UE studies, journal articles, proceedings of professional meetings, newsletters as well as spontaneous reporting sources including the FDAs adverse events databases (CDRH, 2016).
2. Analytical approaches- This involves simulated-use testing to assess the interactions that occur with device and users and can incorporate information obtained from evaluating similar devices. The scenarios created do not mimic true

use cases or include actual users but help to identified unforeseen issues that could occur. Analytical methods include: (a) task analysis, (b) heuristic evaluation and (c) expert analyses (CDRH, 2016).

a) Task analysis- This method uses a systematic approach to dissect the device use process into discrete sequences of tasks. The individual tasks identified are then analyzed to determine the user interface components involved, the use errors that users could make and the potential results of all use errors (CDRH, 2001).

b) Heuristic evaluation- This method provides a process to evaluate a device's user interface in comparison to the design principles for a user interface, as well as heuristic guidelines, to create a comprehensive understanding of the user interface overall, and isolate possible weaknesses in the design, particularly those that could result in harm (CDRH, 2016).

c) Expert analysis- This method uses experts that have knowledge about the device application and HFE/UE area specialists, to evaluate the use of the device, isolate issues observed and provide potential mitigations or solutions. Expert reviews differ from heuristic evaluations in that the former requires that the analyst has expertise in a specific area based on personal experiences and opinions; the assessments provided also reflects this type of knowledge (CDRH, 2016).

3. Empirical approaches- This involves isolation of risks and scenarios in which risks could occur utilizing methods that include: (a) contextual inquiry, (b) interview techniques and (c) formative evaluations (CDRH, 2016).

a) Contextual Inquiry- This method uses actual devices that are similar to the device of interest in its actual use environment and typical users to determine characteristics of the device design that have an effect on safety and effectiveness of the device and then isolate those that are satisfactory and those that are concerning (CDRH, 2016) (Bhutkar, Konkani, Katre, & Ray, 2013).

b) Individual and group interviews (focus groups)- Interviews are conducted to collect qualitative information to understand the sentiments, attitude, specific problems and any thoughts about a similar device to the device of interest, from individual or groups of users, handlers or patients. Information is also collected on what can be implemented to improve a new device (CDRH, 2016) (Bhutkar, Konkani, Katre, & Ray, 2013).

c) Formative evaluations- This approach is conducted during the development of the device and often is used to complement and refine the information determined using the analytical approaches. It also incorporates the tasks that were determined to be critical during the preliminary analyses to evaluate the device as it is being developed (CDRH, 2016) (Bhutkar, Konkani, Katre, & Ray, 2013) (Bhutkar, Konkani, Katre, & Ray, 2013). One form of formative evaluation is a Cognitive Walk-through, where test users are provided guided information while using the device (CDRH, 2016). The evaluators engage in dialogue with test users as they interact with the device to

understand pain-points and issues that occur during the use process (CDRH, 2016) (Bhutkar, Konkani, Katre, & Ray, 2013). Another form of formative evaluation uses simulated- use testing in a similar way as cognitive walk-through except the test users are not guided, but are allowed to use the device independently and naturally (CDRH, 2016).

2.12 Review of Applied Use Error Identification Methods

Limited literature was available on the application of use error identification methods described in the previous section when applied to the design and development phases of products. Available literature was mostly for post manufacturing settings including at device purchase. (Bhutkar, Konkani, Katre, & Ray, 2013). It was evident that when performed in the design and development phases, the methods applied were not published as they were considered proprietary by the manufacturers (Bhutkar, Konkani, Katre, & Ray, 2013). Nevertheless, through a literature study on the use of UE, (Bhutkar, Konkani, Katre, & Ray, 2013) determined that the most used methods in healthcare were heuristic evaluation and cognitive walkthrough usability evaluation methods (UEM). Methods for identifying use errors were also observed to be often applied with some modifications in the methods. (Zhang, Patel, Johnson, Chung, & Turley, 2005) proposed two approaches for evaluating and predicting potential user errors and associated severity for integral information technology medical devices. A heuristic evaluation method, referred to as “modified discount-usability testing”; and a tasks analysis method, referred to as “extended hierarchical tasks analysis (EHTA)” were utilized by the authors in identifying use errors in their study (Zhang, Patel, Johnson, Chung, & Turley, 2005). Both methods require HFE/UE experts to individually evaluate the heuristics and

hierarchical tasks and subtasks required to use a device to determine the challenges encountered and associated severity of each challenge (Zhang, Patel, Johnson, Chung, & Turley, 2005). They showed that the results from the methods correlate with the use errors identified when reviewing the MAUDE database. It is of note that the same MAUDE database that will be used as the data source to identify key use errors in this praxis was used to confirm the results generated from the EHTA methods proposed by (Zhang, Patel, Johnson, Chung, & Turley, 2005) and indicates the consistency and possible accuracy in using the MAUDE database, validating the use of the database as the source for the approach in the praxis. Furthermore, the study also highlighted some of the key drawbacks in using the analytical methods to capture device related errors, which includes requiring expert knowledge, careful curation of a range of possible use errors and expensive set up of experiments. Three aspects that can be substantially reduced using the proposed automated method, and a driver and support for why the proposed model can be a critical part of HFE/UE validation testing.

2.13 Automated Evaluation of Data and Data Driven Approach

Manual analyses including identifying theories, determining which categories or variables to isolate or evaluate or determining the selection or cohort of cases are known to be limited by the accuracy, objectivity, reproducibility, and inferences that can be made (Duggirala, et al., n.d.). However, using data-driven automated approaches, the inputs chosen and the outputs generated are without a priori and systematically identified to generate statistically objective inferences, within the limits of the underlying data (Duggirala, et al., n.d.). In one study aimed at modeling adverse drug interactions (Ho, Le, Thai, & Taewijit, 2016) showed ML to be a powerful tool for adverse drug

interaction detection and prediction. Furthermore, it is generally seen that quantitative and data-driven approaches help minimize some of the deficiencies with subjective inferences. If executed meticulously these approaches often provide results that are reproducible and often generalizable (Alemayehu, Alvir, Levenstein, & Nickerson, 2013). Data-driven methods rely on two components; the source of the data and computational methods to analyze the data. Data is no longer limited to SRS for adverse events or administrative databases, but now includes -omics data such as genomics and proteomics data; social media data including usage and narrative information and electronic medical records (EMRs) (Wu, et al., 2017). Furthermore, advanced methods of statistics, including ML and data mining allows for more effective descriptive, predictive and classification analyses (Duggirala, et al., n.d.). Many methods are available for determining risk propensities, but are usually based on routine statistical models and are affected by their computational limitations. Another drawback is that the routine statistical models that can be applied in risk estimation are parametric and require understanding and explicitly stating the relationship between the input and response variables (Attewell, Monaghan, & Kwong, 2015). ML methods are nonparametric requiring less understanding and reliability on variable relationship leading to improved prediction accuracy (Cafri, Li, Paxton, & Fan, 2018). The approach in this praxis uses ML algorithms to mimic human evaluation of data without the drawbacks related to the human process as well as the restrictions from parametric statistics methods. There are two important advantages that the approach will provide by applying an effective algorithm. First, it will provide an alternative approach for labor intensive and tedious manual tasks measured by time saving (Hypothesis 3) (El-Naqa & Murphy, 2015). A

major benefit is that it can potentially learn more intricate and elusive patterns in the data than manually reviewing and further remove the subjectivity associated with these decisions (El-Naqa & Murphy, 2015). The second is measured by the final algorithm's ability to accurately identify adverse events given product specifications (Hypotheses 1, 2 and 4) and as a result provide consistent results that will not waver between evaluators.

2.13.1Automated Approach-Time Improvement

ML models inherently provide a time saving advantage over using a manual approach (El-Naqa & Murphy, 2015). Firstly, a static model such as the one proposed in this research, requires a negligible amount of time to generate results as there is no need to retrain the model. The model inputs are similar to the requirements to initiate a manual review, and therefore the point after the product characteristics are determined can be projected as the normalized baseline to compare the manual and proposed automated process. Given this baseline reference, a negligible amount of time to generate results can be considered for the proposed static model. Ultimately, static models such as that proposed, will require updating, and research into identifying an updating period and the sensitivity of the results to data change is proposed in the future recommendations section.

A manual approach inherently will require more time and effort to utilize even after a systematic manual process is carefully curated. The curation and development process of an optimal manual process can also be tedious. In the manual classification tool proposed by (Kang, Wang, Yao, Zhou, & Gong, 2019) a lot of time was required to develop the model, and included the training of the reviewers to reach alignment to accurately determine the utility of the model. Additionally, a review of the manual model

proposed by (Kang, Wang, Yao, Zhou, & Gong, 2019), seen in Figure 5, which could also represent a typical manual process, depicts the burdensome requirements in using a manual approach. The time requirement to generate results once the manual approach is developed can consequently be seen as significant, and again would include creating alignment across the reviewers. It is of note that the authors of this research suggested that a ML approach would reduce the burden they encountered in their proposed manual approach (Kang, Wang, Yao, Zhou, & Gong, 2019).

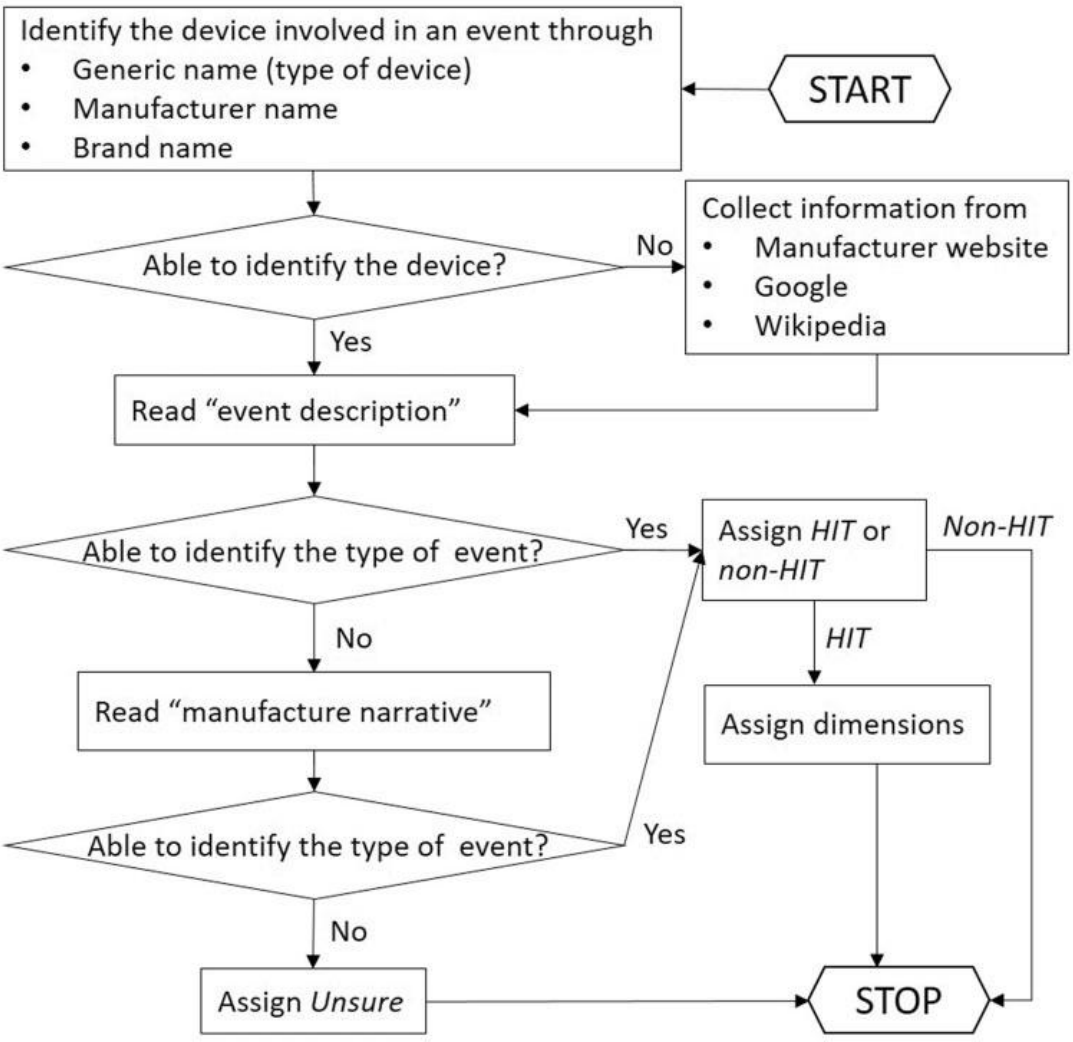


Figure 5 Workflow for reviewing a report from the FDA MAUDE database proposed by (Kang, Wang, Yao, Zhou, & Gong, 2019)

According to Eric Lewis (Safety Development Leader at GlaxoSmithKline) in an article by (Reed, 2018), the manual review time for journal articles for safety signals (issues due to adverse events) was 1.2 to 1.6 minutes per abstract. This may be extrapolated to safety signals or identifying key adverse events in the MAUDE database for an average time to review each record of 1.4 minutes. The total review time can quickly add up when multiple products and ranges and modes of errors are reviewed.

The third research question and hypothesis will aim to determine if there is a time advantage in using the proposed model. A theoretical time of 1.4 minutes (estimated previously) will be used to evaluate the manual time requirement to review records from the MAUDE database for adverse events related to use error for IVD medical devices and the time-advantage using the proposed model.

2.13.2Automated Approach- Quality Improvement

Automated data-driven approaches provide consistency and reduces subjectivity that can plague a manual approach. Data-driven methods rely on the data to evaluate risk factors, recognize relationships, and discover general knowledge (Duggirala, et al., n.d.). Therefore using data-driven methods such as ML, can provide a more general perspective, making it suitable for determining causal factors and root cause of issues and as a surveillance method for early detection of safety issues in medical devices (Samore, et al., 2004).

Manual approaches rely on observation-driven methods particularly using human intelligence and heuristics to focus on a specific situation (Duggirala, et al., n.d.).The inherent variability among human reviewers will challenge the consistency and agreement between the individuals collecting and analyzing the data (McHugh,

2012).Interrater reliability (IRR) is the degree of agreement among data reviewers and determines how much of the resulting variance relates to the true score after accounting for measurement error (Hallgren, 2012). IRR is measured using the Cohen's statistics score for two reviewers and Fleiss Kappa score for more than two reviewers (McHugh, 2012) (Ranganathan, Pramesh, & Aggarwal, 2017). The score ranges from -1 to +1, where +1 indicates complete agreement and as the number approaches 0 the disagreement increases (Ranganathan, Pramesh, & Aggarwal, 2017) (McHugh, 2012). A negative number indicates opposing agreement, where a -1 indicates complete opposing agreement (Ranganathan, Pramesh, & Aggarwal, 2017) (McHugh, 2012). An IRR score of 0.60 indicates that 60% of the resulting variance is based on how similar the reviewers were in their evaluations and is the true score variance; and 40% is based on the error variance or how dissimilar the reviewers were with their evaluations. (Hallgren, 2012).The square of the kappa score extrapolates to the amount of accuracy in the interpreted data as a result of the similarities in data evaluation by the reviewers; and a Kappa score of 0.6 indicates and accuracy in the data interpretation of 36% (McHugh, 2012).

As this is a potential source of error it is important that manual methods measure and calibrate agreement among manual evaluators. This process can often be extensive requiring training and assessing the degree to which similar scores are achieved for the same task by the evaluators (McHugh, 2012). Nonetheless perfect agreement is usually not achieved, and the accuracy of the ensuing results is greatly impacted by the error or amount of disagreement that exists between the evaluators (McHugh, 2012). The inter-rater agreement may also be influenced by the type of information being reviewed and in research conducted by (DeLuca, et al., 2012) on device failures for automated external

defibrillators in the MAUDE database, different agreement scores were obtained depending on the information reviewed. Information that were explicitly stated, observed higher scores (0.69-0.98), but where interpretation of the data was required, the scores were much lower (0.45-0.55). In another study by (Colvin, et al., 2011) the goal was to establish a minimum inter-rater reliability score of 0.6 when developing a manual classification scheme for adverse events related to multiple infusions, intravenous therapy, and intravenous equipment in a medical incident databases. Establishing this score required the use of several trial reports and experts with multidisciplinary backgrounds (Colvin, et al., 2011). Another manual method proposed by (Gupta, et al., 2017) for the da Vinci surgical system, which aimed to identify a structure to classify associated adverse events in the MAUDE database, observed moderate agreement between reviewers with a Kappa score of only 0.52. This study will be used to compare the accuracy advantage of using the proposed model as it also aims to identify a classification approach for adverse events using the MAUDE database albeit for a different subset of medical devices and using a manual approach. Furthermore, this value appears to represent the typical Kappa score observed with data requiring interpretation and the score that is aimed to be reached by reviewers when developing manual approaches. Nevertheless, it is worth noting that although the inter-rater reliability score is often low, the study previously introduced conducted by (Kang, Wang, Yao, Zhou, & Gong, 2019) was able to produce a score of 0.85. However, as previously discussed in the time advantage section, the authors recommended a less burdensome method using ML.

The fourth research question and hypothesis in this praxis will aim to compare the accuracy obtained using the proposed approach with typical inter-rater reliability scores

for manual classification methods that utilize the MAUDE database to establish if there is an advantage in using the proposed method.

2.14 Review of Applications of Automated and Data Driven Methods

Data driven methods have been applied in a number of different areas to identify critical areas of focus. Several statistical and ML methods including the Wilcoxon Rank-Sum test, Latent Class Analysis (LCA), Logistic Regression and Bayesian Modelling were applied to a large set of mostly categorical data by (Alemayehu, Alvir, Levenstein, & Nickerson, 2013), to correlate key indicators with quality issues in clinical trials. The results of the study determined the key variables and pioneered methods to address product quality and monetary consequences from a hazardous material occurrence (Alemayehu, Alvir, Levenstein, & Nickerson, 2013).

A review of the literature also shows that studies have been conducted using adverse event databases to understand problems of interest, identify signals of an issue as well as to build predictive models for a range of outcomes (Chen, 2018) (Jeong, Park, Choi, Park, & Yoon, 2018) (Yeleswarapu, Rao, Joseph, Saipradeep, & Srinivasan, 2014) (Zheng & Xu, 2018) (Botsis, Woo, & Ball, 2013) (Personeni, et al., 2017) (Chai, Anthony, Coiera, & Magrabi, 2013) (Ricci, Pignalberi, Magris, Aquilani, & Altamura, 2012) (Everett, et al., 2016). These studies were not limited to medical device adverse events and included vaccines and prescription drugs. In most cases, the studies conducted, were focused on a particular device, drug or vaccine and in their context of use, for example implantable cardioverter defibrillators (Ricci, Pignalberi, Magris, Aquilani, & Altamura, 2012). The type of use error that occurs with a medical device, is not restricted to a particular device and each error has the potential to affect multiple

types of devices. Hence, research conducted without these restrictions can provide valuable theories. Therefore, the approach in this praxis although limited to one error type- use error, is a culmination of errors in itself and will be investigated across a broad list of similar devices within the IVD medical device sub-field.

Chapter 3—Methodology

3.1 Introduction

This chapter describes the methodologies applied in the praxis to answer the research questions. The methodology includes data collection and pre-processing; data analysis; training; and validation of the generated models; and comparison of the final proposed automated model with the alternative manual approach. A high-level summary of the research methodology is shown in Figure 6.The output of the methodology is a data-driven automated approach to identify focus areas for HFE/UE validation testing that align design improvement goals with use error knowledge models. The previous chapters covered the identification of the problem, solution and data; and provided a background and understanding of the problem and solution as well as the path to determine the effectiveness of the proposed model. The current chapter will continue into the next steps which is the data analysis and pre-processing steps and will then present the analysis approaches used in the praxis.

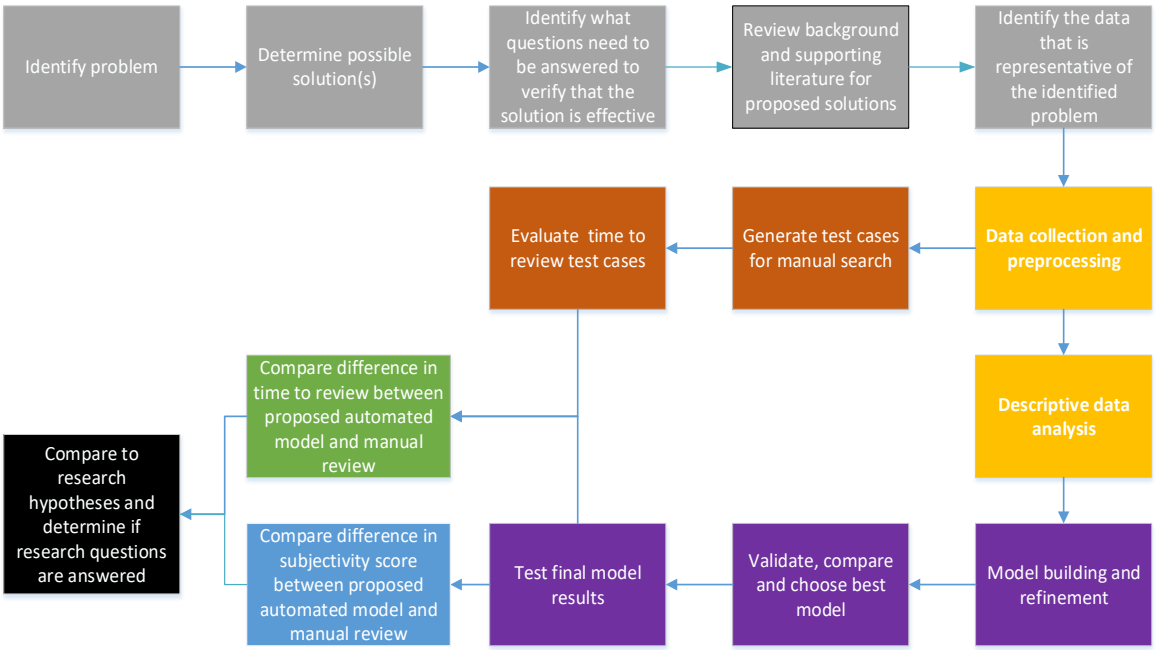


Figure 6 Research methodology used in developing the research questions and answers.

3.2 Data Collection

The data used for the praxis is the Manufacturer and User Facility Device Experience (MAUDE) database. An overview of the MAUDE database was presented in the previous literature review section. This section will present more specific details about the data and elements used to generate the subset of data used in this praxis.

The FDA's CDRH has been collecting adverse event data for medical devices since 1991 (Food and Drug Administration, 2019a). The data can be accessed either through an online search engine (Appendix A) which allows access to the most recent update (conducted monthly) or as zipped data that can be downloaded (updated weekly) (Food and Drug Administration, 2018a). A maximum of 500 records are generated from the search engine, restricted to the preceding 10 years, and are not provided in a downloadable format (Food and Drug Administration, 2018a). Given the limitations of

the search engine, the downloadable files were retrieved for use.

The data files that are downloaded are comprised of manufacturer reports (since 1996), user facility reports (since 1991), distributor reports since (1993) and voluntary reports (since 1993) which are created using information inputted into Medwatch forms 3500A or 3500 (see Appendix B) (Food and Drug Administration, 2018a). All available years (up to the time of retrieval) will be used to build the model separated into training and validation sets. The files are zipped pipe-delimited text files with one record per line and are grouped into four primary files and 2 supplementary files as described in Table 1. The primary files must be combined to generate meaningful information, and the supplementary information enhances the interpretation of the data by adding more meaningful information to the coded text. All record types are linked via a common field within each file - MDR_REPORT_KEY, which is used to combine the files together (Note that throughout this praxis the fields/variables are depicted in small font, all uppercase letters). Additionally, in cases where there are multiple files linked to the same event, the DEVICE SEQUENCE No and PATIENT SEQUENCE NO, are needed to combine the files. The EVENT KEY is unique to each specific event and is used to identify duplicate events. Additional files were created from information obtained from the MAUDE Database site (Food and Drug Administration, 2018a) and were used to recode fields in the downloaded files that contained coded information into corresponding words or details. For example, in the "Event type (H1)" field, "D" was recoded to "Death". Additional details about the files and their included fields are provided in Appendix B.

All the files listed in Table 1 except the text files were downloaded, unzipped (7Zip, Version 18.05) and imported into JMP (JMP, 14.2.0). The Text files were

excluded as they contained narrative information that were not utilized in this praxis. The files were then combined using the MDR_REPORT_KEY, DEVICE SEQUENCE No and PATIENT SEQUENCE No fields. Duplicate files were identified using the EVENT KEY field, and removed, as only the specific events are needed to be captured. The combined file contained 125 unique columns and 1.5 million rows of data after removing duplicates.

Table 1 MAUDE data files description and details overview.

File Type	Description	Number of Fields	File Name(s)	Details
Master Event Data	Master Record through 2017	75	mdrfoithru2017	Separate master event data are created for each reporting source, denoted by a unique EVENT KEY generated internally.
			mdrfoichange	Updates to existing master base data
Patient Data	Patient Record through 2017	5	patientthru2017	Patient details for the related event
			patientchange	Updates to patient base information for associated event record
Device Data	Device Data through 2017	45	foidevthru1997	Device details for the related event
			foidev1998 to foidev2017	Individual device data files for each year from 1998 to 2017
			foidevchange	Updates to existing Device Data base data
Text	Narrative Data through 2017	6	foitextthru1995	Narrative information entered into sections: B5, H3, and H10 of the voluntary or mandatory Medwatch forms
			foitext1996 to foitext2017	
Device Problem codes	Problem codes for each record	2	foidevproblem	Device problem codes
Problem Code Descriptions	Description of problem codes	2	deviceproblemcodes	Maps device problem codes to device problem description

3.3 Data Cohort Subset

The overall steps for creating the data cohort and a usable database from the available files of the MAUDE database that is used in the praxis are provided in Figure 7 and a detailed description follows hereafter. The praxis is limited to one type of medical device and is specific to use error related events. Therefore, only events related to these events were selected as a subset of the combined data. To allow for easier understanding, coded text were recoded using the information listed on the FDA MAUDE Database webpage (Food and Drug Administration, 2018a). The mapping for the recoding is detailed in Appendix B.

To select only IVD medical devices, the field REGULATION_NUMBER was used to identify these devices. The FDA classifies current IVDs in the Code of Federal Regulations according to sections 21 CFR 862, 21 CFR 864, and 21 CFR 866 (Food and Drug Administration, 2019b). Therefore, events associated with codes 862,864 and 866 were selected.

After selection of IVD medical device events, events associated with use error were then selected. The field DEVICE_PROBLEM_CODE DESCRIPTION, was used to identify use error related events. Twenty-nine different problem descriptions were identified and are listed in Appendix C. The use errors were then mapped to six actionable use error groupings (Judgement, Maintenance, Motor, Training, Transfer and Procedural) as discussed in the literature review section, which are based on knowledge error models. The corresponding use error DEVICE_PROBLEM_CODE DESCRIPTION and USE ERROR GROUP mapping is detailed in Appendix C.

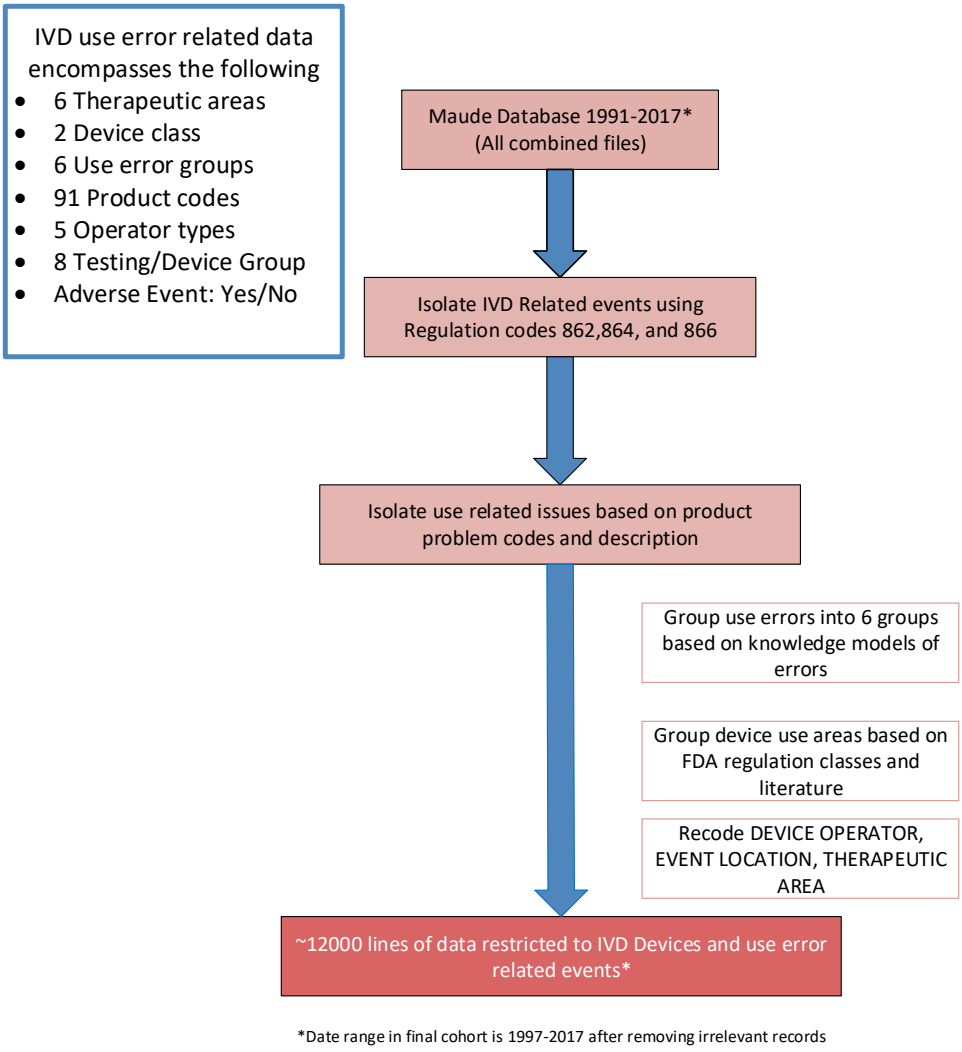


Figure 7 MAUDE database subset creation steps

Finally, columns not used in the analysis were removed. These columns were related to manufacturer or distributor specific information including contact information, device specific information including lot information and did not provide a generalized overview of an adverse event given the goals of the proposed model. The final columns (variables) and their description are listed in Table 2, and the associated parameters are listed in Appendix C. The columns removed and the reasons for removal can also be seen in Appendix C.

