DEVELOPMENT OF A RESEARCH HANDBOOK: A GUIDE FOR NEW RESEARCHERS

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by

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Abstract

Working at an institution with a budding Research Department necessitates the development of additional resources for the education of new researchers. Such an educational gap was noted by key research personnel at Kadlec Regional Medical Center (KRMC). When examining the resources at outside institutions, it was noted that many institutions provided some type of a research handbook for their researchers. The objective of this Capstone Project was to develop a research handbook for the use at KRMC.

When developing a resource such as this, it is important to compile pertinent regulations and institutional requirements so that the handbook is not only useful, but easy to understand. A literature review was conducted of various warning letters issued from the U.S. Food and Drug Administration to institutional sites conducting clinical trials. This examination was vital in the determination of high-risk areas to KRMC so to ensure that these areas were included in the content of the Research Handbook. Other material for the handbook came from assessments of research handbooks from outside institutions. These resources were used to validate content and format so that the most useful information was included in an easy to follow layout.

Upon completion of the initial draft of the Research Handbook, the document was sent to key institutional research stakeholders for review and recommendations. These recommendations were included in the final draft of the document which will be submitted for review and approval at the quarterly Research Committee in January 2019. Once approved, the Research Handbook will be rolled out to KRMC so that all institutional staff has access to the document via the central policy repository. This same portal will route the Research Handbook to designated staff for biennial review to ensure that the information remains up to date and relevant to the institution.
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Chapter 1: Introduction

1.1 Background

Kadlec Regional Medical Center (KRMC) is an affiliate of the larger Providence St. Joseph Health (PSJH) System, which is a Catholic health system that includes institutions across five states. The Research Program at KRMC consists of a staff of eleven employees within the Central Research Department. Currently, KRMC is conducting clinical trials in oncology, rheumatology, neurology, diabetes, stroke and behavioral health. Four years ago, the institution was only conducting research in two of these six indications; therefore, the growth of the KRMC Research Program is quite substantial. Such an expansion in a short amount of time brings growing pains and has resulted in the Research Department staff spending a great deal of time educating institutional staff on the regulations and requirements of conducting clinical research.

For this reason, it was decided that developing a research handbook would be a useful resource for KRMC. This handbook will be a central resource for institutional requirements and federal regulations that all researchers should be aware of. In addition, there will be references to more detailed information either on federal websites or through internal standard operating procedures.

1.2 Statement of the Problem

The problem that KRMC faces is that its personnel do not have extensive experience conducting research. This leaves the institution at risk since there is not a thorough understanding of the requirements and processes related to the conduct of clinical trials. In addition to accessing the centralized research staff, there needs to be supplementary ways to relay the requirements related to the conduct clinical research at KRMC. When interacting with young researchers, it can sometimes be a challenge to ensure that all the requirements are
understood. Therefore, it is crucial to communicate the information in a manner that relays the importance of ensuring that all regulations are maintained. By having a handbook available, the research staff will be able to provide information through multiple pathways.

The establishment of a handbook would fill the education gap that currently exists at KRMC for new researchers. An example of how this handbook could have helped the institution in prior situations would be with physicians wanting to submit for grant funding for their research project. These new researchers often spend too much time trying to find out how to go about navigating the process and are frequently routed to someone at PSJH instead of the local Central Research Department. By making a research handbook, there will be a local resource to guide researchers to the applicable resources to begin their project as well as understand the multiple requirements necessary to conduct clinical research.

1.3 Research Questions

When evaluating this project, the primary question that needed to be addressed is what information should be included in the handbook. The handbook was designed to be a centralized location for all key information related to research. This means that all the main areas of research would need to be included from the initial requirements to be eligible to conduct research through study closure. This resource will provide new researchers with vital information on key areas regarding the conduct of clinical research. Hopefully, this knowledge will better inform KRMC institutional staff about the life cycle of a research project, but also reiterate the importance of protecting human subjects.

The handbook also needs to be easy to read and free of complicated regulatory language so that individuals new to research can understand the content. Another key point to this handbook is that the document needs to be easily accessible. For example, the document should be
printable and located centrally where all institutional staff can access it. By having the document available on the institutional portal, it will become searchable and easy to find for even those unaware of the existence of a Central Research Department at KRMC.

1.4 Objectives

The objective of this project was to create a resource for researchers at KRMC that centralized the key points related to research. This resource will be a compilation of fundamental research regulations and local processes for conducting clinical research that is easy to use and contains the main components of a research project life cycle.

1.5 Significance

This project is important to KRMC since research is expanding quite quickly, and this handbook can hopefully be a useful resource to those new to research. Education around the proper conduct of research is important to mitigate the risk to the institution. Since there are so many requirements surrounding research, it is easy to make a mistake that could have dire consequences to the institution. By having a central source of information, the hope is there will be a better understanding of the research requirements so that the risk of research misconduct is reduced.

1.6 Exclusions and Limitations

The format constraints of a handbook limit how much information could be compiled within a useful document. The primary focus of this project was directed towards a general overview of research processes and the conduct of clinical trials including the use of investigational product. There is an immense amount of information surrounding the conduct of clinical trials, so it was important to limit the content to only the most important information to the institution so to provide an overview opposed to an all-encompassing document. There was avoidance to areas
such as devices, IND submissions and animal research since, at this time, KRMC is not conducting these types of research. In the future, this handbook could be expanded to include these areas as the Research Program continues to expand. The intent is to also ensure that the handbook is periodically updated as needed so that the information remains relevant.

Chapter 2: Literature Review

2.1 Overview of Literature Review

To understand what gaps potentially exist within the Research Program at KRMC, a review was conducted of warning letters to research sites from U.S. Food and Drug Administration (FDA) inspections. These citations were vital in assessing the potential areas of risk at the institution. Attempts were made to find documentation related to investigational sites of similar size so that there was a comparable evaluation of the potential risks at KRMC.

In addition, a search was done to locate similar examples of research handbooks to provide generalized guidance for the handbook development. This document review will offer ideas on key areas that could be included in the KRMC Research Handbook as well as potential layout designs to concisely relay the information in a meaningful way.

2.2 Review of Similar Documents

Research was done on similar research handbooks to provide a basis for the project development. The best handbook that was discovered in this online search was the UC Davis Clinical Research Guidebook¹ developed by the UC Davis Clinical and Translational Science Center. This 176-page document is extremely thorough and provided validation as to the key sections of the handbook that were originally planned for the KRMC Research Handbook. These

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areas include training, start up, Institutional Review Boards (IRBs), contracts, electronic medical record, investigational drug, and informed consent.

The second document evaluated was the Research Handbook of the University of Nebraska Medical Center (UNMC)\(^2\) which was developed for the guidance of researchers at their institution. This document provides extensive guidance on the internal pathways on how to conduct a research project at UNMC. Areas discussed include how to collaborate with outside organizations, how to obtain space for their research project, what research support services are available, required internal forms, and effort reporting. In addition, the group included general guidance on required training to conduct research, indirect costs, and regulations about conducting human subject research. However, there are numerous sections that were included in the UNMC Research Handbook that does not apply to KRMC. Some of these areas include animal research, international export-controlled research, and embryonic stem cell research.

