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Creating, Training, and Implementing the Safety Reporting Processes for a Research Organization's New Clinical Trials Program

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Abstract

Technology is shifting the paradigm of clinical research operations with new non-clinical staff assisting in the conduction of clinical research by helping to create and oversee the programming and capturing of big data. Due to the 21st Century Cures Act focusing on the use of real-world data and real-world evidence, both clinical and non-clinical research staff may be involved in patient safety reporting and necessitate proper training to understand their roles and responsibilities for the proper handling of patient safety reporting. A new research organization (NRO), which currently acts as a healthcare IT company geared towards clinical research, is in this current situation. With the company's focus on eventually conducting their own pragmatic clinical trials, the regulatory team is anticipating the need for staff training as well as the creation of internal controls to meet all Federal regulations. Patient safety was at the top of the team's list to address; it was determined that a training program needed to be created.

FDA and EMA regulations were reviewed to gain a better understanding of the patient safety reporting guidelines, and to also see if either regulatory agencies provided requirements or guidance on the proper training of staff on patient safety reporting. The FDA's Code of Federal Regulations did not provide regulations specifically for staff training, nor were resources made available for institutions to utilize. On the other hand, the EMA's GVP: Module VI addressed staff training requirements on patient safety, including both clinical and non-clinical staff. The EMA also provides a very resourceful website hub of training materials, which institutions may utilize.

National and international institutions were reviewed to find trends and obtain training program ideas. Many institutions use SOPs and training slides as their standard

training methods, which still do not compare to the EMA's abundance of resources. The researcher concluded that the FDA must not only provide further regulations surrounding RWD and RWE, but that the finalized Cures Act should include safety reporting and proper staff training. In order to get ahead of the future regulations, the researcher recommended that the NRO create a general, company-wide training and role-specific training program, complete with training slides, live and recorded training presentations, and to have this program accessible to staff at all times.

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For my parents, Jorge and Carmen Medina, who have provided me with continuous love and support throughout my life, including my many years of study, and have always encouraged me to follow my passions. Much gratitude to Karen Wiercinski, my first manager and mentor, who introduced me to world of clinical research, and unknowingly sparked my passion to pursue a long-term career in the field of clinical research.

Make a habit of at least two things: to help, or at least to do no harm.
- Hippocrates, *Epidemics*

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List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event/Adverse Effect
CFR	Code of Federal Regulations
CRC	Clinical Research Coordinator
CRO	Contract Research Organization
DHHS	Department of Health and Human Services
EMA	European Medicines Agency
EMR	Electronic Medical Records
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
NCI	National Cancer Institute
NIH	National Institutes of Health
NRO	New Research Organization
PHI	Protected Health Information
PI	Principal Investigator
PV	Pharmacovigilance

RQC	Research Quality and Compliance
RWD	Real-world Data
RWE	Real-world Evidence
SAE	Serious Adverse Event/Serious Adverse Effect
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

Chapter 1

Introduction

1.1 Background

The field of clinical research and the conduction of clinical trials has become increasingly competitive around the globe. Sponsors, as well as Contract Research Organizations (CROs), conduct the majority of clinical research trials. However, with the advancement of technology, additional parties are now participating in the clinical research arena, creating a shift in standard clinical research operations. With new laboratories providing clinicogenomic testing, and healthcare IT companies providing new data collection features, clinical research teams are evolving.

The researcher's employer, the NRO, is a healthcare IT company specifically dedicated to oncology research and the collection of real-world cancer patient data. Through its data collection programs and electronic medical records (EMR) program, the company has been capturing intricate cancer data for community oncology providers, pharmaceutical companies, academic institutions, and is now collaborating with the FDA and the National Cancer Institute (NCI) to help streamline and share cancer research datasets. The NRO is now in the process of creating a new Clinical Trials program, which will use real-world data (RWD) from over 2 million cancer patients' structured and unstructured data to find and screen those who may qualify for clinical trials, and will also assist in capturing "real-world evidence" (RWE) for clinical trials; RWE is a new focus for the FDA, who issued the 21st Century Cures Act in 2016.[1] Its purpose is to

[1] U.S. Food & Drug Administration, "Real World Evidence," U.S. Food & Drug Administration - Science & Research, last modified February 15, 2018, accessed February 18, 2018, https://www.fda.gov/ScienceResearch/SpecialTopics/RealWorldEvidence/default.htm.

place “additional focus on the use of these types of data to support regulatory decision making.”[2] However, utilizing and maintaining the technology to capture RWD and RWE for clinical trials does present some challenges.

1.2 Statement of the Problem

When clinical trials are involved, proper training and education is necessary for staff across all teams in the company in order to acknowledge their understanding of proper handling of patients’ protected health information (PHI) and all Federal regulations tied to human subject research. Safety reporting of Adverse Events (AEs), and Serious Adverse Events (SAEs) are a vital portion to a successful clinical trial as well, especially when the objective is to capture real-world evidence. Therefore, the staff would need to be educated and trained on Federal requirements as well as the company’s procedures and internal controls being implemented to ensure the proper handling of safety reporting.

This training element will be included as a portion of the framework currently being created for the Clinical Trials program. Aside from this being a new program with the long-term goal of conducting its own pragmatic clinical trials, the NRO is in a different situation than the typical research organizational structure: there are many non-clinical employees working on building and maintaining the databases and technology who might come across patient information. Other than research oncology professionals, the team consists of engineers and technology specialists.[3] This factor would need to be considered when creating the training element.

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[2] U.S. Food & Drug Administration, “Real World Evidence”
[3] David Zax, “At Flatiron Health, Doctors And Developers Work On Cracking The Code For Better Cancer Treatment,” *Fast Company*, last modified April 19, 2017, accessed December 5, 2017, https://www.fastcompany.com/3067893/at-flatiron-health-keeping-the-doctor-close.

1.3 Research Question

The main question the researcher had was whether or not there are Federal requirements in terms of training clinical research staff on the proper handling of patient safety reporting, or if it is left up to the institutions to create their own training plans. Another question was if there were requirements for non-clinical research staff members to be followed in such instances. The researcher also wanted to know if there were common training activities seen across various institutions, even though the training method(s) used were not simply to meet a Federal requirement.

1.4 Research Objective and Significance

The researcher's objective was to seek out information on what Federal requirements or guidance exist, if any, as well as seek and compare both national and international clinical research institutions. The goal was to see if there were common standards various institutions performed in terms of this training, the differences, as well as ideas the researcher's employer can implement when creating their own internal training plans. Human subject research and the conducting of clinical trials have many regulations to be followed. Proper training is critical in making sure the company is not only following all applicable Federal regulations, but also ensuring that patient safety remains the top priority.

1.5 Exclusions and Limitations

At the time of this research project, the framework for the 21st Century Cures Act (Cures Act) had not been finalized by the FDA.[4] The use of RWE to provide regulatory

[4] CDER Small Business and Industry Assistance (SBIA), "Real-World Data and Evidence in Drug Development" (CDER SBIA Chronicles, August 24, 2017), accessed December 6, 2017, https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm572939.pdf.

support for clinical trials is a fairly new concept. Once finalized, the regulatory framework may provide new requirements surrounding RWE that are not current Federal regulations; this would include new requirements surrounding patient safety reporting, as well as training clinical research staff on the new guidelines. Since RWE is being utilized in “real-time” now more than ever before, it would be expected that the topic of reporting patient safety information such as AEs and SAEs would be included in these new regulations. Overall, the NRO has positioned itself in a newer niche of clinical research data, and therefore, it is expected that not all areas of the company’s work will be covered by current Federal regulations. Since Federal regulations are continuously revisited and amended as research evolves, the findings in this paper may be short-lived once the Cures Act framework is finalized, and Federal regulations are updated to encompass RWE in greater detail.

Chapter Two

Review of the Literature

2.1 Safety Reporting Regulations

In order to understand the current national and international status of patient safety reporting regulations and staff training requirements, the researcher began by reviewing both the FDA's Code of Federal Regulations (CFR) and the EMA's Guideline for Good Pharmacovigilance Practices (GVP). All clinical trials conducted under the FDA or the EMA must ensure all Federal requirements pertaining to the conduction of human subject research are met. Title 21 of the CFR covers Food and Drugs, and includes regulations by the FDA and the Department of Health and Human Services (DHHS).[5] Clinical trial regulations are included in 21 CFR.

