

## **Acknowledgements**

This manual has been developed to assist new research coordinators in the Wayne State University, Karmanos Cancer Institute, Detroit Medical Center, and the John D. Dingell Veterans Administration Medical Center research community. The Coordinator's Advisory Committee for the Wayne State University Human Investigation Committee (HIC) has written this document with the goal of providing research professionals with the guidance needed to function with skill and confidence in their roles. In addition, this manual provides several helpful links for resources that research coordinators may need to complete their responsibilities. The HIC wishes to acknowledge and thank all of the contributors and authors of this document. These individuals spent countless hours over the past year writing, proofing, re-writing, organizing and formatting this manual. The authors and contributors include: Patricia Arballo-Sprong, Vicki Berchou, Barbara Boggs, Megan Burpee, Stephanie Bower, Karen Collins, Jackie Day, Debbie DeCamillo, Marti Farrough, Maryam Fathy, Elizabeth Galvin, Carmen Hughes, Atafeh Jenroe, Cheryl John, Donna Kaveloski, Deborah King, Theresa Kulman, Paula Morton, Rebecca Navarette, Jackie Parker, Jo Anna Risk, Julie Ruterbusch, Lisa Saigh, Ginger Steinhilber, Katie Kelly Toby, and Patti Webber.

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## **Disclaimer**

The content of this handbook does not represent nor supersede the official policies and procedures of the Wayne State University Human Research Protection Program and the Human Investigation Committee. The information presented in this handbook represents the individual authors' opinions and experiences as research coordinators. Each section has been thoroughly researched by the authors and individual members of the Coordinator's Advisory Committee and is meant to provide a broad range of helpful guidance to new coordinators on topics that extend beyond human research protection issues.

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## **Research Coordinator Handbook Introduction**

### Preface

Over the past several years, Wayne State University (WSU) and its affiliate research institutions have been working hard to develop and improve practices designed to protect the integrity and rights of individuals who volunteer for research and at the same time, strengthen and facilitate the conduct of ethical research. As a part of that effort, WSU applied for and obtained full accreditation from the Association for the Accreditation of Human Research Protection Programs (AAHRPP) in December of 2007.

Through accreditation, Wayne State University has demonstrated the highest ethical standards in protecting research participants, which will help to increase public trust in research. AAHRPP's stringent standards helped us raise the quality of our human research protection program. By carefully reviewing our program, we have a more efficient and effective research protection operation. Accreditation signals to sponsors and investigators the efficiency of our operation and the quality of the data produced. Sponsors and investigators now have readily available information about our ability to conduct research ethically and in compliance with regulatory requirements.

This Coordinator's Advisory Committee grew out of the process of self-assessment that was required for the AAHRPP preparation and review. It is a tangible example of how a research institution with complex affiliate relationships can access the talents from all sectors of its research community to solve common problems, develop better communication channels, and help to orient and educate new research coordinators for their role.

### Introduction

Current knowledge of the institutional review boards, investigation, clinical research trials and research outcomes are public domain and easily accessed. However, attempting to identify how the role of the study coordinator developed, what coordinators do, learn about their stories, learning experiences, acquired roles, skills, and knowledge is very difficult. Those of us who have worked in human investigation and research often remain invisible in the records and publications of human investigation. What is equally important to realize is that the work done by these many dedicated study research team members often goes unidentified and unrecognized. That fact in itself is reason enough to communally come together on behalf of those before us and those who follow, in joint effort of this exciting and often unnoticed area of human investigation; and most importantly to capture for future use and hallmark past endeavors of the professionally applied art of protecting the rights of human subjects while conducting research.

Since the 1960's following on the heels of inhuman and unethical events such as withholding treatments, using vulnerable populations in drug testing, and a myriad of exposures to toxins in the name of research, research study coordinators have been taking responsibility in championing and enforcing ethically designed and implemented studies always mindful of individual rights, sensitivity towards the fragility of certain vulnerable populations, and functioning within ethical guidelines of human investigation. In the following pages the reader will find our attempt to place the skills, knowledge and experiences that created successes and hard learned lessons for study coordinators within the eyes of the public domain.

## **Federal Regulations, HIC Policies and Guidance**

### Introduction

All of the HIC policies and procedures have been written to guide IRB Committees and the research community in the protection of the rights and welfare of research participants. The purpose of this chapter is to briefly describe the federal regulations that govern the conduct of research here at WSU and the guidance provided from the federal agencies that are charged with oversight of the regulations. The written regulations, federal guidance documents and the Belmont Report serve as the bases for all of the WSU policies. In addition, the IRB's are also charged with complying with state and local statutes that involve research, although in most cases, these statutes do not contradict the federal rules.