### 2.3 Review of FDA Warning Letters

For the literature review, focus was directed towards FDA warning letters. Four warning letters were of particular interest due to the similarities in size and scope between the institutions cited in the letters and KRMC. The first one examined was warning letter 16-HFD-45-03-01\(^3\) which was issued to Cheta Nand, M.D. March 10, 2018 in Richland, WA; coincidentally, this site is in the same town as the main KRMC hospital campus. This principal investigator (PI) was found to have unacceptable research practices, including enrolling patients onto the clinical trial that did not qualify. For example, there were multiple patients that were on a medication required for eligibility that was not a high enough dose to qualify for the study. There were also

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laboratory tests that were not drawn but expected to be monitored during the study treatment per the protocol. The specific regulation cited by the FDA was 21 CFR 312.60 which states that an investigator must ensure that the trial ran at the institution is done so in accordance with the study protocol. The FDA also stated that the PI was not able to provide a sufficient corrective and preventative action plan to ensure that future subjects are not incorrectly enrolled into clinical trials at the site. Another key point raised by the FDA was that enrolling patients to trial that do not qualify is not only a patient safety concern but raises questions about the quality of data that is being collected at the site.

The second warning letter reviewed was 16-HFD-45-03-03 addressed to Benedict S. Liao, M.D. on March 29, 2016. Similarly, Dr. Liao was cited for enrolling patients onto study that did not qualify and neglecting to run all the protocol specified laboratory tests. However, he was found to have an additional deficiency for failing to maintain adequate records after closure of the study. The site was unable to present all source documentation from their archived records to verify the data that was collected for the study. Failing to maintain study records for the applicable archival timeframe is not in concordance with 21 CFR 312.62(a) and 21 CFR 312.62(b).

The next warning letter that was reviewed was 16-HFD-45-05-01 which was issued on May 19, 2016. This site was located in Florida and was overseen by Jose Giron, M.D. There were a couple large issues noted by the FDA during their visit. First, was a very serious issue of overdosing a patient over the period of a month. The PI provided a shocking response to this finding; he stated that it was corrected and “to the best of my knowledge, no harm has come to”

the patient and failed to mention of any corrective action plan. There were also numerous samples that were not submitted to the central laboratory for multiple patients. The FDA again cited a violation of 21 CFR 312.60 since the PI did not abide by the protocol specifications.

The final warning letter that was reviewed for this project was 16-HFD-45-06-01 which was sent to John Gabriel, M.D. on June 28, 2016. This research center was also cited for enrolling subjects onto trial that did not qualify. Specifically, twenty-five patients were randomized onto the trial and dosed with study drug without verifying the laboratory results. When the laboratory results were received, it took a large period of time before multiple patients were dose reduced due to the patients’ renal insufficiency.

These warning letters reiterate the importance of having controls in place when conducting research. There was also special emphasis on the necessity of having protocol compliance not only for patient safety, but for the validity of the data being collected. In addition, the letters emphasized the need for adequate archival storage of study documents so that the study data can be verified with source documents in the event that there is concern raised in regard to the legitimacy of the data. These citations provide guidance as to some key areas in clinical research that need to be included in the handbook being developed: appropriate training on good clinical practice and human subject’s protection, adequate regulatory file management and archiving of study documents at study closure.

Chapter 3: Project Description

3.1 Description of Project Elements

For this project, extensive research was done to compile research regulations so to provide an easily accessible resource for new researchers. In addition, it is important to understand which areas need to be discussed so that the handbook is comprehensive and contains information about the main elements on the conduct of clinical research.

Chapter 4: Need(s) Assessment

4.1 Determination of Need

Since KRMC is relatively new to the realm of conducting research, there are some large knowledge gaps on requirements as they relate to being part of a clinical trial. There are constantly new projects being brought forward from investigators with little to no prior experience in clinical trials. Recently, a workflow was developed in order to provide a concise way of communicating the required steps to potential investigators (Appendix I). In addition to this workflow, the handbook could be given to these new investigators so to provide some context on what to expect as they move forward through the process. Furthermore, when examining other outside institutions, it was noted that multiple institutions conducting research had research handbooks or research guidebooks available. Since KRMC does not have this resource, it was determined that this was a need for the institution.

4.2 Metrics Used to Establish Need

There were no specific metrics used to evaluate the need for the development of a handbook. Instead, this project is a compilation of information and resources to assist in the day to day activities of clinical research at KRMC. Based on the needs assessment and literature review, it was determined that there was a prominent gap in resources offered for new
researchers at KRMC. Since the current resources fall solely on the research staff employed at the KRMC Research Department, development of a research handbook could provide an intermediary step before inundating staff with questions. This resource will also play a key role in educating researchers on the importance of the proper conduct of research by ensuring that potential areas of risk are addressed within the document. These areas were identified from personal working experience and by analyzing warning letters issued to research sites conducting the same types of clinical research.

4.3 Institutional Committee Assessment

The Research Committee at KRMC was recently formed in 2016 to be a venue for new research projects to be discussed and approved. This committee is the approving body for research standard operating procedures and has been assessing the potential gaps and risks of KRMC research projects being conducted throughout the institution over the last two years. It was determined that an intake process for new research projects was needed; therefore, a guidance document was developed to guide new researchers through the start-up process. This was implemented to ensure that all projects go through the appropriate checks and balances. This workflow was mapped onto a document so it could be utilized as an educational tool and has already been forwarded to numerous potential researchers. However, there is still a lack of information on the key regulations that investigators should be aware of when conducting research. By developing a handbook, the Research Committee will have a resource available to provide to potential researchers.
4.3.1 Role of Committee in Project

The committee is supportive of the plan to develop a research handbook. In addition, this committee will play a large role in the rollout of the new research handbook. The final version of the KRMC Research Handbook will be presented at the next quarterly committee meeting in January 2019 for review and approval. Once the handbook is approved, the document will be rolled out to the institution.

Chapter 5: Methodology

5.1 Methodology and Design

To develop this Research Handbook, federal regulations and institutional policies were thoroughly reviewed. In addition, review of research handbooks from other institutions was completed to aid in the development of a handbook for KRMC. Once these reviews were completed, the main sections were identified and the handbook was written to include local policies and federal regulations. When the first draft of the Research Handbook was developed, the draft was sent to the local Research Compliance Coordinator and the PSJH system level Director of Research Compliance for review and recommendations. The finalized version of the handbook will be presented and reviewed at the quarterly Research Committee which will be held in January 2019 for implementation at the institution. Once approved by the Research Committee, the handbook will be made available to the entire institution by way of KRMC’s internal portal PolicyStat which houses KRMC policies as well as key documents.
Chapter 6: Project Results and Discussion

6.1 Project Result

The result of this project is that the handbook has been completed and reviewed by the Research Compliance Coordinator, locally, and by the Director of Research Compliance at PSJH. Their comments and recommendations were incorporated into the final version of the Research Handbook. Since the document has been reviewed and approved by these research stakeholders, the final version will be presented at the next Research Committee meeting in January 2019 for review and approval. Once the Research Handbook has approval from this committee, the document will be rolled out to the entire institution.

Chapter 7: Recommendations and Discussion

7.1 Recommendations

Recommendations are to ensure that the Research Handbook is accessible to all institutional staff and to support the use of the handbook. It is an extremely valuable resource, especially to those new to research so they understand the key areas related to the conduct of clinical trials. Another recommendation is to ensure that the Research Handbook stays updated. By putting the document on a biennial review with the Research Department Standard Operating Procedures, the document will remain relevant and useful to institutional staff.