The NRO works with several industry sponsors, and some are based in Europe; the company has a goal of the Clinical Trials program eventually extending to an international network. Because of this, the EMA's GVP was analyzed and included in the research. GVP Module VI, "Collection, Management and Submission of Reports of Suspected Adverse Reactions to Medicinal Products," was the module most appropriate for review. The FDA and EMA regulations provided the framework for building the training. Reviewing the two agencies' regulations also allowed the researcher to compare the regulations to determine if one was more thorough than the other in regards to patient safety reporting training requirements, and to provide ideas on what training processes could be included when creating the NRO's training program.

[5] U.S. Food & Drug Administration, "Electronic Code of Federal Regulations: Title 21 Food and Drugs," last modified January 22, 2018, accessed January 22, 2018, https://www.ecfr.gov/cgi-bin/text-idx?gp=&SID=d7f66afa5defb2b48ec9645a36b0dfee&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl.

2.1.1 Regulatory Findings

The researcher first reviewed Federal regulations to gain an understanding of patient safety reporting requirements, which would be the foundation for any training plan(s) that would result from the research findings. The researcher also wanted to know if the regulations included any training requirements surrounding patient safety reporting. Both the FDA's Code of Federal Regulations (CFR) and the European Medicines Agency (EMA) regulations were reviewed. Chart 1 provides summaries and requirements included in the three regulations which pertain to patient safety reporting:

Chart 1. Patient safety reporting regulations

FDA and EMA Patient Safety Reporting Regulations	
Regulation	**Summary**
US FDA - 21 CFR part 312.32 (IND Safety Reporting)[6]	Outlines the sponsor responsibilities in terms of reviewing safety information of an investigational new drug (IND) as well as the appropriate processes for initial and follow-up reporting of adverse events to the FDA. ● All information regarding the safety of a drug must be thoroughly reviewed by the sponsor. ● The sponsor must submit IND safety reports to notify the FDA and all study investigators as soon as possible but no later than 7 days after receiving information of the event for unexpected fatal or life-threatening events, and within 15 calendar days of deeming the event to be reportable for any potential serious risks. ● IND safety reports should include information pertaining to serious and unexpected suspected adverse reaction, findings from other studies, findings from animal or lab testing, as well as frequently occurring serious suspected adverse reactions. ● Any sponsor conducting a clinical trial utilizing a drug that has previously been marketed or approved in the US still must submit IND safety reports for suspected adverse reactions observed during the clinical study.

[6] U.S. Food & Drug Administration, *§312.32 IND Safety Reporting*, *Electronic Code of Federal Regulations*, vol. 21 CFR §312.32, 2018, accessed February 19, 2018, https://www.ecfr.gov/cgi-bin/text-idx?SID=776bfae347cbde4a3b365cb78b480ab6&mc=true&node=se21.5.312_132&rgn=div8.

US FDA - 21 CFR part 314.80 (Postmarketing Reporting of Adverse Drug Experiences)[7]	Outlines the sponsor responsibilities in terms of reviewing safety information associated with a new drug application (NDA) - as well as the appropriate processes for initial and follow-up reporting of adverse events to the FDA. ● New drug applicants must review all adverse drug experience information received or collected from any source, including scientific literature, and postmarketing investigations and/or surveillance studies. ● Postmarketing 15-day "Alert reports" and follow-ups must be submitted as soon as possible but no later than 15 calendar days of the receipt of information. ● A 15-day Alert report does not need to be submitted for adverse drug experiences obtained from a postmarketing study, unless the applicant determines there is a possibility the drug may have caused the adverse experience. ● Periodic reports should be submitted at least quarterly (for the first 3 years after approval) and then at least annually (after 3 years). ● No patient identifiers should be included in reports (such as names and addresses), unless the initial information reported is provided by the patient. ● The FDA may withdraw approval of an application and prohibit the continuation of the marketing of the drug if the applicant fails to meet these requirements.
EMA's GVP module VI section VI.C.1.2.1[8]	The EMA's GVP is composed of 13 modules that cover safety reporting regulations for drugs. The most applicable to this project is Module VI – Management and reporting of adverse reactions to medicinal products. This module covers many items; however, the most applicable information for the NRO is covered in section VI.C.1.2.1: Non-interventional post-authorisation studies. ● The design of non-interventional post-authorisation studies based on secondary use of data are characterised by the use of data previously collected from healthcare professionals for other purposes (e.g. standard of care). Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of EHR, systematic reviews, meta-analyses.

[7] U.S. Food & Drug Administration, *§314.80 Postmarketing Reporting of Adverse Drug Experiences*, *Electronic Code of Federal Regulations*, vol. 21 CFR §314.80, 2018, accessed February 19, 2018, https://www.ecfr.gov/cgi-bin/text-idx?SID=d7f66afa5defb2b48ec9645a36b0dfee&mc=true&node=se21.5.314_180&rgn=div8.

[8] European Medicines Agency, "Guideline on Good Pharmacovigilance Practices (GVP): Module VI – Collection, Management and Submission of Reports of Suspected Adverse Reactions to Medicinal Products (Rev 2)," July 28, 2017, accessed February 19, 2018, http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232767.pdf.

> ● For these studies, the reporting of suspected adverse reactions in the form of individual case safety reports [ICSRs] is not required. Reports of adverse events/reactions should be summarised as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting.[9]

Unfortunately, even though all of the FDA regulations provide detailed safety reporting requirements, there were no instructions on properly training research staff to accomplish the safety reporting tasks outlined. The FDA does have a newer database called the FDA Adverse Event Reporting System (FAERS), which is a database to report adverse events and assists with safety surveillance on post-marketed drugs; a public dashboard is available as well.[10] The only training available for the FAERS is a webinar for those seeking a tutorial on using the FAERS public dashboard.[11] Ultimately, the FDA provides little guidance in terms of training clinical trials staff on patient safety reporting. The lack of requirements shows agencies are leaving it up to institutions to implement their own internal controls to ensure all Federal regulations are met.

Human subject research is heavily regulated with additional policies, to ensure good clinical practice (GCP) principles are followed in accordance with the International Conference on Harmonisation (ICH). It is standard for research staff members to go through GCP training. The researcher reviewed GCP training information, to see if it included patient safety reporting. As noted in a GCP policy issued by the NIH,

> GCP provides a standard for ensuring clinical trial compliance, implementation, data collection, monitoring, and reporting (e.g., safety data, accrual reports, study status, protocol deviations, unanticipated problems, or final data), and outline the

[9] European Medicines Agency, "Guideline on Good Pharmacovigilance Practices (GVP): Module VI"
[10] U.S. Food & Drug Administration, "Questions and Answers on FDA's Adverse Event Reporting System (FAERS)," last modified February 21, 2018, accessed February 22, 2018, https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.
[11] Ibid.

> responsibilities of Institutional Review Boards (IRBs), investigators, sponsors and monitors….
>
> …GCP training may be achieved through a class or course, academic training program, or certification from a recognized clinical research professional organization. Completion of GCP training will demonstrate that individuals have attained the fundamental knowledge of clinical trial quality standards for designing, conducting, recording and reporting trials that involve human research participants. GCP training should be refreshed at least every three years in order remain current with regulations, standards and guidelines.[12]

It is important to note this policy applies to staff in various positions; not only are investigators required to complete GCP training, but the clinical trials staff must complete it as well. The clinical trials staff includes individuals "who are responsible for study coordination, data collection and data management."[13] The researcher took note of this policy, due to the fact that clinical trials staff at the NRO would include non-clinical team members, who would fall under the GCP training policy, since they would be taking part in the data management portion of trials.

Compared to the FDA, the EMA guidelines for human subject research and patient safety reporting goes into much greater detail. The GVP Module VI referenced is designated solely to good pharmacovigilance practices. There are various areas throughout the regulations that discuss staff being properly trained on patient safety reporting. Part VI.B.5 Quality Management states:

> Staff directly performing pharmacovigilance activities should be appropriately trained in applicable pharmacovigilance legislation and guidelines, in addition to specific training in report processing activities for which they are responsible and/or undertake. Data entry staff should be instructed in the use of the appropriate standards and terminologies (see VI.B.8. for ICSRs content and format), and their proficiency confirmed (see VI.C.6.2.4. for EU guidance on training of personnel for pharmacovigilance). Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information,

[12] National Institutes of Health, "Policy on Good Clinical Practice Training for NIH Awardees Involved in NIH-Funded Clinical Trials," last modified September 16, 2016, accessed April 7, 2017, https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-148.html.
[13] Ibid.