Table 2 Columns or variables in the MAUDE database subset and their description

Columns/Variables	Description	Original/ Modified Variable
MDR_REPORT_KEY	Report ID Key	Original
ADVERSE_EVENT_FLAG	Identifies if the problem is an adverse event	Original
DEVICE_OPERATOR	The operator of the device when the error occurred	Original
USE ERROR GROUP	The type of error that occurred based on the knowledge model of user error	Modified
EVENT LOCATION	The location of the error event	Original
DEVICE_REPORT_PRODUCT_CODE	The specific product code for the IVD device	Original
GMPEXEMPTFLAG	Identifies if the product requires Good Manufacturing Practices (GMP)	Original
SINGLE_USE_FLAG	Identifies if the product can be reused	Original
DEVICECLASS	Identifies the regulation class of the device	Original
TESTING/DEVICE GROUP	Grouped device types based on regulation	Modified
SUBMISSION_TYPE DESCRIPTION	Identifies the type of approval submission required by the device	Original
MEDICALSPECIALTY	The medical specialty for the device for regulatory oversight	Original
REGULATIONNUMBER	Identifies the regulation number group for the device	Original

3.4 Data Analysis

The subset created from the MAUDE database as described in the previous section was analyzed for use in the model and to answer the research questions. The MAUDE data subset was divided into training and validation sets, using a 70/30 split. The research methodology used to answer the research questions and evaluate the hypotheses is depicted in Figure 8 and shows the methods and criteria used for testing and validation, as well as the input and output variables. The analysis methods used are the ML methods: Logistic Regression; Random Forest; and Neural Networks, Bootstrap Forest, Boosted Trees and a one-sample test statistics method: Student's t-test or Wilcoxon Signed-Rank test. The ML algorithms were applied to the training data to identify the best model and the final model was then validated using the validation portion of the data. To evaluate the amount of time the automated method saves, a

comparison between the average time to review manual data was compared to the average time to use the proposed model for a hypothetical set of products. The estimated time to use the proposed model as discussed in the literature section of this praxis is theorized to be negligible and equivalent to zero minutes after creating a baseline from similar tasks in the manual approach. Additional time for manual specific tasks including expert training could also be considered, but for the purpose of the calculation are not included, but will be discussed in Chapter 5, when the advantages of the proposed model are discussed.

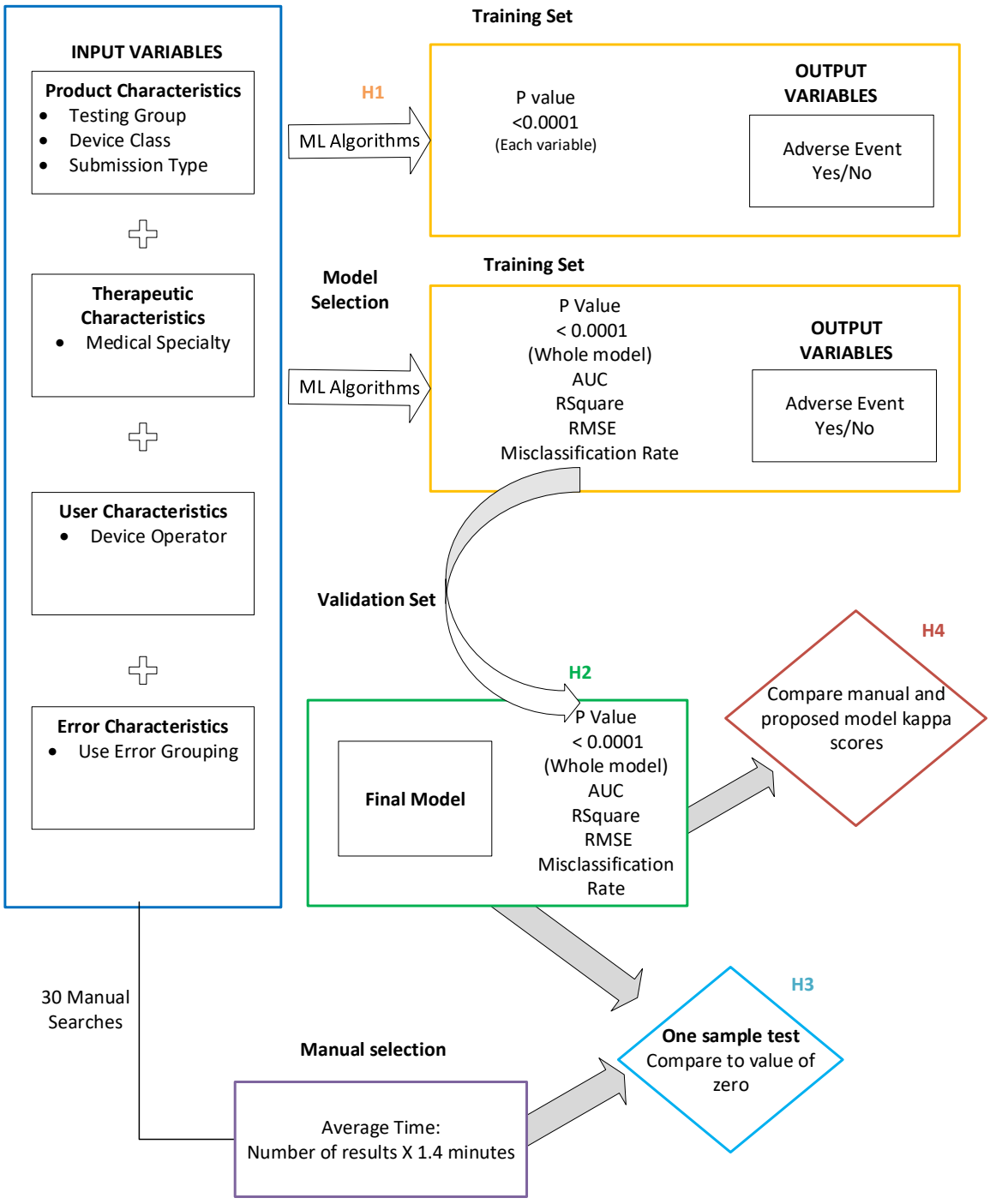


Figure 8 Analysis methodology map showing the input and output variables and criteria.

3.4.1 Descriptive Analysis

Prior to applying the identified modelling and analysis methods, descriptive statistics were generated on the MAUDE database subset to provide an understanding of

the data being used by the models, the distribution of the input variables and the relationship with the output variable. Data imbalances that may skew the analysis and model performance were identified.

3.5 Machine Learning Algorithms

Artificial intelligence (AI) aims to understand by learning the underlying information; and mimic human intelligence by interpreting the information (Panch, Szolovits, & Atun, 2018). ML is a sub-discipline of AI and is the technological development of computer programs referred to as algorithms, which mimic human intelligence by learning associations of predictive power from the information in data without being programmed (El-Naqa & Murphy, 2015) (Panch, Szolovits, & Atun, 2018). One key technique in ML is deep learning, which uses "big data" or large quantities of raw information to identify patterns to detect or classify (Panch, Szolovits, & Atun, 2018). Three basic forms of deep learning are supervised, unsupervised and semi-supervised. Supervised learning is the approach utilized in this praxis and uses known associations (labels) of outputs of interest linked to the inputs, using existing data to predict future instances (Panch, Szolovits, & Atun, 2018). Unsupervised learning learns associations without previously identified associations using the data to discover new predictors (Panch, Szolovits, & Atun, 2018) (El-Naqa & Murphy, 2015). Semi-supervised learning combines supervised and unsupervised learning together, where partially labeled data is used to determine the unlabeled portion (El-Naqa & Murphy, 2015). The next sections will describe the algorithms that are explored in identifying the most suitable algorithm for the MAUDE database subset and the aims of the model. The

models evaluated are: Logistic Regression; Neural Network; Random Forest; Boosted Trees; Bootstrap Forest.

3.5.1 Logistic Regression

Logistic regression algorithms are used to predict the probability that an event will occur or the conditions that make an event more likely to occur (Attewell, Monaghan, & Kwong, 2015). The algorithm fits a regression model to a set of data to develop a regression equation with corresponding coefficients for categorical variables (Grayson, Gardner, & Stephens, 2015). The probability of an event, *p*, is related to predictive factors $(X_1, X_2, \ldots X_K)$ by the mathematical relationship (Grayson, Gardner, & Stephens, 2015):

$$\log(p/(1-p)) = \beta_0 + \beta_1 X_1 + \cdots + \beta_k X_k$$

In the equation $\log(p/(1-p))$ represents the logit or the log-odds. The probability, *p*, is represented by the following equation (Grayson, Gardner, & Stephens, 2015):

$$p = 1/(1 + e^{-(\beta_0 + \beta_1 X_1 + \cdots + \beta_k X_k)})$$

A logistic regression model uses the maximum likelihood method to fit the parameter estimates that are the most consistent with the data (Attewell, Monaghan, & Kwong, 2015). This model can then be used to explain or understand how the probability of an event is influenced by the various factors, or make predictions of the probability of an event or build a classifier based on the predicted probability from an assigned level of classification (Grayson, Gardner, & Stephens, 2015).

Logistic Regression that only includes categorical data requires that several assumptions are met. The first assumption is that the structure of the variables should be

appropriate and in the case of the variables in this praxis where Binary Nominal Logistic Regression method is used, the dependent variable must be dichotomous and nominal and there should be at least one independent variable (Stoltzfus, 2011). Secondly the observations should be independent with no duplicate responses (Stoltzfus, 2011). Thirdly, the predicated outcome should not be very different from the actual outcome due to outliers in the data (Stoltzfus, 2011). Fourthly, the predictor variables should not be redundant and there should be little or no collinearity between the predictor variables (Stoltzfus, 2011).

3.5.2 Random Forest

A decision tree consists of a set of conditional rules, based on simple decision thresholds, where each tree is a set of if-then statements (Attewell, Monaghan, & Kwong, 2015). The individual trees in a forest are grown by repeatedly splitting the data into two at the best node location until a specified criteria is reached (Cafri, Li, Paxton, & Fan, 2018). A random forest is a collection of these decision trees and the final aggregated result leads to a classification or a prediction. Decision trees for continuous response variables predicts the mean of the response and are known as regression tree (Grayson, Gardner, & Stephens, 2015)s. Decision trees for categorical response variables including those in the praxis, predicts the probability of a specific outcome based on a set of predictors, and are known as classification trees (Grayson, Gardner, & Stephens, 2015). In both regression and classification tress, the predictors can be either continuous or categorical (Grayson, Gardner, & Stephens, 2015).

Creation of the trees begins by sub-setting the data into branches (child nodes), known as a split (Attewell, Monaghan, & Kwong, 2015). All possible split locations are

considered and the location of the best split is determined by the measure of the dissimilarity in the proportions between the groups. The best split is where, for the LogWorth value, there is a maximum difference between the heterogeneity of the node or minimal difference in the impurity within the-node (Grayson, Gardner, & Stephens, 2015). The larger the LogWorth the more optimal the split location (Grayson, Gardner, & Stephens, 2015). Within each branch, a node is created after each split, and across all the nodes that are created, the one with the highest Logworth is chosen as the optimal split location (Attewell, Monaghan, & Kwong, 2015) (Grayson, Gardner, & Stephens, 2015). The spitting process occurs at each child node until there is no change in the node purity or on reaching the point determined from the chosen stopping rule (Cafri, Li, Paxton, & Fan, 2018).The terminal nodes represents distinctive combinations of the features of a category and in this case device characteristics (Cafri, Li, Paxton, & Fan, 2018) The culminating results for each node in the tree provides an estimate of the probability for the outcome of interest.

3.5.3 Bootstrap Forest

Bootstrap forest is a type of decision tree method that utilizes a technique called bootstrap aggregation or bagging for short and random sampling of the factors to build a predictive model (Attewell, Monaghan, & Kwong, 2015). The bagging process creates a bootstrap sample by drawing samples from the data the same size as the original data with replacement, resulting in individual observations being sampled one or more times or not at all (Attewell, Monaghan, & Kwong, 2015). The model created is an aggregation and average of several single decision tree models (Attewell, Monaghan, & Kwong,

2015) (Grayson, Gardner, & Stephens, 2015). This results in a model with reduced error variability which can therefore predict better than a single decision tree model.

The algorithm for the Bootstrap Forest begins by drawing a bootstrap sample from the training data set (Attewell, Monaghan, & Kwong, 2015). A tree decision model (T_b) is then built (b representing the tree number built, i.e. for the first tree b =1), splitting at the optimal node across a random set of the factors (Attewell, Monaghan, & Kwong, 2015) (Grayson, Gardner, & Stephens, 2015). This process is repeated B times, (B represents the number of times the process is repeated) and the average of the B trees generated creates the 'aggregated bootstrap forest model' (BF) according to the following formula (Grayson, Gardner, & Stephens, 2015):

$$BF = \frac{1}{B}\sum_{b=1}^{B} T_b$$

3.5.4 Boosted Trees

Boosted trees is a type of decision tree method that utilizes the additive modelling approach technique called boosting (Attewell, Monaghan, & Kwong, 2015). The boosting process builds a sequence of several small (only a few splits in each tree) low-complexity, poorly predicting decision trees called layers (Grayson, Gardner, & Stephens, 2015). Hundreds of these trees are then added together to arrive at the final additive or ensemble model (Grayson, Gardner, & Stephens, 2015). Each decision tree layer predicts a small portion of the remaining residual error of the previous model, effectively reducing the residual error proportion and resulting in a good overall predictive model (Attewell, Monaghan, & Kwong, 2015). Although boosted trees are

more complex than bootstrap forest models, these models can provide better predictive ability requiring less computational power (Grayson, Gardner, & Stephens, 2015).

3.5.5 Neural Networks

Neural Network models can model complex relationships between inputs and outputs and are used for both classification (categorical target variable) and prediction (continuous response) (Attewell, Monaghan, & Kwong, 2015). Each neural network has an input layer, one or more hidden layers, converging to an output layer (Attewell, Monaghan, & Kwong, 2015). In each node in the hidden layer, the input variables are combined into linear functions and are transformed using activations functions that include TanH, linear, and Gaussian (Grayson, Gardner, & Stephens, 2015). A TanH function uses a hyperbolic tangent function (Grayson, Gardner, & Stephens, 2015). Much like a logistic function, a linear function in Neural Networks is similar to a linear regression model without transformation of the predictor variable (Grayson, Gardner, & Stephens, 2015). A Gaussian function is a bell-shaped function similar to a normal distribution density function (Grayson, Gardner, & Stephens, 2015).

3.6 Model Development

Development of the model is an iterative process and involves identifying important variables and tuning the models to optimal performance. An overview of this process is depicted in Figure 9

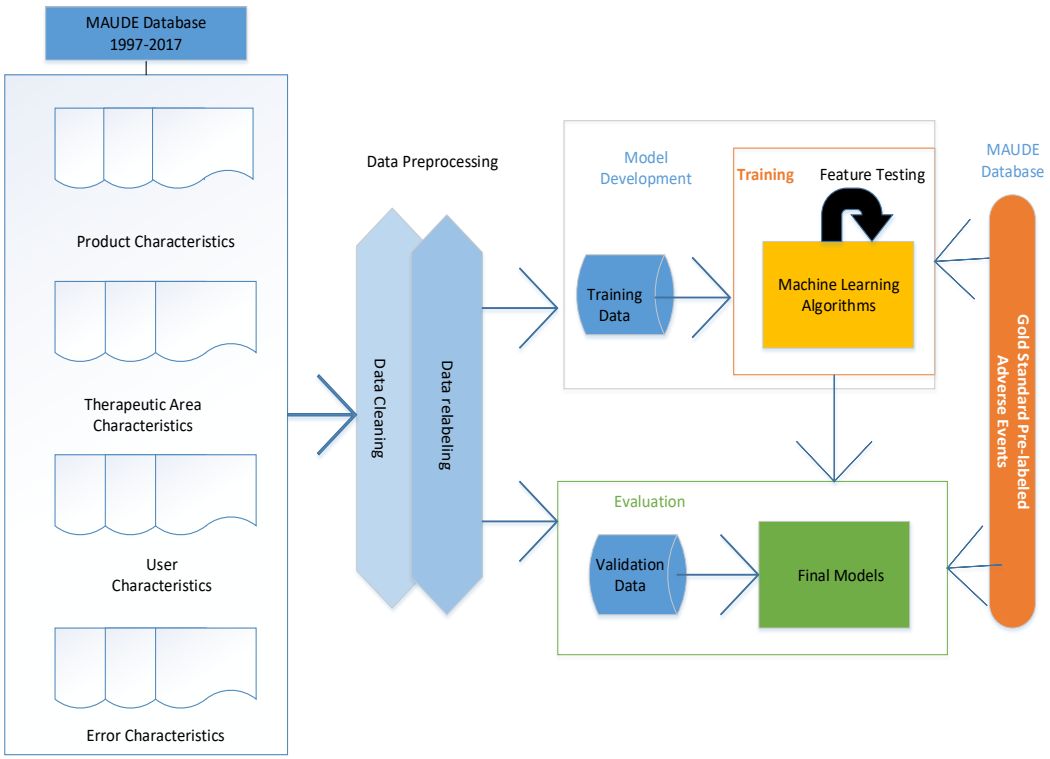


Figure 9 Model development overview

The output or response variable is the pre-labeled adverse events in the MAUDE database. The input or predictor variables based on the literature were taken from four categories of variables that correspond to important factors for the HFE/UE medical device development concentrations: (1) device users, (2) device use environments and (3) device user interfaces (CDRH, 2016). Additional predictors will be considered from feature selection using Stepwise Regression forward and backward selection methods. The ML methods will also be used to determine the importance of the chosen variables based on literature and any other variable identified through stepwise regression, in predicting an adverse event. The key variables will then be used to build the model that will classify an adverse event. Using an iterative process, a model will be built using ML algorithms and tuned to identify the best model for each algorithm. To choose the best model for each algorithm, a comparison of model performance is conducted using the

Chi-square statistic p-value at a significance value of 0.05, R-squared value, Area Under the Curve (AUC), Root Mean Square Error (RMSE), and Misclassification rate; see Table 3.

Table 3 Metrics and criteria use to compare performance of machine learning algorithms.

Metrics	Description	Application
Chi-square statistic p-Value (The observed significance probability)	The chance probability that the Chi-square value is greater than the calculated value. A model or variable is significant if the probability is below 0.05.	(a) Applied to the predictor variables to determine importance in the model. (b) Applied to the whole model to determine model significance .
Area under the curve (AUC)	A measure of how well the model sorts the data. Random sorting has a AUC of 0.5 (represented by a diagonal line on the AUC graph). Perfect sorting has a AUC of 1.0	Applied to the whole model to (a) compare the ML algorithm and (b) validate the final model's ability to sort the adverse event response variable.
Root mean square error (RMSE)	Measures the probability of the fit for the resulting response level, calculated from the differences between 1 and p, where a smaller value indicates a better model.	Applied to the whole model to (a) compare the ML algorithm and (b) validate the final model's fit for predicting the adverse event response variable.
Misclassification Rate	Measures how much difference there is between the assigned response from the highest fitted probability to the actual category. The lower the rate the better the model.	Applied to the whole model to (a) compare the ML algorithm and (b) validate the final model's classification of the adverse event response variable.
R-Squared	The fraction of uncertainty that is related to the fit of the model It is calculated using the likelihood function and ranges from 0, no better than a constant model to a maximum of 1 for a perfect model.	Applied to the whole model to (a) compare the ML algorithm and (b) validate the final model's ability to reduce the uncertainty when predicting the adverse event response variable.

3.6.1 Model Validation

Once the final models are identified for each algorithm the models will be validated with the validation portion of the data, which is the remaining 30% of the data (70% previously used in training the model as detailed previously) to provide an unbiased analysis of the prediction performance of the models (Grayson, Gardner, & Stephens,

2015). This hold out data was created using stratified random sampling (Grayson, Gardner, & Stephens, 2015). The metrics used to choose the best model from each algorithm were also utilized in assessing the performance of the final model. The hold out data set and the predicted response labels will also be compared to the actual response labels.

3.7 Time Advantage of the Proposed Model

To determine the time advantage in using the proposed automated model, a simulation of manual search results was performed and the corresponding review time compared to the theoretical time to use the proposed model for the same selected device characteristics. The input mimics the parameters that would be used if the online search tool was used; see Appendix A.

The estimated time to use the proposed model is negligible and equivalent to zero minutes. This negligible time is proposed as the model created is static and will not require that time is allotted for the user to generate or update it each time it is used. Furthermore, the baseline is assumed to be the point after gathering the characteristics of the product of interest, a task that would be similar to a manual method, and therefore does not need to be accounted for in a comparison between the methods. Using the average time for review of 1.2 to 1.6 minutes per abstract, the review time for each report from a search was extrapolated to safety signals or key adverse events in the MAUDE database for an average time to review per record of 1.4 minutes (Reed, 2018).

To generate the data used to represent the manual approach, 30 combinations of device characteristics were randomly searched in the MAUDE database and the number

of records were counted (RECORD COUNT). To calculate the total review time (REVIEW TIME), the number of records were multiplied by the average review time of 1.4 minutes.

Correlation between the review time using the manual approach and the hypothesized mean/median time of zero to use the proposed model is compared using a one-sample statistics test. After first determining if the manual review time data is normal, using the Normal Quantile Plot and the Shapiro Wilk Goodness of Fit test, either the Student's t-test, a parametric method or the Wilcoxon Signed Rank test, a non-parametric method, is used to determine if there is a significant difference between the manual and automated methods of reviewing adverse event reports.

3.8 Quality Advantage of the Proposed Model

To determine the quality advantage of the proposed automated model over the manual approach, the subjective component of manually reviewing data was taken into consideration. As discussed in the literature review section, the consistency between persons manually reviewing data such as SRS data sources like the MAUDE database leads to errors due to inter-rater reliability or agreement. The inter-rater reliability in one method for the da Vinci Surgical system to classify adverse events in the MAUDE database was determined to have an inter-rater agreement Fleiss Kappa score of 0.52. This indicates inter-rater disagreement Fleiss Kappa score of 0.48 or an error rate of 48%. In another study, a high Fleiss Kappa score of 0.85 was achieved, based on the literature review this is not typical and usually occurs when the interpretation of the data is more explicitly stated and does not require interpretation. The 0.52 and 0.85 Fleiss Kappa scores were extrapolated to be the typical theoretical score and the atypical score (for persons who may be highly trained or if the data required minimal interpretation)

respectively for HFE/UE teams manually reviewing the MAUDE database when classifying use errors and assigning an adverse event probability.

To evaluate the advantages of using the proposed model over a manual method, the Kappa scores for the proposed automated model were compared to the theoretical typical Fleiss Kappa score when reviewing the MAUDE database for use errors and assigning an adverse event probability. The aim of this comparison was to determine the relative difference between the manual and automated methods in terms of quality in reviewing adverse event reports.

Chapter 4—Results

4.1 Introduction

This chapter presents the results from the data analysis using the methodology identified in the previous chapter. A comparison between the tested models and an evaluation of the final model is also presented. Chapter 5 will discuss the presented results and compare to the hypotheses and research questions. The impact of the model relative to a manual approach will also be discussed in Chapter 5.

4.2 Missing Data

The subset created from the MAUDE database was reviewed to identify missing data and data patterns that could potentially affect the analysis and development of the models. As the subset was identified by the product problems related to use error IVD products and the response variable ADVERSE_EVENT_FLAG it was not expected that there would be missing values for these variables. However, as the data is inputted into an online form and populated into the collective database, there is the possibility that sections of the forms are not completed and values may be missing from the corresponding variables for each entry. Review of the variables using JMP Missing Data Pattern tool (JMP, 14.2.0) identified variables of concern and these were removed. The missing data pattern can be viewed in Appendix D, the columns removed and the reasons for removal can also be reviewed in Appendix C.

4.3 Descriptive Statistics

The data was first explored to determine the type of dependent and independent variables in the database cohort. It was determined that the response variable (ADVERSE_EVENT_FLAG) was dichotomous and the independent variables were nominal and

categorical. Frequency distributions were generated for the response variable to identity data imbalance and to determine if data balancing methods should be applied prior to generating ML models. Figure 10 (a) shows the frequency distribution for the response variable ADVERSE_EVENT_FLAG. To address the issue of imbalanced data identified, a bootstrap augmentation was performed on both the training and validation datasets. Using this balancing technique, observations were bootstrapped (and added into the datasets) so the number of rows in the focal group (Y) in the training and validation set achieved approximately 50% ratio of focal to non-focal rows. Figure 10 (b) shows the frequency distribution of adverse events after data balancing, a change from 92% more N to Y, to only 10% more.

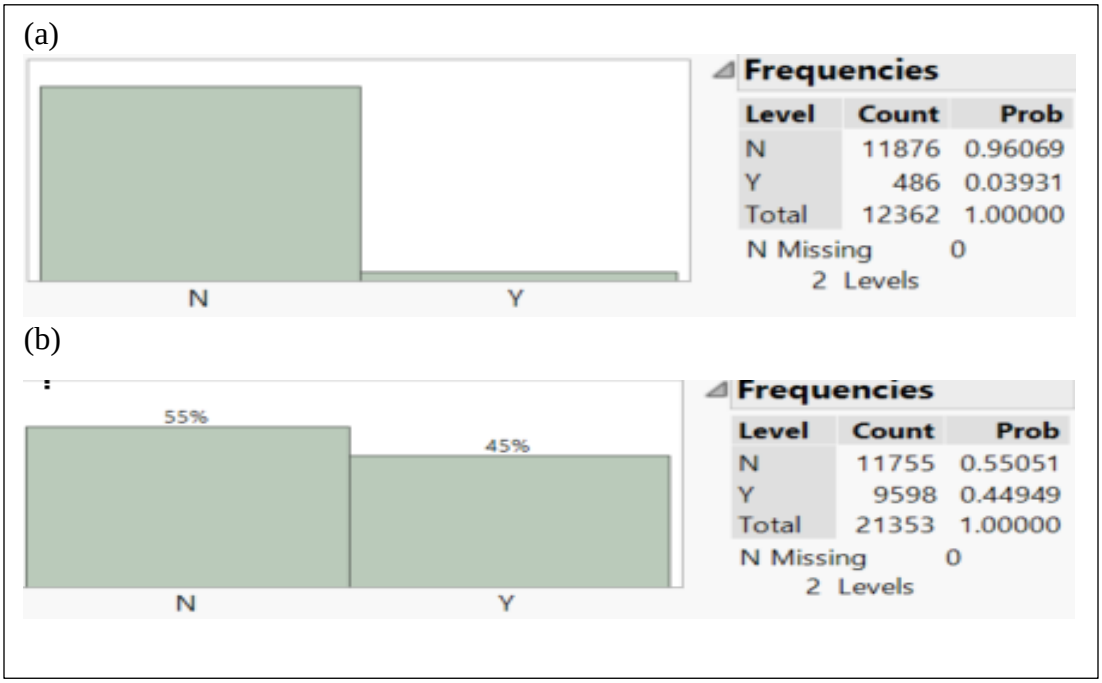


Figure 10 Distribution of response variable ADVERSE_EVENT_FLAG (a) before balancing using Bootstrap Augmentation and (b) after balancing.

Frequency distributions were also generated for the predictor variables to identify disproportionately large or sparse groups; and high number of levels that would require grouping with other similar variables to prevent errors when creating the ML models.

Appendix C shows the distribution of all the variables including the levels. The variables MEDICAL_SPECIALTY and REVIEW PANEL; and DEVICE_OPERATOR were determined to contain disproportionately large groups and sparse groups respectively. For MEDICAL_SPECIALTY and REVIEW PANEL *Immunology, Toxicology* and *Microbiology* were combined into one category to form the combined group *Immunology, Toxicology* and *Microbiology.* For DEVICE_OPERATOR several groups were combined into one group to reduce the number of levels as well as to eliminate sparse groups. See Appendix C also for the mapping of these variables to the combined groups. DEVICE_REPORT_PRODUCT_CODE also showed sparse categories, however as the variable TESTING/DEVICE GROUP was already created as a grouping for similar types of devices based on regulation of similar devices, a second combination of the products by DEVICE_REPORT_PRODUCT_CODE was not created.

4.4 Dimension Reduction

High dimensional data may include variables that are redundant and highly correlated with other variables or do not help to predict the response variable and so does not add value to the model. Furthermore, high dimensional data may create computational issues or be overly complex from a statistical or practical perspective (Grayson, Gardner, & Stephens, 2015) (Cafri, Li, Paxton, & Fan, 2018). The model being developed in this praxis requires input from the user to provide details that will identify the product of interest to be interpreted by the model. If the user is required to provide too many variables or variables that would not readily be available or describe the product of interest, the usability of the model will be low (Cafri, Li, Paxton, & Fan, 2018). A balance is therefore needed between the predictor variables that predict the response variable and predictor variables that are accessible and describe the product of interest.

To identify these variables, two methods were used. The first uses Stepwise Regression forward and backward selection to identify key variables and the second uses literature review to determine the key variables that describe a product and possible relationship with the response variable and the overall goal. The variables used in the evaluated and final models would be a combination of these methods.

4.4.1 Variable Identification-Based on Literature Review

HFE/UE medical device development concentrations are used as the foundation for identifying the predictor categories of interest in the data. Variables that relate to HFE/UE medical device development concentrations: (1) device users, (2) device use environments and (3) device user interfaces (CDRH, 2016) were reviewed in the MAUDE database to identify the fitting response variables; Table 4 shows the identified variables. These variables will also be included in the forward and backward selection methodologies to evaluate their importance to the response variable.

Table 4 Identified predictor variables and mapping based on literature (HFE/UE consideration categories).

HFE/UE Consideration Categories	Data Variables
Environment	EVENT_LOCATION DESCRIPTION
Environment	USE ERROR GROUP
Interface	DEVICE_CLASS
User /Interface	MEDICAL_SPECIALTY GROUP
Interface	SUBMISSION_TYPE DESCRIPTION
User/Environment	DEVICE OPERATOR GROUP
Interface	DEVICE_REPORT_PRODUCT_CODE
Interface	TESTING/DEVICE GROUP
Interface	GMP_EXEMPT_FLAG

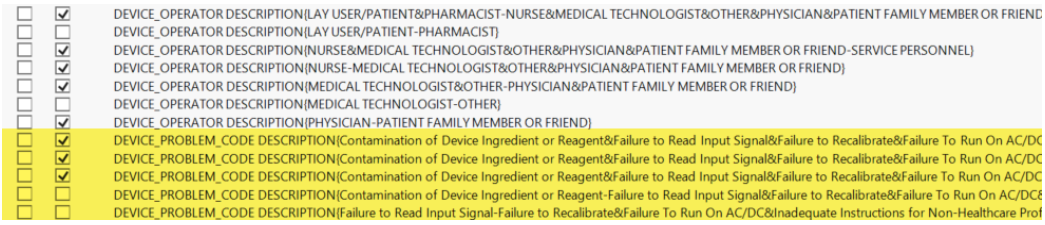
4.4.2 Forward Selection and Backward Selection

Stepwise regression with forward and backward selection was performed on all the variables that remained after removing outcome specific, manufacturer specific,

device specific and report specific variables as these would not be useful as input variables for the user when using the proposed model. Figure 11 shows a section of the results, the complete results can be reviewed in Appendix E. The results of the forward and backward selection showed the following:

1. Moderate R-Squared values were obtained for both forward (0.5840) and backward (0.5780) selection.
2. Forward and backward selection did not identify all the same predictors determined based on literature.
3. In some cases, the predictors identified were related to the original predictor variables before they were combined into groups.
4. Forward and backward selection identified similar predictors with small differences within the levels identified in each predictor.
5. The predictors are separated into multiple levels and all levels are not included.