7.2 Discussion

There are so many minute details that must be known when conducting clinical trials that it is relatively easy to not fully understand a requirement or regulation. It is apparent given the sheer mass of knowledge needed to conduct clinical trials that the requirements can appear quite daunting. By having a handbook, it will be easier to relay to new investigators just a portion of the knowledge required and dedication needed to be commit in order to conduct research.
Chapter 8: Conclusion

In conclusion, through the process of this project, an institutional Research Handbook was developed. The document was developed through extensive research of current regulations and examination of research handbooks from outside institutions. Overall, the experience of developing this handbook has been gratifying. It is something that has been recognized as an educational gap for KRMC for some time, so having the opportunity to commit time to develop this resource has been very rewarding.
Appendix 1: Research Intake Workflow

Research Project Intake Workflow

Applies to research being requested outside of the established research programs at ERMC

1. Project Identified → Contact Research Manager
   - Complete Research credentialing requirements: CITI Training (Good Clinical Practice, Human Subjects in Research Protection, Conflict of Interest in Research); COIR SMART

2. Study not Opened
   - Scientific Merit/ Peer Review
     - Feasibility Assessment (e.g., staffing, etc.), Assess Funding vs Expense

3. Denied
   - Present project at Research Committee Meeting (convene quarterly)
     - Approved

   - Central Regulatory Process:
     - * IRB processing/submission
     - * Regulatory document preparation

   - Clinical Trial Agreement and Budget Negotiation:
     - * Budget Research Manager
     - * CTA: Providence
     - * Contract HUB
     - * Activity Code Creation

   - Approved
   - Fully Executed Contract

   - EPIC Build Request, if applicable
     - Fully Executed
     - Build complete

   - Velos
     - Account Created

   - Project Can Begin
Appendix 2: Kadlec Regional Medical Center Research Handbook
Introduction

The intent of this Handbook is to provide information in a centralized location for those looking to conduct research at Kadlec Regional Medical Center (KRMC). This book will also help guide research staff to applicable regulations as they relate to vital topics in the conduct of research. It is extremely important that all those involved in research understand the severity of not complying with local, state and federal regulations as they relate to research. Care should be taken to ensure that both the researcher and the researcher’s institution maintains compliance with these regulations in addition to institutional policies.

This Handbook is broken out into sections so that readers can quickly access the topics of interest. Keep in mind that the intent of this Handbook is to provide general guidance to the conduct of research and every effort has been made to ensure that the most current regulations and processes are outlined at the time of the publication of this Handbook. Consult the references for links to the most up to date regulatory information.

In addition to having access to this Handbook, all institutional staff have access to the KRMC Central Research Department. The research staff will be available to guide new researchers through the entire life cycle of a research project from pre-award to study closure. Researchers at KRMC will work closely with the central research team on all sections discussed within this Handbook.
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1.1 National Regulations: Department of Health and Human Services (HHS)

1.1.1 What is HHS?

HHS includes eight agencies in public health and human services. These agencies are committed to protecting and serving the American people by way of numerous services including the funding of research projects\(^1\). The mission of HHS is “to enhance and protect the health and well-being of all Americans. We fulfill that mission by providing for effective health and human services and fostering advances in medicine, public health, and social services.”\(^2\) The following sections outline some of the primary agencies in HHS that apply to the conduct of clinical research.

1.1.2 Centers for Medicare and Medicaid Services (CMS)

CMS is a federal agency within HHS that manages Medicare and partners with state government to oversee Medicaid. CMS also supervises the standards for the Health Insurance Portability and Accountability Act of 1996 (HIPAA), nursing homes, the Clinical Laboratory Improvement Amendments (CLIA) as well as HealthCare.gov\(^3\). Research sites work with CMS when dealing with clinical trials that bill routine procedures to Medicare as part of the clinical trial. Refer to Section 5.2 for further detail.

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1.1.3 Food and Drug Administration (FDA)

The FDA “ensures that food is safe, pure and wholesome; humans and animal drugs, biological products, and medical devices are safe and effective; and electronic products that emit radiation are safe.” This agency is in charge of new drug approvals and oversees the conduct of clinical trials within the United States of America. The FDA uses the Code of Federal Regulations when reviewing institutional regulatory compliance.

1.1.3.1 Code of Federal Regulations (CFR)

The Code of Federal Regulations (CFR) includes rules published by departments and agencies within the Federal Government. The CFR is divided into 50 different titles and are updated annually. Clinical trials fall under the FDA which is governed by Title 21: Food and Drugs.

1.1.4 Office of Human Research Protections (OHRP)

OHRP protects the “rights, welfare, and wellbeing of human subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS).” OHRP provides education and materials in addition to overseeing regulatory and ethical issues in both behavioral and biomedical research. OHRP is intimately involved in the protection of human subjects in research. One way OHRP does this is by requiring institutions to have a Federal Wide Assurance.

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1.1.4.1 Federal Wide Assurance (FWA)

An FWA is a statement by an institution that verifies that they will be guided by a set of principles to protect the rights and welfare of human subjects in research. Kadlec Regional Medical Center (KRMC) is guided by the ethical principles of the Belmont Report. The Belmont Report holds three primary ethical principles in the conduct of human research: respect for persons, beneficence and justice.\(^7\)

As part of declaring an institutional FWA, the institution is claiming to have established written procedures for prompt reporting to the Institutional Review Board (IRB), applicable institutional officials and any federal agencies supporting the conduct of such research. These reportable events include the following:\(^8\):

1. Unanticipated problems that include risks to human subjects;
2. Noncompliance that is either serious or reoccurring based on guidelines set forth by the IRB or funding agency;
3. IRB approval that is suspended or terminated;
4. Continuing review must be performed by the IRB at least once annually;
5. Any proposed changes to the research project must be reviewed by the IRB prior to initiating those changes unless doing so is to eliminate potential of immediate harm to the research subject(s).

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1.1.5 National Institute of Health (NIH)

The NIH promotes the collection and sharing of medical knowledge by way of research activities in the biomedical and behavioral field. NIH’s mission is “to seek fundamental knowledge about the nature and behavior of living systems and application of that knowledge to enhance health, lengthen life, and reduce illness and disability.”

1.2 Kadlec Regional Medical Center (KRMC) Research Policies

All policies can be found on PolicyStat which is located online on the KWeb home page. Once in PolicyStat, policies are searchable by titles as well as policy areas. Selecting Research in the filter section of Policy Area will pull up all the current policies related to Research.

1.3 Collaborative Institutional Training Initiative (CITI)

Prior to conducting research, it is required that key research personnel complete the appropriate training in the responsible conduct of research. Key research personnel include all those with a significant role in the design and conduct of the trial (refer to policy 699.68.00: Key Research

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Personnel for further clarification). The training program that is widely recognized, as well as the training that KRMC requires, is provided by the Collaborative Institutional Training Initiative (CITI). Required modules include education on the protection of human subjects, good clinical practice and conflicts of interest in research. By affiliating with Providence Health Care Institutional Review Board, your certificate of completion will be available during pre-study review and allow your application to proceed in the process. The training is good for three years and it is the responsibility of the researcher to maintain their certificate by completing the refresher course prior to the certificate lapsing. Failure to maintain human subject protection training could impact your ability to continue participation in research at KRMC.

1.4 Conflict of Interest-Smart

Conflict of Interest-Smart (also called COI-Smart) is the program that Providence utilizes to review potential conflicts of interest as it relates to the research projects being conducted at KRMC. This is required to be completed annually and updated within 30 days of any new potential conflict in order to conduct research at KRMC. Contact the Research Department if you have not completed this submission and need the link to be resent to your institutional email. Refer to PSJH system-wide policy PROV-ICP-724: Conflict of Interest in Research for additional clarification.