> legal, quality control) should be trained in adverse events/reactions collection and submission to the pharmacovigilance department in accordance with internal policies and procedures.[14]

The EMA not only directly addresses staff training, but it also includes additional resources within Module VI to provide further guidance on safety reporting training. This main statement also addressed "other personnel" and the safety reporting training that should be completed by personnel that fall into the category. Similar to the CFR, the emphasis on internal controls is seen in the EMA.

Module VI's initial training statement references additional information found in Section VI.C.6.2.4. It explains that any staff member who participates in pharmacovigilance activities must complete initial training in regards to their roles and responsibilities, and should complete recurrent refresher training as well. Should the institution ever be audited or inspected, all "training plans and records for documenting, maintaining and developing the competences of personnel based on an assessment of the training" needs to be kept on file.[15] In addition to these requirements in the GVP Module VI, the EMA provides supporting, external resources for institutions to utilize for training their staff on pharmacovigilance. It is located on the EudraVigilance training website, which provides "a detailed training plan and catalogue based on a modular training approach focusing on the management of individual safety reports, signals management, and EudraVigilance."[16] EudraVigilance is the EMA's centralized safety reporting system

[14] European Medicines Agency, "Guideline on Good Pharmacovigilance Practices (GVP): Module VI"
[15] Ibid.
[16] Ibid.

used for reporting and analyzing suspected adverse reactions to both approved drugs and INDs used in clinical trials.[17]

The EudraVigilance Training and Support website is a very robust resource hub. It provides an initial document of the EudraVigilance Training and Plan Curriculum which provides information on the modular training available and the resources designated to accomplish each section. Training is offered through various methods (figure 1). Three-day face-to-face training courses are available; the target audience and learning outcomes are listed, as well as training dates available throughout London and other locations throughout Europe. Registration links and documents are available for these courses. Support webinars are offered on a monthly basis, each lasting two hours; the webinars are also designated for question and answer sessions. Information Days are offered to provide updates and also discuss "regulatory, procedural, or technical questions."[18]

Guidance documentation is provided in PDF files, as well as e-Learning modules; the majority of pharmacovigilance training utilizes the e-Learning modules. Videos are available, as well as the training slides used. There are optional quizzes provided, and a competency assessment at the end of training; the competency assessment is mandatory for new staff involved with safety reporting.[19]

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[17] European Medicines Agency, "EudraVigilance," last modified 2018, accessed January 4, 2018, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5.

[18] European Medicines Agency, "EudraVigilance Training and Support," last modified 2018, accessed January 4, 2018, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000162.jsp&mid=WC0b01ac0580a1a1fb%20-%20section1.

[19] European Medicines Agency, "Introduction to Training Offering by EMA: Training Module PhV-M0," 2016, accessed January 4, 2018, http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/06/WC500208958.pdf.

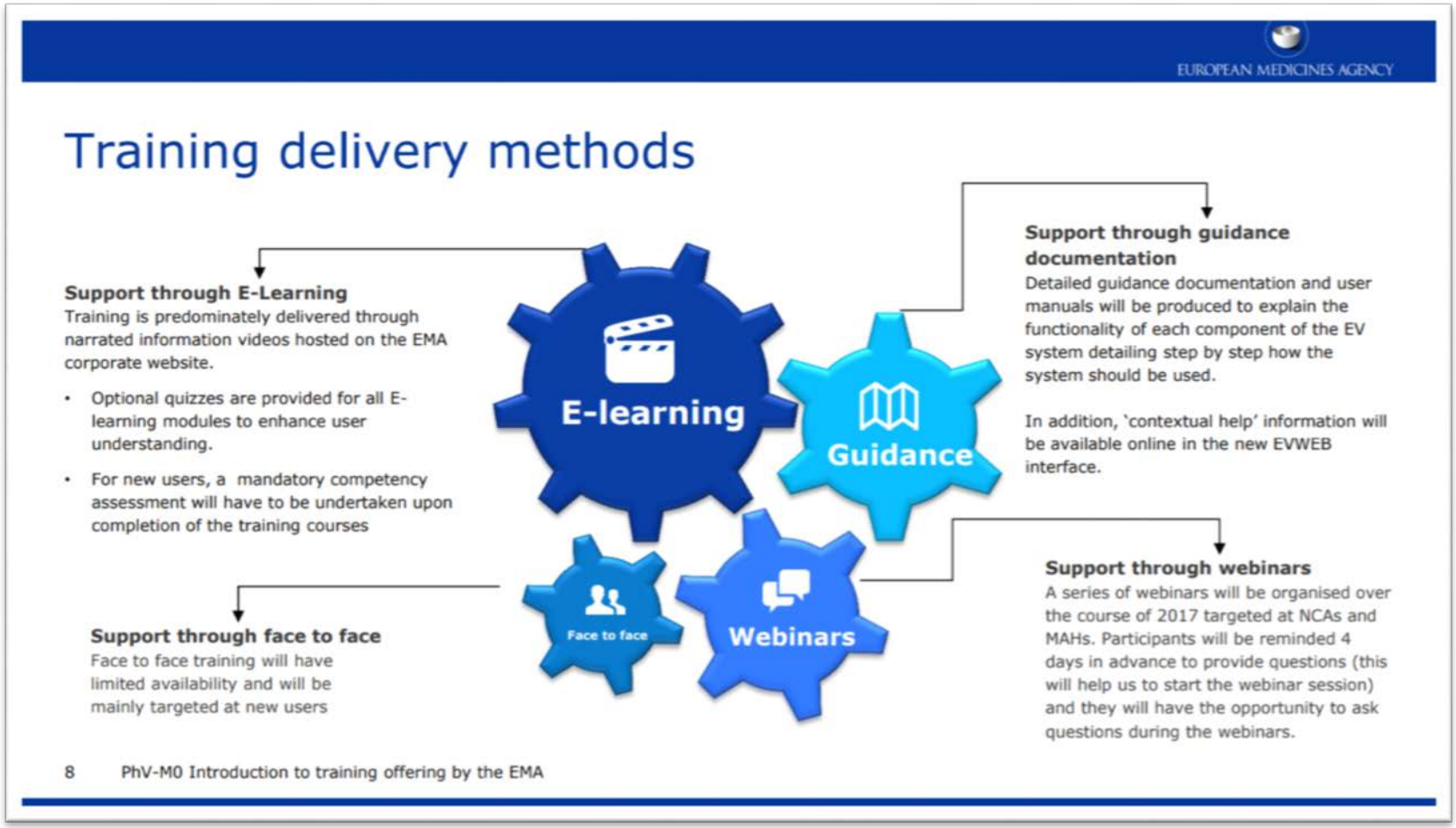

Figure 1. European Medicines Agency, Training Delivery Methods[20]

[20] European Medicines Agency, "Introduction to Training Offering by EMA: Training Module PhV-M0," 2016: Slide 8, accessed January 4, 2018, http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/06/WC500208958.pdf

The EMA's EudraVigilance Training and Support website, which includes training on pharmacovigilance and patient safety reporting, provides various options for users to choose from, as well as different training formats and environments, and is flexible for those with busy schedules. Aside from the training requirements specified in the GVP Module VI, the training website provides institutions and clinical trial sponsors in-depth training resources and materials. Staff participating in the conduction of a clinical trial under EMA regulations should have no reservations as to what is expected of them in terms of the proper handling of patient safety reporting, nor a basis for having weak staff training processes and procedures.

After reviewing both the FDA's CFR and the EMA's GVP, the researcher saw similarities between the two regulations, but noted that the EMA provided much more detailed requirements and training resources. The main areas compared are identified in Chart 2. The results show how many key areas the EMA covers which are not specified by the FDA: addressing both the clinical staff and non-clinical staff training on safety reporting, utilizing a streamlined database for IND safety reporting, and most importantly, providing additional resources and materials which institutions may utilize to train their staff on safety reporting.