(a) Forward Selection



(b) Backward Selection

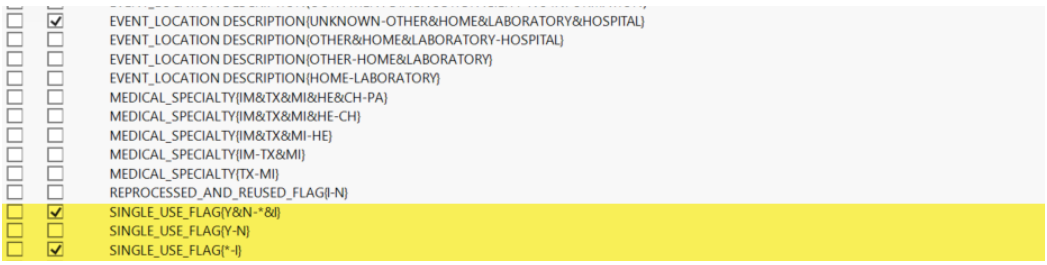


Figure 11 Input variables and variables selected by Stepwise Regression (a) forward and (b) backward selection

Although the Stepwise Regression forward and backward selection did not explicitly identify the predictors that were based on literature, the predictors that were identified were related to some of the same categories. The process identified the original variables DEVICE_OPERATOR DESCRIPTION, DEVICE_PROBLEM_CODE DESCRIPTION and TEST TYPE GROUP, that were ungrouped but are represented by the modified grouped variables. This suggests that the device characteristics, therapeutic area and operator are important predictors, but there may be specific levels that are more important in classification of an adverse event. One additional variable identified was SINGLE_USE_FLAG, and included all the levels of the variable. Based on these inferences the SINGLE_USE_FLAG variable will be included in the model development process and the variables already chosen based on literature will be used as predictors. Any further tuning of the variables used as predictors will be considered during the actual model development process.

4.5 Logistic Regression

Logistic Regression was performed using the literature based variables in addition to the variable SINGLE_USE_FLAG identified using the forward and backward selection process. Assumptions for Logistic Regression were first checked to ensure there were no violations that could impact the results and interpretation; all assumptions were met. Assumptions for the data to include a dichotomous dependent/response variable and nominal categorical variables; and determination that there are no repeated responses were addressed in previous sections and confirm that the data subset meets these two assumptions. The remaining two assumptions are assessed further on when the results from the analysis are evaluated.

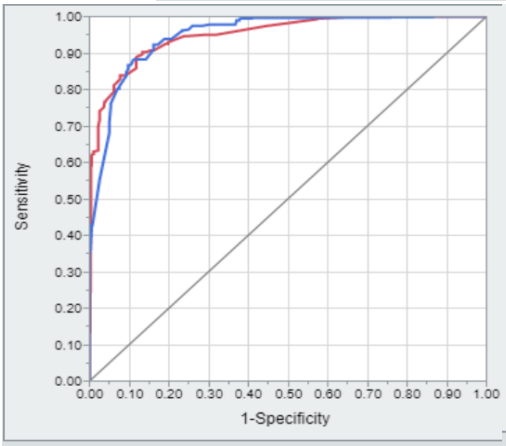
As noted in the previous section, forward and backward selection identified levels

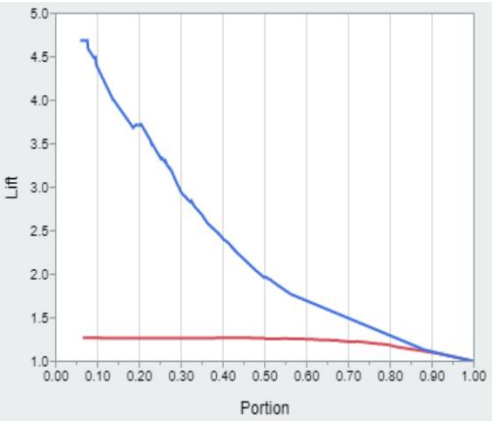
within categories as important but not all levels within a category. This would not be a practical approach given the aim of the model, for inputting product characteristics, but as the variables were related to the literature based variables, conferred their importance. Nevertheless, to allow a complete analysis, model generation was also carried out with the identified variables selecting only the levels within those categories as identified using the Stepwise Regression forward and backward selection process. A comparison will be made between these models to determine if there are any advantages to consider.

Figure 12 shows the results of the Logistics Regression using the predictors (with levels) from the forward selection and Figure 13 backward selection. The models are significant based on the ChiSquare value of < 0.0001 and shows low false negative and false positive rate; misclassification rate of only 0.0931 and 0.0935 and a AUC of 0.9507 and 0.9510 respectively. The misclassification rate also shows that the assumption is satisfied that the predicted outcome is not very different from the actual outcome. The generalized R Squared value at 0.7018 and 0.7008 indicates that a moderately high proportion of the predictor variables explain a large percentage of the variation in the response variable. Note that as the variables are chosen using Stepwise Regression, the assumption that the variables are not redundant or correlated is satisfied as part of the selection criteria in the Stepwise Regression process.

Model	-LogLikelihood	DF	ChiSquare	Prob>ChiSq
Difference	1873.8677	50	3747.735	**<.0001***
Full	1321.4177			
Reduced	3195.2854			

Measure	Training	Validation	Definition
Entropy RSquare	0.5864	0.5819	1-Loglike(model)/Loglike(0)
Generalized RSquare	0.7066	0.7018	(1-(L(0)/L(model))^(2/n))/(1-L(0)^(2/n))
Mean -Log p	0.2158	0.2166	∑ -Log(ρ[j])/n
RMSE	0.2589	0.2618	√ ∑(y[j]-ρ[j])²/n
Mean Abs Dev	0.1346	0.1363	∑ |y[j]-ρ[j]|/n
Misclassification Rate	0.0874	0.0931	∑ (ρ[j]≠ρMax)/n
N	6122	2600	n





ADVERSE_EVENT_FLAG	Area
Y	0.9507
N	0.9507

ADVERSE_EVENT_FLAG
Y
N

	Actual	Predicted Count
ADVERSE_EVENT_FLAG	Y	N
Y	1937	109
N	133	422

Figure 12 Logistic Regression results using predictors identified from forward selection

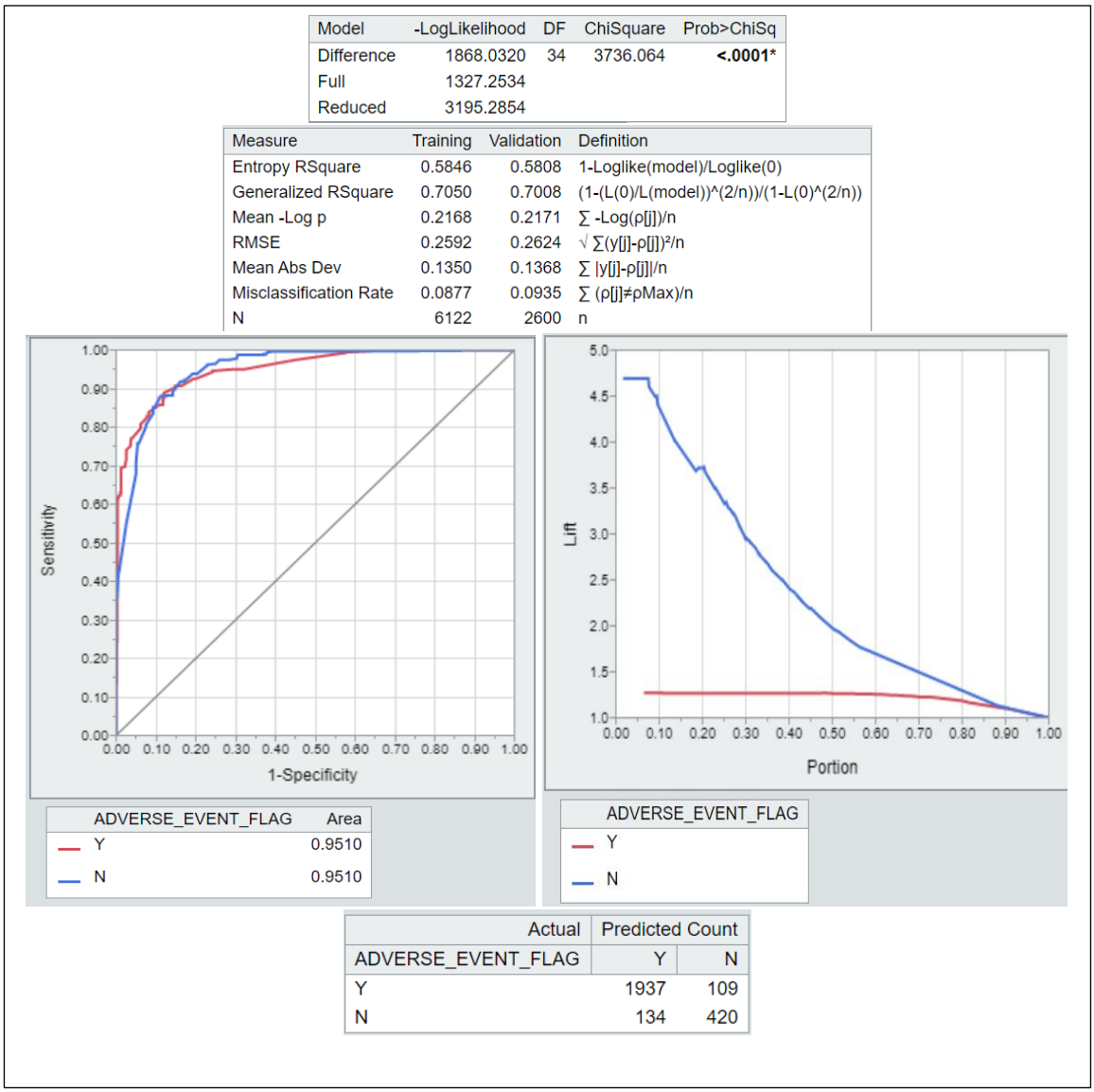


Figure 13 Logistic Regression results using predictors identified from backward selection

Logistic regression after tuning resulted in only predictor variables identified through literature. Figure 14 shows that these predictors satisfy the assumption that the variables overall are not highly correlated with each other or redundant in the model. Note that a snapshot of the actual correlation values and variables compared can be seen in Appendix E. Figure 15 shows the final results of the model which is significant based on the ChiSquare value of < 0.0001 and shows a low false negative and false positive rate; misclassification rate of 0.0916 and AUC of 0.9649. The misclassification rate also

shows that the assumption is satisfied that the predicted outcome is not very different from the actual outcome. The generalized R Squared value at 0.8006 indicates that a moderately high proportion of the predictor variables explain a large percentage of the variation in the response variable. To arrive at this model, the iterative process required removal of several variables to ensure higher R-Square and AUC values and lower misclassification rate. The variables removed were SINGLE_USE_FLAG (from Stepwise Regression), GMP_EXCEPT_FLAG, DEVICE_CALSS, SUBMISSION TYPE, and EVENT LOCATION DESCRIPTION. It is worth noting that although EVENT LOCATION DESCRIPTION was observed to have a very low and significant p-value indicating importance, its removal substantially improved the model. Although this variable may be an interesting variable to include in the model as it identifies where the device is used, it contained a fairly high number of missing values, but was not initially removed during the missing value evaluations given perceived value as an input. Finally, it is of note that one variable, TESTING/DEVICE GROUP, identified through literature was not observed to be significant in creating the Logistic Regression model, however it did not change the model performance when removed.

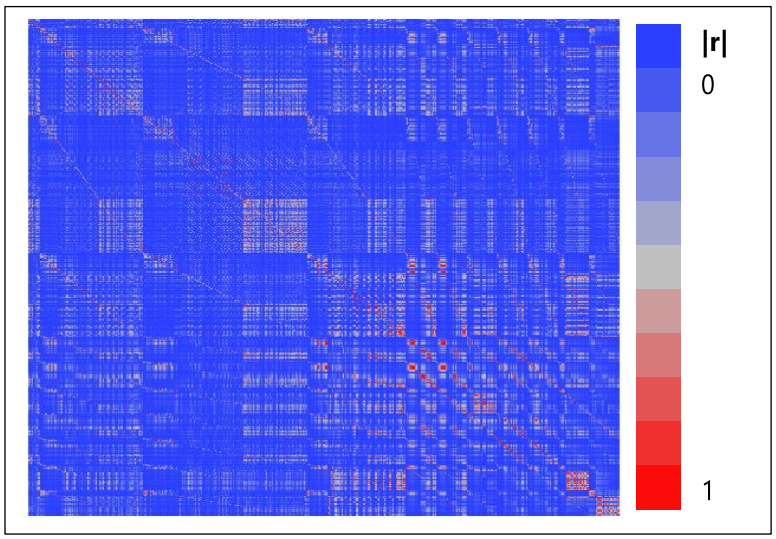


Figure 14 Correlation color map showing comparison between all possible pairs of variables in the model

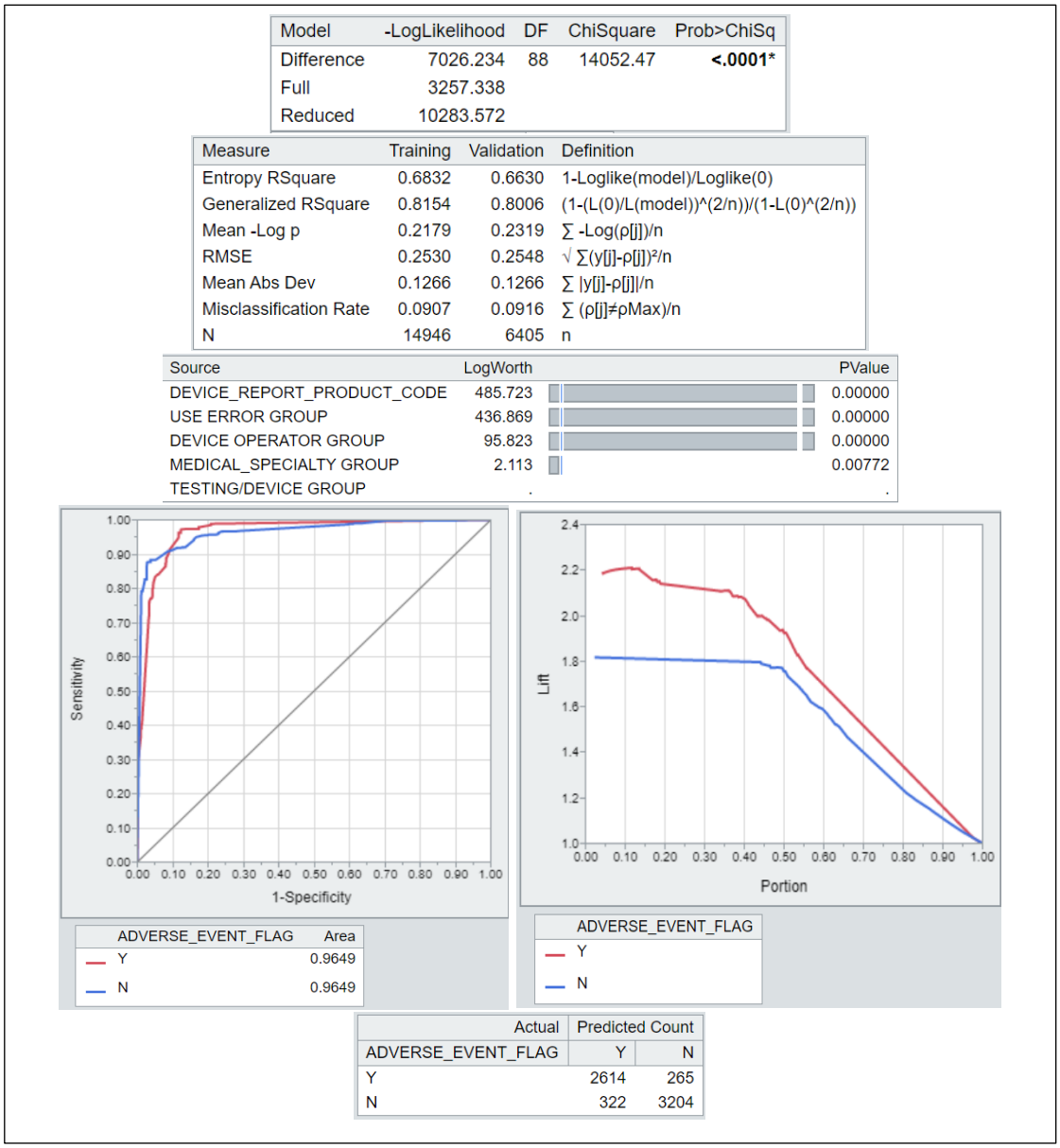


Figure 15 Logistic Regression results using predictors identified from iterative tuning process.

Table 5 shows the comparison between the logistic regression models with all variables; with and without forward and backward selection variables; and with only the literature based variables. Better overall model performance was obtained with the variables identified from literature, and as already mentioned, the additional variable SINGLE_USE_FLAG was subsequently removed during the iterative model building process, along with other literature based variables.

Table 5 Comparison of logistic regression models with forward and backward selected variables with sublevels; variables based on literature with and without additional variable categories from forward and backward selection.

ML Algorithm	Logistic Regression No forward or backward selection (Literature variables)	Logistic Regression Before removing high p-value variables)	Logistic Regression with forward selection sublevels	Logistic Regression with backward selection sublevels
P value	<0.001	<0.001	<0.001	<0.001
RSquare	0.8006	0.4417	0.7018	0.7008
AUC	0.9649	0.8910	0.9507	0.9510
RMSE	0.2548	0.3156	0.2618	0.2624
Misclass.Rate	0.0916	0.1362	0.0931	0.0935

Note: Green-Best values; Yellow- Middle values; Red- Lowest values

4.6 Boosted Trees

Boosted trees was performed using predictor variables identified from literature and the additional variable SINGLE_USE_FLAG (from Stepwise Regression), the results are presented in Figure 16. After tuning, some variables were removed, and final variables are seen in Figure 16. The model is significant based on the ChiSquare value of < 0.0001 and using the validation data shows a low false negative and false positive rate; misclassification rate of 0.0709 and AUC of 0.9716. The generalized R Squared value at 0.8431 is slightly lower than the training data value of 0.8441 and indicates that a high proportion of the predictor variables explain a large percentage of the variation in the response variables and there is minimal overfitting.

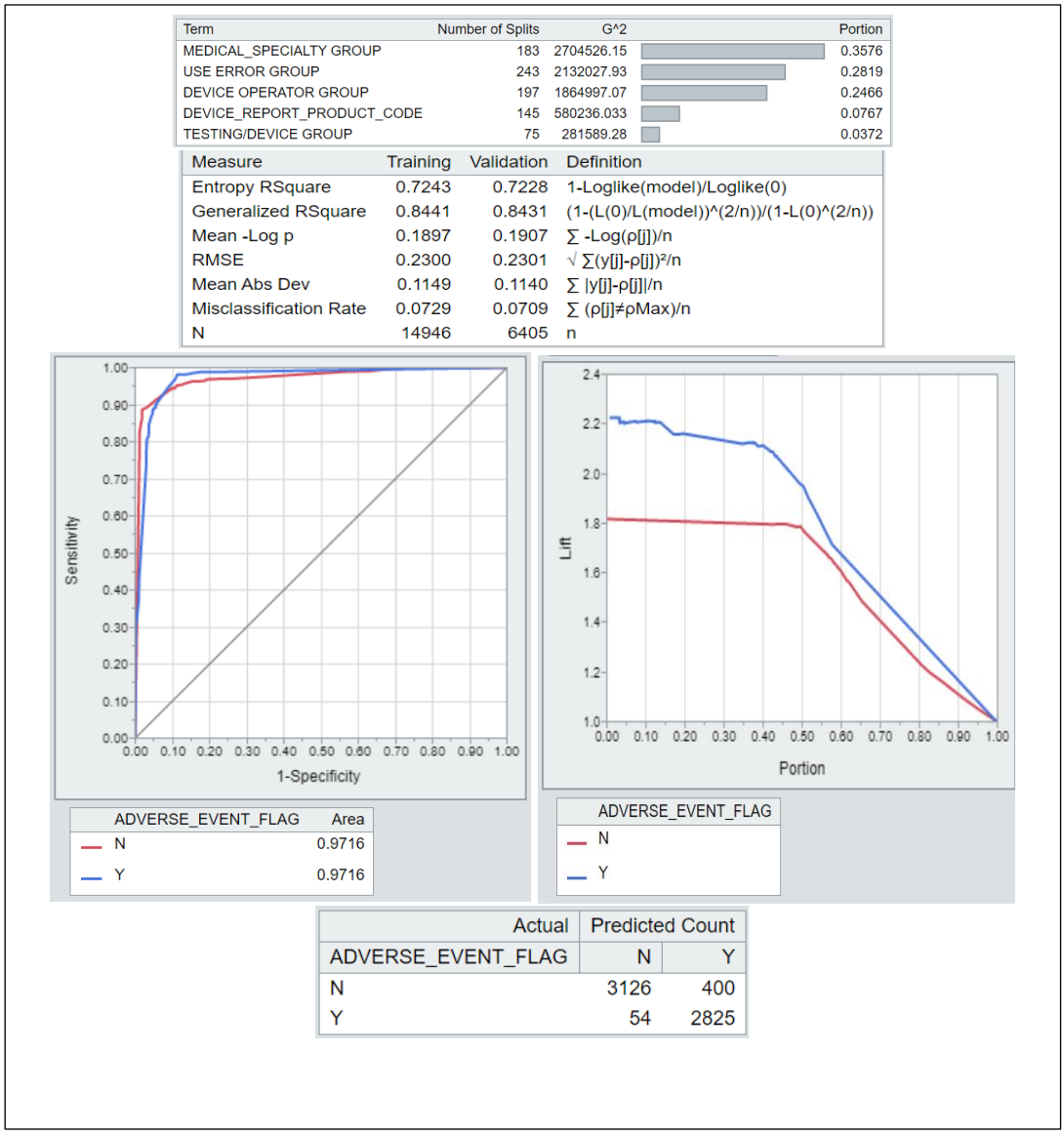


Figure 16 Boosted trees model with literature-based predictor variables

4.7 Random Forest

Random Forest was performed using predictor variables identified from literature and the additional variable SINGLE_USE_FLAG (from Stepwise Regression). The results are presented in Figure 17. After tuning, some variables were removed, and final variables are seen in Figure 17. The model is significant based on the ChiSquare value of < 0.0001 and using the validation data shows a low false negative and false positive rate;

misclassification rate of 0.0698 and AUC of 0.9740. The generalized R Squared value at 0.8575 is slightly lower than the training data value of 0.8614 and indicates that a high proportion of the predictor variables explain a large percentage of the variation in the response variables and there is minimal overfitting.

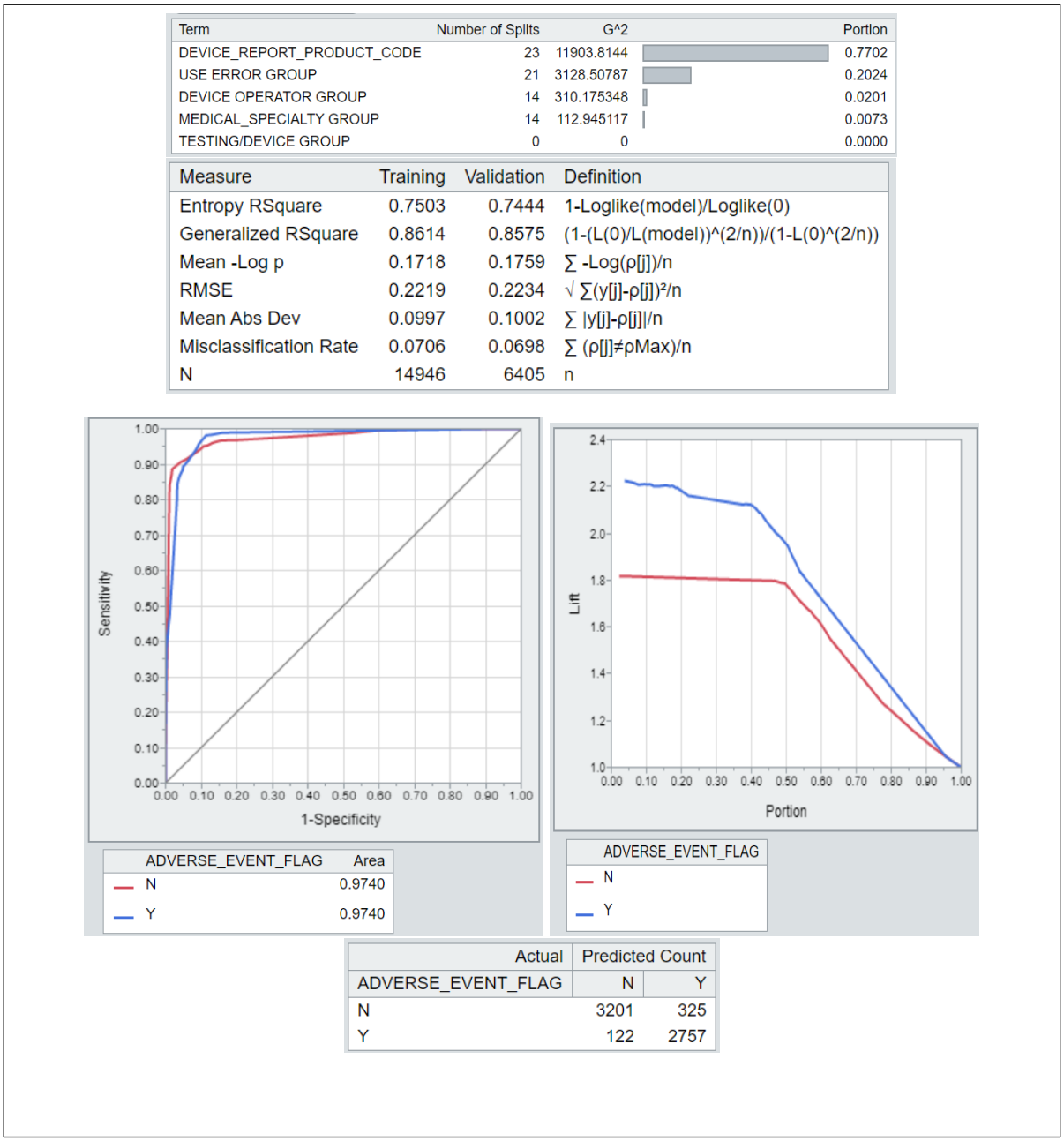


Figure 17 Random Forest model with literature-based predictor variables

4.8 Neural Networks

Neural Networks was performed using predictor variables identified from literature and the additional variable SINGLE_USE_FLAG (from Stepwise Regression). The results are presented in Figure 18. After tuning, some variables were removed, and final variables are seen in Figure 18. The model is significant based on the ChiSquare value of < 0.0001 and using the validation data shows a low false negative and false positive rate; misclassification rate of 0.0715 and AUC of 0.9729. The generalized R Squared value at 0.8545 is slightly lower than the training data value of 0.8557 and indicates that a high proportion of the predictor variables explain a large percentage of the variation in the response variables and there is minimal overfitting.

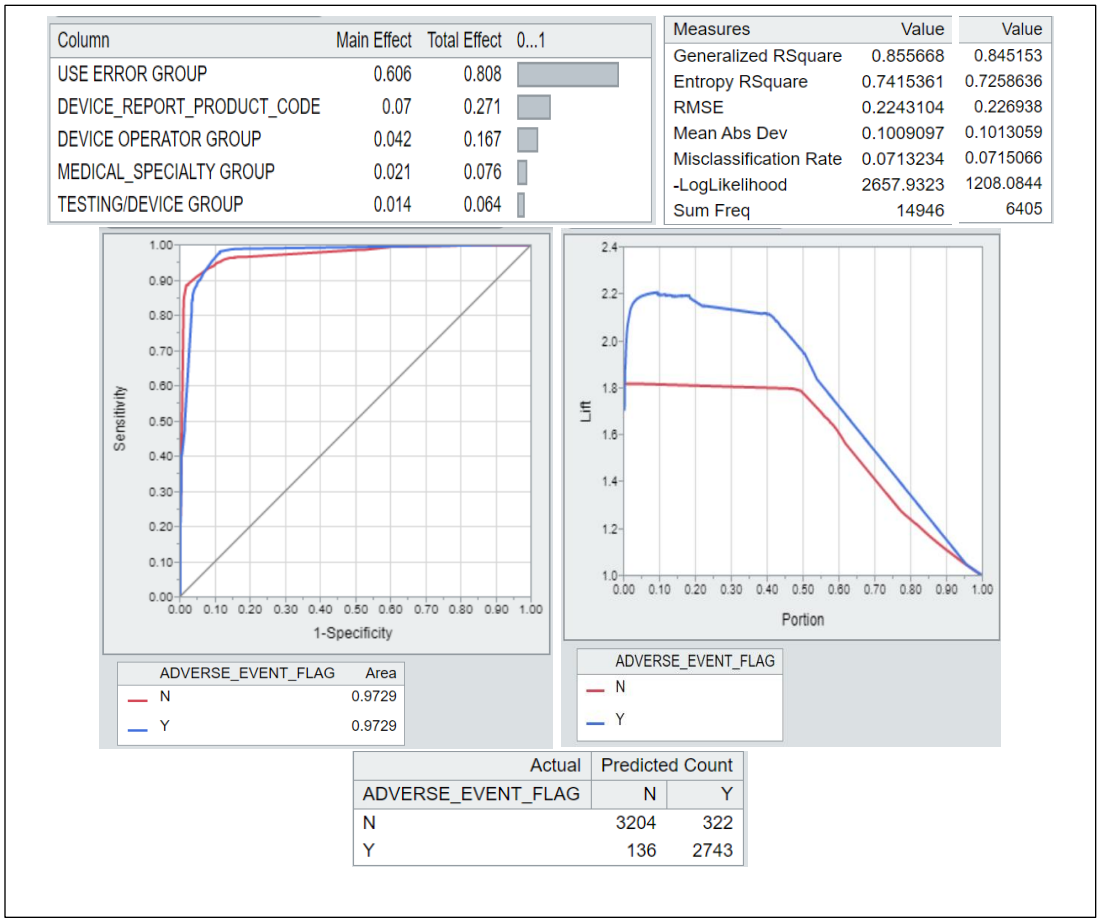


Figure 18 Neural Networks model with literature-based predictor variables

4.9 Bootstrap Forest

Bootstrap Forest was performed using predictor variables identified from literature and the additional variable SINGLE_USE_FLAG (from Stepwise Regression). The results are presented in Figure 19. After tuning, some variables were removed, and final variables are seen in Figure 19. The model is significant based on the ChiSquare value of < 0.0001 and using the validation data shows a low false negative and false positive rate; misclassification rate of 0.0695 and AUC of 0.9753. The generalized R Squared value at 0.8587 is slightly lower than the training data value of 0.8604 and indicates that a high proportion of the predictor variables explain a large percentage of the variation in the response variables and there is minimal overfitting.