1.5 Dangerous Goods Shipping for Infectious Substances and Dry Ice

International Air Transport Association (IATA) training is required for persons shipping dangerous goods. Dangerous goods include, but is not limited to, patient blood or tissue samples and dry ice. KRMC Research utilizes a program called Eduware to fulfill this regulatory
requirement. Reach out to the Research Department for approval to proceed with IATA training under the Research Client account. The certificate is effective for two years, and it is the responsibility of designated staff to take the refresher course prior to the certification lapsing.
CHAPTER 2
FEASIBILITY AND STUDY START UP

2.1  Research Department Assistance
As part of the Providence network, KRMC researchers have access to support services to aid in
the research development process. There is also a dedicated Centralized Research Department to
help with regulatory, data, clinical and financial management. If you have identified a potential
funding source for your project or an industry sponsored trial that you are interested in pursuing,
contact the research team to discuss your next steps.

The team can be contacted via email at Research@kadlec.org or by phone at (509) 783-4637.

2.2  Providence St. Joseph Health (PSJH) Medical Data Research Center
The Providence Medical Data Research Center (MDRC) provides KRMC researcher’s access to
biostatisticians for a multitude of services. Services include trial design and robust statistical
analyses including:

- Statistical plan
- Sample size and power analysis
- Population representativeness evaluation
- Survey sampling
- Randomization and cohort matching
• Data management: validation, accuracy, completeness
• Statistical modeling and model evaluation
• Descriptive statistics, advanced statistical inference
• Prediction and interim analyses
• Result interpretation and conclusion suggestion
• Presentations and publications

The MDRC supports all service lines. For more information, visit the PSJH Intranet website: https://sssteams.providence.org/sites/ces/mdrc.

The MDRC group can be contacted via email at MDRC@providence.org.

2.3 Providence St. Joseph Health (PSJH) System Library Services

The PSJH System Library Services provide all caregivers, providers and affiliated medical staff with access to an extensive collection of electronic resources. Services include:

• Librarians to perform literature searches for employees
• Provide full-text articles
• Current awareness searches – librarians can provide staff with searches delivered by email on a regular basis to allow the employee to stay current on new evidence in their area of specialty
• Table of contents service – employees can request the table of contents for numerous journals and request the full articles for those of interest
• One-on-one training of database searching
• Specialized research – employees can request a more in depth search than a traditional literature search
• Access to 2000+ electronic medical journals

More information can be located at the PSJH System Library Services website:
http://www.psjhealth.org/library.

The PSJH System Library Group can be contacted via email at librarian@providence.org.

2.4 Providence St. Joseph Health (PSJH) Digital Commons

The PSJH Digital Commons serves as a system-wide repository of PSJH research and other scholarly activities. The website allows for end users to search articles and is organized by Clinical Institutes and Departments. Content available includes publications, conference abstracts, book citations, and other multimedia. The Digital Commons team will also assist with bringing your work to the top of Google searches.


For the current contacts by service area, visit http://www.psjhealth.org/library/locations.
CHAPTER 3
FACILITY REVIEW AND APPROVAL PROCESS

3.1 Research Request Intake Form

On KWeb, there is a link for potential researchers to route their proposal requests to the Central Research Office. This is required for research being requested outside of the established Research Programs at KRMC. The KRMC Research Request Intake Form can be accessed via: https://redcap.providence.org/redcap/surveys/?s=AXRNH7WCRT.

3.2 Research Committee

The Research Committee was formed by KRMC in conjunction with Providence State Mary’s in Walla Walla, WA to review the current institutional research activities as well as new project requests from both institutions. It is important for new researchers to review the Research Intake Workflow (Appendix II) to understand the expectations of the institution prior to presenting their request to conduct research at the Committee. The Research Committee will review new research projects to verify that appropriate resources are available to conduct the study and that risks to the patient and the institution are minimized.

3.3 Providence Institutional Review Board (IRB) Facility Form

Prior to any KRMC researcher submitting their project to one of the Providence IRBs, they will be required to fill out a Facility Approval Form (Appendix III) that allows a KRMC institutional official to review and approve the project prior to it being reviewed by the IRB. This form
provides a summary of the project, who will be the principal investigator of the study, points out any conflicts of interest and if required training is complete followed by a place for a KRMC Executive’s signature to approve the project. For questions related to this form (including the submission of this form for institutional approval and signature), reach out to the Central Research Office at Research@kadlec.org.

3.4 Student Education Requirements: Dissertation, Thesis and Capstone Project

Students planning on conducting a project at KRMC as part of their dissertation, thesis or capstone project must have their project reviewed through the established approval process. This applies to projects that are deemed quality improvement or research. Outlined below are the steps required prior to any project implementation:

1. Contact the KRMC Education Department at (509) 942-2600 for the most current application form on file. Students will need to review their project with their sponsor at KRMC. Typically, the sponsor will be the student’s manager.

2. Once approved by their KRMC sponsor, the Facility Approval Form (Appendix III) needs to be completed by the student and signed the KRMC sponsor. Once complete, the facility approval form needs to be routed to Education for final approval and signature by senior leadership.

3. Once the project has been approved by senior leadership, the student will submit their application form and project summary/protocol to the Providence Institutional Review Board – Spokane at institutional.review.board@providence.org for final determination of the project being deemed quality improvement (QI) or research. If the project is deemed research, the protocol will need to be submitted through eClick for approval (see Section
1.3) after all applicable research specific trainings have been completed.
4.1 Reporting to the Institutional Review Board

An Institutional Review Board (IRB) is responsible for reviewing research projects to ensure that they are conducted ethically and protect the rights, welfare and safety of human research subjects. When the IRB is reviewing a research project, they are making sure the risk to human subjects is minimized, there is reasonable risk compared to the potential benefit, special care is be taken in regards to vulnerable populations, and that informed consent is appropriately documented.

The researcher is required to provide information about the study so that the IRB can determine if the project meets all federal requirements as stated in 45 CFR 46.111(a)(1-7)(b)\(^\text{10}\). Along with the initial IRB application submission, the protocol and applicable study documents must be submitted for review (i.e. informed consent documents, all patient facing materials including questionnaires, investigator brochures, advertising, etc.).

4.2 Central IRB versus Local IRB

A central IRB is an IRB that has been selected by the funding agency of the project. By doing so, the sponsoring agency has committed to submitting the majority of the regulatory documents to that designated IRB on behalf of the site. This allows for a reduction in staff time and effort due

to the institution not being responsible for completing the applicable paperwork with those IRB submissions. This is commonly seen with industry sponsored trials. The site is still responsible for ensuring all local requirements are adhered to; this includes, but is not limited to, informed consent wording containing applicable HIPAA language as well as local maintenance of regulatory documents.

A local IRB is utilized when the funding agency has not designated an IRB for the study. This is also the pathway for investigator initiated and retrospective chart review studies. In the event that there is not a designated IRB, researchers will submit their research projects to the Providence IRB HUB via eClick at https://eirb.providence.org/ClickIRB or another outside IRB, if desired.

### 4.3 Initial Submission to the IRB

The initial submission to the IRB will includes an application that will gather information through many study specific questions related to the project. Each IRB will have varying application questions that will need to be answered; however, typical questions may include ones related to consent forms, patient stipends, satellite site utilization and investigator history (i.e. if the investigator has been investigated or disbarred).

#### 4.3.1 Special Considerations

There are special considerations with some clinical trials that require an additional layer of oversight and review by the IRB. This section will review some of these special requirements.
4.3.1.1 Patient Facing Materials

Anything related to a research trial that is going to be provided to a patient needs to be reviewed by the IRB. This includes, but is not limited to, questionnaires, pill diaries, information cards, and brochures.

4.3.1.2 Advertising/Recruitment Materials

The IRB must review any advertising that will be used for the recruitment of subjects to ensure that there are no unduly coercive statements. They will also verify that the statements in the advertisement are in alignment with the protocol and consent form11. Examples of information that is required to be reviewed by the IRB include: any signs, fliers or written advertisement materials; the final taped broadcast, or the script that will be used in the advertisement; and screen shots of any website pages.