### 45 CFR 46: The Code of Federal Regulations 45 Part 46

This set of regulations was written as a part of the Federal Policy for the protection of human subjects in research. The provisions of the Code were written in 1980. In the 1990's, these regulations were adopted by many other federal agencies where human subject research is being conducted. The sections then came to be known as "The Common Rule" and provide regulations for the definition of an IRB, how it must be constituted and conduct its work, the types of review that must be done, what should be involved in the consent documentation and process, what criteria need to be evident in order for the IRB to approve the research, and special protections for vulnerable groups-pregnant women, fetuses, children, prisoners, and persons with decision-making incapacities.

The federal agency that is charged with oversight of these regulations is the Office for Human Research Protection (OHRP). It is housed within the Department of Health and Human Services (DHHS) and is under the authority of the Secretary of DHHS. Guidance documents have been written and a great section on Frequently Asked Questions was recently developed. These are on the OHRP website that I suggest you visit. ([www.ohrp.gov](http://www.ohrp.gov)). At anytime, the OHRP can conduct a site visit of the Human Research Protection Program at WSU if they have identified potential problems, or as a result of a complaint. They have the regulatory authority to shut down any or all research being conducted at this institution if they find serious non-compliance with the regulations governing protection of human subjects.

### 21 CFR 50, 56, 312, 812, 814: Protection of Human Subjects, The IRB, and Drug and Devices-Food and Drug Administration

The FDA follows the Common Rule regarding regulations for the IRB and protection of human subjects. For drug and device studies being conducted at WSU, not only do PI's need to adhere to the Common Rule and the FDA regulations, but the IRB must do so as well. Sponsors focus on the FDA specific regulations written to provide policy for drug and device studies, but the HIC policies and procedures have been written with both in mind and the IRB must follow both sets of rules. So when a monitor asks why a certain practice is required at WSU and it isn't in the Drug and Device regulations for the FDA, the practice probably was required by OHRP for oversight of the Common Rule.

In addition to regulations for IRBs and protecting participants, the FDA has specific regulations for drugs and devices that guide your work with clinical trials: (21 CFR 312 (Drugs

for human use-INDs), 314( Drugs for human use-Applications for Approval, 330-Over the Counter Drugs, 601-Biologics, 812-Investigational Device Exemptions, and 814-Premarket Approval. All of the HIC policies on drugs, devices, single-time use, off-label use, "compassionate use" and humanitarian use devices were written from these regulations and the guidance provided by the FDA.

Helpful links for these guidance documents and regulations include:

<http://www.fda.gov/oc/ohrt/irbs/default.htm>

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=312>

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=812>

In addition to the above citations, an excellent two-volume "Guide to Good Clinical Practice" by Mary Bernadette Ott and Gary Yingling provides information on FDA regulations and requirements in a very complete format. These books (published by Thompson Publishing Group, a Food and Drug Series) provide information and access to all federal regulations and guidance, including international standards for research. Also included are tools to use to keep your study on track. If you wish to examine them before purchasing them, they are available at the HIC office for you to review.

### Veterans Administration Research

The Common Rule (as previously described) is codified by the Department of Veterans Affairs at 38 CFR 16-Protection of Human Subjects. These are identical to those written in the other sets of regulations, with a few exceptions. The VA regulations do not include Sub-Part B-D which describes additional protections for vulnerable groups. There is a VHA Handbook 1200.5 that outlines procedures for implementing 38 CFR 16 and serves as the primary source of guidance concerning agency interpretation of the Common Rule where research is conducted by VA personnel on official VA time or in VA facilities (including approved off-site locations).

When VA research is being reviewed by the WSU IRB, a special VA checklist is used by IRB members, two VA members must be present at the IRB meeting, and the protocol must be approved for scientific integrity by a special committee at the VAMC prior to submission for IRB review. The Office of Research Oversight is the federal agency that is charged with regulatory oversight and can audit, monitor, and request corrective actions from PI's and IRB's that are conducting VA research.