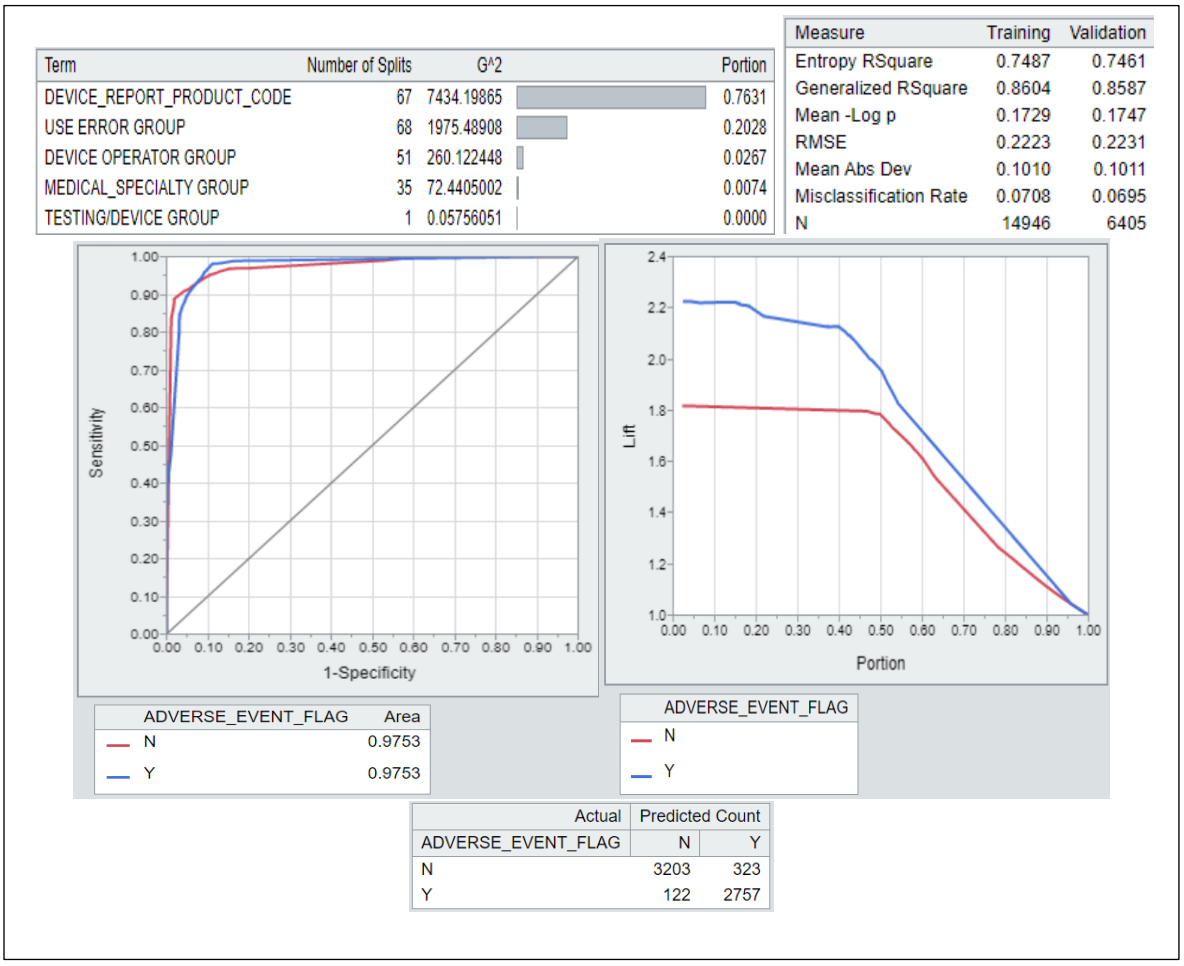


Figure 19 Bootstrap Forest model with literature-based predictor variables

4.10 Comparison of Features

Predictor variables were identified using Stepwise Regression forward and backward selection as previously discussed. Additionally, each algorithm evaluated also identified variable importance. Table 6 shows a comparison of the variable importance. In most cases the algorithms determined that the chosen predictor variables were important in predicting the response variable ADVERSE_EVENT_FLAG. TESTING/DEVICE GROUP was identified as an important variable except with the Logistic Regression and Random Forest algorithms. All the algorithms except Neural Networks and Boosted Trees have the same order for all the predictor variables; in order: DEVICE_REPORT_PRODUCT_CODE, USE ERROR GROUP, DEVICE OPERATOR GROUP, MEDICAL_SPECIALTY GROUP and lastly TESTING/DEVICE GROUP. For Neural Networks and Boosted Trees there is switch in the order of the last three predictors for the former; or switching of the first and fourth for the latter. Overall, the results show a consistency with variable importance as well as confirm their importance in predicting the response variable.

Table 6 Comparison of important predictor variables and their relative importance for each algorithm

Machine Learning Algorithm	Logistic Regression	Random Forest	Neural Networks	Boosted Trees	Bootstrap Forest
Variables					
DEVICE_REPORT_PRODUCT_CODE	1	1	1	4	1
USE ERROR GROUP	2	2	2	2	2
DEVICE OPERATOR GROUP	3	3	5	3	3
MEDICAL_SPECIALTY GROUP	4	4	3	1	4
TESTING/DEVICE GROUP	5*	5*	4	5	5
Legend	Most Important----------Least Important 1 5				

*Variable does not show importance based on machine learning algorithm; ranking is based on being the fifth variable.

4.11 Comparison of Algorithm Models

The selected model generated from each algorithm's iterative training process was compared to determine the final model for the outcome from this research. These individual results were presented in the previous sections. Overall, Bootstrap Forrest has the best performance and Logistic Regression has the worst performance. However, all the models performed well and could be utilized for the goals of the praxis. This may also indicate that the data and the parameters chosen are stable and are ideally suited for the goal of identifying use error probabilities using the MAUDE database and device characteristics.

Table 7 Comparison between evaluated algorithms

Validation	Y	Creator	0...1	Entropy RSquare	Generalized RSquare	Mean -Log p	RMSE	Mean Abs Dev	Misclassification Rate	N	AUC
Validation	Predicted Adverse Event Bootstrap Forest Y	Bootstrap Forest		0.7461	0.8587	0.1747	0.2231	0.1011	0.0695	6405	0.9753
Validation	Predicted Adverse Event Random Forest Y	Partition		0.7444	0.8575	0.1759	0.2234	0.1002	0.0698	6405	0.9749
Validation	Predicted Adverse Event Neural Network Y	Neural		0.7259	0.8452	0.1886	0.2269	0.1013	0.0715	6405	0.9729
Validation	Predicted Adverse Event Boosted Trees Y	Boosted Tree		0.7228	0.8431	0.1907	0.2301	0.1140	0.0709	6405	0.9716
Validation	Predicted Adverse Event Logistics Regression Selected Y	Fit Nominal Logistic		0.6630	0.8006	0.2319	0.2548	0.1266	0.0916	6405	0.9649
Validation	Predicted Adverse Event Logistics Regression Backward Y	Fit Nominal Logistic		0.5808	0.7008	0.2171	0.2624	0.1368	0.0935	2600	0.9510
Validation	Predicted Adverse Event Logistics Regression Forward Y	Fit Nominal Logistic		0.5790	0.7001	0.2198	0.2638	0.1382	0.0945	2562	0.9496
Validation	Predicted Adverse Event Logistics Regression All Y	Fit Nominal Logistic		-0.135	-0.230	0.573	0.3157	0.1967	0.1362	2782	0.8619

4.12 Time Advantage Evaluation

To evaluate the time advantage of using the proposed model over a manual review the created database from the downloaded MAUDE files were used instead of an actual search using the online tool (see Appendix A). The downloaded files are a representation of the online search tool, and allows for easier analysis with identical results to the online search tool. The results from 30 possible product specifications combinations chosen at random are depicted in Appendix F. The average time for reviewing a combination was 61.93 minutes with a minimum of 1.4 minutes and a

maximum of 876.4 minutes. Figure 20 shows the results of the normal plot and goodness of fit test performed to determine if a parametric or nonparametric test would be used to evaluate the time advantage between the proposed automated model and a manual search. The results of the test indicate that the review time data is not from a normal distribution and therefore the nonparametric test Wilcoxon Signed-Rank test was used to evaluate the difference between the median time using a manual approach and the hypothesized median time to use the proposed automated model.

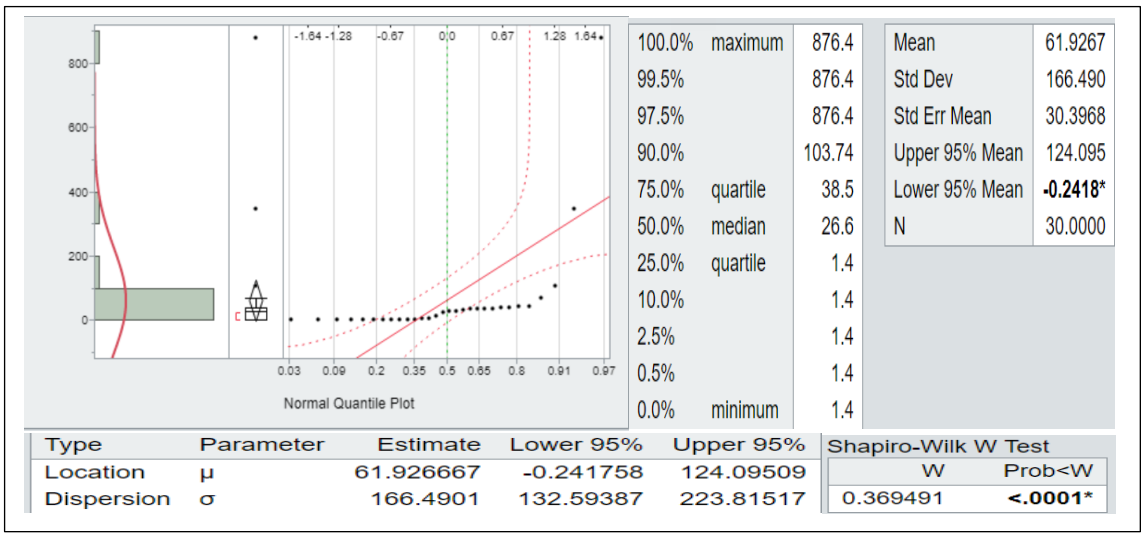


Figure 20 Normal Quantile Plot and Goodness of Fit test showing that the data is not normal

The results of the Wilcoxon Signed Rank test is seen in Figure 21. The results show that the Prob >t is less than 0.05, and therefore the null hypothesis is rejected that the true median is less than or equal to a time of 0 minutes and is about 166.49 minutes or approximately 3 hours longer. The compounding time advantage in reviewing several errors and device characteristics can be substantial during the development of a device, and will be discussed further in Chapter 5.

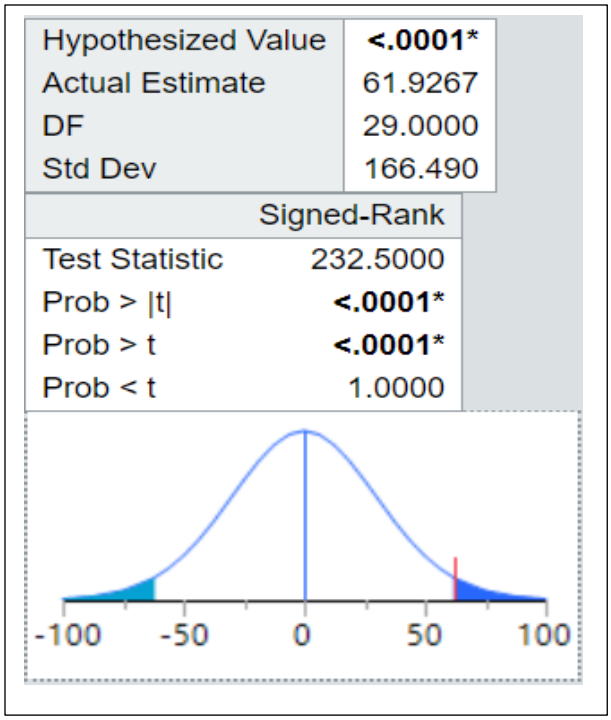
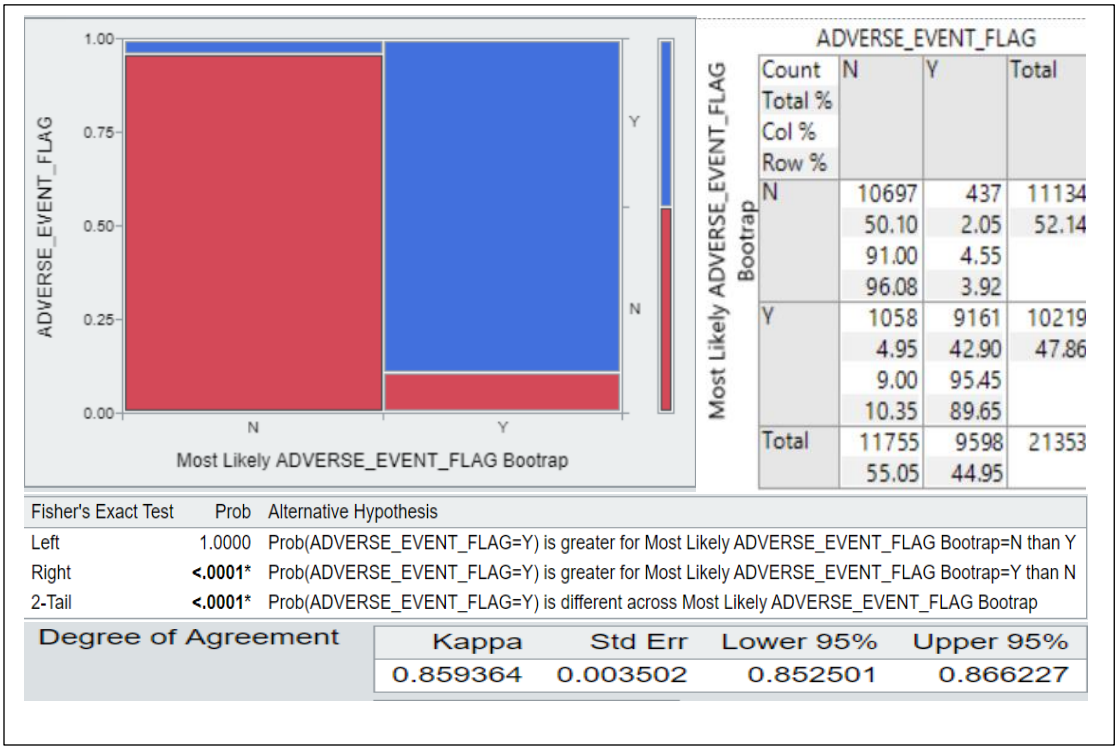


Figure 21 Wilcoxon Signed-Ranked test showing that the median manual review time is different from the hypothesized value of zero for the model

4.13 Accuracy Advantage Evaluation

To evaluate the accuracy advantage of using the proposed model over a manual review process, the identified typical inter-rater reliability score for a manual approach used for analyzing the MAUDE database of 0.52 (Gupta, et al., 2017) was compared to the Kappa score for the chosen final model for the automated approach. Depending on the performance of the automated approach, it can be expected to highly correlate with the actual data-labeled gold standard classifications, and will also provide consistent results between each use and therefore less errors when utilized. To generate the Kappa score for the final model, a contingency table was first generated comparing the actual result from the model to the labeled data result for adverse events. The results are presented in Figure 22. The results from the Fisher's exact test showed that there was no

statistical difference between the predicted adverse events classification from the Bootstrap Forest model and the actual classifications.



ADVERSE_EVENT_FLAG

Most Likely ADVERSE_EVENT_FLAG Bootrap	Count / Total % / Col % / Row %	N	Y	Total
N		10697	437	11134
		50.10	2.05	52.14
		91.00	4.55	
		96.08	3.92	
Y		1058	9161	10219
		4.95	42.90	47.86
		9.00	95.45	
		10.35	89.65	
Total		11755	9598	21353
		55.05	44.95	

Fisher's Exact Test	Prob	Alternative Hypothesis
Left	1.0000	Prob(ADVERSE_EVENT_FLAG=Y) is greater for Most Likely ADVERSE_EVENT_FLAG Bootrap=N than Y
Right	**<.0001***	Prob(ADVERSE_EVENT_FLAG=Y) is greater for Most Likely ADVERSE_EVENT_FLAG Bootrap=Y than N
2-Tail	**<.0001***	Prob(ADVERSE_EVENT_FLAG=Y) is different across Most Likely ADVERSE_EVENT_FLAG Bootrap

Degree of Agreement

Kappa	Std Err	Lower 95%	Upper 95%
0.859364	0.003502	0.852501	0.866227

Figure 22 Contingency table, Fisher's exact test results, and degree of agreement Kappa test results

Using an agreement test, the Kappa coefficient was determined to be 0.86 for the final model, indicating a high degree of agreement or an error rate between the model and gold standard result of 14%, an accuracy in the reported results from the model of 74%. As shown in Table 8 , this is a substantial improvement compared to a typical manual review agreement Kappa score of 0.52 or an error rate of 48%, an accuracy in the reported results from the manual reviewers of 27%. The impact overall can be substantial during the development of a device when considering the contributions that the identification of potential errors has in designing a product, and will be discussed further in Chapter 5.

Table 8 Comparison between agreement score, error rate and accuracy for the proposed automated model and a manual approach

Statistics	Proposed Model	Manual Review
Kappa Score	0.86	0.52
Error Rate	14%	48%
Accuracy	74%	27%
Reliability Interpretation	Almost perfect agreement (Range 0.81-1.0)	Moderate agreement (Range 0.41-0.60)

Chapter 5—Discussion and Conclusions

5.1 Discussion

In this study, the MAUDE database was used as the source to create an automated model that is able to estimate the probability of use related errors for IVD devices. The research showed that an automated model that is accurate and saves time can be created to determine use error probabilities based on characteristics of an IVD device. The next sections will evaluate the research questions and the hypotheses tested to arrive at this statement as well as the potential impact when the model is applied. The chapter will culminate with the conclusions and contributions to the body of knowledge and some suggestions for future research to enhance the current findings in this research

5.2 Research Questions 1 and 2 and Hypotheses 1 and 2

The first task of the research was to identify if variables related to the device type description and therapeutic area within the database are key contributors to predicting adverse event classifications and then determine if a model could be generated using these variables to predict the classification of an adverse event to be utilized in identifying critical use error probabilities.

RQ1: How is the classification of an adverse event due to use error related to device type and therapeutic area using the MAUDE Database?

- **H1:** *The device type and therapeutic area are significant contributors to the classification of an adverse event due to use error using the MAUDE Database.* **ACCEPT THE HYPOTHESIS**

The research showed that there are several characteristics:

DEVICE_REPORT_PRODUCT_CODE, USE ERROR GROUP, DEVICE OPERATOR GROUP, MEDICAL_SPECIALTY

GROUP, and TESTING/DEVICE GROUP of an IVD device that are important in identifying the probabilities of a user error related adverse event. Most importantly these characteristics are readily available to a user of the proposed model and do not require a burdensome number of characteristics to generate accurate probability results.

RQ2: Can an automated model be created that can classify adverse events related to use error based on device type and therapeutic area?

- **H2:** *Supervised machine learning methods can be used to automate detection of use error related adverse events given the device characteristics and therapeutic area.* **ACCEPT THE HYPOTHESIS**

The chosen final model uses the Bootstrap Forest algorithm to provide a highly accurate method with a low misclassification rate of 6.95% and is an effective model for distinguishing if an event is an adverse event with a high AUC of 97.5%. Additionally, the characteristics chosen are able to explain the adverse event response with a good generalized R-squared value of 0.8587. Although Logistics Regression appears to be the most commonly used method in the medical field, it requires that the variables are accurately specified, otherwise the prediction or classification accuracy may be low. In this case where the data does not follow typical patterns and the collection of information is without restrictive conditions, it is not surprising that Bootstrap Forest has generated the best performing model and Logistic Regression performed the worst among the algorithms explored. Bootstrap Forest and other decision tree models have been shown to be a good alternative especially in cases of rare event data like adverse events in the MAUDE database because these methods are less susceptible to issues with bias,

variance and convergence, seen with statistical methods and other ML methods (Attewell, Monaghan, & Kwong, 2015).

In addition to the creation of an optimal model, the model is advantageous in grouping use error problems into more actionable categories for design improvement and provide the probabilities of these issues to aid in the prioritization of resources. These use error groupings provide an understanding from a human factor and usability perspective and allows the design team to address the design based on the cognitive areas that are impacted for the new device rather than a specific design issue identified with a similar device that may not in fact be applicable to the new device.

5.3 Research Questions 3 and 4 and Hypotheses 3 and 4

One of the main motivations for this research is to identify a method that is able to improve the identification of use errors when using the MAUDE database. It has been discussed in the previous section that a model can be achieve that can accurately represent the MAUDE database. To show the advantages over the current manual methods and therefore the reason to utilize the proposed model over the current manual approach, two components were reviewed: time advantage and subjectivity improvement.

RQ3: Is the proposed automated method faster than the manual approach?

- **H3**: *There is a statistically significant difference between the time it takes to review the data using the proposed automated model and a manual approach*. **ACCEPT THE HYPOTHESIS**

A random sample was created that would represent several searches, and the median time to review the information from each search result was compared to the median time to review the information generated from the proposed model. A theoretical

time of 0 minutes was used based on the negligible amount of time that would be required to use the model given a normalized baseline in both the manual and automated approach after the product characteristics have been identified. The results showed that the median time saved by using the model is 166 minutes or approximately 3 hours per product and for each use error category of interest.

Time advantage is increased as other types of use errors are evaluated across multiple devices under the development or improvement process. For example, the dollar amount saved is approximately $6795 if a company develops or improves 10 medical devices annually; reviewing 6 use error categories for each device at an average hourly salary for a Human Factors Engineering of $37.75 (PayScale, 2019). Although this is not a substantial amount for a large company, on the scale of a department budget this is a considerable cost savings from one aspect of the development process. Furthermore, the time savings and associated dollar amount calculated only considers the use of the model for reviewing the specific records from the MAUDE database and does not include the time required for training of the reviewers to allow for consistency in reviewing between and within device evaluations. The training in one study included review of a written tutorial providing instructive information; review and analysis of sample reports; test cases with annotated answer key followed by 20 practice reviews to determine the reviewer's consistency and accuracy (DeLuca, et al., 2012). This was an iterative process requiring training, retraining and assessment and although there are no specific numbers provided in the study for how long this training took, given the number of tasks, could be estimated to have taken 1-4 weeks and required at least two persons (the trainer and the trainee). This would add to the annual costs savings for using the proposed automated

model for 10 products under the development or improvement process; an additional $30200 for 1 week of training, 8 hours each day for two persons at an average hourly salary of $37.75 (PayScale, 2019).

RQ4: Is the proposed automated model more accurate in interpretation of the MAUDE database?

- **H4**: *There is an improved reliability score when reviewing the MAUDE database using the proposed automated model than a manual approach.*

  ACCEPT THE HYPOTHESIS

Inter-rater reliability testing is a method for estimating the degree of agreement between independent reviewers of the same data and is measured using the Kappa coefficient. In preforming usability evaluation, it is important that the evaluators are consistent when they review the MAUDE database to ensure that similar conclusions are made for all products using the same information. However, as noted by the FDA, manual review of the MAUDE database is very subjective. If the MAUDE database reviewing agreement is high, then individual biases are reduced, in turn reducing subjectivity and increasing the objectivity of the assessment. Furthermore, if the assessment is more objective, then there is an expectation that the results will be more consistent with an expected result and therefore more accurate. To compare the level of agreement for the adverse event data between manual reviewing and the proposed automated model, the level of agreement between (1) the expected results generated from the automated model and the known adverse event results and (2) the expected level of agreement between different reviewers if they reviewed the adverse event data, were compared to each other using the inter-rater reliability score (Kappa coefficient). The

research showed that proposed model would provide an 86% agreement to the known classification of adverse event compared to an expected agreement between manual reviewers to the known classification of the adverse event of only 52%. In other words, if a set of manual reviewers reviewed the adverse event data to determine the classification of adverse event, they would disagree from each other on the classification 48% of the time and the accuracy of the interpretation would only be 27%, whereas the model would disagree only 14% of the time and the accuracy of the interpretation would be 74%. Consequently, an evaluation using the proposed model would be more consistent and accurate and ultimately more objective.

The utility of the model is to identify critical tasks that if not adequately addressed could result in harm. An accuracy of only 27% using a manual review could translate into the potential of missing 73% of the critical tasks. If this is extended over 10 devices under the development or improvement process in a given year, and considering that there are hypothetically 24 critical tasks that would be identified for each device, the manual approach would miss 176 out of 240 tasks (see Table 9).

Table 9 Missed tasks comparison between proposed model and manual review

Approach	**Accuracy**	**Tasks Identified***	**Tasks Missed***
Manual review	27%	64	176
Proposed model	74%	177	63

*For 10 devices under the development or improvement process and 24 potential tasks in a given year

These missed tasks would have the potential to result in adverse events because they were not identified during the design requirements capture process. As previously discussed in the literature section of the praxis, the identification process feeds into the design development and design validation process and would result in a cascading effect

not only for the design of the device in reducing potential adverse events but lessen the benefits outlined in Figure 3 and could possibly result in the following:

- Delayed time to market due to identifying user interface issues late in the development cycle
- Increased customer training and support requirements
- Complexed user manuals and related tools
- Reduced sales from diminished interface quality
- Reduced user satisfaction
- Reduced market life
- Increased exposure to liability claims
- Reduced clarity with regulatory compliance
- Reduced marketing positioning due to usability and productivity issues

5.4 Conclusions

The FDA, the MHRA and other regulatory authorities recommends that during the development process of a device, manufacturers should aim to understand the use errors of comparable devices to the ones of interest. Knowing the probability and severity of use errors for similar products, they can be eliminated or reduce by implementing HFE/UE principles related to them. The research provides an alternative to a manual approach that is an accurate and time-saving automated method to classify use error related adverse events for IVD devices and therefore an estimation of the use error probabilities. Figure 23 shows the utility and application of the model for three products under development and the identification of high risk or critical use errors. These

probabilities can then be used to determine focus areas to inform the risk management efforts and protocol development for human factors validation testing. The long term goal is to facilitate device design improvements to ensure safety and prevent patient injury and death caused by adverse events associated with use errors with IVD medical devices.

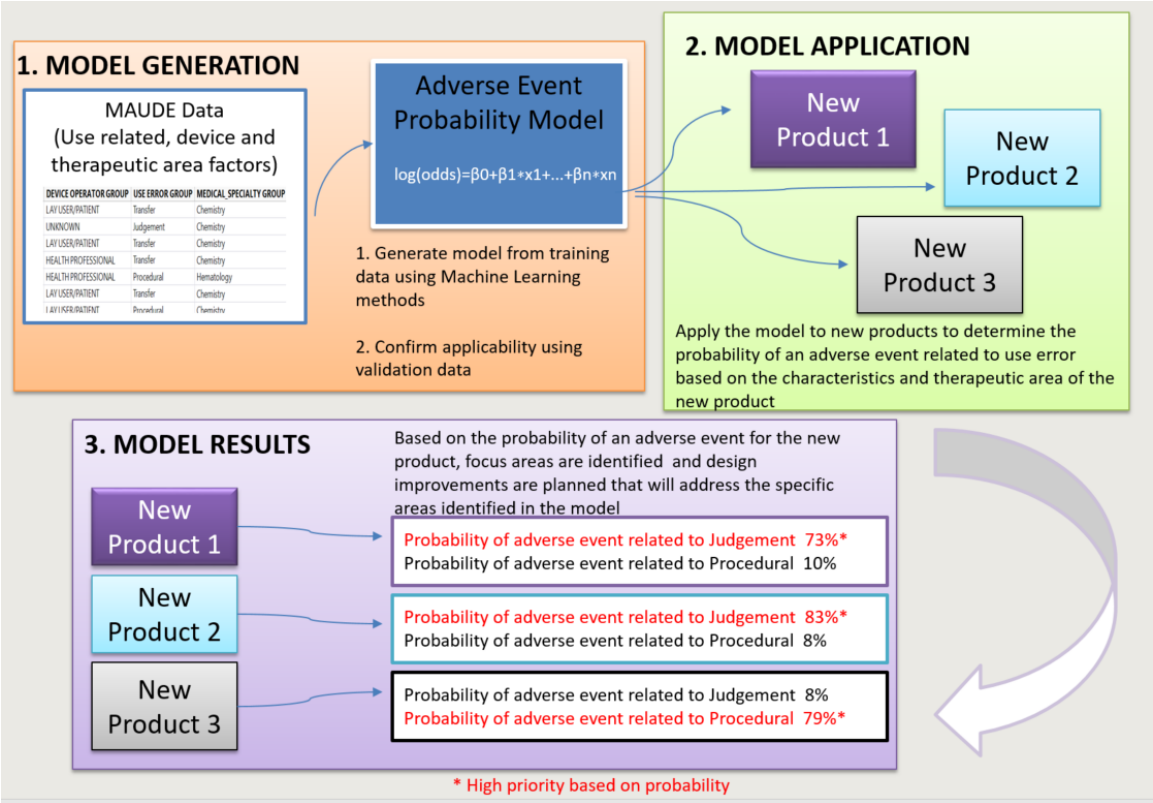


Figure 23 Utility of the proposed model during the development process.

5.5 Contributions to Body of Knowledge

The following contributions are a result of the work completed within this praxis:

1. An estimation tool is created that can automate the determination of the relative probability of adverse event related use error issues which can be used in the decision making process for focus areas in HFE/UE validation testing.

2. An alternative method is provided to a manual approach that improves speed, consistency and objectivity with which focus areas related to use errors for IVD medical devices are determined.
3. A method is identified that uses an automated machine learning model that aligns use error related cognitive knowledge models with device design improvement areas.
4. Confirmed that there is an important relationship between the product characteristics and therapeutic areas within the MAUDE database for predicting use related adverse events.

5.6 Recommendations for Future Research.

The research presented in this praxis provides evidence that a model that saves time and is objective in estimating use error probabilities can be derived using the information collected in the MAUDE database from labeled adverse event information from manufacturers and users of IVD medical devices. Future research should focus on improving the model using narrative information, applying the model to actual device design HFE/UE studies, exploring the method within other error areas and devices, and finally determining how often the model should be recalibrated.

5.6.1 Semi-Supervised Learning Using Narrative Text

To further improve the identified model, a semi-supervised learning approach could be evaluated to use both the labeled information and narrative text information in the MAUDE database. This semi-supervised approach could be utilized to (1) identify additional reports that were excluded from the analysis because there were missing information in coded fields including the product code, adverse event classification,

problem identification, location, operator; and (2) correct coded information that may have been incorrectly coded in the labeled fields but better explanations are contained within the narrative fields. In creating the subset of the MAUDE database that was utilized to generate the model, there were potential reports from thousands of unlabeled reports that could not be identified and therefore were not included in the model training. Additionally, it has been shown that there are instances where the coding inputted differed from the narrative field or indicated the final route cause rather than the error observed (Harris & North, 2012). Including the missing information and more accurate reflection of the issue reported should improve the overall accuracy of the model.