4.3.1.3 Translation of Documents

All patient facing documents must be provided in a language that is understandable to the subject. It is important to evaluate the potential patient population and request translations at the initial submission to the IRB so that all materials are available at the time of subject recruitment.

4.4 Periodic Submissions to the IRB

No less than once per year, the IRB must review the study at each study site. Factors considered

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during this review process include: if the subjects have received appropriate informed consent, the consent process is appropriately documented, evaluation of any potential issues at the site, and a risk assessment of the study\textsuperscript{12}. Assessing the risk is one of the most important tasks of the IRB. They will also review any new safety information provided from the sponsor and/or investigational site to determine if the risks to subjects are reasonable as compared to the potential benefit.

\subsection*{4.4.1 Continuing Review}

At a minimum of once per year, the researcher is required to submit a continuing review report to the IRB to request continued oversight over the research project. The site will provide an update to the IRB about the number of patients enrolled, number of patients completed, any unanticipated problems or patient complaints.

\subsection*{4.4.2 Change in Research}

If there is a change from the initial study submission to the IRB, such as a change in the principal investigator or a location of study procedures, the study staff needs to submit a change in research to the IRB to make them aware of the changes. The IRB needs to approve those changes prior to making any changes to the conduct of the trial.

In the event that there is an amendment to any key research documents, they will need to be submitted to the IRB for review and approval. This includes amendment to documents

such as the protocol, investigator brochure, consent forms and any patients facing materials.

4.4.3 Reporting Serious Adverse Events

When a research subject has experienced a serious adverse event, the research site may be required to submit this information to the IRB. A serious adverse events (SAE) is an adverse event that is deemed life threatening or prolongs a hospitalization. The requirements around when a researcher is required to submit this information is dependent on the guidelines set forth by the IRB of record. Please refer to the study protocol for any additional reporting requirements.

4.4.4 Reporting Protocol Deviations

Protocol deviations are instances when the research study is not conducted as designed and approved by the IRB. Examples include missed study procedures or procedures being done out of the specified time frame. Any time there is a protocol deviation on a study, the research team needs to consult the IRB reporting guidelines to see if the event is reportable to the IRB or not. The reporting guidelines vary from IRB to IRB, so it is imperative that the guidelines are consulted with every event. These guidelines will also direct the research team on how many days from discovery that the deviation needs to be reported.

4.4.5 Submitting Amendments

In the event that there is an amendment to any key research documents, they will need to
be submitted to the IRB for review and approval. This includes amendments to
documents such as the protocol, investigator brochure, consent forms and any patient
facing materials.

4.5 Providence IRB HUB and eClick

KRMC has access to the three IRBs through the Providence IRB HUB. These services are
accessed through the eClick website: https://eirb.providence.org/ClickIRB/. KRMC researchers
will work with the Central Research Department to request access to the eClick portal. Once
approved, the researcher will log onto the eClick portal with their Providence credentials.
5.1 Providence Research Contract HUB

The Clinical Trial Agreement (CTA) is an integral component of performing research. To assist with the review and negotiating of contract language, KMRC has access to the central Providence Research Contract HUB located at Swedish Medical Center. The study budget is generally an exhibit or attachment to the larger CTA and is negotiated locally by the Central Research Department (see Section 5.3).

5.2 Medicare Coverage Analysis

Medicare covers routine costs for qualifying clinical trials in addition to services that are reasonable and necessary for the treatment of complications from participating in a research study. They will not cover services that are done for the sole purpose of data collection. Some examples of items covered by Medicare in a clinical trial include: services typically done regardless of enrollment into the study, administration of the study medication, clinical monitoring of potential side effects of the study medication, prevention of potential complications from the study medication and services to diagnose and treat complications that arise from receiving the study medication. For a trial to be deemed as a qualifying clinical trial, the service needs to fall within the benefit category, the trial must have therapeutic intent and cannot be for the purpose of monitoring toxicity, is funded by the NIH, CDC, AHRQ, CMS, DOD or the VA, or is being conducted under a new drug application (IND) that is reviewed by the FDA.
For a full description of Medicare coverage of clinical trials, visit:

The Medicare Coverage Analysis (MCA) is developed by the KRMC Research Department and is required for all clinical trials that include billable tests or procedures. The MCA will document all procedures that will be billed to Medicare/third party payor or the sponsor and will be used during the conduct of the trial to ensure that there is appropriate and compliant billing.

5.3 Budget Development

It is important to make sure that all costs are recovered when conducting a trial. Developing a comprehensive budget is key to making sure KRMC can continue to conduct research. Work with the Research Department staff to help develop a budget that accounts for all study costs. In a clinical trial, there are a multitude of factors to consider and the following sections outline a few of these topics.

5.3.1 Per Visit Costs

Clinical trial budgets typically reimburse the site for study costs per patient visit. Utilization of an MCA will ensure that all the out of pocket costs are included in the per visit cost. This may include labs or procedures such as administration of study medications. Less obvious costs to consider when evaluating the per visit costs are the research staff salary for collecting and recording the research data, the PI time and the
facilities and administrative (F&A) cost (see Section 5.3.4).

5.3.2 Invoicable Costs

There are some research costs that will not be automatically paid to KRMC. As part of conducting the study, research staff must ensure that procedure costs that are covered by the research sponsor are billed to the Research Department and not to the patient’s insurance. This will trigger designated research staff to send an invoice to the sponsoring agency for reimbursement to recoup the costs incurred by the institution.

5.3.3 Outside Services Costs

If the research project has services or procedures conducted outside of KRMC, the Research Department needs to establish a contract for these purchased services. Research staff will make sure that costs covered by the sponsor are ordered as “Bill Client” and route those charges to the Research Department account.

5.3.4 Facilities and Administrative Costs

Facilities and administrative (F&A) costs is sometimes referred to as indirect or overhead costs. These are the costs that are not easily identifiable to any specific study. Examples include rent, building depreciation, office supplies, and management and accounting staff. See 2 CFR § 200.414 for further guidance on the cost accounting principles related to F&A costs.

5.4 **Budget Negotiation**

The Research Department Manager will negotiate the budget terms in parallel with contract negotiations. Often, this process will take several weeks before the two parties come to an agreement. During this process the study protocol will be examined thoroughly, and an MCA will be developed. The MCA be used to determine what procedures within the protocol are deemed routine care and will be billed to the patient’s insurance and which ones are deemed research and will be covered by the sponsoring agency.

5.5 **Types of Binding Agreements**

When conducting research, there are various types of agreements that may be put into place. The type of agreement executed will be in relation to the type of business between two or more parties.

5.5.1 **Confidentiality Disclosure Agreements**

Confidentiality Disclosure Agreements (CDA) are sometimes referred to as a Non-Disclosure Agreements (NDA). This is a contract that outlines how the parties within the contract agree to protect the proprietary information that is shared between groups.

5.5.2 **Business Associate Agreements**

A Business Associate Agreement (BAA) is a legally binding contract that describes how the parties will handle Protected Health Information (PHI) (see Section 7.1.3). The agreement will also illustrate how the business associate will adhere to HIPAA regulations (see Section 7.1.1).
5.5.3 Data Use Agreements

A Data Use Agreement (DUA) is a contractual agreement that is put in place when data not publicly available needs to be transferred to another entity. This agreement will describe any restrictions related to the transferred data as well as how the data can be used.