Chart 2. FDA CFR vs. EMA GVP comparison of training staff on patient safety reporting

Regulation	FDA CFR	EMA GVP
Addresses clinical staff training on safety reporting		√
Addresses non-clinical staff training on safety reporting		√
Utilizes a streamlined database for IND safety reporting		√
Utilizes a streamlined database for post-market reporting	√	√
Additional guidance on required training	√	√
Provides resources for additional safety reporting training		√
Encourages institutions to utilize internal controls	√	√

The EMA provides many more regulatory details and training resources than the FDA. One factor which may be hindering the FDA is that many industry sponsors utilize their own safety reporting databases for clinical sites to submit AEs/SAEs through. The CFR also emphasizes the use of internal controls at the institutional level.

2.2 National and International Safety Reporting Training

2.2.1 National Safety Reporting Training

To supplement the regulations, the researcher selected six institutions in the United States to see if staff training on patient safety reporting was available, and if so, what each institution's training entailed. For national institutions, the researcher selected Stanford Medicine Cancer Clinical Trials Office, Jefferson University Clinical Research Institute, University of California, Los Angeles (UCLA) Clinical and Translational Science Institute, Duke University Office of Clinical Research, the University of California, San Francisco (UCSF) Clinical and Translational Science Institute, and Ohio State University Office of Research.

2.2.2 International Safety Reporting Training and Third-Party Training Programs

The researcher selected five international institutions: Oxford University Hospitals, Australia's Melbourne Health Office for Research, the Australian Government: National Health and Medical Research Council's Therapeutic Goods Administration, the Norfolk and Suffolk NHS Foundation Trust, and Ireland's Health Products Regulatory Authority to review. Aside from studying these institutions that conduct clinical trials, the researcher also investigated external parties who provide training on patient safety reporting; third-party companies may provide training services

and resources to institutions. Analyzing institutional training around the globe, as well as third party training programs, provided a solid awareness as to current models for training being utilized.

2.3 Research Studies and Journal Articles

The researcher was able to locate studies and journal articles which pertain to training clinical research staff on patient safety reporting, and the efficacy of current Federal regulations surrounding safety reporting. A study reviewed SAEs that had been reported to an academic sponsor; "Quality of Serious Adverse Events Reporting to Academic Sponsors of Clinical Trials: Far from Optimal" discovered high percentages of missing information in the SAE reports, including causality, seriousness of the event, the investigational product, the onset date of the SAE, and the patient outcome.[21] The conclusion of the study determined poor quality in both completeness and accuracy of SAE reporting. The authors suggest "the training of investigators in SAE reporting must be improved."[22]

"Training in Post-authorization Pharmacovigilance" offers a detailed breakdown on the criticality of training, the choice of trainings and management system, types of trainings, topics for the training, timing of the trainings, training modalities, management of trainings, the assessment of training effectiveness, documentation of training, and the challenges.[23] Though the article's focus is on Adverse Drug Reaction (ADR) reporting

[21] Sabrina Crépin, Claire Villeneuve, and Louis Merle, "Quality of Serious Adverse Events Reporting to Academic Sponsors of Clinical Trials: Far from Optimal," *Pharmacoepidemiology and Drug Safety* 25, no. 6 (June 1, 2016): 719–724.
[22] Ibid.
[23] Vivek Ahuja and Varun Sharma, "Training in Post-Authorization Pharmacovigilance," *Perspectives in Clinical Research* 1, no. 2 (2010): 70–75.

for post-authorized drugs, the material discussed may be beneficial for any clinical research site to apply or model their training after.

Ahuja and Sharma note:

> How much training is required and whether external trainers are required, who should undergo which type of training, whether all personnel should receive the same set of trainings, whether there should be a separate function in the company which manages the trainings are some of the questions which can be answered after careful assessment of the company's profile and desired objectives.[24]

The article addresses types of pharmacovigilance training and topics which would be beneficial to include in the training. Two different types of training were mentioned: "training of pharmacovigilance staff," and "training of other company employees." The authors explain the reasoning for training other company employees, by stating "As a good pharmacovigilance practice and to fulfill regulatory requirement in many countries, the company needs to ensure that all its employees (including consultants and temporary staff) are trained to identify and report any ADR coming to their notice to the pharmacovigilance department on an expedited basis."[25]

Two training types are provided as examples of topics to discuss in the general staff training, and more detailed topics for staff members in roles with pharmacovigilance responsibilities. Examples of modalities for internal and external training are listed as well, including self-training, face-to-face training via classroom training or one-on-one training, video conferencing, telephonically, or web-based.[26] Ahuja and Sharma make an impactful statement which underscores the lack of training resources available for patient safety reporting, saying "It is interesting to note that not many resources, be it internet,

[24] Vivek Ahuja and Varun Sharma, "Training in Post-Authorization Pharmacovigilance"
[25] Ibid.
[26] Ibid.

literature or books, are available specifically addressing the need of the industry to guide them on training requirements to set up and maintain a competent pharmacovigilance department."[27] For that reason, the article's purpose was to provide clinical sites helpful information and suggestions on creating a training program for patient safety reporting.

2.4 Additional Patient Safety and Ethical Considerations

The researcher acknowledged the importance of continuously ensuring patient safety during clinical research studies. Ethical considerations in human subject research, such as clinical trials, must be made in order to assess and ensure that the risks do not outweigh the benefits. The Declaration of Helsinki (Declaration), by the World Medical Association, underscores the importance of this, stating "every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others."[28]

The Declaration provides ethical principles in regards to the safety and wellbeing of human subject research participants. Some of these key principles iterate that "considerations related to the well-being of the human subject should take precedence over the interests of science and society," as well as it being the physician's duty to "protect the life, health, privacy, and dignity of the human subject."[29] With this in mind, it is understood that patient safety is the number one priority during the conducting of human subject research. Additionally, the protection of clinical research participants outlined in the Declaration should not be reduced by and legal or regulatory

[27] Vivek Ahuja and Varun Sharma, "Training in Post-Authorization Pharmacovigilance"
[28] World Medical Association, "Declaration of Helsinski" (World Health Organization, 2001), accessed August 13, 2017, http://www.who.int/bulletin/archives/79%284%29373.pdf.
[29] Ibid.

requirement.[30] With such thorough emphasis on ethical principles, institutions should assess potential risks which may occur during the study, and ensure internal controls are implemented to help reduce any risks the clinical research patients may encounter.

[30] World Medical Association, "Declaration of Helsinski"

Chapter 3

Project Description

3.1 Discussion of Project Elements

The purpose of the project was to assist in the creation of training materials on the proper handling of patient safety reporting, by first outlining the framework for handling patient safety information and reporting processes. Reviewing the NRO's current internal documents, SOPs, and internal controls would provide insight on what further research would need to be performed. Analyzing Federal regulations, specifically the FDA and the EMA, assisted in the understanding and collection of the safety reporting regulations to be followed. This in turn assisted the researcher with the creation of an initial internal patient safety reporting document which would be distributed companywide, and defined terms, regulations, as well as outlined the roles within the company that would be involved in safety reporting activities.

In order to contribute to the creation of a full staff training program on patient safety reporting processes, researching national and global training processes and programs currently utilized by institutions would help guide the creation of the training program at the NRO. Analyzing and comparing various institutions would assist in identifying common trends, well-structured training programs, as well as weakened processes from which the researcher could collectively learn from in order to build a comprehensive training program.

Project elements would be composed of researching both internal documentation and external documents, studying FDA and EMA regulations, analyzing current training resources and programs found both nationally and internationally, identifying strong

training modules as well as weak processes, communicating with regulatory staff to report research findings, and assist with the creation and future implementation of a staff training program on proper patient safety reporting processes at the NRO.

The end goal of the research project from the company standpoint was to determine and solidify roles and responsibilities of each team, and its staff members, when it pertains to the NRO's Clinical Trials program and safety reporting, create a general training program for staff on Federal Regulations and the proper handling of safety information, and also create supplemental training programs customized by role to address their direct responsibilities in the safety reporting process. Once training programs are solidified, the internal controls and training would be the foundation used when creating any trial-specific safety reporting guidance as necessary.