5.6.2 Model Application and Probability Verification

The model has been shown to be able to accurately represent the information within the MAUDE database, and it is also known that knowledge of use errors from similar device can help to improve the design of future products. To add further credibility as well as to solidify the utility of the proposed model it would be interesting to understand the impact in reducing specific use errors by addressing these issues within the device design given the identified knowledge from the proposed model and as an added bonus compared to a similar device that did not utilized the use error probabilities from the proposed model.

5.6.3 Application to Other Areas

Successful application with use errors for IVD medical devices has been described in this praxis. The application of machine learning methods with other types of errors and medical devices have been explored as described in the literature section, however, its application to the specific approach proposed in the praxis to identify

probability of an adverse event related to the device characteristics has not been explored. This is a novel use of machine learning as well as a novel method for determining probability of errors to improve medical device design. The proposed approach can provide an alternative method for determining probabilities of an adverse event for other types of errors as well as other medical devices and given that it has been determined through this research that the proposed method is faster and more reliable, may provide an advantage to the gold standard manual approach currently in use.

5.6.4 Model Recalibration

The proposed model is expected to be utilized as a static model and does not require re-training each time it is used. However, the use error probabilities in the model is based on information that is currently available and represents a snapshot from 1997 to 2017. As more information is added to the MAUDE database along with changes in designs and available technology, the use errors and their probabilities will also change. It is therefore important that the model is recalibrated to reflect these updates and changes. Further research can be conducted to determine the recalibration period or to identify a quality check method that can determine if an update is required.

References

7Zip. (Version 18.05). Copyright 2019: Igor Pavlov.

AAMI. (2001). *ANSI/AAMI HE74-2001 Human factors.* Arlington, VA: Association for the Advancement of Medical Instrumentation.

Alemayehu, D., Alvir, J., Levenstein, M., & Nickerson, D. (2013). A Data-driven Approach to Quality Risk Management. *Perspectives in Clinical Research*, 4(4), 221–226.

Altayyar, S. S. (2016). Medical Devices and Patient Safety. *Journal of Analytical & Pharmaceutical Research*, 2(5): 00034.

Attewell, P., Monaghan, D. B., & Kwong, D. (2015). *Data Mining for the Social Sciences: An Introduction.* Oakland, CA: University of California Press.

Barg-Walkow, L. H., Walsh, D. R., & Rogers, W. A. (2012). Understanding Use Errors for Medical Devices: Analysis of the MAUDE Database. *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, 56(1), 872–876.

Bhardwaj, R., Nambiar, A. R., & Dutta, D. (2017). A Study of Machine Learning in Healthcare. *2017 IEEE 41st Annual Computer Software and Applications Conference (COMPSAC)* (pp. 236-241). Turin: IEEE.

Bhutkar, G., Konkani, A., Katre, D., & Ray, G. G. (2013). A Review: Healthcare Usability Evaluation Methods. *Biomedical Instrumentation & Technology*, 47(2), 45-53.

Botsis, T., Woo, E. J., & Ball, R. (2013). Application of Information Retrieval: Approaches to Case Classification in the Vaccine Adverse Event Reporting System. *Drug Safety*, 36, 573–582.

Cafri, G., Li, L., Paxton, E. W., & Fan, J. (2018). Predicting Risk for Adverse Health Events Using Random Forest. *Journal of Applied Statistics*, 45(12), 2279-2294.

CDRH. (2001). *Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers.* Rockville. MD: U.S. Department of Health and Human Services: Food and Drug Administration; Center for Devices and Radiological Health.

CDRH. (2016). *Applying Human Factors and Usability Engineering to Medical Devices. Guidance for Industry and Food and Drug Administration Staff.* Rockville, MD: Center for Devices and Radiological Health (CDRH).

Chagpar, A., & Cafazzo, J. A. (2010). Human Factors Recommendations and Testing Considerations for FDA Premarket Medical Device Submissions. *Biomedical Instrumentation & Technology*, 33-39.

Chai, J. Y. (2000). Medical Device Regulation in the United States and the European Union: A Comparative Study. *Food and Drug Law Journal*, 55(1), 57-80.

Chai, K. E., Anthony, S., Coiera, E., & Magrabi, F. (2013). Using Statistical Text Classification to Identify Health Information Technology Incidents. *Journal of the American Medical Informatics Association*, 20(5), 980–985.

Chen, A. (2018). Predicting Adverse Drug Reaction Outcomes with Machine Learning. *International Journal of Community Medicine and Public Health* , 5, 901-904.

Clark, R. M., & Besterfield-Sacre, M. E. (2009). A New Approach to Hazardous Materials Transportation Risk Analysis: Decision Modeling to Identify Critical Variables. *Risk Analysis*, 29, 344-354.

Colvin, C., Fan, M., Cheng, R., Pinkney, S., Sabovitch, S., Shier, A., . . . Easty, A. (2011). Effectiveness of Medical Incident Databases as Tools for Adverse Event Analysis. *CMBES Proceedings*, 34(1).

DeLuca, L. A., Simpson, A., Beskind, D., Grall, K., Stoneking, L., Stolz, U., . . . Denninghoff, K. R. (2012). Analysis of Automated External Defibrillator Device Failures Reported to the Food and Drug Administration. *Annals of Emergency Medicine*, 59,103-111.

Duggirala, H. J., Tonning, J. M., Smith, E., Bright, R. A., Baker, J. D., Ball, R., . . . Khaled, B. (n.d.). *Data Mining at FDA -- White Paper*. Rockville, MD: The Food and Drug Administration.

El-Naqa, I., & Murphy, M. (2015). What Is Machine Learning? In I. El-Naqa, R. Li, & M. Murphy, *Machine Learning in Radiation Oncology.* Springer, Cham.

Everett, K. D., Conway, C., Desany, G. J., Baker, B. L., Choi, G., Taylor, C. A., & Edelman, E. R. (2016). Structural Mechanics Predictions Relating to Clinical Coronary Stent Fracture in a 5 Year Period in FDA MAUDE Database. *Annals of Biomedical Engineering*, 44(2), 391-403.

Feigal, D. W., Gardner, S. N., & McClellan, M. (2003). Ensuring Safe and Effective Medical Devices. *The New England Journal of Medicine*, 348,191-192.

Food and Drug Administration. (2011, October 31). *Understanding Barriers to Medical Device Quality.* Retrieved from US Food and Drug Administration: https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM277323.pdf

Food and Drug Administration. (2016a). *List of Highest Priority Devices for Human Factors Review: Draft Guidance for Industry and Food and Drug Administration Staff.* Rockville, MD: Food and Drug Administration.

Food and Drug Administration. (2016b, February 01). *What is a Serious Adverse Event?* Retrieved from US Food and Drug Administration: https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm

Food and Drug Administration. (2017, December 23). *Human Factors Considerations.* Retrieved from US Food and Drug Administration: https://www.fda.gov/medical-devices/human-factors-and-medical-devices/human-factors-considerations

Food and Drug Administration. (2018a, September 11). *Manufacturer and User Facility Device Experience Database - (MAUDE).* Retrieved from US Food and Drug Administration: https://www.fda.gov/medical-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities/manufacturer-and-user-facility-device-experience-database-maude

Food and Drug Administration. (2018b, September 14). *Medical Device Overview.* Retrieved from US Food and Drug Administration: https://www.fda.gov/forindustry/importprogram/importbasics/regulatedproducts/ucm510630.htm

Food and Drug Administration. (2018c). *Overview of IVD Regulation.* Retrieved from US Food and Drug Administration: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm123682.htm

Food and Drug Administration. (2018d, February 21). *Forms for Reporting to FDA.* Retrieved from US Food and Drug Administration: https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda

Food and Drug Administration. (2019a). *MAUDE - Manufacturer and User Facility Device Experience.* Retrieved from US Food and Drug Administration: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm

Food and Drug Administration. (2019b, May 16). *Overview of IVD Regulation*. Retrieved from US Food and Drug Administration: https://www.fda.gov/medical-devices/ivd-regulatory-assistance/overview-ivd-regulation

Food and Drug Administration. (2019c, June 30). *MAUDE - Manufacturer and User Facility Device Experience* . Retrieved from US Food and Drug Administration: Manufacturer and User Facility Device Experience Database - (MAUDE)

Gawron, V. J., Drury, C. G., Fairbanks, R. J., & Berger, R. C. (2006). Medical Error and Human Factors Engineering: Where Are We Now? *American Journal of Medical Quality*, 21(1), 57-67.

Grayson, J., Gardner, S., & Stephens, M. L. (2015). *Building Better Models with JMP Pro.* Cary: SAS Institute Inc.

Gupta, P., Schomburg, J., Krishna, S., Adejoro, O., Wang, Q., Marsh, B., . . . Konety, B. R. (2017). Development of a Classification Scheme for Examining Adverse Events Associated with Medical Devices, Specifically the DaVinci Surgical System as Reported in the FDA MAUDE Database. *Journal of Endourology*, 31(1), 27-31.

Gupta, S., & Pidgeon, A. (2016). An Analytical Approach to Identifying Potential Use-related Issues Concerning a Medical Device Under Development. *Journal of Medical Engineering and Technology*, 40(3), 61-71.

Gurtcheff, S. E. (2008). Introduction to the MAUDE Database. *Clinical Obstetrics and Gynecology*, 51(1), 120–123.

Hallgren, K. A. (2012). Computing Inter-Rater Reliability for Observational Data: An Overview and Tutorial. *Tutorials in Quantitative Methods for Psychology*, 8(1), 23–34.

Harris, S. D., & North, R. A. (2012). *Mining MAUDE: Human Factors Perspectives on EHR and Device Design from the FDA Manufacturers and Users Device Experience Database.* 2012 Symposium on Human Factors and Ergonomics in Health Care.

Hernández-Cruz, L., & Medina, L. A. (2017). A Predictive Model to Estimate the FDA's Decision Time for Medical Device Development of 510(k)s. *IIE Annual Conference*, 1673-1678.

Ho, T.-B., Le, L., Thai, D. T., & Taewijit, S. (2016). Data-driven Approach to Detect and Predict Adverse Drug Reactions. *Current Pharmaceutical Design*, 22(23), 3498-526.

Hu, N., Huang, L., & Tiwari, R. C. (2015). Signal detection in FDA AERS database using Dirichlet process. *Statistics in Medicine*, 34(19), 2725-42.

ISO 14971:2007. (n.d.). *Medical Devices - Application of Risk Management to Medical Devices.*

Jeong, E., Park, N., Choi, Y., Park, R. W., & Yoon, D. (2018). Machine learning model combining features from algorithms with different analytical methodologies to detect laboratory-event-related adverse drug reaction signals. *PLoS One*, 13(11) .

JMP. (14.2.0). Copyright:1998-2014 Neil Hodgson.

Kang, H., Wang, J., Yao, B., Zhou, S., & Gong, Y. (2019). Toward Safer Health Care: A Review Strategy of FDA Medical Device Adverse Event Database to Identify and Categorize Health Information Technology Related Events. *JAMIA Open*, 2(1),179–186.

Kaye, R. D., North, R., & Peterson, M. (2003). UPCARE: An analysis, description, and educational tool for medical device use problems. *Proceedings of the Eighth*

Annual International Conference of Industrial Engineering Theory, Applications and Practice, 27.

Maak, T. G., & Wylie, J. (2016). Medical Device Regulation: A Comparison of the United States and the European Union. *The Journal of the American Academy of Orthopaedic Surgeons*, 8, 537-43.

McHugh, M. L. (2012). Interrater Reliability: The Kappa Statistic. *Biochemia Medica*, 22(3), 276–282.

MedPAC. (2017). *An Overview of the Medical Device Industry.* Washington, D.C.: The Medicare Payment Advisory Commission.

MHRA. (2016). *Medicines & Medical Devices Regulations: What You Need to Know.* The Medicines and Healthcare Products Regulatory.

Money, A. G., Barnett, J., Kuljis, J., Craven, M. P., Martin, J. L., & Young, T. (2011). The Role of the User within the Medical Device Design and Development Process: Medical Device Manufacturers' Perspectives. *BMC Medical Informatics and Decision Making*, 11,15.

Norman, D. A. (1981). Categorization of Action Slips. *Psychological Review*, 88,1-55.

Norman, D. A. (1983). Design Rules Based on Analyses of Human Error. *Communications of the ACM*, 26(4), 254-258.

Orme, J., & Buehler, C. (2001). Introduction to Multiple Regression for Categorical and Limited Dependent Variables. *Social Work Research*, 25(1), 49-61.

Panch, T., Szolovits, P., & Atun, R. (2018). Artificial Intelligence, Machine Learning and Health Systems. *Journal of Global Health*, 8(2):020303.

PayScale. (2019). *Human Factors Engineer*. Retrieved from PayScale: https://www.payscale.com/research/US/Job=Human_Factors_Engineer/Salary

Personeni, G., Bresso, E., Devignes, M.-D., Dumontier, M., Smail-Tabbone, M., & Coule, A. (2017). Discovering Associations between Adverse Drug Events Using Pattern Structures and Ontologies. *Journal of Biomedical Semantics*, 8(1), 29.

Ranganathan, P., Pramesh, C. S., & Aggarwal, R. (2017). Common Pitfalls in Statistical Analysis: Measures of Agreement. *Perspectives in Clinical Research*, 8(4),187–191.

Reason, J. (1990). *Human error.* Cambridge: Cambridge University Press.

Reason, J. (2000). Human Error: Models and Management. *BMJ*, 320(7237), 768–770.

Reason, J. (2005). Safety in the Operating Theatre - Part 2: Human Error and Organisational Failure. *Quality & Safety in Health Care*, 14(1), 56-60.

Reed, J. (2018, February 23). *Text Mining for Pharmacovigilance and Drug Safety.* Retrieved from Linguamatics: https://www.linguamatics.com/blog/text-mining-pharmacovigilance-and-drug-safety

Ricci, R. P., Pignalberi, C., Magris, B., Aquilani, S., & Altamura, V. (2012). Can we predict and prevent adverse events related to high-voltage implantable cardioverter defibrillator lead failure? *Journal of Interventional Cardiac Electrophysiology*, 33(1),113-121.

Samore, M., Evans, R., Lassen, A., Gould, P., Lloyd, J., Gardner, R., . . . Bright, R. (2004). Surveillance of Medical Device-related Hazards and Adverse Events in Hospitalized Patients. *The Journal of the American Medical Association*, 291(3), 325-34.

Stern, A. D., Kramer, D. B., Ouellet, M., & Kesselheim, A. S. (2017). Review Times and Adverse Events for Cardiovascular Devices. *Nature Biomedical Engineering*, 1(13), 1-3.

Stoltzfus, J. C. (2011). Logistic Regression: A Brief Primer. *Academic Emergency Medicine* , 18 (10), 1099-1104.

Van Den Bos, J., Rustagi, K., Gray, T., Halford, M., Ziemkiewicz, E., & Shreve, J. (2011). The $17.1 Billion Problem: The Annual Cost of Measurable Medical Errors. *Health Affairs*, 30(4), 596-603.

Ward, J. R., & Clarkson, P. J. (2003). An Analysis of Medical Device-related Errors: Prevalence and Possible Solutions. *Journal of Medical Engineering and Technology*, 28(1), 2-21.

WHO. (2010). *Baseline Country Survey on Medical Devices.* World Health Organization.

WHO. (2015). *Post-market Surveillance for In Vitro Diagnostics (IVDs).* Retrieved from World Healh Organization: https://apps.who.int/iris/bitstream/handle/10665/255576/9789241509213-eng.pdf?sequence=1

WHO. (2019). *Laboratory and In Vitro Diagnostics.* Retrieved from World Health Organiation: https://www.who.int/in-vitro-diagnostic/en/

Wu, P.-Y., Cheng, C.-W., Kaddi, C. D., Venugopalan, J., Hoffman, R., & Wang, M. D. (2017). -Omic and Electronic Health Record Big Data Analytics for Precision Medicine. *IEEE Transactions on Biomedical Engineering*, 64(2), 263–273.

Yeleswarapu, S., Rao, A., Joseph, T., Saipradeep, V. G., & Srinivasan, R. (2014). A Pipeline to Extract Drug-adverse Event Pairs from Multiple Data Sources. *BMC Medical Informatics and Decision Making*, 14(1),13.

Zhang, J., Patel, V. L., Johnson, T. R., Chung, P., & Turley, J. P. (2005). Evaluating and Predicting Patient Safety for Medical Devices with Integral Information

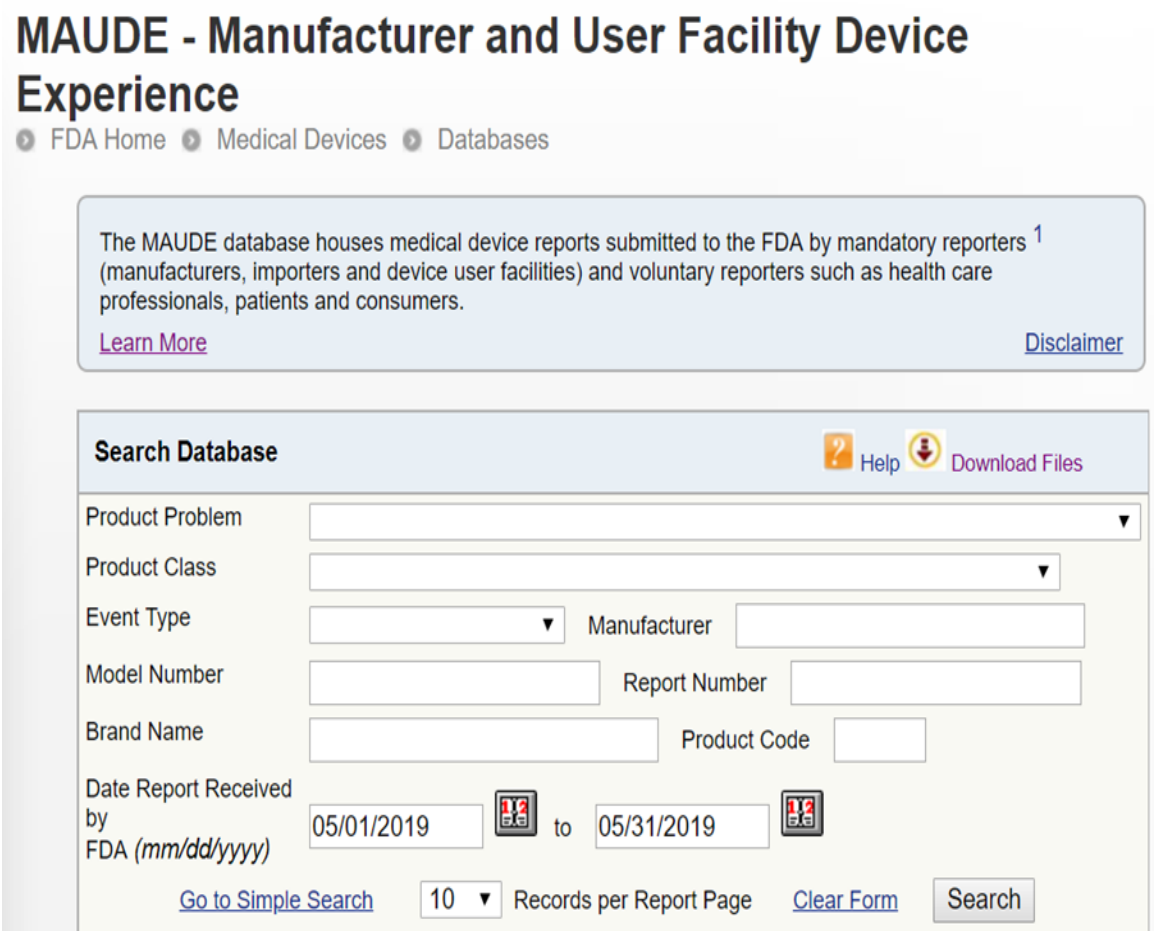
Technology. In K. Henriksen, J. B. Battles, E. S. Marks, & etal, *Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology).* Rockville, MD: Agency for Healthcare Research and Quality.

Zheng, C., & Xu, R. (2018). Large-scale Mining Disease Comorbidity Relationships from Post-market Drug Adverse Events Surveillance Data. *BMC Bioinformatics*, 19(Suppl 17):500.

Zippel, C., & Bohnet-Joschko, S. (2017). Innovation for Safe and Effective Medical Devices: Contributions from Postmarket Surveillance. *Therapeutic Innovation & Regulatory Science*, 51(2), 237-245.

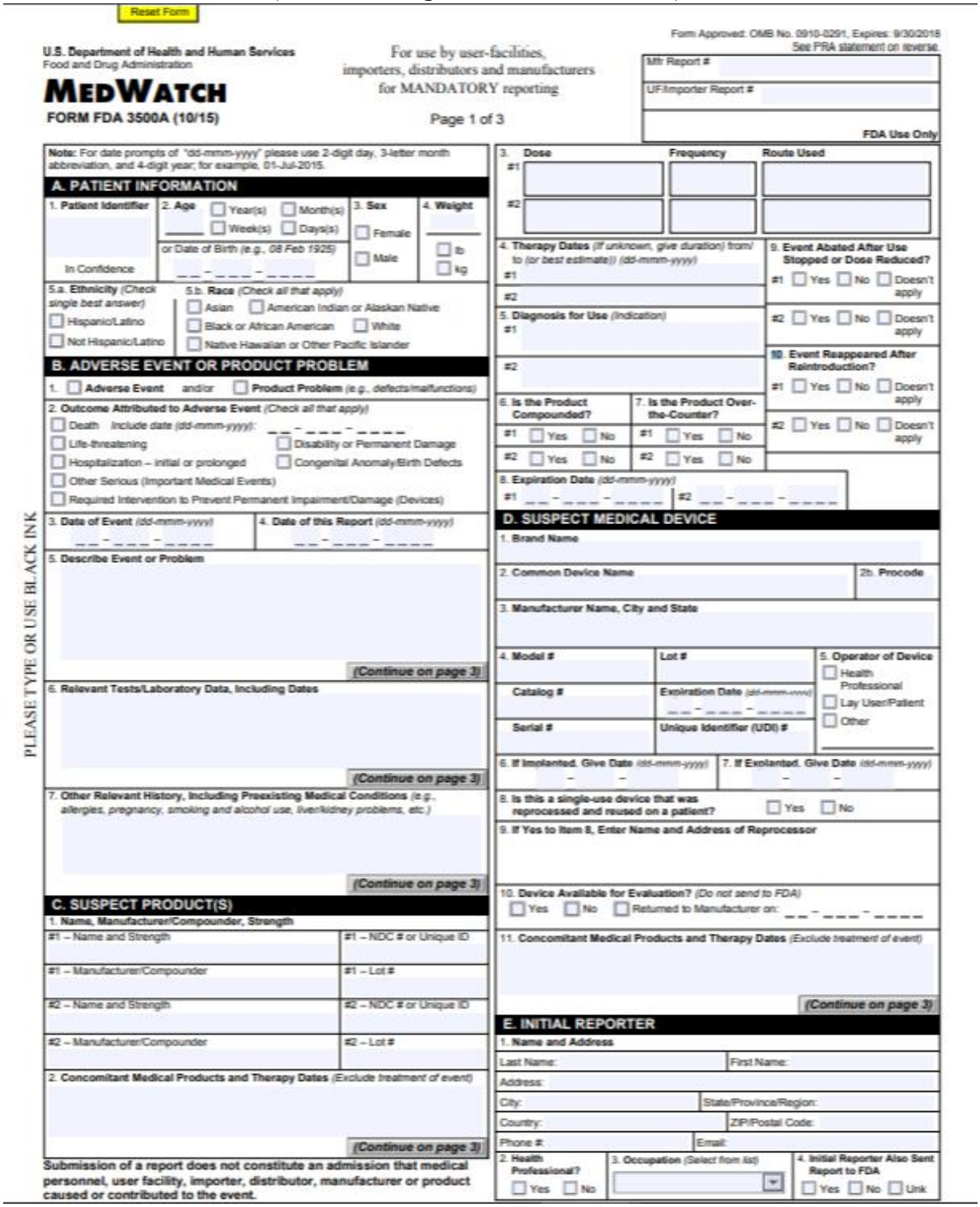
Appendix A

MAUDE Database Online Search Interface (Food and Drug Administration, 2019c)



Appendix B

Medwatch Form 3500A (Food and Drug Administration, 2018d)



Reset Form

Form Approved: OMB No. 0910-0291, Expires: 9/30/2018
See PRA statement on reverse.

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500A (10/15)

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page 1 of 3

Mfr Report #

UF/Importer Report #

FDA Use Only

PLEASE TYPE OR USE BLACK INK

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2015.

A. PATIENT INFORMATION

1. Patient Identifier — In Confidence
2. Age — Year(s) Month(s) Week(s) Days(s) — or Date of Birth (e.g., 08 Feb 1925)
3. Sex — Female Male
4. Weight — lb kg
5.a. Ethnicity (Check single best answer) — Hispanic/Latino; Not Hispanic/Latino
5.b. Race (Check all that apply) — Asian; American Indian or Alaskan Native; Black or African American; White; Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. Adverse Event and/or Product Problem (e.g., defects/malfunctions)
2. Outcome Attributed to Adverse Event (Check all that apply) — Death (Include date (dd-mmm-yyyy)); Life-threatening; Disability or Permanent Damage; Hospitalization – initial or prolonged; Congenital Anomaly/Birth Defects; Other Serious (Important Medical Events); Required Intervention to Prevent Permanent Impairment/Damage (Devices)
3. Date of Event (dd-mmm-yyyy)
4. Date of this Report (dd-mmm-yyyy)
5. Describe Event or Problem — (Continue on page 3)
6. Relevant Tests/Laboratory Data, Including Dates — (Continue on page 3)
7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.) — (Continue on page 3)

C. SUSPECT PRODUCT(S)

1. Name, Manufacturer/Compounder, Strength
#1 – Name and Strength | #1 – NDC # or Unique ID
#1 – Manufacturer/Compounder | #1 – Lot #
#2 – Name and Strength | #2 – NDC # or Unique ID
#2 – Manufacturer/Compounder | #2 – Lot #
2. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) — (Continue on page 3)

3. Dose | Frequency | Route Used — #1, #2
4. Therapy Dates (If unknown, give duration) from/to (or best estimate)) (dd-mmm-yyyy) — #1, #2
5. Diagnosis for Use (Indication) — #1, #2
6. Is the Product Compounded? — #1 Yes No; #2 Yes No
7. Is the Product Over-the-Counter? — #1 Yes No; #2 Yes No
8. Expiration Date (dd-mmm-yyyy) — #1, #2
9. Event Abated After Use Stopped or Dose Reduced? — #1 Yes No Doesn't apply; #2 Yes No Doesn't apply
10. Event Reappeared After Reintroduction? — #1 Yes No Doesn't apply; #2 Yes No Doesn't apply

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name | 2h. Procode
3. Manufacturer Name, City and State
4. Model # | Lot # | 5. Operator of Device: Health Professional; Lay User/Patient; Other
Catalog # | Expiration Date (dd-mmm-yyyy)
Serial # | Unique Identifier (UDI) #
6. If Implanted, Give Date (dd-mmm-yyyy)
7. If Explanted, Give Date (dd-mmm-yyyy)
8. Is this a single-use device that was reprocessed and reused on a patient? Yes No
9. If Yes to Item 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? (Do not send to FDA) Yes No Returned to Manufacturer on:
11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) — (Continue on page 3)

E. INITIAL REPORTER

1. Name and Address
Last Name: | First Name:
Address:
City: | State/Province/Region:
Country: | ZIP/Postal Code:
Phone #: | Email:
2. Health Professional? Yes No
3. Occupation (Select from list)
4. Initial Reporter Also Sent Report to FDA Yes No Unk

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

Reset Form

MEDWATCH

FORM FDA 3500A (10/15) *(continued)*

FDA USE ONLY

F. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. **Check One** ☐ User Facility ☐ Importer
2. **UF/Importer Report Number**
3. **User Facility or Importer Name/Address**
4. **Contact Person**
5. **Phone Number**
6. **Date User Facility or Importer Became Aware of Event** *(dd-mmm-yyyy)*
7. **Type of Report** ☐ Initial ☐ Follow-up #
8. **Date of This Report** *(dd-mmm-yyyy)*
9. **Approximate Age of Device**
10. **Event Problem Codes** *(Refer to coding manual)* Patient Code / Device Code
11. **Report Sent to FDA?** *(If Yes, enter date (dd-mmm-yyyy))* ☐ Yes ☐ No
12. **Location Where Event Occurred** ☐ Hospital ☐ Home ☐ Nursing Home ☐ Outpatient Treatment Facility ☐ Outpatient Diagnostic Facility ☐ Ambulatory Surgical Facility ☐ Other: *(Specify)*
13. **Report Sent to Manufacturer?** *(If Yes, enter date (dd-mmm-yyyy))* ☐ Yes ☐ No
14. **Manufacturer Name/Address**

G. ALL MANUFACTURERS

1. **Contact Office (and Manufacturing Site for Devices)** Name / Address / Email Address / Compounding Outsourcing Facility 503B? ☐ Yes
2. **Phone Number**
3. **Report Source** *(Check all that apply)* ☐ Foreign ☐ Study ☐ Literature ☐ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other:
4. **Date Received by Manufacturer** *(dd-mmm-yyyy)*
5. NDA # / ANDA # / IND # / BLA # / PMA/510(k) # / Combination Product ☐ Yes / Pre-1938 ☐ Yes / OTC ☐ Yes
6. **If IND, Give Protocol #**
7. **Type of Report** *(Check all that apply)* ☐ 5-day ☐ 7-day ☐ 10-day ☐ 15-day ☐ 30-day ☐ Periodic ☐ Initial ☐ Follow-up # ____
8. **Adverse Event Term(s)**
9. **Manufacturer Report Number**

H. DEVICE MANUFACTURERS ONLY

1. **Type of Reportable Event** ☐ Death ☐ Serious Injury ☐ Malfunction
2. **If Follow-up, What Type?** ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. **Device Evaluated by Manufacturer?** ☐ Not Returned to Manufacturer ☐ Yes ☐ Evaluation Summary Attached ☐ No *(Attach page to explain why not)* or provide code:
4. **Device Manufacture Date** *(dd-mmm-yyyy)*
5. **Labeled for Single Use?** ☐ Yes ☐ No
6. **Event Problem and Evaluation Codes** *(Refer to coding manual)* Patient Code / Device Code / Method / Results / Conclusions
7. **If Remedial Action Initiated, Check Type** ☐ Recall ☐ Repair ☐ Replace ☐ Relabeling ☐ Notification ☐ Inspection ☐ Patient Monitoring ☐ Modification/Adjustment ☐ Other:
8. **Usage of Device** ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. **If action reported to FDA under 21 USC 360(f), list correction/removal reporting number:**
10. ☐ **Additional Manufacturer Narrative** and / or 11. ☐ **Corrected Data**

This section applies only to requirements of the Paperwork Reduction Act of 1995.