5.5.4 Clinical Trial Agreements

A Clinical Trial Agreement (CTA) is a legally binding agreement between a sponsor and an institution. The CTA explains the responsibilities of each party including funding, obligations and the protection of intellectual property. Throughout the life of a study, the CTA will be amended to reflect changes that occur. This may include changes to the principal investigator, site name changes or any budgetary changes as it relates to procedural changes as reflected in amendments to the protocol.
6.1 Purpose of Informed Consent

The purpose of an informed consent form (ICF) is to protect human subjects in research. This requirement is based on the Belmont Report\textsuperscript{14} which states that human subjects should be treated as autonomous agents who are individuals that are able to deliberate and make decisions based upon those deliberations. Informed consent consists of disclosing information to the potential study subject so they can appropriately make an informed decision. Subjects should be able to understand the information that was provided in the consent form and given the ability to voluntarily choose to participate or not participate in the research.

Informed consent is a continuous process that occurs throughout the study. The consent process allows the researcher to communicate changes to the subject both verbally and on paper. The subject should always have adequate time to review the material and decide if they wish to participate, continue to participate or not continue participation based on the new information presented. In the event a patient decides to not continue to participate in a study, they will withdraw their consent.

6.2 Informed Consent Process and Documentation

In accordance with 45 CFR 46.117\textsuperscript{15}, the informed consent process needs to be documented. A copy of the signed informed consent form must be provided to the research subject and it must be documented that the patient had sufficient time to review the consent form, had an opportunity to review the document with delegated staff in a private area and had sufficient time to ask questions. Refer to policy 699.67.00: Informed Consent for further clarification. This process needs to be documented either in the electronic medical record or on paper source documents that get filed into the patient’s shadow chart.

6.3 Language Specifications

The ICF needs to be in a language that is understandable to the research subject per 45 CFR 46.116\textsuperscript{16}. In addition to the translated document, a person who reads and speaks that language should be present to conduct the informed consent or a translator should be present to facilitate the discussion. In the event a translated ICF is needed for a study, reach out to the Central Research Department in order to process the translation request.

6.4 Readability Specifications

The ICF should be readable and be free of complex terminology. The consent should be written at an 8\textsuperscript{th} grade reading level or below and use common words\textsuperscript{17}. The sentences should also not be too long and contain less than 15 words. The document should include formatting that allows the


subject to easily follow and understand the document. This can include bullets, spacing between paragraph and visual aids when appropriate.

6.5 Special Considerations

There are several special circumstances that may arise when consenting a patient to a study. This section will explain how to handle some of these circumstances.

6.5.1 Illiterate Patients

Subjects that understand English, but cannot read or write are able to enroll into a research study. This can be achieved by the subject “making their mark” on the ICF. An impartial third party should be present during the entire informed consent process and sign the ICF confirming that the person obtaining consent read the entire document word-for-word to the subject and that the subject voluntarily consents to participate in the study.

6.5.2 Vulnerable Populations

When enrolling vulnerable patient populations to a study, there are additional safeguards that need to be in place to make certain that the study protects the rights and welfare of that population. Examples of vulnerable populations are children, pregnant women, prisoners and those with impaired mental capacity.

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6.5.3 Assent of Children

When the potential research subject is a minor, it is important that the researcher reviews the guidance in 45 CFR 46, Subpart D\(^{19}\). Special care should be taken as minors are unable consent to treatments or procedures from a legal standpoint. Consent can be obtained from the biological or adoptive parents or the child’s legally authorized representative.

6.5.4 Legally Authorized Representatives

A Legally Authorized Representative (LAR) is a person that has been authorized under applicable law to consent on behalf of the potential research subject. The allowability of who can serve as an LAR is dependent on local and/or state law. If there are no applicable laws in regard to LARs, the local institutional policy related to acceptable consent process in the non-research setting shall prevail\(^{20}\).

6.5.5 Subject Injury

HHS and the FDA require that informed consent forms include information related to the compensation and treatment of injuries that could occur due to participation in the research study. This requirement is only for research that involves more than minimal risk to the research subject. There should also be information about how those treatments will be billed as well as contact information for the research subject to contact if they


\(^{20}\) “Title 45: Public Welfare, Part 46 – Protection of Human Subjects,” Government Publishing Office, last modified July 19, 2018, accessed November 11, 2018, [https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5e6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML#se45.1.46_1116](https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5e6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML#se45.1.46_1116)
have questions or concerns\textsuperscript{21}. Prior to the study opening, subject injury coverage will be negotiated in the CTA and this information will be included in the informed consent so to relay this information to the patient.

### 6.5.6 Patient Financial Responsibility

It is important to ensure that the details regarding financial responsibility to the patient is included in the ICF. This will allow the patient to be properly informed about what will be billed to their insurance or what they may need to pay out of pocket. This is an essential element of informed consent so that the research subject can understand what expenses are expected with participation in the trial.

### 6.5.7 Compensation to Subjects

In the event that the study provides monetary compensation to the study patient, this should also be included in the ICF. Compensation may include reimbursement for travel, food, parking or stipends. The total amount provided to the patient should be an amount that is not deemed as coercive. The site will be required to inform the IRB of the compensation amount by including this information in the initial IRB application. The amount should not exceed the additional costs that is expected to be incurred due to the patient participating in the study.

### 6.6 Waiver of Informed Consent

An IRB can waive the requirement of informed consent (or alter some or all of the required


- There is minimal risk to the research subjects
- The waiver of consent does not affect the rights and welfare of the research subjects
- The research could not be realistically conducted within the waiver/alteration
- Research subjects should be given information about the research after the project is completed, if appropriate

The request for waiver of consent would be included in the IRB application. The IRB will review the request and let the institution know if the request was approved or denied.

\section*{6.7 Re-Consenting Subjects}

Periodically throughout the course of a study, there may be changes to the study that needs to be communicated to the study participants. It is the responsibility of the principal investigator or delegated staff to communicate these changes throughout the study by updating the ICF and presenting the new information to the research subject. The subject is then given the opportunity to review the new information and decide if they wish to continue participation and sign the new ICF (called re-consenting) or opt to not consent to continue participation on the study.
CHAPTER 7
PRIVACY ISSUES

7.1 Patient Privacy

7.1.1 Health Insurance Portability and Accountability Act of 1996

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) was set into law and “included Administrative Simplification provisions that required HHS to adopt national standards for electronic health care transactions and code sets, unique health identifiers, and security.”23 It is important to ensure that information related to HIPAA is included in the ICF to appropriately inform the patient.

7.1.2 De-identification of Patient Information

When sending out information to study sponsors or Contract Research Organizations (CROs), such as for eligibility confirmation for sponsor approval to enroll a patient into a clinical trial, it is absolutely imperative that the personal identifiable information is removed from the document prior to being sent. Examples of patient information include, but are not limited to: name, order number, pathological block number, address, phone number, social security number, and medical record number. In addition to de-identifying the patient information, encryption should be used when emailing these documents out by entering #secure# in the subject line.

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7.1.3 Access to Protected Health Information (PHI)

When Contract Research Associates (CRAs) are onsite monitoring data on a study, they will need to have access to the electronic medical record (i.e. EPIC) to source verify the data. This requires the research staff to request read-only access to the patient charts for only the patients consented to the study. The CRA will need to request this access from the Central Research Department when scheduling their onsite visit. The research staff will work with the Health Information Management team to ensure that the read only access is available when the CRA is onsite.

7.2 Data Security

It is the responsibility of the researcher to protect the personal identifiable information of research subjects. This is done by developing a data management plan.