Chapter 4

Need Assessment

4.1 How the Need for the Project Was Assessed

The need for the project came about when the researcher's company announced plans to build a Clinical Trials program as an extension to their current services. The framework for the program was in the process of being constructed, and the new Clinical Trials team held a presentation for staff on the future program. The Research Quality and Compliance (RQC) Director welcomed any staff member with clinical trials experience to reach out to him if he/she would like to help in building parts of the framework. The researcher, having clinical trials experience, contacted the RQC Director to offer assistance in building the Clinical Trials framework.

4.2 Metrics Used

The researcher reviewed the current internal research documents and slide decks which discussed portions of the Clinical Trials framework, but did not come across any training materials to educate and prepare staff for the new Clinical Trials operations and processes. At the time, the researcher was working on the oncology research team and responsible for data collection and reporting; however, she had former clinical trial experience and was familiar with the various facets of conducting clinical trials. Additionally, the researcher was aware that an internal "playbook" on the handling of patient safety was in the works, but no training had been held.

4.3 Who the Researcher Conferred with on Establishing the Need

The RQC Director was initially conferred with via e-mail communications. A video-conferencing meeting was scheduled to discuss where the most help was needed in

the creation of the Clinical Trails framework. Different areas where assistance was needed were discussed, and based on researcher's clinical trials background in data management and AE/SAE reporting, the RQC Director and researcher decided and agreed that the researcher could help create the training programs and materials on proper patient safety reporting processes.

4.4 Committees Established to Assist in Assessing the Need

The main point of contact throughout the project was the RQC Director via video-conference meetings, e-mail communications, and messages through an internal messenger system. The researcher did participate with other RQC team members when assisting with the creation of the initial patient safety reporting "playbook," which is considered an internal training document and project charter. Communications with RQC team members were conducted via e-mails as well as conversations within the playbook Google document suggestions and comments windows. The company's internal messenger system was used as well to communicate with one another.

Chapter 5

Methodology

5.1 Methods Used to Conduct the Project

The majority of tasks involved for the project pertained to performing external research to collect, analyze, and understand current staff training programs for patient safety reporting activities, as well as review regulations which govern safety reporting processes and training requirements.

5.1.1 Review Federal Regulations and Provide High-Level Synthesis of Each

Three specific Federal regulations were focused on, as they each pertain to safety reporting for INDs and post-marketed drugs: U.S. FDA's 21 CFR §312.32 on "IND Safety Reporting,"[31] U.S. FDA's 21 CFR §314.80 on "Postmarketing Reporting of Adverse Drug Experience,"[32] and EMA's GVP Module VI – "Collection, management and submission of reports of suspected adverse reactions to medicinal products," Section VI.C.1.2, "Management of individual safety reports for non-interventional post-authorisation studies, compassionate use and named patient use."[33]

[31] U.S. Food & Drug Administration, *§312.32 IND Safety Reporting*, *Electronic Code of Federal Regulations*, vol. 21 CFR §312.32, 2018, accessed February 19, 2018, https://www.ecfr.gov/cgi-bin/text-idx?SID=776bfae347cbde4a3b365cb78b480ab6&mc=true&node=se21.5.312_132&rgn=div8.
[32] U.S. Food & Drug Administration, *§314.80 Postmarketing Reporting of Adverse Drug Experiences*, *Electronic Code of Federal Regulations*, vol. 21 CFR §314.80, 2018, accessed February 19, 2018, https://www.ecfr.gov/cgi-bin/text-idx?SID=d7f66afa5defb2b48ec9645a36b0dfee&mc=true&node=se21.5.314_180&rgn=div8.
[33] European Medicines Agency, "Guideline on Good Pharmacovigilance Practices (GVP): Module VI – Collection, Management and Submission of Reports of Suspected Adverse Reactions to Medicinal Products (Rev 2)," July 28, 2017, accessed February 19, 2018, http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232767.pdf.

These regulations provided a starting point which the patient safety reporting process and its training program could use to initiate the analysis. It was critical for both to follow all Federal requirements. The "High-Level Synthesis" of each regulation was included in the Standard Operating Procedure (SOP) for the proper handling of patient safety information.

5.1.2 Review of Other Research Institutions' Safety Reporting Processes and Training Programs (if Available)

The researcher gathered data from other research institutions, both nationally and internationally, to analyze if and/or how each institution has implemented patient safety reporting processes, and also what methods were used to train research staff on the proper handling of patient safety information. The objective was to compare and contrast institutions' training programs for similarities, as well as any creative training methods used which the NRO may consider utilizing.

5.1.3 Review Third-Party Training Programs

To supplement the analyses of Federal regulations as well as safety reporting processes and training programs at institutions, third-party training programs were reviewed. This provided insight on outside resources that are currently available for institutions to utilize when training staff on patient safety reporting.

5.2 Study Design

5.2.1 Outline the Framework for Handling Safety Information and Reporting as Well as How Each Internal Team Will be Working with Clinical Trials

Meetings with the RQC team helped determine which internal controls should be implemented to ensure the NRO was meeting all Federal regulations in terms of handling

patient safety information. The review of the various teams involved in the Clinical Trials program aided in the decisions of how each role would be responsible for the handling of safety information, and which teams would need more thorough, role-specific training.

5.2.2 Create a General Training Program as Well as Role-Specific Training

The focus was to create a company-wide general training program on the Federal regulations, and an overview of how the NRO would be meeting all requirements with the safety reporting process. In addition, the researcher helped produce role-specific training programs to focus on each team's responsibilities and where they "fit in" during the safety reporting process.

5.2.3 Present Training Programs to the Research Quality and Compliance Team

The training programs were presented to the RQC team via training slides, and a live presentation. After further feedback and meetings, finalized materials would be provided to the RQC team. Time-permitting, a company-wide general training session would be held live or pre-recorded. The live session would also be recorded and posted internally for all staff to access at any time.

Chapter 6

Project Results and Discussion

6.1 Training at National Institutions

Once FDA and EMA regulations pertaining to patient safety reporting and proper staff training on patient safety reporting processes were studied, as discussed in Chapter 2: Review of the Literature, the researcher investigated how institutions around the United States were training their clinical trials staff on patient safety reporting, and if there were any similarities between institutions. While the EMA provides clinical research institutions a resourceful training website to either utilize or model their training program after, the FDA has yet to provide such resources or guidance for institutions. Thus reviewing a selection of clinical research institutions' staff training on patient safety reporting provided a snapshot of how institutions are implementing processes to train their staff; it also assisted in finding common trends as well as different training methods that are currently being utilized.

6.1.1 Stanford Medicine Cancer Clinical Trials Office

Stanford's Cancer Clinical Trials Office (CCTO) provides many resources for their staff, which includes clinical research "Supervision and Oversight FAQs," a full orientation program, standard operating procedures, information on their quality assurance program and the Data and Safety Monitoring Committee, monthly educational meetings, and an annual all-day educational program.[34] All new clinical staff members must go through a 7-session clinical research orientation, which must be completed

[34] Stanford Medicine - Cancer Clinical Trials Office, "Training and Quality Assurance," last modified 2017, accessed October 27, 2017, http://med.stanford.edu/ccto/about/AboutCCTO.html#training_and_qualityassurance.

within their first 6 months; some sessions may be used as refresher courses for existing staff depending on their role.[35] Sessions cover study conduct, regulatory, financial management, training on the use of Stanford's OnCore program, and safety documentation and reporting.