### HIPAA

The Privacy Rule for research allows institutions to establish Privacy Boards to review all human subject research in terms of use of protected health information for research purposes. As you well know, the IRBs here serve as the Privacy Board for WSU and its affiliate institutions. The HIPAA regulations that govern research are found at 45 CFR 160-164. These regulations govern privacy and security of information. Basically, any time research requires use of a medical record (paper, electronic, database developed from medical records) for research purposes, the HIPAA regulations apply and HIPAA review must be done prior to the beginning of a research study. WSU has developed a HIPAA Summary Form and Authorization (see [hic.wayne.edu](http://hic.wayne.edu) at forms and informed consent links) and policies and checklists to help investigators wade through the process. In addition, NIH has excellent descriptions of

everything HIPAA that applies to research. The website for this is: <http://NIH.gov> Search for HIPAA once you have accessed that site.

### General Helps

The WSU policies and procedures are written to provide structure to all research involving human subjects at WSU and its affiliate institutions. Because of the federal requirements, entities within WSU and its affiliates that are conducting research must follow the WSU policy for that activity. The PI and research team do not have the choice of whether or not to follow the HIC policies. Our office is available to answer specific questions about the policies and how to apply them. Please call if you have trouble locating a policy, difficulty in understanding what it means, and how to apply it, and if you identify problems, please let the HIC know. We are constantly changing our information to be more user-friendly.

### The Department of Defense

If you are working with a study that will be receiving Department of Defense (DOD) funding, you may be asked, in the future, to make sure you meet the requirements of a special amendment to our FWA for whichever branch is doing the funding (Army, Navy, etc).

For new studies when the contract is being negotiated, the DOD may state this upfront. What we know thus far is that there are special educational modules that will be required for all IRB members reviewing the protocol, and every member of the research team. The people at the Department of the Navy have accepted the WSU modules for the protection of human subjects for most of this FWA Amendment, however, there will likely be two specific "Navy" modules found in the CITI training program that will be required. In addition to training, WSU must verify that the FWA we now hold does cover the PI doing the work.

The important thing to determine at the outset is whether or not any FWA Amendment would be required for the contract to be approved. There will be joint paperwork required on the part of the IRB and research team and the earlier we know about the requirements, the sooner the studies can be funded.

There are currently funded DOD studies at WSU and its affiliate institutions where this has not been required. However, for new studies, for certain branches of the DOD, it will be an expectation.

## **Clinical Research and Vulnerable Participants**

There are several considerations the clinical researcher must address when criteria for enrollment into the trial includes vulnerable populations. Vulnerable populations include the cognitively impaired, pregnant women, newborns and fetuses, children, as well as captive populations such as soldiers, prisoners or students. In the following sections, regulations are reviewed and recommendations are included to guide the clinical researcher, whose responsibility it is to protect these participants from unethical practice.

### The Regulations

U.S. Department of Health and Human Services, National Institutes of Health, and Office for Human Research Protections, The Common Rule, Title 45 (Public Welfare), Code of Federal Regulations, Part 46 (Protection of Human Subjects), Subparts A-D (Washington D.C.: DHHS, revised November 13, 2001; effective December 13, 2001)  
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>

- Subpart A-Federal Policy for the Protection of Human Subjects (Basic DHHS Policy for Protection of Human Research Subjects)
- Subpart B-Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C-Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D-Additional DHHS Protections for Children Involved as Subjects in Research

Regulation Highlight - 46.111 Criteria for IRB Approval of Research. (b) 'When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.'

### Cognitively Impaired Participants

The Common Rule does not provide specific guidelines, as with other vulnerable populations, for the inclusion of cognitively impaired participants, therefore the researcher has a large responsibility to ensure ethical inclusion of these participants in any research study.

Though there is not a specific subpart in the Federal Regulations addressing this population, the National Bioethics Advisory Commission formulated a report which includes considerations and recommendations for the conduct of research with cognitively impaired participants. Through review of public and expert testimony, publications, professional and patient organizations, as well as research protocols and consent documents, over an 18 month period, the Commission reached the following conclusions:

- Research regarding cause and treatment of mental illness is important and will only expand in the future.

- IRBs lack practical and expert knowledge of mental illness and are many times unequipped to adequately review these studies.
- Communication is essential between researchers and the participant(s)/family member(s)/caregiver(s) who may benefit from newly-approved therapy. It is the responsibility of the researcher to ensure proper ethical oversight is occurring in this complicated field, as research continues to grow in an ever-changing environment.

The NBAC made 21 recommendations focusing on Review Bodies, Research Design, Informed Consent and Capacity, Categories of Research, and Surrogate Decision Making. One recommendation is that the Legally Authorized Representative (LAR) be available to follow the subject's participation in the study, to ensure ethical accordance with the Protocol and protection of the individual. The LAR is a family member or someone the subject has assigned through court order, who can authorize the subject's involvement in the study. This individual should have the participant's best interests in mind and, as mentioned previously, be aware and involved in the subject's participation in the study.