The public reporting burden for this collection of information has been estimated to average 73 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

Please DO NOT RETURN this form to the above PRA Staff email address.

OMB Statement: "An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Reset Form

(CONTINUATION PAGE)
For use by user-facilities,
importers, distributors, and manufacturers
for MANDATORY reporting
Page 3 of 3

MEDWATCH
FORM FDA 3500A (10/15) *(continued)*

Back to Item B.5

B.5. **Describe Event or Problem** *(continued)*

Back to Item B.6

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

Back to Item B.7

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)* *(continued)*

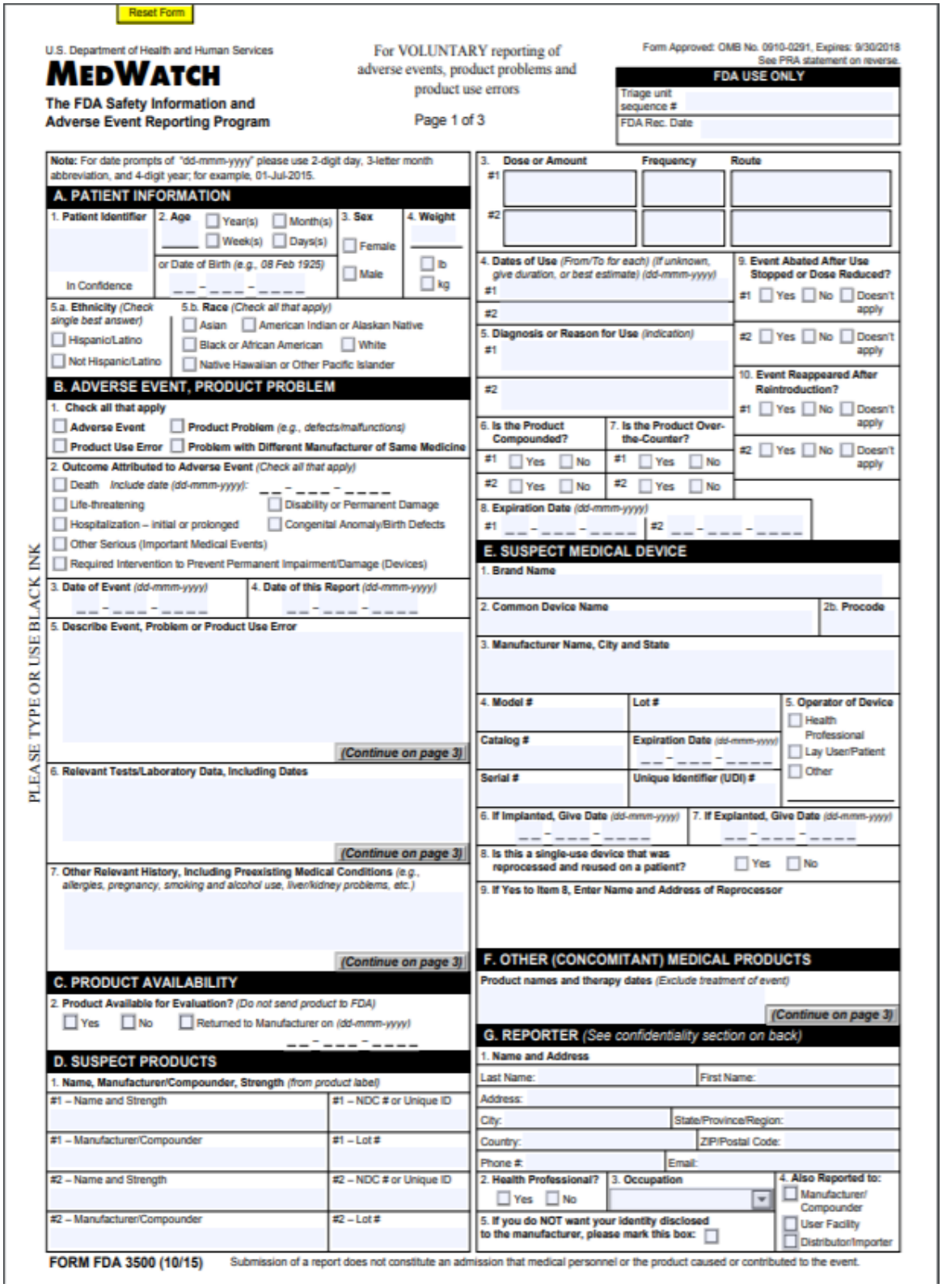
Back to Item C.2

Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)* *(For continuation of C.2 and/or D.11; please distinguish)*

Back to Item D.11

Other Remarks

Medwatch Form 3500 (Food and Drug Administration, 2018d)



Reset Form

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of 3

Form Approved: OMB No. 0910-0291, Expires: 9/30/2018
See PRA statement on reverse.

FDA USE ONLY

Triage unit sequence #

FDA Rec. Date

PLEASE TYPE OR USE BLACK INK

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2015.

A. PATIENT INFORMATION

1. Patient Identifier — In Confidence
2. Age — Year(s) Month(s) Week(s) Days(s) — or Date of Birth (e.g., 08 Feb 1925) __ - ___ - ____
3. Sex — Female Male
4. Weight — lb kg
5.a. Ethnicity (Check single best answer) — Hispanic/Latino; Not Hispanic/Latino
5.b. Race (Check all that apply) — Asian; American Indian or Alaskan Native; Black or African American; White; Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM

1. Check all that apply
Adverse Event; Product Problem (e.g., defects/malfunctions); Product Use Error; Problem with Different Manufacturer of Same Medicine

2. Outcome Attributed to Adverse Event (Check all that apply)
Death Include date (dd-mmm-yyyy): __ - ___ - ____
Life-threatening; Disability or Permanent Damage; Hospitalization – initial or prolonged; Congenital Anomaly/Birth Defects; Other Serious (Important Medical Events); Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (dd-mmm-yyyy) __ - ___ - ____
4. Date of this Report (dd-mmm-yyyy) __ - ___ - ____

5. Describe Event, Problem or Product Use Error
(Continue on page 3)

6. Relevant Tests/Laboratory Data, Including Dates
(Continue on page 3)

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
(Continue on page 3)

C. PRODUCT AVAILABILITY

2. Product Available for Evaluation? (Do not send product to FDA)
Yes No Returned to Manufacturer on (dd-mmm-yyyy) __ - ___ - ____

D. SUSPECT PRODUCTS

1. Name, Manufacturer/Compounder, Strength (from product label)

#1 – Name and Strength	#1 – NDC # or Unique ID
#1 – Manufacturer/Compounder	#1 – Lot #
#2 – Name and Strength	#2 – NDC # or Unique ID
#2 – Manufacturer/Compounder	#2 – Lot #

3. Dose or Amount / Frequency / Route
#1
#2

4. Dates of Use (From/To for each) (If unknown, give duration, or best estimate) (dd-mmm-yyyy)
#1
#2

5. Diagnosis or Reason for Use (Indication)
#1
#2

6. Is the Product Compounded? #1 Yes No; #2 Yes No

7. Is the Product Over-the-Counter? #1 Yes No; #2 Yes No

8. Expiration Date (dd-mmm-yyyy)
#1 __ - ___ - ____ #2 __ - ___ - ____

9. Event Abated After Use Stopped or Dose Reduced?
#1 Yes No Doesn't apply
#2 Yes No Doesn't apply

10. Event Reappeared After Reintroduction?
#1 Yes No Doesn't apply
#2 Yes No Doesn't apply

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name
2b. Procode
3. Manufacturer Name, City and State
4. Model #
Lot #
Catalog #
Expiration Date (dd-mmm-yyyy) __ - ___ - ____
Serial #
Unique Identifier (UDI) #
5. Operator of Device: Health Professional; Lay User/Patient; Other
6. If Implanted, Give Date (dd-mmm-yyyy) __ - ___ - ____
7. If Explanted, Give Date (dd-mmm-yyyy) __ - ___ - ____
8. Is this a single-use device that was reprocessed and reused on a patient? Yes No
9. If Yes to Item 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (Exclude treatment of event)
(Continue on page 3)

G. REPORTER (See confidentiality section on back)

1. Name and Address
Last Name: First Name:
Address:
City: State/Province/Region:
Country: ZIP/Postal Code:
Phone #: Email:
2. Health Professional? Yes No
3. Occupation
4. Also Reported to: Manufacturer/Compounder; User Facility; Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, please mark this box:

FORM FDA 3500 (10/15)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Detailed instructions available at: http://www.fda.gov/medwatch/report/consumer/instruct.htm

Report adverse events, product problems or product use errors with:

- Medications *(drugs or biologics)*
- Medical devices *(including in-vitro diagnostics)*
- Combination products *(medication & medical devices)*
- Human cells, tissues, and cellular and tissue-based products
- Special nutritional products *(dietary supplements, medical foods, infant formulas)*
- Cosmetics
- Food *(including beverages and ingredients added to foods)*

Report product problems - quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures (product didn't work)

-Fold Here-

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- Death
- Life-threatening
- Hospitalization - initial or prolonged
- Disability or permanent damage
- Congenital anomaly/birth defect
- Required intervention to prevent permanent impairment or damage (devices)
- Other serious (important medical events)

Report even if:

- You're not certain the product caused the event
- You don't have all the details

How to report:

- Just fill in the sections that apply to your report
- Use section D for all products except medical devices
- Attach additional pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer *(or both)*

Other methods of reporting:

- 1-800-FDA-0178 - To FAX report
- 1-800-FDA-1088 - To report by phone
- www.fda.gov/medwatch/report.htm - To report online

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

-Fold Here-

If your report involves a serious adverse event with a vaccine, call 1-800-822-7967 to report.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

The information in this box applies only to requirements of the Paperwork Reduction Act of 1995

The burden time for this collection of information has been estimated to average 40 minutes per response, including the time to review instructions, search existing data sources, gather and maintain the data needed, and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

Please DO NOT RETURN this form to the PRA Staff e-mail to the left.

OMB statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FORM FDA 3500 (10/15) (Back) **Please Use Address Provided Below -- Fold in Thirds, Tape and Mail**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

Reset Form

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

FORM FDA 3500 (10/15) *(continued)*

(CONTINUATION PAGE)

For VOLUNTARY reporting of adverse events and product problems

Back to Form

B.5. **Describe Event or Problem** *(continued)*

Back to Form

B.6. **Relevant Tests/Laboratory Data, Including Dates** *(continued)*

Back to Form

B.7. **Other Relevant History, Including Preexisting Medical Conditions** *(e.g., allergies, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) (continued)*

Back to Form

F. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event) (continued)*

MAUDE Database Fields and Recoding Information (Food and Drug Administration, 2018a)

MDRFOI file contains following 75 fields, delimited by pipe (|), one record per line:

1. MDR Report Key
2. Event Key
3. Report Number
4. Report Source Code

P = Voluntary report
U = User Facility report
D = Distributor report
M = Manufacturer report

5. Manufacturer Link Flag (internal information flag)
6. Number Devices in Event (if source code is 'P', field will be null)
7. Number Patient in Event (if source code is 'P', field will be null)
8. Date Received

SECTION-B

9. Adverse Event Flag (B1)
10. Product Problem Flag (B1)
11. Date Report (B4)
12 Date of Event (B3) -- new added, 2006
13 Single Use Flag (Reprocessor Flag) (D8) -- new added, 2006
14 Reporter Occupation Code (E3) -- new added, 2006

* INVALID DATA
000 OTHER
001 PHYSICIAN
002 NURSE
0HP HEALTH PROFESSIONAL
0LP LAY USER/PATIENT
100 OTHER HEALTH CARE PROFESSIONAL
101 AUDIOLOGIST
102 DENTAL HYGIENIST
103 DIETICIAN
104 EMERGENCY MEDICAL TECHNICIAN
105 MEDICAL TECHNOLOGIST
106 NUCLEAR MEDICINE TECHNOLOGIST
107 OCCUPATIONAL THERAPIST
108 PARAMEDIC
109 PHARMACIST
110 PHLEBOTOMIST
111 PHYSICAL THERAPIST
112 PHYSICIAN ASSISTANT
113 RADIOLOGIC TECHNOLOGIST
114 RESPIRATORY THERAPIST
115 SPEECH THERAPIST
116 DENTIST

300 OTHER CAREGIVERS
301 DENTAL ASSISTANT
302 HOME HEALTH AIDE
303 MEDICAL ASSISTANT
304 NURSING ASSISTANT
305 PATIENT
306 PATIENT FAMILY MEMBER OR FRIEND
307 PERSONAL CARE ASSISTANT
400 SERVICE AND TESTING PERSONNEL
401 BIOMEDICAL ENGINEER
402 HOSPITAL SERVICE TECHNICIAN
403 MEDICAL EQUIPMENT COMPANY TECHNICIAN/REPRESENTATIVE
404 PHYSICIST
405 SERVICE PERSONNEL
499 DEVICE UNATTENDED
500 RISK MANAGER
600 ATTORNEY
999 UNKNOWN
NA NOT APPLICABLE
NI NO INFORMATION
UNK UNKNOWN

SECTION-E (if source code is 'P', Section E to H will contain no data)

15. Health Professional (E2)
16. Initial Report to FDA (E4)

Y = Yes
N = No
U = Unknown
* = No answer provided

SECTION-F

17. Distributor Name (F3) -- if report source code = 'M' and Manufacturer link flag is 'Y', fields 14 - 20 will contain data; otherwise they will be null
18. Distributor Address line 1 (F3)
19. Distributor Address line 2 (F3)
20. Distributor City (F3)
21. Distributor State Code (F3)
22. Distributor Zip Code (F3)
23. Distributor Zip Code Ext (F3)
24. Date Facility Aware (F6)
25. Type of Report (F7) !multiple submission type, separate by ','

I = Initial submission
F = Followup
X = Extra copy received
O = Other information submitted

26. Report Date (F8)
27. Report to FDA (F11)
28. Date Report to FDA (F11)
29. Event Location (F12)
30. Report to Manufacturer (F13)
31. Date Report to Manufacturer (F13)
32. Manufacturer Name (F14)
33. Manufacturer Address line 1 (F14)
34. Manufacturer Address line 2 (F14)
35. Manufacturer City (F14)
36. Manufacturer State Code (F14)
37. Manufacturer Zip Code (F14)
38. Manufacturer Zip Code Ext (F14)
39. Manufacturer Country Code (F14)
40. Manufacturer Postal Code (F14)

SECTION-G (only for report source 'M', others sources will be null)

41. Manufacturer Contact Title Name (G1)
42. Manufacturer Contact First Name (G1)
43. Manufacturer Contact Last Name (G1)
44. Manufacturer Contact Street 1 (G1)
45. Manufacturer Contact Street 2 (G1)
46. Manufacturer Contact City (G1)
47. Manufacturer Contact State Code (G1)
48. Manufacturer Contact Zip Code (G1)
49. Manufacturer Contact Zip Code Ext (G1)
50. Manufacturer Contact Country Code
51. Manufacturer Contact Postal Code
52. Manufacturer Contact Phone No Area Code (G1)
53. Manufacturer Contact Phone No Exchange (G2)
54. Manufacturer Contact Phone No (G2)
55. Manufacturer Contact Phone No Ext (G2)
56. Manufacturer Contact Phone No Country Code
57. Manufacturer Contact Phone No City Code
58. Manufacturer Contact Phone No Local
59. Manufacturer G1 Name (G1)
60. Manufacturer G1 Street 1 (G1)
61. Manufacturer G1 Street 2 (G1)
62. Manufacturer G1 City (G1)
63. Manufacturer G1 State Code (G1)
64. Manufacturer G1 Zip Code (G1)
65. Manufacturer G1 Zip Code Ext (G1)
66. Manufacturer G1 Country Code
67. Manufacturer G1 Postal Code
68. Source Type (G3) -- multiple source type, separate by ','

00 Other
01 Foreign
02 Study
03 Literature
04 Consumer
05 Health Professional
06 User facility
07 Company representation
08 Distributor
99 Unknown
* Invalid data

69. Date Manufacturer Received (G4)

SECTION-H
70. Device Date Of Manufacture (H4)
71. Single Use Flag (H5)
72. Remedial Action (H7) -- multiple source type, separate by ','

RC = Recall
RP = Repair
RL = Replace
RB = Relabeling
OT = Other
NO = Notification
IN = Inspection
PM = Patient Monitoring
MA = Modification/Adjustment
* = Invalid Data

73. Previous Use Code (H8)
74. Removal/Correction Number (H9)
75. Event type (H1) -- only relevant for report sourcetype 'M'

D = Death
IN = Injury
IL = Injury
IJ = Injury
M = Malfunction
O = Other
* = No answer provided

DEVICE file contains following 45 fields, delimited by pipe (|), one record per line:

1. MDR Report Key
2. Device Event key
3. Implant Flag -- D6, new added; 2006
4. Date Removed Flag -- D7, new added; 2006; if flag in M or Y, print Date

U = Unknown
A = Not available
I = No information at this time
M = Month and year provided only, day defaults to 01
Y = Year provided only, day defaulted to 01, month defaulted to January

5. Device Sequence No -- from device report table
6. Date Received (from mdr_document table)

SECTION-D

7. Brand Name (D1)
8. Generic Name (D2)
9. Manufacturer Name (D3)
10. Manufacturer Address 1 (D3)
11. Manufacturer Address 2 (D3)
12. Manufacturer City (D3)
13. Manufacturer State Code (D3)
14. Manufacturer Zip Code (D3)
15. Manufacturer Zip Code ext (D3)
16. Manufacturer Country Code (D3)
17. Manufacturer Postal Code (D3)
18. Expiration Date of Device (D4)
19. Model Number (D4)
20. Catalog Number (D4)
21. Lot Number (D4)
22. Other ID Number (D4)
23. Device Operator (D5)
24. Device Availability (D10)

Y = Yes
N = No
R = Device was returned to manufacturer
* = No answer provided

25. Date Returned to Manufacturer (D10)
26. Device Report Product Code
27. Device Age (F9)
28. Device Evaluated by Manufacturer (H3)

Y = Yes
N = No
R = Device not returned to manufacturer
* = No answer provided

BASELINE SECTION (for records prior to 2009)

29. Baseline brand name
30. Baseline generic name
31. Baseline model no
32. Baseline catalog no
33. Baseline other id no
34. Baseline device family
35. Baseline shelf life contained in label

Y = Yes
N = No
A = Not applicable
* = No answer provided

36. Baseline shelf life in months
37. Baseline PMA flag
38. Baseline PMA no
39. Baseline 510(k) flag
40. Baseline 510(k) no
41. Baseline preamendment
42. Baseline transitional
43. Baseline 510(k exempt flag
44. Baseline date) first marketed
45. Baseline date ceased marketing

PATIENT file contains following 5 fields, delimited by pipe (|), one record per line:

1. MDR Report Key (from patient report table)
2. Patient Sequence Number (from patient report table)
3. Date Received (from mdr_document table)
4. Sequence Number||','|| Treatment -- multiple source type, separate by ';'
5. Sequence Number||','|| Outcome -- multiple source type, separate by ';'

L - Life Threatening
H - Hospitalization
S - Disability
C - Congenital Anomaly
R - Required Intervention
O - Other
* - Invalid Data
U - Unknown
I - No Information
A - Not Applicable
D - Death

TEXT file contains following 6 fields, delimited by pipe (|), one record per line:

1. MDR Report Key
2. MDR Text Key
3. Text Type Code (D=B5, E=H3, N=H10 from mdr_text table)
4. Patient Sequence Number (from mdr_text table)
5. Date Report (from mdr_text table)
6. Text (B5, or H3 or H10 from mdr_text table)

FOIDEVPROBLEM contains following 2 fields, delimited by pipe (|), one record per line:

1. MDR Report Key
2. Device Problem Code -- (F10) new added; 2006

DEVICEPROBLEMCODES contains following 2 fields, delimited by pipe (|),
one record per line:

1. Device Problem Code
2. Problem Description

Appendix C

Variables and Reasons for Removal

REASON FOR REMOVAL	FACTURER SPECIFIC INFORM	REPORT SPECIFIC
COLUMN NAMES/VARIABLES	GENERIC_NAME	DEVICE_EVENT_KEY
	MANUFACTURER_D_NAME	REPORT_SOURCE_CODE
	MANUFACTURER_D_ADDRESS_1	SOURCE_TYPE
	MANUFACTURER_D_ADDRESS_2	TYPE_OF_REPORT
	MANUFACTURER_D_CITY	DATE_REMOVED_FLAG
	MANUFACTURER_D_STATE_CODE	DEVICE_SEQUENCE_NO
	MANUFACTURER_D_ZIP_CODE	REVIEWCODE
	MANUFACTURER_D_ZIP_CODE_EXT	EVENT_KEY
	MANUFACTURER_D_COUNTRY_COD	DATE_RECEIVED
	MANUFACTURER_D_POSTAL_CODE	DEVICE_AVAILABILITY
	THIRDPARTYFLAG	DATE_RETURNED_TO_MANUFACTURER
	BASELINE_BRAND_NAME	DEVICE_EVALUATED_BY_MANUFACTUR
	BASELINE_GENERIC_NAME	SummaryMalfunctionReporting
	BASELINE_MODEL_NO	REPORT_NUMBER
	BASELINE_CATALOG_NO	NUMBER_DEVICES_IN_EVENT
	BASELINE_OTHER_ID_NO	NUMBER_PATIENTS_IN_EVENT
	BASELINE_DEVICE_FAMILY	DATE_REPORT
	BASELINE_SHELF_LIFE_CONTAINED	DATE_OF_EVENT
	BASELINE_SHELF_LIFE_IN_MONTHS	REPORTER_OCCUPATION_CODE
	BASELINE_PMA_FLAG	HEALTH_PROFESSIONAL
	BASELINE_PMA_NO	INITIAL_REPORT_TO_FDA
	BASELINE_510_K__FLAG	DATE_FACILITY_AWARE
	BASELINE_510_K__NO	REPORT_DATE
	BASELINE_PREAMENDMENT	REPORT_TO_FDA
	BASELINE_TRANSITIONAL	DATE_REPORT_TO_FDA
	BASELINE_510_K__EXEMPT_FLAG	DATE_REPORT_TO_MANUFACTURER
	BASELINE_DATE_FIRST_MARKETED	DATE_MANUFACTURER_RECEIVED
	BASELINE_DATE_CEASED_MARKET	REMOVAL_CORRECTION_NUMBER
	MANUFACTURER_LINK_FLAG_	REPORT_TO_MANUFACTURER
	MANUFACTURER_CONTACT_T_NAM	DATE_ADDED
	MANUFACTURER_CONTACT_F_NAM	DATE_CHANGED
	MANUFACTURER_CONTACT_L_NAM	
	MANUFACTURER_CONTACT_STREE	
	MANUFACTURER_CONTACT_STREE	
	MANUFACTURER_CONTACT_CITY	
	MANUFACTURER_CONTACT_STATE	
	MANUFACTURER_CONTACT_ZIP_CO	
	MANUFACTURER_CONTACT_ZIP_EX	
	MANUFACTURER_CONTACT_COUNT	
	MANUFACTURER_CONTACT_POSTA	
	MANUFACTURER_CONTACT_AREA_	
	MANUFACTURER_CONTACT_EXCHA	
	MANUFACTURER_CONTACT_PHONE	
	MANUFACTURER_CONTACT_EXTENS	
	MANUFACTURER_CONTACT_PCOUN	
	MANUFACTURER_CONTACT_PCITY	
	MANUFACTURER_CONTACT_PLOCA	
	MANUFACTURER_G1_NAME	
	MANUFACTURER_G1_STREET_1	
	MANUFACTURER_G1_STREET_2	
	MANUFACTURER_G1_CITY	
	MANUFACTURER_G1_STATE_CODE	
	MANUFACTURER_G1_ZIP_CODE	
	MANUFACTURER_G1_ZIP_CODE_EXT	
	MANUFACTURER_G1_COUNTRY_COI	
	MANUFACTURER_G1_POSTAL_COD	
	DISTRIBUTOR_NAME	
	DISTRIBUTOR_ADDRESS_1	
	DISTRIBUTOR_ADDRESS_2	
	DISTRIBUTOR_CITY	
	DISTRIBUTOR_STATE_CODE	
	DISTRIBUTOR_ZIP_CODE	
	DISTRIBUTOR_ZIP_CODE_EXT	
	MANUFACTURER_NAME	
	MANUFACTURER_ADDRESS_1	
	MANUFACTURER_ADDRESS_2	
	MANUFACTURER_CITY	
	MANUFACTURER_STATE_CODE	
	MANUFACTURER_ZIP_CODE	
	MANUFACTURER_ZIP_CODE_EXT	
	MANUFACTURER_COUNTRY_CODE	
	MANUFACTURER_POSTAL_CODE	

REASON FOR REMOVAL	DEVICE SPECIFIC	LE PREDICTORS (with Insufficient Infor	MOVED DURING MODEL REFINEMI	OUTCOME/ACTION
COLUMN NAMES/VARIABLES	DEVICENAME	TARGETAREA	GMP_EXEMPT_FLAG	
	DEFINITION	TECHNICALMETHOD	DEVICE_CLASS	REMEDIAL_ACTION
	BRAND_NAME	IMPLANT_FLAG	SUBMISSION_TYPE DESCRIPTION	EVENT_TYPE
	EXPIRATION_DATE_OF_DEVICE	UNCLASSIFIED_REASON	EVENT_LOCATION	PATIENT_SEQUENCE_NUMBER
	MODEL_NUMBER	PHYSICALSTATE	REVIEW_PANEL	SEQUENCE_NUMBER_TREATMENT
	CATALOG_NUMBER	PREVIOUS_USE_CODE	EVENT_LOCATION DESCRIPTION	SEQUENCE_NUMBER_OUTCOME
	LOT_NUMBER	Life_Sustain_ruppart_flag	GMP_EXEMPT_FLAG	
	OTHER_ID_NUMBER			
	DEVICE_AGE_TEXT			
	DEVICE_DATE_OF_MANUFACTURE			

Grouping and Mapping of Predictors and Potential Variables with Counts

EVENT_LOCATION	EVENT_LOCATION DESCRIPTION	N
0	OTHER	731
1	HOSPITAL	1037
2	HOME	275
5	OUTPATIENT DIAGNOSTIC FACILITY	152
611	LABORATORY	27
I	UNKNOWN	7664
NI	NO INFORMATION	10

SUBMISSION_TYPE_ID	SUBMISSION_TYPE DESCRIPTION	N
1	510(K)	17824
4	510(K) Exempt	3527

DEVICE_CLASS	N
1	3560
2	17791

GMP_EXEMPT_FLAG	N
N	20953
Y	398

SINGLE_USE_FLAG	N
*	648
I	40
N	18807
Y	1044

MEDICAL_SPECIALTY GROUP	MEDICAL_SPECIALTY	REVIEW_PANEL GROUP	REVIEW_PANEL	REVIEW_PANEL DESCRIPTION	N
Chemistry	CH	Chemistry	CH	Clinical Chemistry	17922
Chemistry	CH	Immunology, Toxicology and Microbiology	MI	Microbiology	26
Chemistry	CH	Immunology, Toxicology and Microbiology	TX	Clinical Toxicology	2
Hematology	HE	Hematology	HE	Hematology	1546
Immunology, Toxicology and Microbiology	IM	Immunology, Toxicology and Microbiology	IM	Immunology	1
Immunology, Toxicology and Microbiology	IM	Pathology	PA	Pathology	1
Immunology, Toxicology and Microbiology	MI	Immunology, Toxicology and Microbiology	IM	Immunology	28
Immunology, Toxicology and Microbiology	MI	Immunology, Toxicology and Microbiology	MI	Microbiology	204
Immunology, Toxicology and Microbiology	TX	Immunology, Toxicology and Microbiology	TX	Clinical Toxicology	2
Pathology	PA	Pathology	PA	Pathology	1619

DEVICE OPERATOR GROUP	DEVICE_OPERATOR	DEVICE_OPERATOR DESCRIPTION	N
HEALTH PROFESSIONAL	1	PHYSICIAN	62
HEALTH PROFESSIONAL	2	NURSE	60
HEALTH PROFESSIONAL	100	OTHER HEALTH CARE PROFESSIONAL	78
HEALTH PROFESSIONAL	105	MEDICAL TECHNOLOGIST	163
HEALTH PROFESSIONAL	109	PHARMACIST	38
HEALTH PROFESSIONAL	110	PHLEBOTOMIST	183
HEALTH PROFESSIONAL	114	RESPIRATORY THERAPIST	2
HEALTH PROFESSIONAL	303	MEDICAL ASSISTANT	1
HEALTH PROFESSIONAL	0HP	HEALTH PROFESSIONAL	4314
LAY USER/PATIENT	305	PATIENT	4076
LAY USER/PATIENT	306	PATIENT FAMILY MEMBER OR FRIEND	23
LAY USER/PATIENT	0LP	LAY USER/PATIENT	9949
OTHER	0	OTHER	1719
OTHER	401	BIOMEDICAL ENGINEER	1
OTHER	405	SERVICE PERSONNEL	78
UNKNOWN	UNK	UNKNOWN	22

USE ERROR GROUP	Device Problem Code (F10)	DEVICE_PROBLEM_CODE DESCRIPTION	N
Judgement	1397	Misapplication	32
Judgement	1581	Failure to Read Input Signal	2
Judgement	2913	Device Operates Differently Than Expected	1850
Maintenance	1120	Contamination During Use	357
Maintenance	1379	Device Maintenance Issue	96
Maintenance	1563	Failure To Service	1
Maintenance	2303	Microbial Contamination of Device	87
Maintenance	2895	Contamination / decontamination Problem	1
Maintenance	2974	Maintenance Does Not Comply To Manufacturers Recommendations	41
Motor	1398	Misassembled	1
Motor	1399	Misconnection	3
Motor	1670	Use of Device Problem	1583
Motor	2949	Human-Device Interface Problem	194
Motor	2958	Inadequate User Interface	81
Motor	3133	Misassembly by Users	47
Procedural	1001	Failure To Run On AC/DC	3
Procedural	1494	Off-Label Use	398
Procedural	1517	Failure to Recalibrate	3
Procedural	2410	Miscalibration	39
Procedural	2901	Contamination of Device Ingredient or Reagent	9
Procedural	2914	Device Operational Issue	547
Procedural	3265	Device Handling Problem	3339
Training	1318	Labelling, Instructions for Use or Training Problem	112

USE ERROR GROUP	Device Problem Code (F10)	DEVICE_PROBLEM_CODE DESCRIPTION	N
Training	1319	Inadequate Instructions for Healthcare Professional	124
Training	1643	Inadequate or Insufficient Training	82
Training	2017	Improper or Incorrect Procedure or Method	2117
Training	2956	Inadequate Instructions for Non-Healthcare Professional	4
Transfer	1126	Use of Incorrect Control Settings	9673
Transfer	2948	Human Factors Issue	525