Stanford CCTO's orientation designates Session 5 specifically for "Safety Documentation and Reporting." It is an hour and a half long training course that must be completed after working for at least one month; it reviews "Serious Adverse Event documentation, Unanticipated Problems and IRB Reporting, Protocol Deviations, and Outside Safety Reports."[36] Further details were inaccessible, as login information was necessary to view and register for the orientation sessions; however, Session 5 demonstrates the Stanford CCTO has implemented patient safety reporting training for their staff to complete. Though these sessions are designated for clinical staff, the orientation page did mention "specific Orientation Sessions may also be required of non-clinical staff."[37]

6.1.2 Jefferson University Clinical Research Institute

The Manager of Education and Training at the Jefferson Clinical Research Institute, created PowerPoint training slides which cover "Adverse Events, Unanticipated Problems, and Protocol Deviations."[38] The presentation provides staff thorough information by defining AEs and SAEs, distinguishing Expected versus Unexpected AEs,

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[35] Stanford Medicine - Cancer Clinical Trials Office, "New Employee Orientation: Clinical Research Orientation," last modified 2018, accessed January 2, 2018, http://med.stanford.edu/ccto/staff-resources/orientation.html#orientation_sessions.
[36] Ibid.
[37] Ibid.
[38] Kathleen O'Malley, "Adverse Events, Unanticipated Problems, and Protocol Deviations" (Jefferson Clinical Research Institute, n.d.), accessed November 4, 2017, http://www.jefferson.edu/content/dam/university/skmc/dept-of-medicine/Research/JCCCR/Adverse_Events_Unanticipated_Problems_and_Protocol_Deviations.pptx.

listing examples of AEs as well as what are not considered AEs, explaining regulations, and discussing Institutional Review Boards (IRBs). In addition, the presentation outlines a specific guidance and staff responsibilities. It specifies where in patient records the staff members are going to find AEs, how they are going to identify AEs, as well as how to document them.[39] The training slides inform staff on how to properly grade AEs/SAEs according to severity, and even offers a "decision tree" to assist staff with determining if an AE is considered unexpected and reportable. The presentation also displays a safety reporting visual (figure 2), which shows the communication processes, and the parties involved in safety reporting activities. Though this appeared to be the main training at the Jefferson Clinical Research Institute for safety reporting, it offers clinical research staff a strong overview of safety reporting regulations, in-depth explanations regarding the subject matter and decision-making, as well as guidance on internal responsibilities.

[39] Kathleen O'Malley, "Adverse Events, Unanticipated Problems"

Figure 2. Jefferson Clinical Research Institute, Reporting AEs: All About Safety![40]

6.1.3 University of California, Los Angeles Clinical and Translational Science Institute

The University of California, Los Angeles (UCLA) Clinical and Translational Science Institute provides training on safety and study integrity in clinical research via a data monitoring presentation by the Regulatory Knowledge and Research Ethics Co-Leader. Though many slides are overviews of data and safety monitoring boards and plans (DSMB and DSMP), adverse events and safety reporting are addressed. The training slides define AEs, the Investigator responsibilities, regulatory requirements on

[40] Kathleen O'Malley, "Adverse Events, Unanticipated Problems, and Protocol Deviations" (Jefferson Clinical Research Institute, n.d.), Slide 31, accessed November 4, 2017, http://www.jefferson.edu/content/dam/university/skmc/dept-of-medicine/Research/JCCCR/Adverse_Events_Unanticipated_Problems_and_Protocol_Deviations.pptx

data collection and reporting of AEs, grading AEs, as well as "practical pointers" on safety reporting.[41] Shaker-Irwin explains how significant safety reporting is for a clinical research study:

> The most important component of data and safety monitoring is the adverse event reporting and its completeness and accuracy. The DSMB makes important decisions about the study and thus needs the most up-to-date accurate and detailed data to do so…
> … Inaccurate and/or inadequate reporting of adverse events leads to an incomplete or misinterpreted final AE compilation and statistical analysis.[42]

6.1.4 Duke University Office of Clinical Research

Duke University's Office of Clinical Research has many resources available for clinical research staff, most of which are designated for Investigators. Unfortunately, not many resources were located by the researcher in terms of patient safety reporting. Duke's IRB does provide a "Safety Events and Correspondence Reference Guide" document. It offers "step-by-step instructions for creating and submitting Safety Events and Correspondence in the eIRB," along with visuals of the eIRB system.[43] The Office of Clinical Research does have a new website, which could have affected previous documents and resources, or the website is still being finalized and reorganized.

6.1.5 University of California, San Francisco (UCSF) Clinical and Translational Science Institute (CTSI)

Similar to Jefferson University and UCLA, UCSF's Clinical and Translational Science Institute (CTSI) also provides their Clinical Research Coordinators (CRCs) with

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[41] Laurie Shaker-Irwin, "Data Monitoring: Assuring Safety & Study Integrity in Clinical Research" (UCLA Clinical and Translational Science Institute, 2012), accessed November 4, 2017, http://ctsi.ucla.edu/education/files/view/training/docs/module5-shaker-irwin-feb12.pdf.
[42] Ibid.
[43] Duke University Institutional Review Board, "eIRB Training: Safety Events and Correspondence Reference Guide," last modified 2016, accessed May 24, 2017, https://irb.duhs.duke.edu/training-and-education/eirb-training.

online training slides on safety reporting. The training covers Federal regulations, Investigator responsibilities, and CRC responsibilities in AE/SAE reporting. It also provides documents that are to be used, and both internal and external deadlines that must be met. Topics also discussed include what AEs/SAEs should and should not be reported to UCSF's Committee on Human Research (CHR), and an overview of the DSMB and DSMP.[44] UCSF's CTSI training on safety reporting provides useful information for CRCs; however, aside from CRCs and Investigators, it does not outline the responsibilities of other clinical research staff when it comes to safety reporting activities.

6.1.6 Ohio State University Office of Research

The Office of Research at Ohio State University educates clinical research staff of institutional and Federal requirements with the use of SOPs and policies. Policy #22b covers "Event Reporting - Unanticipated Problems Involving Risks to Subjects or Others, Adverse Events, and Other Problems."[45] Definitions of the key terms are provided, as most SOPs usually include. The document describes what AEs require "prompt reporting," and which AEs do not require prompt reporting, as well as timeframes which must be met when reporting safety events.[46] Other topics discussed in the SOP include the event reporting review process, IRB actions, institutional reporting, record retention, and regulations and guidance that pertain to the SOP. The last four pages, a sample of which is provided in Figure 3, provide clinical research staff with "Event Examples and Reporting Requirements," which offers scenarios staff may encounter, the reporting

[44] University of California, San Francisco: Clinical and Translational Science Institute, "Safety for the Research Subject: Adverse Event Reporting," February 3, 2014, accessed November 3, 2017, http://hub.ucsf.edu/sites/hub.ucsf.edu/files/7.%20Reporting%20Adverse%20Events.pdf.
[45] Ohio State University: Office of Research, "Event Reporting - Unanticipated Problems Involving Risks to Subjects or Others, Adverse Events, and Other Problems," last modified 2017, accessed November 4, 2017, http://orrp.osu.edu/files/2011/10/Event-Reporting.pdf.
[46] Ohio State University, "Event Reporting"

criteria, as well as how to report the event.[47] Though only training SOPs were found for Ohio State University, the information explains the essentials, and the safety reporting examples are helpful.

Event Examples and Reporting Requirements
Contact ORRP With Questions: (614) 688-8457

Event	Examples (not all-inclusive)	Reporting Criteria	How to Report
Adverse Event (AE)	◦ Participant with acute renal failure at a site **under Ohio State IRB jurisdiction**, probably related to study drug administration, resulting in hospitalization, renal failure not listed as a known risk in the informed consent document or investigator's brochure. ◦ Participant with suicidal ideation at a site **not under Ohio State IRB jurisdiction but engaged in Ohio State research,** resulting in hospitalization, unexpected, related to protocol behavioral intervention, not listed as a known risk in the informed consent.	**An adverse event that is:** ✓ Serious, ✓ Unanticipated, **and** ✓ Related	**Buck IRB Event Report within 10 Days**

Figure 3. Ohio State University, Event Examples and Reporting Requirements.[48]

[47] Ohio State University, "Event Reporting"
[48] Ibid.

6.2 Training at International Institutions and Third-Party Training Programs

6.2.1 Training at International Institutions and Agencies

Oxford University Hospitals: NHS Trust,[49,50] Australia's Melbourne Health Office for Research,[51] Australian Government: National Health and Medical Research Council's Therapeutic Goods Administration,[52] Norfolk and Suffolk NHS Foundation Trust,[53] and Ireland's Health Products Regulatory Authority[54] were reviewed and compared altogether, as there were common training trends among them (Chart 3).