Source: The National Bioethics Advisory Commission, *Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity, Volume I* (Rockville, MD.: NBAC, December 1998), [bioethics.georgetown.edu/nbac/pubs.html](http://bioethics.georgetown.edu/nbac/pubs.html)

When enrolling participants who have a diminished capacity, the researcher should pay particular attention to the degree of impairment. Though it is not required, it is recommended that the Protocol include an independent capacity assessment tool, which will assess the participant's ability to provide informed consent and make decisions. This assessment tool should not only evaluate the individual's intellectual comprehension of the research activities, but also their emotional state. For example, a participant with a mood disorder may be more inclined to consent to a greater than minimal risk trial, as their judgment and affect may be impaired and they simply may not care or pay attention to the risks involved, as outlined in the consent document. A capacity assessment tool can be utilized in the screening process, and used throughout the study to document the participant's level of capacity. The informed consent process begins during the screening process, but should be reinforced throughout the duration of the trial, particularly if the population studied includes individuals with transient or changing levels of capacity. Reinforced use of a tool establishes the participant's cognitive attunement and decision-making capacity. For example, repeated use of an assessment tool throughout the course of the study would be extremely important if the population being researched were those individuals with Alzheimer's Disease, as they suffer from periods of increasing confusion and memory loss and decreasing lucidity.

All tools can provide basic comprehension questions, but consideration should be made in the event the study is focusing on a specific disease process such as Depression. The Mini Mental State Exam was developed for clinicians to assess memory and reasoning ability (Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975 Nov;12(3):189-98.) Though this may be a sufficient instrument for some studies, it is important to eliminate therapeutic misconception of the participant, whereby the individual believes the research procedures are clinically necessary for treatment of their medical condition. Other assessment tool alternatives are presented in the following publications:

Jeste DV, Palmer BW, Appelbaum PS, Golshan S, Glorioso D, Dunn LB, Kim K, Meeks T, Kraemer HC. A new brief instrument for assessing decisional capacity for clinical research. *Arch Gen Psychiatry.* 2007 Aug;64(8):966-74.

Dunn LB, Nowrangi MA, Palmer BW, Jeste DV, Saks ER. Assessing decisional capacity for clinical research or treatment: a review of instruments. *Am J Psychiatry*. 2006 Aug;163(8):1323-34.

### Additional Resources

Ten Myths About Decision-Making Capacity. A Report by the National Ethics Committee of the Veterans Health Administration, Department of Veterans Affairs. September 2002. ([www.ethics.va.gov/ETHICS/docs/necrpts/NEC\\_Report\\_20020201\\_Ten\\_Myths\\_about\\_DMC.pdf](http://www.ethics.va.gov/ETHICS/docs/necrpts/NEC_Report_20020201_Ten_Myths_about_DMC.pdf))

Decision-making and Dementia. Ethel L. Mitty, EdD, RN, New York University College of Nursing. ([www.hartfordign.org/publications/trythis/DecisionMakingandDementia.pdf](http://www.hartfordign.org/publications/trythis/DecisionMakingandDementia.pdf))

MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR). Paul S. Appelbaum, MD. June 2001.

Evaluation of Patients with Advanced Cancer Using the Karnofsky Performance Status. Jerome W. Yates, MD, Bruce Chalmer, MS, F. Patrick McKegey, MD. *Cancer* 45:2220-2224, 1980.

A New Brief Instrument for Assessing Decisional Capacity for Clinical Research. Dilip V. Jeste, MD, Barton W. Palmer, PhD, Paul S. Appelbaum, MD, Shahrokh Golshan, PhD, Danielle Glorioso, BS, Laura B. Dunn, MD, Kathleen Kim, MD, MPH, Thomas Meeks, MD, Helena C. Kraemer, PhD. *Arch Gen Psychiatry/Vol 64 (No. 8), Aug 2007, 966-974.*

In addition to federal regulations, local IRBs also provide guidance regarding research involving vulnerable participants. The Wayne State University Human Investigation Committee outlines guidelines in the Human Research Protection Program Manual, under Section 8 (<http://www.hic.wayne.edu/>). The following populations are discussed: Fetuses and Neonates, Children, Cognitively Impaired & Mentally Disabled, Prisoners, Terminally Ill, Normal Volunteers, and Students, Trainees and Employees. All researchers should be aware of their local IRB policies and procedures, in addition to federal regulations as they also incorporate State law and procedure. For example, the State of Michigan does not have a formal policy regarding proxy consent for research, therefore the local IRBs hold oversight and the responsibility to ensure safeguards are maintained in the consenting documents and process when proxies are being used by study participants.