7.2.1 Data Management Plan

When the data is collected on paper, the Data Management Plan (DMP) may include storing information in locked rooms and filing cabinets only accessible by study staff. However, when it comes to electronic data, the DMP becomes more complicated. The DMP may include firewalls, encryption methods or restricted access. When developing a new protocol, a DMP will be required and should outline how the personal identifiable information will be maintained confidentially.
8.1 Study Entry into the Electronic Medical Record

The research team will put the trial information into the electronic medical record (EMR). When opening a new clinical trial, be sure to contact the research team to see if the research project will require a build within the EMR. Whenever there is a study drug being used in an interventional trial, the treatment regimen needs to be inputted into the EMR so that the clinical team has the information they need to safely treat the patient. Elements in the treatment regimen include: the protocol number, the arm the patient was randomized to, the starting dose for that arm/cohort, and special instructions for pharmacy and nursing staff. Pharmacy information included are instructions on how to properly mix the study drug and special instructions such as keeping IV bag out of direct sunlight. Information for the nursing staff will contain guidance on the route the study drug is given, infusion time or any additional instructions such as requirements of observation after completion of the treatment.

8.2 Associating Study Patient to a Study

Associating a patient with a study is done by the research team and will prompt the charges to be routed through the research billing review system, if applicable. There are multiple statuses that can be added to a patient’s chart to indicate where they are in the course of a study (such as screening versus completed). This allows for a centralized area that displays the timeframe that a patient is enrolled into a clinical trial as well as prompts specialized routing of charges so that the patient is not billed for services being covered by the sponsor as indicated in the CTA and ICF.
8.3 Linking Encounters and Orders to a Study

“Linking” is a functionality within EPIC (the EMR used at KRMC) that will indicate that the visit or procedure is being completed as outlined in the study protocol. When something is linked, a flask will appear next to the order or encounter. This is an important step that is done by the research staff to ensure that the charges for a patient on study are billed correctly. This step will not only ensure that the charge is routed to the appropriate payor (research vs. insurance) but will also notify the staff member completing the order that the order is being done as part of a study.

8.4 Billing Review

Charges within the EMR will be routed to designated research staff for review to ensure that the charges being paid for by the research study are appropriately billed. It is important for procedures related to a study be linked within the EMR to ensure these charges are routed to this pathway. This pathway will also add the applicable billing modifiers as required by CMS to indicate that the procedure was being completed on a study.
9.1 Investigational Product Accountability

An investigational product can include study drugs or study devices. Study drug may include product that is swallowed, injected, applied topically or infused. When a site conducts a clinical trial that includes investigational study drugs or devices, the product will typically be provided by the sponsor. When the investigational product is received at the site, it is required that delegated staff verify that the shipment was received in proper condition (i.e. frozen product is received frozen or refrigerated drug is cold) and log it on an accountability log. Sometimes these shipments will use a form of temperature monitoring (i.e. TempTale) that will record the temperature of the investigational product from leaving the manufacturer to being received at the site. This is another method used to ensure product quality. This log is crucial in accounting for the amount of product onsite throughout the study. Periodically, the sponsor or assigned CRA will verify that the investigational product is accounted for and that the accountability log correctly reflects the amount of product onsite.

9.2 Investigational Product Management

Investigational product will have varying temperature requirements based on the stability of the compound. It is the responsibility of the research site to ensure that the study drug is maintained at the sponsor specified temperature to sustain the integrity of the product for the safe dispensing to study patients. This will require a mechanism of periodic temperature monitoring and an alert pathway for notifying key staff in the event of a temperature excursion. If a temperature
excursion occurs, the research staff will need to quarantine the study drug and report to the sponsor for further guidance. For the safety of the patient(s), it is vital that the quarantined drug not be dispensed to study patients until the sponsor has verified that it is safe to be moved out of quarantine into the study stock.

On occasion, some study drug might have additional requirements such as restrictions from light exposure. It is important for the research staff to consult the pharmacy manual and onsite pharmacy staff to ensure that all precautions are taken with storing and dispensing the drug.

9.3 Investigational Product Dispensing

Each study will have different requirements for dispensing the study drug to a patient. This may include an electronic dispensing system (sometimes referred to as IVRS, IWRS or IXRS). Typically, a container number will be dispensed by the system, so the research staff needs to pay special attention to the study requirements before pulling study drug for a patient. When a study is double-blinded, the computer system is vital in ensuring that everyone, including the site, sponsor and patient, remain blinded to what medication is being dispensed.

9.4 Investigational Product Compounding

For study drugs that require compounding, the compounding instructions need to be inputted into the treatment regimen in the EMR. These specific requirements are typically found in the pharmacy manual.
9.5  Concomitant Medications

Research staff need to pay special attention to the contraindicated section of the protocol. Sometimes, there are concomitant medications that are processed in the body through pathways that need to be avoided because they can diminish or increase the study drug concentration in the patient. There are also medications that can affect the patient’s heart (such as QTc prolongation), so extra care should be taken to not give multiple medications that can have a compounding effect on the heart. It is important to review all medications a patient is taking at each clinic visit and instruct a patient to not start any new medications without first consulting with their study doctor.
10.1 Study Binder Maintenance

The study binder houses the documents that are processed during the conduct of a study. Often, these binders are separated into multiple binders so to organize the documents in a manner that is creates ease in finding them at a future date.

10.1.1 Regulatory Binder

The regulatory binder will house the key study documents. This may include the 1572, financial disclosure forms, delegation of duties, IRB approvals, protocol and investigator brochure, and all study related training. All versions of the documents must be maintained.

10.1.2 Patient Shadow Chart

The research team will create a shadow chart in order to centralize the key data that is being captured on the clinical trial. This is also the location of source documents that are collected during the course of the trial that are not directly documented into the EMR (such as questionnaires; adverse event assessment of grade, relatedness and causality; and original consent form documents).
10.1.3 Investigational New Drug Reports

Throughout the study, investigational new drug (IND) safety reports will be sent to the PI. IND safety reports are serious adverse events that other research sites using that investigational new drug reported to the study sponsor. When utilizing a central IRB, the sponsor will be responsible for submitting the IND safety report to the IRB, if applicable. When the site is utilizing a local IRB, the research staff will refer to the reporting requirements of the local IRB reviewing the study. Research staff will also ensure that the PI has reviewed all the IND reports by sending them to the PI via email. Once reviewed, the PI will sign off the tracking log provided by designated research staff as verification of the review process. See Section 4.2 for additional information on central versus local IRBs.

10.2 Trial Monitoring and Audits

Data integrity is crucial to the results of a study. This means that steps need to be taken to verify that an institution is not only conducting the study as written, but that the data being reported is valid. Therefore, the funding agency and the regulatory body need to have avenues to validate data integrity. This is accomplished through monitoring and inspections.

10.2.1 Industry Sponsor Monitoring

Often, the sponsor will hire an outside entity called a Contract Research Organization (CRO) to visit sites to verify that the study is being conducted as written in the protocol, verify source documents match the data that is being reported to the sponsor and confirms

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that the investigational product, if applicable, in being handled in accordance with the pharmacy manual. The CRO will send Contract Research Associates (CRAs) to the site to conduct these monitoring visits.

10.2.2 FDA Inspections

Investigators are required to allow the FDA and/or sponsor to have access to the site study documents per 21 CFR 312.68\textsuperscript{25} and GCP 4.1.4\textsuperscript{26}. In the event that the site is notified of an inspection, the research team will need to notify the Providence Risk and Integrity Services – Research Compliance office within 24 hours of becoming aware of the inspection. The research team will work with the Providence Research Compliance team to prepare for the audit. When the auditor arrives to conduct the audit, it is important to verify the credentials of the auditor before taking them to a private area to review the study. Prior to the exit meeting, every effort should be made to resolve all issues raised by the auditor. After completion of the audit, the research team will need to send a copy of the audit report to the IRB. For further clarification, refer to policy 45.26.00 External Audits and Inspections.