TESTING/DEVICE GROUP	REGULATION GROUP	REGULATION_NUMBER	REGULATION_NUMBER DESCRIPTION	N
Clinical Kits Reagents and Devices	862	862.112	Blood gases (PCO2, PO2) and blood pH test system.	94
Clinical Kits Reagents and Devices	862	862.115	Calibrator.	17
Clinical Kits Reagents and Devices	862	862.1155	Human chorionic gonadotropin (HCG) test system.	18
Clinical Kits Reagents and Devices	862	862.1205	Cortisol (hydrocortisone and hydroxycorticosterone) test system.	1
Clinical Kits Reagents and Devices	862	862.1215	Creatine phosphokinase/creatine kinase or isoenzymes test system.	285
Clinical Kits Reagents and Devices	862	862.1225	Creatinine test system.	125
Clinical Kits Reagents and Devices	862	862.134	Urinary glucose (nonquantitative) test system.	9
Clinical Kits Reagents and Devices	862	862.1345	Glucose test system.	15298
Clinical Kits Reagents and Devices	862	862.1495	Magnesium test system.	3
Clinical Kits Reagents and Devices	862	862.1545	Parathyroid hormone test system.	12
Clinical Kits Reagents and Devices	862	862.155	Urinary pH (nonquantitative) test system.	24
Clinical Kits Reagents and Devices	862	862.16	Potassium test system.	30
Clinical Kits Reagents and Devices	862	862.166	Quality control material (assayed and unassayed).	204
Clinical Kits Reagents and Devices	862	862.1665	Sodium test system.	1
Clinical Kits Reagents and Devices	862	862.1675	Blood specimen collection device.	302
Clinical Kits Reagents and Devices	862	862.1678	Tacrolimus test system.	1
Clinical Kits Reagents and Devices	862	862.1785	Urinary urobilinogen (nonquantitative) test system.	2
Clinical Kits Reagents and Devices	862	862.205	General purpose laboratory equipment labeled or promoted for a specific medical use.	134
Clinical Kits Reagents and Devices	862	862.21	Calculator/data processing module for clinical use.	327
Clinical Kits Reagents and Devices	862	862.215	Continuous flow sequential multiple chemistry analyzer for clinical use.	2
Clinical Kits Reagents and Devices	862	862.216	Discrete photometric chemistry analyzer for clinical use.	512
Clinical Kits Reagents and Devices	862	862.23	Colorimeter, photometer, or spectrophotometer for clinical use.	2
Clinical Kits Reagents and Devices	862	862.231	Clinical sample concentrator.	30
Clinical Kits Reagents and Devices	862	862.256	Fluorometer for clinical use.	58
Clinical Kits Reagents and Devices	862	862.257	Instrumentation for clinical multiplex test systems.	13
Clinical Kits Reagents and Devices	862	862.275	Pipetting and diluting system for clinical use.	223
Clinical Kits Reagents and Devices	862	862.286	Mass spectrometer for clinical use.	1
Clinical Kits Reagents and Devices	862	862.29	Automated urinalysis system.	222
Clinical Kits Reagents and Devices	862	862.355	Lead test system.	1

TESTING/DEVICE GROUP	REGULATION GROUP	REGULATION_NUMBER	REGULATION_NUMBER DESCRIPTION	N
Clinical Kits Reagents and Devices	862	862.384	Sirolimus test system.	1
Diagnostic Devices	866	866.164	Antimicrobial susceptibility test powder.	1
Diagnostic Devices	866	866.1645	Fully automated short-term incubation cycle antimicrobial susceptibility system.	6
Diagnostic Devices	866	866.17	Culture medium for antimicrobial susceptibility tests.	2
Hematology Kits Reagents and Devices	864	864.52	Automated cell counter.	30
Hematology Kits Reagents and Devices	864	864.522	Automated differential cell counter.	398
Hematology Kits Reagents and Devices	864	864.54	Coagulation instrument.	96
Hematology Kits Reagents and Devices	864	864.5425	Multipurpose system for in vitro coagulation studies.	78
Hematology Kits Reagents and Devices	864	864.57	Automated platelet aggregation system.	32
Hematology Kits Reagents and Devices	864	864.67	Erythrocyte sedimentation rate test.	1
Hematology Kits Reagents and Devices	864	864.729	Factor deficiency test.	1
Hematology Kits Reagents and Devices	864	864.747	Glycosylated hemoglobin assay.	90
Hematology Kits Reagents and Devices	864	864.7675	Leukocyte peroxidase test.	1
Hematology Kits Reagents and Devices	864	864.775	Prothrombin time test.	122
Hematology Kits Reagents and Devices	864	864.7925	Partial thromboplastin time tests.	1
Hematology Kits Reagents and Devices	864	864.8625	Hematology quality control mixture.	29
Immunology Kits Reagents and Devices	866	866.47	Automated fluorescence in situ hybridization (FISH) enumeration systems.	1
Immunology Kits Reagents and Devices	866	866.551	Immunoglobulins A, G, M, D, and E immunological test system.	1
Microbiology Devices	866	866.245	Supplement for culture media.	15
Microbiology Devices	866	866.25	Microtiter diluting and dispensing device.	18
Microbiology Devices	866	866.256	Microbial growth monitor.	119
Microbiology Devices	866	866.266	Microorganism differentiation and identification device.	23
Microbiology Devices	866	866.29	Microbiological specimen collection and transport device.	18
Pathology Instrumentation and Accessories	864	864.301	Tissue processing equipment.	263
Pathology Instrumentation and Accessories	864	864.325	Specimen transport and storage container.	1
Pathology Instrumentation and Accessories	864	864.33	Cytocentrifuge.	2
Pathology Instrumentation and Accessories	864	864.38	Automated slide stainer.	46
Pathology Instrumentation and Accessories	864	864.3875	Automated tissue processor.	1307
Products Used In Establishments That Manufacture Blood and Blood Products	864	864.905	Blood bank supplies.	1
Products Used In Establishments That Manufacture Blood and Blood Products	864	864.91	Empty container for the collection and processing of blood and blood components.	1
Products Used In Establishments That Manufacture Blood and Blood Products	864	864.9165	Blood establishment computer software and accessories.	1
Products Used In Establishments That Manufacture Blood and Blood Products	864	864.9175	Automated blood grouping and antibody test system.	10

TESTING/DEVICE GROUP	REGULATION GROUP	REGULATION_NUMBER	REGULATION_NUMBER DESCRIPTION	N
Products Used In Establishments That Manufacture Blood and Blood Products	864	864.9205	Blood and plasma warming device.	26
Products Used In Establishments That Manufacture Blood and Blood Products	864	864.9245	Automated blood cell separator.	628
Serological Reagents	866	866.3235	Epstein-Barr virus serological reagents.	1
Serological Reagents	866	866.3372	Nucleic acid-based in vitro diagnostic devices for the detection of Mycobacterium tuberculosis complex in respiratory specimens.	1
Serological Reagents	866	866.351	Rubella virus serological reagents.	26
Serological Reagents	866	866.378	Toxoplasma gondii serological reagents.	2

DEVICE_REPORT_PRODUCT_CODE	N
BSB	26
CDM	2
CEM	30
CEW	12
CFR	1
CGA	30
CGL	19
CGX	106
CHL	94
DEW	1
DHA	18
DOF	1
DOP	1
GGM	29
GGN	22
GGP	1
GGW	1
GIM	32
GJS	122
GKN	25
GKP	71
GKT	609
GKZ	391
IDO	157
IDP	105
IDW	1
IEO	1307
IFB	2
JFT	1
JGJ	3
JGS	1
JIL	9
JIT	1
JIX	16
JJC	2
JJE	512
JJH	29
JJQ	2
JJX	34
JJY	94
JKA	270
JPA	56

DEVICE_REPORT_PRODUCT_CODE	N
JPH	1
JQC	107
JQP	327
JQW	221
JSK	15
JSO	2
JTC	18
JTO	1
JWX	1
JXA	2
KHO	58
KPA	46
KQO	222
KSR	1
KSS	1
KSZ	10
LCP	90
LFR	9543
LGD	2
LIO	18
LJX	1
LKM	30
LON	6
LQL	19
LQN	26
LRG	1
LSE	1
LXG	27
MDB	91
MJX	26
MLM	1
MMH	1
MMI	285
MWA	1
MZC	28
NBW	5724
NNL	1
NQM	24
NSU	11
NTH	1
OBW	32
OHQ	50
OOI	1
ORG	19
OUF	1
OUL	1
OYE	7
PCA	1
PER	2

Appendix D

Missing Variables Mapping

Count	Count of columns missing	Patterns	DEVICE	USE ERROR	MEDICAL_SPECIA	DEVICE_REPORT_	TESTING/DEVICE	SINGLE_USE_FLAG	GMP_EXEMPT_FLA	DEVICE_CLASS	SUBMISSION_TYPE	EVENT_LOCATION	ADVERSE_EVENT_	MEDICAL_SPECIA	REPROCESSED_AN	REVIEW_PANEL	REVIEW_PANEL	DEVICE_OPERATO	DEVICE_PROBLEM	REGULATION_NU	REGULATION	TEST TYPE GROUP	PREVIOUS_USE_CO	TARGETAREA	TECHNICALMETH	IMPLANT_FLAG	UNCLASSIFIED_RE	PHYSICALSTATE	Life_Sustain_support
61	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
8553	4	110110	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	0
50	2	100000000100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	0	0
532	5	100000110110	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	1	0	1	1	0
110	5	100000000110110	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	1	1	0	1	1	0
3	2	100000000000000	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
11207	5	100000000000110000	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	0
1	6	100000000001110000	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	0
24	6	100100000000110000	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	1	1	0	1	1	0
366	5	100000000000000000000	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	0
225	6	100000000000000000000	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	0
112	7	100000010000000000000	0	0	0	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	1	1	0	1	1	0
24	3	100010000000000000000	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0
26	6	100010000000000000000	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	0
59	7	100010000000000000000	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	1	1	1	0	1	1	0

Appendix E

Backward Selection

DEVICE OPERATOR GROUP{HEALTH PROFESSIONAL-LAY USER/PATIENT&OTHER}

DEVICE OPERATOR GROUP{LAY USER/PATIENT-OTHER}

DEVICE_REPORT_PRODUCT_CODE{DEW&JPH&KSS&CFR&CGA&KSR&JPA&JJH&KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH&LON&MDB&CHL-GKZ&GKT&JQP&JJE&JQC&GJS&NBW&JJX&LXG&LFR&ORG&IEO&CEM&CGX&JKA&MMI&JSK&IDP&JTC&IDO&LQL&LQN&GKP&GKN&KPA&DHA&BSB&MZC&CGL&NNL&OBW&CEW&OUF&JQW&LKM}

DEVICE_REPORT_PRODUCT_CODE{GKZ&GKT&JQP&JJE&JQC&GJS&NBW&JJX-LXG&LFR&ORG&IEO&CEM&CGX&JKA&MMI&JSK&IDP&JTC&IDO&LQL&LQN&GKP&GKN&KPA&DHA&BSB&MZC&CGL&NNL&OBW&CEW&OUF&JQW&LKM}

DEVICE_REPORT_PRODUCT_CODE{GKZ&GKT&JQP&JJE-JQC&GJS&NBW&JJX}

DEVICE_REPORT_PRODUCT_CODE{LXG&LFR&ORG&IEO&CEM-CGX&JKA&MMI&JSK&IDP&JTC&IDO&LQL&LQN&GKP&GKN&KPA&DHA&BSB&MZC&CGL&NNL&OBW&CEW&OUF&JQW&LKM}

DEVICE_REPORT_PRODUCT_CODE{CGX&JKA&MMI-JSK&IDP&JTC&IDO&LQL&LQN&GKP&GKN&KPA&DHA&BSB&MZC&CGL&NNL&OBW&CEW&OUF&JQW&LKM}

SUBMISSION_TYPE DESCRIPTION

EVENT_LOCATION DESCRIPTION{OUTPATIENT DIAGNOSTIC FACILITY&NO INFORMATION-UNKNOWN&OTHER&HOME&LABORATORY&HOSPITAL}

EVENT_LOCATION DESCRIPTION{UNKNOWN-OTHER&HOME&LABORATORY&HOSPITAL}

SINGLE_USE_FLAG{Y&N-*&I}

SINGLE_USE_FLAG{*-I}

DEVICE_OPERATOR DESCRIPTION{BIOMEDICAL ENGINEER&MEDICAL ASSISTANT&PATIENT&RESPIRATORY THERAPIST&OTHER HEALTH CARE PROFESSIONAL&PHLEBOTOMIST&HEALTH PROFESSIONAL-LAY USER/PATIENT&PHARMACIST&NURSE&MEDICAL TECHNOLOGIST&OTHER&PHYSICIAN&PATIENT FAMILY MEMBER OR FRIEND&SERVICE PERSONNEL}

DEVICE_OPERATOR DESCRIPTION{BIOMEDICAL ENGINEER&MEDICAL ASSISTANT&PATIENT&RESPIRATORY THERAPIST-OTHER HEALTH CARE PROFESSIONAL&PHLEBOTOMIST&HEALTH PROFESSIONAL}

DEVICE_OPERATOR DESCRIPTION{OTHER HEALTH CARE PROFESSIONAL-PHLEBOTOMIST&HEALTH PROFESSIONAL}

DEVICE_OPERATOR DESCRIPTION{PHLEBOTOMIST-HEALTH PROFESSIONAL}

DEVICE_OPERATOR DESCRIPTION{LAY USER/PATIENT&PHARMACIST-NURSE&MEDICAL TECHNOLOGIST&OTHER&PHYSICIAN&PATIENT FAMILY MEMBER OR FRIEND&SERVICE PERSONNEL}

DEVICE_OPERATOR DESCRIPTION{NURSE&MEDICAL TECHNOLOGIST&OTHER&PHYSICIAN&PATIENT FAMILY MEMBER OR FRIEND-SERVICE PERSONNEL}

DEVICE_OPERATOR DESCRIPTION{NURSE-MEDICAL TECHNOLOGIST&OTHER&PHYSICIAN&PATIENT FAMILY MEMBER OR FRIEND}

DEVICE_OPERATOR DESCRIPTION{MEDICAL TECHNOLOGIST&OTHER-PHYSICIAN&PATIENT FAMILY MEMBER OR FRIEND}

DEVICE_OPERATOR DESCRIPTION{PHYSICIAN-PATIENT FAMILY MEMBER OR FRIEND}

DEVICE_PROBLEM_CODE DESCRIPTION{Contamination of Device Ingredient or Reagent&Failure to Read Input Signal&Failure to Recalibrate&Failure To Run On AC/DC&Inadequate Instructions for Non-Healthcare Professional&Labelling, Instructions for Use or Training Problem&Microbial Contamination of Device&Misapplication&Misassembled&Misconnection&Inadequate Instructions for Healthcare Professional&Use of Incorrect Control Settings&Contamination During Use&Off-Label Use&Device Operational Issue&Device Operates Differently Than Expected&Inadequate User Interface&Maintenance Does Not Comply To Manufacturers Recommendations-Use of Device Problem&Improper or Incorrect Procedure or Method&Human Factors Issue&Device Maintenance Issue&Human-Device Interface Problem&Device Handling Problem&Misassembly by Users}

DEVICE_PROBLEM_CODE DESCRIPTION{Contamination of Device Ingredient or Reagent&Failure to Read Input Signal&Failure to Recalibrate&Failure To Run On AC/DC&Inadequate Instructions for Non-Healthcare Professional&Labelling, Instructions for Use or Training Problem&Microbial Contamination of Device&Misapplication&Misassembled&Misconnection&Inadequate Instructions for Healthcare Professional-Use of Incorrect Control Settings&Contamination During Use&Off-Label Use&Device Operational Issue&Device Operates Differently Than Expected&Inadequate User Interface&Maintenance Does Not Comply To Manufacturers Recommendations}

DEVICE_PROBLEM_CODE DESCRIPTION{Contamination of Device Ingredient or Reagent&Failure to Read Input Signal&Failure to Recalibrate&Failure To Run On AC/DC&Inadequate Instructions for Non-Healthcare Professional&Labelling, Instructions for Use or Training Problem&Microbial Contamination of Device&Misapplication&Misassembled&Misconnection-Inadequate Instructions for Healthcare Professional}

DEVICE_PROBLEM_CODE DESCRIPTION{Use of Incorrect Control Settings&Contamination During Use&Off-Label Use&Device Operational Issue-Device Operates Differently Than Expected&Inadequate User Interface&Maintenance Does Not Comply To Manufacturers Recommendations}

DEVICE_PROBLEM_CODE DESCRIPTION{Use of Incorrect Control Settings&Contamination During Use-Off-Label Use&Device Operational Issue}

DEVICE_PROBLEM_CODE DESCRIPTION{Off-Label Use-Device Operational Issue}

DEVICE_PROBLEM_CODE DESCRIPTION{Device Operates Differently Than Expected-Inadequate User Interface&Maintenance Does Not Comply To Manufacturers Recommendations}

DEVICE_PROBLEM_CODE DESCRIPTION{Use of Device Problem&Improper or Incorrect Procedure or Method-Human Factors Issue&Device Maintenance Issue&Human-Device Interface Problem&Device Handling Problem&Misassembly by Users}

DEVICE_PROBLEM_CODE DESCRIPTION{Human Factors Issue-Device Maintenance Issue&Human-Device Interface Problem&Device Handling Problem&Misassembly by Users}

TEST TYPE GROUP{Immunological Test Systems&Manual Hematology Devices&Diagnostic Devices&Hematology Kits and Packages&Clinical Toxicology Test Systems&Clinical Laboratory Instruments&Microbiology Devices&Products Used In Establishments That Manufacture Blood and Blood Products-Automated and Semi-Automated Hematology Devices&Clinical Chemistry Test Systems&Serological Reagents&Pathology Instrumentation and Accessories}

TEST TYPE GROUP{Automated and Semi-Automated Hematology Devices&Clinical Chemistry Test Systems-Serological Reagents&Pathology Instrumentation and Accessories}

TEST TYPE GROUP{Automated and Semi-Automated Hematology Devices-Clinical Chemistry Test Systems}

Forward Selection

DEVICE OPERATOR GROUP{HEALTH PROFESSIONAL-LAY USER/PATIENT&OTHER}
DEVICE OPERATOR GROUP{LAY USER/PATIENT-OTHER}

DEVICE_REPORT_PRODUCT_CODE{DEW&JPH&KSS&CFR&CGA&KSR&JPA&JJH&KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH&LON&MDB&CHL-GKZ&GKT&JQP&JJE&JQC&GJS&NBW&JJX&LXG&LFR&ORG&IEO&CEM&CGX&JKA&MMI&JSK&IDP&JTC&IDO&LQL&LQN&GKP&GKN&KPA&DHA&BSB&MZC&CGL&NNL&OBW&CEW&OUF&JQW&LKM}

DEVICE_REPORT_PRODUCT_CODE{DEW&JPH&KSS&CFR&CGA&KSR&JPA&JJH&KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH-LON&MDB&CHL}

DEVICE_REPORT_PRODUCT_CODE{DEW-JPH&KSS&CFR&CGA&KSR&JPA&JJH&KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}

DEVICE_REPORT_PRODUCT_CODE{JPH-KSS&CFR&CGA&KSR&JPA&JJH&KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}

DEVICE_REPORT_PRODUCT_CODE{KSS-CFR&CGA&KSR&JPA&JJH&KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}

DEVICE_REPORT_PRODUCT_CODE{CFR-CGA&KSR&JPA&JJH&KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}

DEVICE_REPORT_PRODUCT_CODE{CGA-KSR&JPA&JJH&KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}

DEVICE_REPORT_PRODUCT_CODE{KSR-JPA&JJH&KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}

DEVICE_REPORT_PRODUCT_CODE{JPA-JJH&KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}

DEVICE_REPORT_PRODUCT_CODE{JJH-KQO&DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}

DEVICE_REPORT_PRODUCT_CODE{KQO-DOF&FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}

DEVICE_REPORT_PRODUCT_CODE{DOF-FMH&GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}
DEVICE_REPORT_PRODUCT_CODE{FMH-GGN&GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}
DEVICE_REPORT_PRODUCT_CODE{GGN-GGP&JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}
DEVICE_REPORT_PRODUCT_CODE{GGP-JIT&KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}
DEVICE_REPORT_PRODUCT_CODE{JIT-KHO&JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}
DEVICE_REPORT_PRODUCT_CODE{KHO-JXA&JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}
DEVICE_REPORT_PRODUCT_CODE{JXA-JGS&JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}
DEVICE_REPORT_PRODUCT_CODE{JGS-JWX&JSO&JIL&LCP&OYE&LGD&PER&LRG&MMH}

DEVICE_REPORT_PRODUCT_CODE{GKZ&GKT&JQP&JJE&JQC&GJS&NBW&JJX-LXG&LFR&ORG&IEO&CEM&CGX&JKA&MMI&JSK&IDP&JTC&IDO&LQL&LQN&GKP&GKN&KPA&DHA&BSB&MZC&CGL&NNL&OBW&CEW&OUF&JQW&LKM}
DEVICE_REPORT_PRODUCT_CODE{GKZ&GKT&JQP&JJE-JQC&GJS&NBW&JJX}

DEVICE_REPORT_PRODUCT_CODE{LXG&LFR&ORG&IEO&CEM-CGX&JKA&MMI&JSK&IDP&JTC&IDO&LQL&LQN&GKP&GKN&KPA&DHA&BSB&MZC&CGL&NNL&OBW&CEW&OUF&JQW&LKM}

DEVICE_REPORT_PRODUCT_CODE{CGX&JKA&MMI-JSK&IDP&JTC&IDO&LQL&LQN&GKP&GKN&KPA&DHA&BSB&MZC&CGL&NNL&OBW&CEW&OUF&JQW&LKM}
SUBMISSION_TYPE DESCRIPTION

EVENT_LOCATION DESCRIPTION{OUTPATIENT DIAGNOSTIC FACILITY&NO INFORMATION-UNKNOWN&OTHER&HOME&LABORATORY&HOSPITAL}
EVENT_LOCATION DESCRIPTION{UNKNOWN-OTHER&HOME&LABORATORY&HOSPITAL}
SINGLE_USE_FLAG{Y&N-*&I}
SINGLE_USE_FLAG{*-I}

DEVICE_OPERATOR DESCRIPTION{BIOMEDICAL ENGINEER&MEDICAL ASSISTANT&PATIENT&RESPIRATORY THERAPIST&OTHER HEALTH CARE PROFESSIONAL&PHLEBOTOMIST&HEALTH PROFESSIONAL-LAY USER/PATIENT&PHARMACIST&NURSE&MEDICAL TECHNOLOGIST&OTHER&PHYSICIAN&PATIENT FAMILY MEMBER OR FRIEND&SERVICE PERSONNEL}

DEVICE_OPERATOR DESCRIPTION{BIOMEDICAL ENGINEER&MEDICAL ASSISTANT&PATIENT&RESPIRATORY THERAPIST-OTHER HEALTH CARE PROFESSIONAL&PHLEBOTOMIST&HEALTH PROFESSIONAL}
DEVICE_OPERATOR DESCRIPTION{OTHER HEALTH CARE PROFESSIONAL-PHLEBOTOMIST&HEALTH PROFESSIONAL}
DEVICE_OPERATOR DESCRIPTION{PHLEBOTOMIST-HEALTH PROFESSIONAL}
DEVICE_OPERATOR DESCRIPTION{LAY USER/PATIENT&PHARMACIST-NURSE&MEDICAL TECHNOLOGIST&OTHER&PHYSICIAN&PATIENT FAMILY MEMBER OR FRIEND&SERVICE PERSONNEL}

DEVICE_OPERATOR DESCRIPTION{NURSE&MEDICAL TECHNOLOGIST&OTHER&PHYSICIAN&PATIENT FAMILY MEMBER OR FRIEND-SERVICE PERSONNEL}

DEVICE_OPERATOR DESCRIPTION{NURSE-MEDICAL TECHNOLOGIST&OTHER&PHYSICIAN&PATIENT FAMILY MEMBER OR FRIEND}
DEVICE_OPERATOR DESCRIPTION{MEDICAL TECHNOLOGIST&OTHER-PHYSICIAN&PATIENT FAMILY MEMBER OR FRIEND}
DEVICE_OPERATOR DESCRIPTION{PHYSICIAN-PATIENT FAMILY MEMBER OR FRIEND}

DEVICE_PROBLEM_CODE DESCRIPTION{Contamination of Device Ingredient or Reagent&Failure to Read Input Signal&Failure to Recalibrate&Failure To Run On AC/DC&Inadequate Instructions for Non-Healthcare Professional&Labelling, Instructions for Use or Training Problem&Microbial Contamination of Device&Misapplication&Misassembled&Misconnection&Inadequate Instructions for Healthcare Professional&Use of Incorrect Control Settings&Contamination During Use&Off-Label Use&Device Operational Issue&Device Operates Differently Than Expected&Inadequate User Interface&Maintenance Does Not Comply To Manufacturers Recommendations-Use of Device Problem&Improper or Incorrect Procedure or Method&Human Factors Issue&Device Maintenance Issue&Human-Device Interface Problem&Device Handling Problem&Misassembly by Users}

DEVICE_PROBLEM_CODE DESCRIPTION{Contamination of Device Ingredient or Reagent&Failure to Read Input Signal&Failure to Recalibrate&Failure To Run On AC/DC&Inadequate Instructions for Non-Healthcare Professional&Labelling, Instructions for Use or Training Problem&Microbial Contamination of Device&Misapplication&Misassembled&Misconnection&Inadequate Instructions for Healthcare Professional-Use of Incorrect Control Settings&Contamination During Use&Off-Label Use&Device Operational Issue&Device Operates Differently Than Expected&Inadequate User Interface&Maintenance Does Not Comply To Manufacturers Recommendations}

DEVICE_PROBLEM_CODE DESCRIPTION{Contamination of Device Ingredient or Reagent&Failure to Read Input Signal&Failure to Recalibrate&Failure To Run On AC/DC&Inadequate Instructions for Non-Healthcare Professional&Labelling, Instructions for Use or Training Problem&Microbial Contamination of Device&Misapplication&Misassembled&Misconnection-Inadequate Instructions for Healthcare Professional}

DEVICE_PROBLEM_CODE DESCRIPTION{Use of Incorrect Control Settings&Contamination During Use&Off-Label Use&Device Operational Issue-Device Operates Differently Than Expected&Inadequate User Interface&Maintenance Does Not Comply To Manufacturers Recommendations}

DEVICE_PROBLEM_CODE DESCRIPTION{Use of Incorrect Control Settings&Contamination During Use-Off-Label Use&Device Operational Issue}
DEVICE_PROBLEM_CODE DESCRIPTION{Off-Label Use-Device Operational Issue}
DEVICE_PROBLEM_CODE DESCRIPTION{Device Operates Differently Than Expected-Inadequate User Interface&Maintenance Does Not Comply To Manufacturers Recommendations}

DEVICE_PROBLEM_CODE DESCRIPTION{Use of Device Problem&Improper or Incorrect Procedure or Method-Human Factors Issue&Device Maintenance Issue&Human-Device Interface Problem&Device Handling Problem&Misassembly by Users}
DEVICE_PROBLEM_CODE DESCRIPTION{Human Factors Issue-Device Maintenance Issue&Human-Device Interface Problem&Device Handling Problem&Misassembly by Users}

TEST TYPE GROUP{Immunological Test Systems&Manual Hematology Devices&Diagnostic Devices&Hematology Kits and Packages&Clinical Toxicology Test Systems&Clinical Laboratory Instruments&Microbiology Devices&Products Used In Establishments That Manufacture Blood and Blood Products-Automated and Semi-Automated Hematology Devices&Clinical Chemistry Test Systems&Serological Reagents&Pathology Instrumentation and Accessories}
TEST TYPE GROUP{Automated and Semi-Automated Hematology Devices&Clinical Chemistry Test Systems-Serological Reagents&Pathology Instrumentation and Accessories}
TEST TYPE GROUP{Automated and Semi-Automated Hematology Devices-Clinical Chemistry Test Systems}

Correlation Table for Variable Pairs in Logistic Regression Model

Effect Names	DEVICE OPERATOR GROUP 1	DEVICE OPERATOR GROUP 2	DEVICE OPERATOR GROUP 3	USE ERROR GROUP 1	USE ERROR GROUP 2	USE ERROR GROUP 3	USE ERROR GROUP 4	USE ERROR GROUP 5	MEDICAL_SPECIALTY GROUP 1	MEDICAL_SPECIALTY GROUP 2	MEDICAL_SPECIALTY GROUP 3	DEVICE OPERATOR GROUP*USE ERROR GROUP 1	DEVICE OPERATOR GROUP*USE ERROR GROUP 2	DEVICE OPERATOR GROUP*USE ERROR GROUP 3	DEVICE OPERATOR GROUP*USE ERROR GROUP 4	DEVICE OPERATOR GROUP*USE ERROR GROUP 5	DEVICE OPERATOR GROUP*USE ERROR GROUP 6	DEVICE OPERATOR GROUP*USE ERROR GROUP 7	DEVICE OPERATOR GROUP*USE ERROR GROUP 8	DEVICE OPERATOR GROUP*USE ERROR GROUP 9	DEVICE OPERATOR GROUP*USE ERROR GROUP 10	DEVICE OPERATOR GROUP*USE ERROR GROUP 11	DEVICE OPERATOR GROUP*USE ERROR GROUP 12	DEVICE OPERATOR GROUP*USE ERROR GROUP 13	DEVICE OPERATOR GROUP*USE ERROR GROUP 14	DEVICE OPERATOR GROUP*USE ERROR GROUP 15	DEVICE OPERATOR GROUP*MEDICAL_SPECIALTY GROUP
DEVICE OPERATOR GROUP 1	1.0	0.7	0.1	0.4	0.3	0.3	0.0	0.1	0.1	0.4	0.1	0.0	0.3	0.4	0.2	0.4	0.2	0.2	0.2	0.2	0.1	0.0	0.0	0.1	0.1	0.1	0.6
DEVICE OPERATOR GROUP 2	0.7	1.0	0.2	0.5	0.4	0.4	0.0	0.2	0.5	0.4	0.1	0.2	0.5	0.4	0.1	0.6	0.3	0.2	0.4	0.2	0.0	0.1	0.0	0.0	0.3	0.0	0.5
DEVICE OPERATOR GROUP 3	0.1	0.2	1.0	0.2	0.2	0.2	0.0	0.4	0.5	0.0	0.0	0.0	0.2	0.0	0.0	0.2	0.2	0.0	0.2	0.2	0.0	0.0	0.0	0.0	0.1	0.5	0.1
USE ERROR GROUP 1	0.4	0.5	0.2	1.0	0.5	0.4	0.3	0.2	0.2	0.3	0.1	0.4	0.7	0.8	0.2	0.7	0.4	0.0	0.5	0.2	0.1	0.4	0.4	0.0	0.3	0.0	0.2
USE ERROR GROUP 2	0.3	0.4	0.2	0.5	1.0	0.5	0.5	0.3	0.3	0.3	0.1	0.1	0.6	0.5	0.5	0.5	0.5	0.1	0.4	0.3	0.0	0.4	0.4	0.0	0.3	0.0	0.1
USE ERROR GROUP 3	0.3	0.4	0.2	0.4	0.5	1.0	0.2	0.1	0.2	0.0	0.0	0.1	0.4	0.4	0.0	0.5	0.4	0.7	0.1	0.3	0.1	0.3	0.2	0.1	0.2	0.0	0.2
USE ERROR GROUP 4	0.0	0.0	0.0	0.3	0.5	0.2	1.0	0.0	0.1	0.0	0.0	0.1	0.4	0.4	0.0	0.4	0.4	0.1	0.4	0.2	0.3	0.7	0.8	0.0	0.0	0.0	0.0
USE ERROR GROUP 5	0.1	0.2	0.4	0.2	0.3	0.1	0.0	1.0	0.4	0.2	0.1	0.0	0.3	0.2	0.0	0.3	0.2	0.0	0.3	0.1	0.0	0.0	0.0	0.5	0.3	0.2	0.0
MEDICAL_SPECIALTY GROUP 1	0.1	0.5	0.5	0.2	0.3	0.2	0.1	0.4	1.0	0.4	0.1	0.1	0.3	0.2	0.1	0.3	0.2	0.0	0.3	0.1	0.0	0.0	0.0	0.1	0.1	0.3	0.1
MEDICAL_SPECIALTY GROUP 2	0.4	0.4	0.0	0.3	0.3	0.0	0.0	0.2	0.4	1.0	0.1	0.2	0.2	0.3	0.1	0.2	0.2	0.1	0.2	0.1	0.1	0.0	0.0	0.2	0.1	0.1	0.1
MEDICAL_SPECIALTY GROUP 3	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.1	0.1	0.1	1.0	0.0	0.1	0.1	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0
DEVICE OPERATOR GROUP*USE ERROR G	0.0	0.2	0.0	0.4	0.1	0.1	0.1	0.0	0.1	0.2	0.0	1.0	0.1	0.4	0.1	0.2	0.1	0.1	0.2	0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.1
DEVICE OPERATOR GROUP*USE ERROR G	0.3	0.5	0.2	0.7	0.6	0.4	0.4	0.3	0.3	0.2	0.1	0.1	1.0	0.6	0.0	0.7	0.4	0.1	0.5	0.2	0.0	0.4	0.4	0.0	0.3	0.0	0.2
DEVICE OPERATOR GROUP*USE ERROR G	0.4	0.4	0.0	0.8	0.5	0.4	0.4	0.2	0.2	0.3	0.1	0.4	0.6	1.0	0.1	0.6	0.2	0.0	0.4	0.1	0.1	0.4	0.3	0.0	0.3	0.1	0.2
DEVICE OPERATOR GROUP*USE ERROR G	0.2	0.1	0.0	0.2	0.5	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.0	0.1	1.0	0.3	0.4	0.1	0.1	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.2
DEVICE OPERATOR GROUP*USE ERROR G	0.4	0.6	0.2	0.7	0.5	0.5	0.4	0.3	0.3	0.2	0.0	0.2	0.7	0.6	0.3	1.0	0.4	0.1	0.7	0.3	0.0	0.5	0.4	0.0	0.4	0.0	0.3
DEVICE OPERATOR GROUP*USE ERROR G	0.2	0.3	0.2	0.4	0.5	0.4	0.4	0.2	0.2	0.2	0.1	0.1	0.4	0.2	0.4	0.4	1.0	0.1	0.3	0.2	0.0	0.3	0.3	0.0	0.2	0.0	0.1
DEVICE OPERATOR GROUP*USE ERROR G	0.2	0.2	0.0	0.0	0.1	0.7	0.1	0.0	0.0	0.1	0.0	0.1	0.1	0.0	0.1	0.1	0.1	1.0	0.4	0.5	0.1	0.0	0.1	0.1	0.1	0.0	0.2
DEVICE OPERATOR GROUP*USE ERROR G	0.2	0.4	0.2	0.5	0.4	0.1	0.4	0.3	0.3	0.2	0.1	0.2	0.5	0.4	0.1	0.7	0.3	0.4	1.0	0.0	0.1	0.4	0.4	0.1	0.2	0.0	0.1

*snapshot only

Appendix F

Combinations from MAUDE Database for Searched Characteristics.