Chart 3. Comparison of methods used internationally to train staff on patient safety reporting

Institution	SOP/ Policy	Guidance	Flowchart
Oxford University Hospitals: NHS Trust	√	-	√
Australia's Melbourne Health Office for Research	√	-	√
Australian Gov't: Therapeutic Goods Admin	-	√	√
Norfolk and Suffolk: NHS Trust	√	-	√
Ireland: Health Products Regulatory Authority	-	-	-

[49] Heather House, "Safety Reporting in Clinical Research Policy" (Oxford University Hospitals: NHS Trust, September 2017), accessed October 27, 2017, http://www.ouh.nhs.uk/researchers/documents/documents/safety-reporting.pdf.

[50] Clare Riddle, "Safety Reporting for CTIMPs - Standard Operating Procedure" (University of Oxford, 2017), accessed November 4, 2017, https://researchsupport.admin.ox.ac.uk/sites/default/files/researchsupport/documents/media/university_core_sop_3_safety_reporting_for_ctimps.pdf.

[51] Melbourne Health: Office for Research, "Monitoring and Reporting of Safety in Clinical Trials Involving Therapeutic Products and Other Clinical Research," March 20, 2017, accessed October 27, 2017, https://www.thermh.org.au/sites/default/files/media/documents/research/Guidelines%20for%20clinical%20trial%20monitoring-safety%20reporting%20updated%2030.03.2017.pdf.

[52] Australian Government: Therapeutic Goods Administration, "Guidance: Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods" (National Health and Medical Research Council, November 2016), accessed October 27, 2017, https://www.thermh.org.au/sites/default/files/media/documents/research/NHMRC%20Safety%20Monitoring%20Clinical%20Trials%202016.pdf.

[53] Bonnie Teague, "Research Adverse Event and Safety Reporting Procedures" (Norfolk and Suffolk NHS Foundation Trust, 2013), http://nsft.nhs.uk/Get-involved/Documents/RnD016.pdf.

[54] Health Products Regulatory Authority, "National Reporting of Adverse Drug Reactions," last modified 2014, accessed November 4, 2017, http://www.hpra.ie/homepage/medicines/regulatory-information/pharmacovigilance-and-post-authorisation-safety/national-reporting-of-adverse-drug-reactions.

All of the institutions provide resources for clinical research staff, which include definitions, an outline of staff responsibilities, reporting requirements, AE reporting flowcharts, as well as supplemental documents and websites affiliated with safety reporting; most of the institutions utilized an SOP for training, and the Australian government's Therapeutic Goods Administration issued a guidance. The only outlier was Ireland's "National Reporting of Adverse Drug Reactions" page, which directs staff to the EMA website and also references the EMA's GVP, and the EudraVigilance for safety reporting:

> In accordance with European and national legislation, marketing authorisation holders (MAHs) are required to ensure that an appropriate system for pharmacovigilance is in place in order to assume responsibility for marketed medicines and to ensure appropriate action may be taken when necessary in accordance with relevant EU guidance included in GVP…
> ...Irish SUSAR reports are reportable to the HPRA in parallel with reporting to the EudraVigilance clinical trials module.[55]

Though the majority shared common characteristics and resources, it is important to note three of the five institutions and agencies fall under EMA regulations: Oxford University Hospitals, Norfolk and Suffolk NHS Trust, and Ireland's Health Products Regulatory Authority. The extensive EMA training resources are available for their use in addition to the SOPs and Guidance found.

6.2.2 Third-Party Training Programs

Aside from institutions providing clinical staff internal training on patient safety reporting, some may utilize external or third-party companies to train the staff. TransCelerate BioPharma, Inc. provides training for clinical research sites. It includes GCP training, form documents sites can use for clinical research studies, and

[55] Health Products Regulatory Authority, "National Reporting of Adverse Drug Reactions"

informational programs.[56] The informational programs include one designated for "Adverse Events and Safety," which provides definitions, the Investigator's responsibilities for subject safety, as well as SAE reporting requirements.[57] TransCelerate BioPharma, Inc. collaborates with the Society for Clinical Research Sites (SCRS) to provide the programs. The programs are in module format, and are "being offered to simplify and enhance the clinical trial site qualification and training process."[58]

Rho World, Inc. is an external company which clinical research sites and sponsors may utilize for all safety reporting processes. The company provides product safety and pharmacovigilance services on a global level with their own safety team. Aside from handling safety reporting procedures and creating documentation for sites to use, Rho World also "supports and educates site staff" on safety reporting.[59] No further details were provided on the extent or format of the site staff education; however, this external company is an option for both sites and sponsors to use for not only safety reporting training, but for all safety reporting activities.

6.3 Overall Findings

The FDA's CFR and the EMA's GVP do not provide similar regulations when it came to safety reporting and the proper training of staff on safety reporting activities. The EMA's safety reporting regulations are much more detailed compared to the FDA's regulations; additionally, it also provides guidance on training both clinical and non-

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[56] TransCelerate BioPharma, Inc., "Site Qualification and Training," last modified 2017, accessed November 4, 2017, http://www.transceleratebiopharmainc.com/assets/site-qualification-and-training/.
[57] Ibid.
[58] Society for Clinical Research Sites, "Site Management Modules," last modified 2017, accessed November 4, 2017, http://myscrs.org/learningcampus/site-management-modules/.
[59] Rho World, Inc., "Product Safety and Pharmacovigilance Services," last modified 2017, accessed October 27, 2017, http://www.rhoworld.com/rho/services/stand-alone-services/product-safety-and-pharmacovigilance-services.

clinical staff. It offers a website that houses various training resources and materials to accomplish both mandatory and supplemental training, which clinical research sites may utilize.

The FDA does not provide a hub with training materials, and only offers a webinar tutorial on how to utilize the dashboard of the FDA Adverse Event Reporting System (FAERS) for post-marketed drugs. A major factor which may play a role in the EMA providing more regulations and resources is their use of a streamlined database for IND safety reporting, which the FDA currently does not have.

Institutions studied in the United States primarily utilize training slides to educate staff on safety reporting, while others issue an SOP describing the processes, responsibilities, and AE/SAE reporting flowcharts. Orientation training sessions were also noted, which cover safety reporting. There are additional options of calling on external parties to train clinical research staff via modules or on-site training. There was not much consistency in the training program modalities or how in-depth each one was. The international institutions and agencies studied shared common characteristics, where most provided similar SOPs and AE/SAE reporting flowcharts. The findings do come with the caveat that most of the institutions fall under EMA regulations, which means those institutions all have access to the EMA's training resources available for patient safety reporting, with different training modalities offered.

An SAE report research study as well as a journal article regarding staff training on pharmacovigilance were both reviewed. The research study observed poor quality SAE reporting, with many reports missing critical information. The study concluded the lack of accuracy and completeness seen in SAEs showed the training on SAE reporting

needs to improve. The journal article was a very detailed document, providing examples and information on ways clinical research sites could create a strong staff training program for patient safety reporting activities. The main reason the article had been created was due to the lack of guidance from regulatory agencies and not having many resources available online or in literature to address the topic. Both the research study and journal article highlight the need for stronger staff training on patient safety reporting and supplemental resources to conduct the training.

Chapter 7

Recommendations and Conclusions

At the time of this research project, the FDA does not provide sufficient guidance on staff training for patient safety reporting activities. In addition to that, there are not many Federal regulations pertaining to data management.[60] With clinical research evolving and shifting the focus to RWD and RWE, the researcher concludes that the FDA must address both topics in greater detail, and provide additional regulations and resources to fulfill both.

It would be conducive for the Cures Act to address safety reporting and proper staff training when it is issued, since safety reporting will be tied into the collection of RWD and RWE.

> **Recommendation 1:** The NRO should anticipate future regulations and prepare by creating internal processes and a training program to cover patient safety reporting procedures in the interim.

Even though there are not many data management regulations or resources available to utilize for training both clinical and non-clinical staff on patient safety reporting, the NRO needs to be proactive in anticipating changes to federal regulations and should start the process by creating internal processes and a training program. Internal controls are heavily emphasized in Federal regulations, which leaves institutions responsible for implementing their own internal processes in order to meet the requirements. The lack of guidance from the FDA on the appropriate training needed to

[60] Elliott C Kulakowski and Lynne U Chronister, *Research Administration and Management* (Sudbury, Mass.: Jones & Bartlett Learning, 2011).

fulfill proper handling of patient safety reporting shows the institutions need to create their own training for their staff to complete.