CHAPTER 11
STUDY CLOSURE

11.1 Study Closure with the IRB

When a study has ended and all study requirements have been completed, research staff will submit an official request to close the study with the IRB. A copy of the IRB closure letter should be filed in the regulatory binder.

11.2 Investigational Product Final Reconciliation/Disposal

When a study is being closed, the designated research staff will verify that all study drugs and/or devices have been accounted for. Depending on the contractual arrangement with the study sponsor, the remaining study drug and/or devices will be either destroyed onsite or shipped back to the sponsor. This should be documented on the site investigational product accountability log.

11.3 Archiving of Study Documents

According to 21 CFR 312.62(c), a researcher will retain study records for drug trials for 2 years following the marketing approval date for the indication that was under study. In the event that no application for approval is submitted to the FDA, the researcher should retain all study records for 2 years after the FDA is notified of the study discontinuation.

According to 21 CFR 812.140(d), a researcher will retain study records for device trials for 2 years.

years after the following two dates: date that the study was completed or terminated, or the date that the records are no longer needed for the application for premarket approval or the product development protocol was completed\textsuperscript{28}.

Always refer to the CTA to verify that there are not additional requirements related to the archiving of study records.

11.4 Publications

Before publishing data from any trial, make sure to consult the CTA for potential terms or conditions related to the use of study data.

Glossary

**Adverse Event (AE)** – A symptom or medical event that a research subject experiences during participation on a clinical trial. The adverse event (AE) can be related or not related to the investigational product in the study.

**Code of Federal Regulations (CFR)** – These are a compilation of regulations that are developed by agencies of the federal government.

**Contract Research Associate (CRA)** – They are sometimes referred to as “monitors.” These are individuals that work at CROs as part of a contractual agreement with a funding agency. CRAs are most commonly used at investigational sites to verify data integrity.

**Contract Research Organization (CRO)** – These are organizations that are hired by funding agencies to manage potentially numerous portions of the conduct of a trial. This may include verification of data integrity, payment management to sites, or contract and budget negotiations.

**Electronic Medical Record (EMR)** – An EMR is an electronic system that holds the medical information of patients within a given medical facility. Medical staff will document directly into the EMR since it is a replacement for paper patient charts.

**Food and Drug Administration (FDA)** – The United States Food and Drug Administration (FDA) is responsible for the safety of food and drugs in the U.S. This federal agency is responsible for the approval of new drugs and will periodically audit investigational sites to ensure that patients are being treated per the investigational plan and that the data being collected is accurate and not altered in any way.

**Health Insurance Portability and Accountability Act (HIPAA)** – This federal law protects an individual’s health information so that it is accessible to only authorized individuals.
**Institutional Review Board (IRB)** – The IRB is an ethics review board that reviews and monitors the conduct of a research project to make sure the rights and welfare of human subjects are protected.

**Investigational New Drug (IND)** - The Investigational New Drug Program is overseen by the FDA and is the way pharmaceutical companies obtain approval to start new clinical trials with new investigational drugs in human subjects. The IND also allows for a pharmaceutical company to have approval to ship the drugs across the United States.

**Principal Investigator (PI)** – The investigator that takes primary responsibility for the conduct of the research project. The PI can delegate tasks to staff as he/she sees fit, but the PI cannot delegate responsibility for the conduct of the trial. By signing the 1572, the PI is acknowledging that the study will be conducted in accordance with all applicable regulations and that they are ultimately responsible for the conduct of the trial at the site.

**Quality Improvement (QI)** – Evaluation of a current practice or process so to analyze and implement a new method in order to improve that practice or process.

**Serious Adverse Event (SAE)** – An adverse event that is life threatening, causes hospitalization, prolongs hospitalization or results in death.
APPENDIX I: Key Research Contacts

KRMC Central Research Department
Phone: (509) 783-4637
Email: Research@kadlec.org

PSJH Medical Data Research Center
Email: MDRC@providence.org
Website: https://sssteams.providence.org/sites/ced/mdrc

PSJH System Library Services
Email: Librarian@providence.org
Website: http://www.psjhealth.org/library

PSJH Commons
Contacts by service area: http://www.psjhealth.org/library/locations
Website: https://digitalcommons.psjhealth.org

Providence Institutional Review Board Spokane
Phone: (509) 474-3632
Email: institutional.review.board@providence.org
eClick Website: https://eirb.providence.org/ClickIRB

KRMC Education Department
Phone: (509) 942-2600
APPENDIX II: Research Intake Workflow

Research Project Intake Workflow

 Applies to research being requested outside of the established research programs at ERMC

- Project Identified
- Contact Research Manager
- Complete Research credentialing requirements: CITI Training (Good Clinical Practice, Human Subjects in Research Protection, Conflict of Interest in Research); COI SMART
- Study not Opened
- Feasibility Assessment (ie. staffing, etc.), Assess Funding vs Expense
- Present project at Research Committee Meeting (convenes quarterly)
- Approved

Central Regulatory Process:
- IRE processing/submission
- Regulatory document preparation

Clinical Trial Agreement and Budget Negotiation:
- Budget Research Manager
- CTA Providence Contract HUB
- Activity Code Creation

EPIC Build Request, if applicable

Velos

Account Created

Project Can Begin
APPENDIX III: Facility Approval Form

FACILITY APPROVAL

This form must be completed and signed by the designated authority (PI and/or SI not acceptable) for each facility listed on the IRB application or IRB Modification Request (when adding any Providence entity as a research site or adding any key research personnel in which the research is conducted at any Providence entity or personnel is employed by a Providence entity). The signed form must be submitted with your IRB application.

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Name of Local Regulatory Contact Person delegated by PI to fulfill IRB requirements:

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HOSPITAL/FACILITY/ORGANIZATION

- Providence Holy Family Hospital
- Providence Sacred Heart Medical Center and Children’s Hospital
- St. Luke’s Rehabilitation Institute
- Other: ______________________________

APPROVAL

- Approved for conduct at facility(ies) following IRB approval
- Contingent approval to allow for simultaneous review by IRB and facility*
  - *Full facility approval required prior to final IRB approval

SIGNATURE OF AUTHORIZED FACILITY PERSONNEL

By checking boxes below you are certifying the following:

- The Principal Investigator has the appropriate expertise and ability to provide adequate oversight for this study.
- The Principal Investigator/key research personnel are approved/credentialed to conduct this study at facility(ies) indicated in the IRB Application.
This study has been reviewed and is feasible (per facility guidelines) for conduct at facility(ies) listed, including but not limited to:

- Appropriate scientific merit
- Adequate staffing levels (i.e., investigators, coordinators, ancillary departments)
- Provision/support for protocol training of all key research personnel and ancillary departments as applicable.

Conflict of interest disclosure has been reviewed and all conflicts (real or perceived) pertaining to this study, along with mediated (if applicable) plan for conflict disclosure have been submitted to the IRB.

- No Conflict of Interest
- Conflict exists, COI disclosure form, mediation plan are attached

__________________________
Printed Name

__________________________
Signature of Authorized Representative

__________________________ Date
References


Bibliography


Biography

Heather Johansen conferred her Bachelor of Science from Eastern Oregon University with a major in Biology and a minor in Chemistry. She is currently the Research Manager for the Research Program at Kadlec Regional Medical Center which conducts clinical trials in oncology, rheumatology, neurology, diabetes, stroke and behavioral health. She has been working for this institution in clinical research since 2007. Job duties have included all aspects of clinical trial management including data management, regulatory document maintenance, direct patient care, contract and budget negotiation, and Medicare Coverage Analysis development.