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
HEALTH PROFESSIONAL	Judgement	CH	CDM	Clinical Kits Reagents and Devices	2
HEALTH PROFESSIONAL	Judgement	CH	CHL	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	CH	DOP	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	CH	JJE	Clinical Kits Reagents and Devices	57
HEALTH PROFESSIONAL	Judgement	CH	JJH	Clinical Kits Reagents and Devices	2
HEALTH PROFESSIONAL	Judgement	CH	JKA	Clinical Kits Reagents and Devices	65
HEALTH PROFESSIONAL	Judgement	CH	JQC	Clinical Kits Reagents and Devices	35
HEALTH PROFESSIONAL	Judgement	CH	JQP	Clinical Kits Reagents and Devices	38
HEALTH PROFESSIONAL	Judgement	CH	KHO	Clinical Kits Reagents and Devices	3
HEALTH PROFESSIONAL	Judgement	CH	KQO	Clinical Kits Reagents and Devices	209
HEALTH PROFESSIONAL	Judgement	CH	LXG	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	CH	MMI	Clinical Kits Reagents and Devices	152
HEALTH PROFESSIONAL	Judgement	CH	NBW	Clinical Kits Reagents and Devices	27
HEALTH PROFESSIONAL	Judgement	CH	NSU	Clinical Kits Reagents and Devices	8
HEALTH PROFESSIONAL	Judgement	CH	OOI	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	CH	OUL	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	CH	PCA	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	CH	PER	Clinical Kits Reagents and Devices	2
HEALTH PROFESSIONAL	Judgement	HE	GGP	Hematology Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	HE	GJS	Hematology Kits Reagents and Devices	1

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
HEALTH PROFESSIONAL	Judgement	HE	GKN	Hematology Kits Reagents and Devices	25
HEALTH PROFESSIONAL	Judgement	HE	GKP	Hematology Kits Reagents and Devices	43
HEALTH PROFESSIONAL	Judgement	HE	GKT	Products Used In Establishments That Manufacture Blood and Blood Products	209
HEALTH PROFESSIONAL	Judgement	HE	GKZ	Hematology Kits Reagents and Devices	24
HEALTH PROFESSIONAL	Judgement	HE	KSZ	Products Used In Establishments That Manufacture Blood and Blood Products	5
HEALTH PROFESSIONAL	Judgement	HE	LCP	Hematology Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	HE	LJX	Hematology Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	IM, TX, MI	DEW	Immunology Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	IM, TX, MI	LON	Diagnostic Devices	2
HEALTH PROFESSIONAL	Judgement	IM, TX, MI	LQN	Serological Reagents	26
HEALTH PROFESSIONAL	Judgement	IM, TX, MI	LRG	Diagnostic Devices	1
HEALTH PROFESSIONAL	Judgement	IM, TX, MI	MDB	Microbiology Devices	5
HEALTH PROFESSIONAL	Judgement	IM, TX, MI	NTH	Immunology Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Judgement	PA	FMH	Pathology Instrumentation and Accessories	2
HEALTH PROFESSIONAL	Judgement	PA	IEO	Pathology Instrumentation and Accessories	40
HEALTH PROFESSIONAL	Judgement	PA	IFB	Pathology Instrumentation and Accessories	2
HEALTH PROFESSIONAL	Maintenance	CH	CEM	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Maintenance	CH	GIM	Clinical Kits Reagents and Devices	32
HEALTH PROFESSIONAL	Maintenance	CH	JGS	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Maintenance	CH	JJE	Clinical Kits Reagents and Devices	3
HEALTH PROFESSIONAL	Maintenance	CH	JKA	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Maintenance	CH	JQC	Clinical Kits Reagents and Devices	20

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
HEALTH PROFESSIONAL	Maintenance	CH	JQP	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Maintenance	CH	JQW	Clinical Kits Reagents and Devices	29
HEALTH PROFESSIONAL	Maintenance	CH	NSU	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Maintenance	HE	BSB	Products Used In Establishments That Manufacture Blood and Blood Products	1
HEALTH PROFESSIONAL	Maintenance	HE	GKT	Products Used In Establishments That Manufacture Blood and Blood Products	75
HEALTH PROFESSIONAL	Maintenance	HE	GKZ	Hematology Kits Reagents and Devices	193
HEALTH PROFESSIONAL	Maintenance	HE	JPA	Hematology Kits Reagents and Devices	2
HEALTH PROFESSIONAL	Maintenance	IM, TX, MI	JSO	Diagnostic Devices	2
HEALTH PROFESSIONAL	Maintenance	IM, TX, MI	JTC	Microbiology Devices	1
HEALTH PROFESSIONAL	Maintenance	IM, TX, MI	JXA	Microbiology Devices	2
HEALTH PROFESSIONAL	Maintenance	IM, TX, MI	MDB	Microbiology Devices	61
HEALTH PROFESSIONAL	Maintenance	IM, TX, MI	MWA	Serological Reagents	1
HEALTH PROFESSIONAL	Motor	CH	CGA	Clinical Kits Reagents and Devices	27
HEALTH PROFESSIONAL	Motor	CH	CGL	Clinical Kits Reagents and Devices	19
HEALTH PROFESSIONAL	Motor	CH	CHL	Clinical Kits Reagents and Devices	51
HEALTH PROFESSIONAL	Motor	CH	JIL	Clinical Kits Reagents and Devices	5
HEALTH PROFESSIONAL	Motor	CH	JIT	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Motor	CH	JJE	Clinical Kits Reagents and Devices	192
HEALTH PROFESSIONAL	Motor	CH	JJY	Clinical Kits Reagents and Devices	22
HEALTH PROFESSIONAL	Motor	CH	JKA	Clinical Kits Reagents and Devices	77
HEALTH PROFESSIONAL	Motor	CH	JQC	Clinical Kits Reagents and Devices	13
HEALTH PROFESSIONAL	Motor	CH	JQP	Clinical Kits Reagents and Devices	125
HEALTH PROFESSIONAL	Motor	CH	JQW	Clinical Kits Reagents and Devices	28

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
HEALTH PROFESSIONAL	Motor	CH	KQO	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Motor	CH	LFR	Clinical Kits Reagents and Devices	48
HEALTH PROFESSIONAL	Motor	CH	LXG	Clinical Kits Reagents and Devices	25
HEALTH PROFESSIONAL	Motor	CH	MJX	Clinical Kits Reagents and Devices	26
HEALTH PROFESSIONAL	Motor	CH	MLM	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Motor	CH	MMI	Clinical Kits Reagents and Devices	48
HEALTH PROFESSIONAL	Motor	CH	NBW	Clinical Kits Reagents and Devices	276
HEALTH PROFESSIONAL	Motor	HE	BSB	Products Used In Establishments That Manufacture Blood and Blood Products	25
HEALTH PROFESSIONAL	Motor	HE	GGN	Hematology Kits Reagents and Devices	13
HEALTH PROFESSIONAL	Motor	HE	GJS	Hematology Kits Reagents and Devices	3
HEALTH PROFESSIONAL	Motor	HE	GKP	Hematology Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Motor	HE	GKT	Products Used In Establishments That Manufacture Blood and Blood Products	74
HEALTH PROFESSIONAL	Motor	HE	GKZ	Hematology Kits Reagents and Devices	3
HEALTH PROFESSIONAL	Motor	HE	JPA	Hematology Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Motor	HE	KSR	Products Used In Establishments That Manufacture Blood and Blood Products	1
HEALTH PROFESSIONAL	Motor	HE	LCP	Hematology Kits Reagents and Devices	2
HEALTH PROFESSIONAL	Motor	HE	ORG	Products Used In Establishments That Manufacture Blood and Blood Products	1
HEALTH PROFESSIONAL	Motor	IM, TX, MI	JTO	Microbiology Devices	1
HEALTH PROFESSIONAL	Motor	IM, TX, MI	LON	Diagnostic Devices	1
HEALTH PROFESSIONAL	Motor	IM, TX, MI	LQL	Microbiology Devices	19
HEALTH PROFESSIONAL	Motor	IM, TX, MI	OUF	Clinical Kits Reagents and Devices	1

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
HEALTH PROFESSIONAL	Motor	PA	IDO	Pathology Instrumentation and Accessories	27
HEALTH PROFESSIONAL	Motor	PA	IDP	Pathology Instrumentation and Accessories	59
HEALTH PROFESSIONAL	Motor	PA	IDW	Pathology Instrumentation and Accessories	1
HEALTH PROFESSIONAL	Motor	PA	IEO	Pathology Instrumentation and Accessories	50
HEALTH PROFESSIONAL	Procedural	CH	CEW	Clinical Kits Reagents and Devices	12
HEALTH PROFESSIONAL	Procedural	CH	CGX	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Procedural	CH	CHL	Clinical Kits Reagents and Devices	24
HEALTH PROFESSIONAL	Procedural	CH	DHA	Clinical Kits Reagents and Devices	18
HEALTH PROFESSIONAL	Procedural	CH	JIL	Clinical Kits Reagents and Devices	4
HEALTH PROFESSIONAL	Procedural	CH	JIX	Clinical Kits Reagents and Devices	6
HEALTH PROFESSIONAL	Procedural	CH	JJE	Clinical Kits Reagents and Devices	142
HEALTH PROFESSIONAL	Procedural	CH	JJY	Clinical Kits Reagents and Devices	29
HEALTH PROFESSIONAL	Procedural	CH	JKA	Clinical Kits Reagents and Devices	49
HEALTH PROFESSIONAL	Procedural	CH	JQP	Clinical Kits Reagents and Devices	88
HEALTH PROFESSIONAL	Procedural	CH	JQW	Clinical Kits Reagents and Devices	73
HEALTH PROFESSIONAL	Procedural	CH	KHO	Clinical Kits Reagents and Devices	36
HEALTH PROFESSIONAL	Procedural	CH	KQO	Clinical Kits Reagents and Devices	12
HEALTH PROFESSIONAL	Procedural	CH	LXG	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Procedural	CH	MMI	Clinical Kits Reagents and Devices	85
HEALTH PROFESSIONAL	Procedural	HE	GGM	Hematology Kits Reagents and Devices	29
HEALTH PROFESSIONAL	Procedural	HE	GKP	Hematology Kits Reagents and Devices	27
HEALTH PROFESSIONAL	Procedural	HE	GKT	Products Used In Establishments That	42

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
				Manufacture Blood and Blood Products	
HEALTH PROFESSIONAL	Procedural	HE	GKZ	Hematology Kits Reagents and Devices	27
HEALTH PROFESSIONAL	Procedural	HE	JPA	Hematology Kits Reagents and Devices	30
HEALTH PROFESSIONAL	Procedural	HE	KSZ	Products Used In Establishments That Manufacture Blood and Blood Products	1
HEALTH PROFESSIONAL	Procedural	HE	LCP	Hematology Kits Reagents and Devices	86
HEALTH PROFESSIONAL	Procedural	HE	LKM	Hematology Kits Reagents and Devices	30
HEALTH PROFESSIONAL	Procedural	HE	OYE	Hematology Kits Reagents and Devices	7
HEALTH PROFESSIONAL	Procedural	IM, TX, MI	JWX	Microbiology Devices	1
HEALTH PROFESSIONAL	Procedural	IM, TX, MI	LGD	Serological Reagents	2
HEALTH PROFESSIONAL	Procedural	IM, TX, MI	LON	Diagnostic Devices	2
HEALTH PROFESSIONAL	Training	CH	CHL	Clinical Kits Reagents and Devices	2
HEALTH PROFESSIONAL	Training	CH	JGJ	Clinical Kits Reagents and Devices	3
HEALTH PROFESSIONAL	Training	CH	JJC	Clinical Kits Reagents and Devices	2
HEALTH PROFESSIONAL	Training	CH	JJE	Clinical Kits Reagents and Devices	25
HEALTH PROFESSIONAL	Training	CH	JKA	Clinical Kits Reagents and Devices	56
HEALTH PROFESSIONAL	Training	CH	JQC	Clinical Kits Reagents and Devices	39
HEALTH PROFESSIONAL	Training	CH	JQP	Clinical Kits Reagents and Devices	32
HEALTH PROFESSIONAL	Training	CH	JQW	Clinical Kits Reagents and Devices	33
HEALTH PROFESSIONAL	Training	CH	NBW	Clinical Kits Reagents and Devices	103
HEALTH PROFESSIONAL	Training	CH	NQM	Clinical Kits Reagents and Devices	24
HEALTH PROFESSIONAL	Training	HE	GGN	Hematology Kits Reagents and Devices	7
HEALTH PROFESSIONAL	Training	HE	GJS	Hematology Kits Reagents and Devices	23
HEALTH PROFESSIONAL	Training	HE	GKT	Products Used In Establishments That	205

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
				Manufacture Blood and Blood Products	
HEALTH PROFESSIONAL	Training	HE	GKZ	Hematology Kits Reagents and Devices	71
HEALTH PROFESSIONAL	Training	HE	JPA	Hematology Kits Reagents and Devices	23
HEALTH PROFESSIONAL	Training	HE	JPH	Hematology Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Training	HE	KSS	Products Used In Establishments That Manufacture Blood and Blood Products	1
HEALTH PROFESSIONAL	Training	HE	KSZ	Products Used In Establishments That Manufacture Blood and Blood Products	2
HEALTH PROFESSIONAL	Training	HE	MMH	Products Used In Establishments That Manufacture Blood and Blood Products	1
HEALTH PROFESSIONAL	Training	HE	OBW	Hematology Kits Reagents and Devices	32
HEALTH PROFESSIONAL	Training	HE	ORG	Products Used In Establishments That Manufacture Blood and Blood Products	18
HEALTH PROFESSIONAL	Training	IM, TX, MI	DOF	Clinical Kits Reagents and Devices	1
HEALTH PROFESSIONAL	Training	IM, TX, MI	JTC	Microbiology Devices	17
HEALTH PROFESSIONAL	Training	IM, TX, MI	LON	Diagnostic Devices	1
HEALTH PROFESSIONAL	Training	IM, TX, MI	MDB	Microbiology Devices	25
HEALTH PROFESSIONAL	Training	IM, TX, MI	MZC	Microbiology Devices	28
HEALTH PROFESSIONAL	Training	PA	IDO	Pathology Instrumentation and Accessories	20
HEALTH PROFESSIONAL	Training	PA	IEO	Pathology Instrumentation and Accessories	20
HEALTH PROFESSIONAL	Transfer	CH	CGX	Clinical Kits Reagents and Devices	105
HEALTH PROFESSIONAL	Transfer	CH	CHL	Clinical Kits Reagents and Devices	13
HEALTH PROFESSIONAL	Transfer	CH	JJE	Clinical Kits Reagents and Devices	28
HEALTH PROFESSIONAL	Transfer	CH	JQP	Clinical Kits Reagents and Devices	7
HEALTH PROFESSIONAL	Transfer	CH	KHO	Clinical Kits Reagents and Devices	2
HEALTH PROFESSIONAL	Transfer	CH	LFR	Clinical Kits Reagents and Devices	247

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
HEALTH PROFESSIONAL	Transfer	CH	NBW	Clinical Kits Reagents and Devices	55
HEALTH PROFESSIONAL	Transfer	HE	GGN	Hematology Kits Reagents and Devices	2
HEALTH PROFESSIONAL	Transfer	HE	GKT	Products Used In Establishments That Manufacture Blood and Blood Products	1
HEALTH PROFESSIONAL	Transfer	HE	GKZ	Hematology Kits Reagents and Devices	3
HEALTH PROFESSIONAL	Transfer	IM, TX, MI	LSE	Serological Reagents	1
HEALTH PROFESSIONAL	Transfer	PA	IDO	Pathology Instrumentation and Accessories	54
HEALTH PROFESSIONAL	Transfer	PA	IDP	Pathology Instrumentation and Accessories	15
LAY USER/PATIENT	Judgement	CH	CGA	Clinical Kits Reagents and Devices	1
LAY USER/PATIENT	Judgement	CH	JJX	Clinical Kits Reagents and Devices	5
LAY USER/PATIENT	Judgement	CH	LFR	Clinical Kits Reagents and Devices	4
LAY USER/PATIENT	Judgement	CH	NBW	Clinical Kits Reagents and Devices	626
LAY USER/PATIENT	Judgement	HE	GJS	Hematology Kits Reagents and Devices	1
LAY USER/PATIENT	Judgement	IM, TX, MI	JSK	Microbiology Devices	15
LAY USER/PATIENT	Maintenance	CH	NBW	Clinical Kits Reagents and Devices	46
LAY USER/PATIENT	Maintenance	HE	GKZ	Hematology Kits Reagents and Devices	1
LAY USER/PATIENT	Motor	CH	LFR	Clinical Kits Reagents and Devices	86
LAY USER/PATIENT	Motor	CH	NBW	Clinical Kits Reagents and Devices	95
LAY USER/PATIENT	Motor	HE	GJS	Hematology Kits Reagents and Devices	1
LAY USER/PATIENT	Procedural	CH	LFR	Clinical Kits Reagents and Devices	26
LAY USER/PATIENT	Procedural	CH	NBW	Clinical Kits Reagents and Devices	3110
LAY USER/PATIENT	Procedural	HE	GJS	Hematology Kits Reagents and Devices	19
LAY USER/PATIENT	Procedural	PA	NNL	Pathology Instrumentation and Accessories	1

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
LAY USER/PATIENT	Training	CH	JJX	Clinical Kits Reagents and Devices	28
LAY USER/PATIENT	Training	CH	LFR	Clinical Kits Reagents and Devices	61
LAY USER/PATIENT	Training	CH	NBW	Clinical Kits Reagents and Devices	525
LAY USER/PATIENT	Training	HE	GJS	Hematology Kits Reagents and Devices	43
LAY USER/PATIENT	Transfer	CH	JJX	Clinical Kits Reagents and Devices	1
LAY USER/PATIENT	Transfer	CH	LFR	Clinical Kits Reagents and Devices	8942
LAY USER/PATIENT	Transfer	CH	NBW	Clinical Kits Reagents and Devices	380
LAY USER/PATIENT	Transfer	HE	GJS	Hematology Kits Reagents and Devices	31
OTHER	Judgement	CH	CGA	Clinical Kits Reagents and Devices	2
OTHER	Judgement	CH	LFR	Clinical Kits Reagents and Devices	25
OTHER	Judgement	CH	NBW	Clinical Kits Reagents and Devices	178
OTHER	Judgement	HE	GKZ	Hematology Kits Reagents and Devices	4
OTHER	Judgement	HE	KSZ	Products Used In Establishments That Manufacture Blood and Blood Products	2
OTHER	Judgement	PA	IEO	Pathology Instrumentation and Accessories	8
OTHER	Maintenance	CH	CEM	Clinical Kits Reagents and Devices	29
OTHER	Maintenance	CH	JJE	Clinical Kits Reagents and Devices	2
OTHER	Maintenance	CH	JKA	Clinical Kits Reagents and Devices	1
OTHER	Maintenance	CH	KHO	Clinical Kits Reagents and Devices	11
OTHER	Maintenance	CH	LFR	Clinical Kits Reagents and Devices	1
OTHER	Maintenance	CH	NBW	Clinical Kits Reagents and Devices	1
OTHER	Maintenance	HE	GKZ	Hematology Kits Reagents and Devices	39

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
OTHER	Maintenance	PA	IEO	Pathology Instrumentation and Accessories	25
OTHER	Motor	CH	CHL	Clinical Kits Reagents and Devices	3
OTHER	Motor	CH	JFT	Clinical Kits Reagents and Devices	1
OTHER	Motor	CH	JJE	Clinical Kits Reagents and Devices	29
OTHER	Motor	CH	JQW	Clinical Kits Reagents and Devices	20
OTHER	Motor	CH	LFR	Clinical Kits Reagents and Devices	28
OTHER	Motor	CH	NBW	Clinical Kits Reagents and Devices	2
OTHER	Motor	HE	GKT	Products Used In Establishments That Manufacture Blood and Blood Products	1
OTHER	Motor	PA	IDP	Pathology Instrumentation and Accessories	30
OTHER	Motor	PA	IEO	Pathology Instrumentation and Accessories	252
OTHER	Motor	PA	KPA	Pathology Instrumentation and Accessories	18
OTHER	Procedural	CH	CFR	Clinical Kits Reagents and Devices	1
OTHER	Procedural	CH	JIX	Clinical Kits Reagents and Devices	10
OTHER	Procedural	CH	JQP	Clinical Kits Reagents and Devices	28
OTHER	Procedural	CH	JQW	Clinical Kits Reagents and Devices	20
OTHER	Procedural	CH	KHO	Clinical Kits Reagents and Devices	5
OTHER	Procedural	PA	IEO	Pathology Instrumentation and Accessories	47
OTHER	Training	CH	JQW	Clinical Kits Reagents and Devices	18
OTHER	Training	CH	LFR	Clinical Kits Reagents and Devices	53
OTHER	Training	CH	NBW	Clinical Kits Reagents and Devices	120
OTHER	Training	HE	GKZ	Hematology Kits Reagents and Devices	26
OTHER	Training	IM, TX, MI	LIO	Microbiology Devices	18

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
OTHER	Training	PA	IEO	Pathology Instrumentation and Accessories	711
OTHER	Transfer	CH	LFR	Clinical Kits Reagents and Devices	22
OTHER	Transfer	CH	NBW	Clinical Kits Reagents and Devices	7
UNKNOWN	Judgement	CH	JJE	Clinical Kits Reagents and Devices	11
UNKNOWN	Judgement	CH	JJQ	Clinical Kits Reagents and Devices	2
UNKNOWN	Judgement	CH	KHO	Clinical Kits Reagents and Devices	1
UNKNOWN	Judgement	CH	NSU	Clinical Kits Reagents and Devices	2
UNKNOWN	Judgement	HE	GKT	Products Used In Establishments That Manufacture Blood and Blood Products	2
UNKNOWN	Judgement	HE	LCP	Hematology Kits Reagents and Devices	1
UNKNOWN	Motor	CH	JJE	Clinical Kits Reagents and Devices	22
UNKNOWN	Motor	CH	JJY	Clinical Kits Reagents and Devices	23
UNKNOWN	Motor	HE	GGW	Hematology Kits Reagents and Devices	1
UNKNOWN	Motor	PA	IEO	Pathology Instrumentation and Accessories	1
UNKNOWN	Motor	PA	KPA	Pathology Instrumentation and Accessories	28
UNKNOWN	Procedural	CH	JJH	Clinical Kits Reagents and Devices	27
UNKNOWN	Procedural	CH	JQP	Clinical Kits Reagents and Devices	7
UNKNOWN	Procedural	CH	NBW	Clinical Kits Reagents and Devices	173
UNKNOWN	Training	CH	JKA	Clinical Kits Reagents and Devices	21
UNKNOWN	Transfer	CH	JJE	Clinical Kits Reagents and Devices	1
UNKNOWN	Transfer	CH	JJY	Clinical Kits Reagents and Devices	20
UNKNOWN	Transfer	CH	JQP	Clinical Kits Reagents and Devices	1

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	Number of Events
UNKNOWN	Transfer	CH	OHQ	Clinical Kits Reagents and Devices	50
UNKNOWN	Transfer	PA	IDO	Pathology Instrumentation and Accessories	56
UNKNOWN	Transfer	PA	IDP	Pathology Instrumentation and Accessories	1
UNKNOWN	Transfer	PA	IEO	Pathology Instrumentation and Accessories	153

Results from Random Selection of Simulated Online Search

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_ SPECIALTY GROUP	DEVICE_REPO RT_PRODUCT_ CODE	TESTING/DEVICE GROUP	# of Events	Time to Review (mins)
HEALTH PROFESSIONAL	Judgement	CH	NSU	Clinical Kits Reagents and Devices	8	11.2
HEALTH PROFESSIONAL	Judgement	HE	GKZ	Hematology Kits Reagents and Devices	24	33.6
HEALTH PROFESSIONAL	Judgement	IM,TX, MI	DEW	Immunology Kits Reagents and Devices	1	1.4
HEALTH PROFESSIONAL	Judgement	IM,TX, MI	LQN	Serological Reagents	26	36.4
HEALTH PROFESSIONAL	Maintenance	CH	JKA	Clinical Kits Reagents and Devices	1	1.4
HEALTH PROFESSIONAL	Maintenance	HE	BSB	Products Used In Establishments That Manufacture Blood and Blood Products	1	1.4
HEALTH PROFESSIONAL	Maintenance	HE	JPA	Hematology Kits Reagents and Devices	2	2.8
HEALTH PROFESSIONAL	Motor	CH	JIL	Clinical Kits Reagents and Devices	5	7
HEALTH PROFESSIONAL	Motor	CH	JKA	Clinical Kits Reagents and Devices	77	107.8
HEALTH PROFESSIONAL	Motor	CH	KQO	Clinical Kits Reagents and Devices	1	1.4
HEALTH PROFESSIONAL	Motor	CH	LFR	Clinical Kits Reagents and Devices	48	67.2
HEALTH PROFESSIONAL	Motor	HE	LCP	Hematology Kits Reagents and Devices	2	2.8
HEALTH PROFESSIONAL	Procedural	CH	DHA	Clinical Kits Reagents and Devices	18	25.2
HEALTH PROFESSIONAL	Procedural	HE	GGM	Hematology Kits Reagents and Devices	29	40.6
HEALTH PROFESSIONAL	Procedural	HE	LKM	Hematology Kits Reagents and Devices	30	42
HEALTH PROFESSIONAL	Training	CH	JJE	Clinical Kits Reagents and Devices	25	35
HEALTH PROFESSIONAL	Training	HE	JPA	Hematology Kits Reagents and Devices	23	32.2
HEALTH PROFESSIONAL	Training	IM,TX, MI	LON	Diagnostic Devices	1	1.4
HEALTH PROFESSIONAL	Training	PA	IEO	Pathology Instrumentation and Accessories	20	28
HEALTH PROFESSIONAL	Transfer	CH	LFR	Clinical Kits Reagents and Devices	247	345.8
HEALTH PROFESSIONAL	Transfer	HE	GKT	Products Used In Establishments That Manufacture Blood and Blood Products	1	1.4

DEVICE OPERATOR GROUP	USE ERROR GROUP	MEDICAL_ SPECIALTY GROUP	DEVICE_REPORT_PRODUCT_CODE	TESTING/DEVICE GROUP	# of Events	Time to Review (mins)
HEALTH PROFESSIONAL	Transfer	IM,TX, MI	LSE	Serological Reagents	1	1.4
LAY USER/PATIENT	Judgement	CH	NBW	Clinical Kits Reagents and Devices	626	876.4
LAY USER/PATIENT	Motor	HE	GJS	Hematology Kits Reagents and Devices	1	1.4
OTHER	Maintenance	CH	JKA	Clinical Kits Reagents and Devices	1	1.4
OTHER	Motor	PA	IDP	Pathology Instrumentation and Accessories	30	42
OTHER	Procedural	CH	KHO	Clinical Kits Reagents and Devices	5	7
OTHER	Training	HE	GKZ	Hematology Kits Reagents and Devices	26	36.4
UNKNOWN	Procedural	CH	JJH	Clinical Kits Reagents and Devices	27	37.8
UNKNOWN	Transfer	CH	JJY	Clinical Kits Reagents and Devices	20	28