Seeing that patient safety and efficacy is the number one priority when conducting clinical trials, this training should be regulated by both the FDA and the EMA, or at the very least, a training program be issued by the agencies. The EMA provides much stronger oversight, detailed regulations, and training resources for the clinical research studies they oversee. The FDA should take note of the EMA's current model and work towards creating similar regulations and resources.

Lack of, or weak, training processes may compromise patient safety and efficacy. The researcher believes the gravity of that in itself underscores how vital it is for the FDA and EMA to ensure all clinical research being conducted have clinical trial staff who are properly educated through a streamlined, "blanket" training across the board. Similar to GCP training, and many institutions requiring CITI certifications in order to work on clinical research studies, an additional patient safety reporting training would help cover the most important part of the trial: patients and their health and wellbeing. This will in turn result in clinical data providing the most accurate patient safety information for sponsors who are seeking approval of an IND from the FDA.

Recommendation 2: The NRO should create both a general training program and supplemental role-specific training for those clinical staff who are responsible for patient safety reporting.

After studying various institutions across the nation and in other countries, the researcher recommends that the NRO be proactive in developing and conducting a general training program and supplemental role-specific training for those clinical staff

who are responsible for patient safety reporting. While SOPs and internal controls are commonalities, additional training modalities will assist in properly training staff. This is essential to ensure good patient care.

To facilitate the creation of a general training program, the researcher met with the RQC Director to go over research findings and discuss ways the NRO can implement the training. The researcher proposed, and offered to assist, the RQC team in creating training slides, as well as producing pre-recorded presentations, and to make these available and accessible to all staff.

The NRO hosts internal company-wide meetings and presentations regularly; the RQC Director suggested that the general training slides on patient safety reporting could be presented at one of the company-wide meetings, where time would be allotted for questions and answers by staff members. Documentation of all training activities and records of completion by the staff would be kept on file with the RQC team. For being a healthcare IT company with plans on building a clinical trials program, the NRO would already be implementing a staff training program on patient safety reporting that is more thorough than many research institutions are currently utilizing. In addition to SOPs and policies, the company would provide training slides, pre-recorded presentations, live presentations, and a documentation system for both clinical and non-clinical staff within the company.

Once further regulations are issued by the FDA and the Cures Act is finalized and implemented, the NRO would adjust its internal processes and training modalities as needed to fulfill the new requirements as they are issued. Regulations are continuously evolving, but human subjects remain constant. Research institutions must conform to new

requirements so that human research subjects' safety is never disrupted or compromised. The researcher is hopeful new safety reporting regulations and training resources will soon become available, as they would ensure patient safety is handled with the utmost care by well-trained clinical staff.

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Appendix A:

Johns Hopkins University Homewood Institutional Review Board Approval Letter

JOHNS HOPKINS
U N I V E R S I T Y

Homewood Institutional Review Board
3400 N. Charles Street
Baltimore MD 21218-2685
410-516-6580
hp://web.jhu.edu/Homewood-IRB/

Michael McCloskey, PhD
Chair

Date: November 27, 2017

PI Name: Marianne Woods
Study #: HIRB00006654
Study Name: "Creating, Training, and Implementing the Safety Reporting Processes for a Research Organization's New Clinical Trials Program"

Date of Review: 11/27/2017
Date of Approval: 11/27/2017

The Homewood IRB reviewed the information provided for the above-mentioned project and has determined that this research does not qualify as federally-regulated human subjects research, and therefore does not require IRB approval. This determination has been made with the understanding that the proposed research either (a) does not involve a systematic research investigation designed to develop or contribute to generalizable knowledge, or (b) does not collect identifiable private data about a human participant.

You may proceed with the study at any time. No further communications with the HIRB are necessary unless the procedures in your project are changed in such a manner that would require IRB review or approval.

Please keep this message in your files for future reference. Thank you for contacting the Homewood IRB about this research and for providing the requested information to make this determination. Your cooperation is greatly appreciated.

Study Team Members:
Angelica Medina

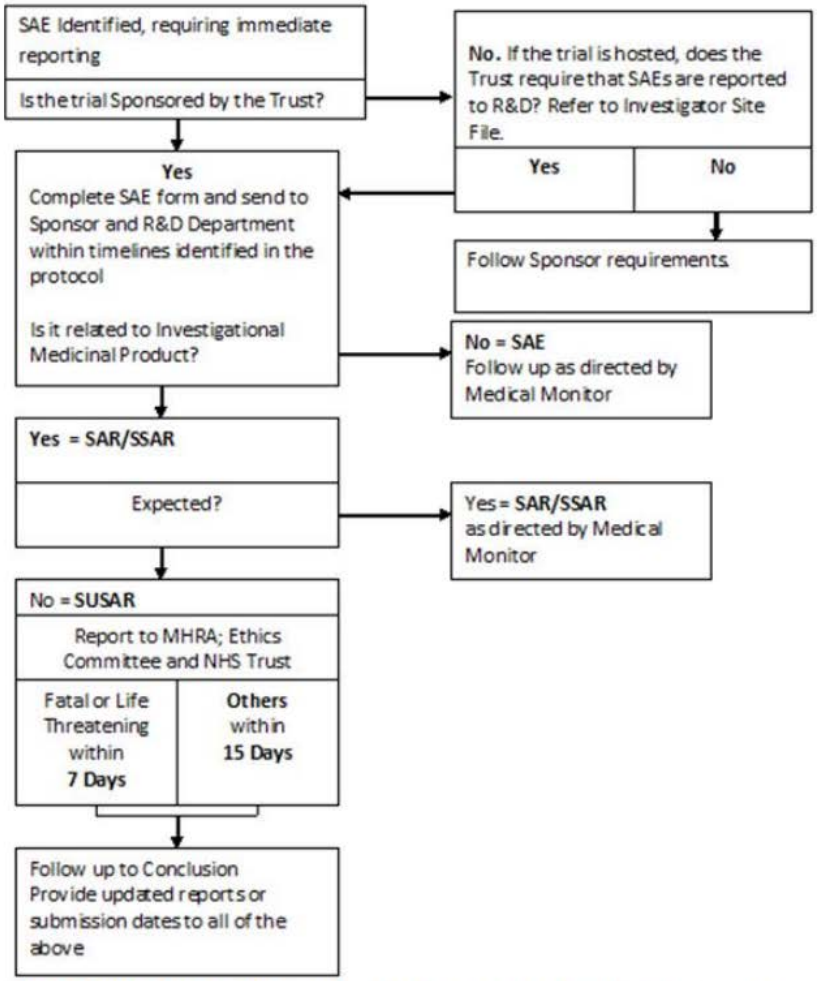
APPROVAL IS GRANTED UNDER THE TERMS OF FWA00005834 FEDERAL-WIDE ASSURANCE OF COMPLIANCE WITH DHHS REGULATIONS FOR PROTECTION OF HUMAN RESEARCH SUBJECTS

Appendix B

Oxford University Hospitals' Flowchart of the Reporting Process

Oxford University Hospitals

Appendix 1: Flowchart of the Reporting Process



PLEASE NOTE: For any type of report, if there are any safety concerns for patients or potential for adverse publicity, please contact the Trust R&D Department.

N.B. Where the SAE also constitutes an untoward incident, this must also be reported to Clinical Governance using the appropriate system.

Appendix 1: Flowchart of the Reporting Process Page 10 of 12

Heather House, *"Safety Reporting in Clinical Research Policy"* (Oxford University Hospitals: NHS Trust), Page 10, last modified September 2017, accessed October 27, 2017, http://www.ouh.nhs.uk/researchers/documents/documents/safety-reporting.pdf.

Curriculum Vitae

Angelica Medina, MS, BS
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Angelica ("Gel") Medina, born January 24, 1985, is an Orlando, FL native and graduate of the Master of Science in Research Administration program at Johns Hopkins University. She is currently a Senior Oncology Data Abstractor on the Research Oncology team for Flatiron Health, where she performs activities surrounding the data collection and analyses of oncology patient data points requested from clients. Of her 14 years working in the healthcare field thus far, nine years have been in clinical research, mostly involving data management activities for solid tumor clinical trials; other experiences were obtained in the operating room as a Surgical Technologist, as well as emergency medicine. Angelica also holds a Bachelor of Science degree in Biomedical Sciences, and an Associate of Science degree in Surgical Technology.