### Pregnant Women, Neonates & Fetuses

The researcher should be familiar with Subpart B of the Federal Regulations, as well as State policies regarding parental permission for research activities. In Michigan, the minor is required to sign an assent, while the parent or LAR signs the consent document. The Assent document should be at the appropriate level of comprehension so the minor fully understands what is involved by agreeing to participate. The minor can consent for her child to be a research participant as well as to receive medical care. Also in Michigan, the minor can consent to receive medical care for reproductive health, i.e. prenatal care or care received during labor and delivery. Each Protocol must undergo individual IRB Review and approval will be based on level of risk. It is the investigator's role to ensure the IRB and more importantly the participant knows the risk(s) associated with participation in the study, not only to herself but also to her unborn child.

## Children

Additional protections for children are outlined in Subpart D of the Federal Regulations. Children are defined as ‘persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.’ For example, in the state of Michigan the legal age of consent is 18. The researcher must be aware of local policies regarding the legal age of consent. Assent is defined as ‘a child’s affirmative agreement to participate in research.’ Furthermore the child must positively agree to the study, simply perceived omission of objection is not acceptable assent. If the research is deemed greater than minimal risk-no prospect of direct benefit, assent must be obtained, as well as parental permission from both parents or legally authorized representative/guardian. In cases in which this is not feasible, i.e. one parent is deceased/unknown/incompetent/not reasonably available or one parent has legal custody for the child, signature from the responsible parent present is sufficient. Parental permission should be obtained prior to approaching the child for assent. Local IRBs may waive this requirement and specify the terms of consent necessary for the practice of the Protocol. As with consenting adult participants, this process should be clearly documented in the research records, and can be documented in the medical record at the researcher’s discretion.

The actual Assent document should be tailored to the studied population’s age and level of comprehension. For example, the ability of the adolescent to think abstractly is greater than that of a child, therefore the assent document could reflect this accordingly if adolescents were the population included. Local IRBs may have an Assent document template that can be utilized, such as the Wayne State University Human Investigation Committee.

Local IRBs will follow State regulations regarding the inclusion of emancipated minors, in which parental/guardian permission is not required. In the State of Michigan, children 16 years of age or older may be emancipated without a court order, under specific circumstances (i.e. the minor is married or the minor is on duty with the US armed forces) or by court order, in which specific circumstances are outlined (i.e. the minor is financially independent, including proof of employment, etc.) Local regulation will also outline the exact ages and the type of assent required. For example the WSU HIC does not require assent for children under the age of 6, oral assent is sufficient for children ages 7-12 with a documented parental permission form, and written assent is required for children ages 13-17 with a documented parental permission form. Again the requirement of assent is determined by the local IRB and is directly linked to how the federal regulations define level of risk associated with the study.

Note: Special consideration is given to children who are wards of the State in the federal regulations.

In summary, it is the role of the researcher to establish safeguards in the research Protocol and consent documents, to protect potential participants from coercion or undue influence. Vulnerable participants can include individuals with diminished capacity, pregnant women, fetuses or newborns, as well as captive populations such as soldiers, prisoners or students. Though individuals are typically students by choice they may be unduly influenced by their perceived benefit to participate. Researchers must be aware of federal and local state regulations regarding the inclusion of these populations. The considerations outlined above should be included and implemented in research studies to which they apply, and specifications should be made as necessary.

Additional Source:

Ethical and Regulatory Aspects of Clinical Research. Edited by Ezekial J. Emmanuel, Robert A. Crouch, John D. Arras, Jonathan D. Moreno & Christine Grady. The Johns Hopkins University Press. Baltimore & London (2003).

## **When the FDA Comes Knocking at your Door**

Federal law allows an FDA investigator who provides written notice (called a Form 482) and shows appropriate credentials to enter a regulated establishment.

The FDA may inspect a site to see if protocol procedures were followed and that records are in order. An inspection will last a minimum of 3 days and as much as 5 weeks. The inspection is accomplished by interview of study personnel and document review. The inspector will look for evidence of PI involvement in the study through documentation that patients met eligibility criteria, that adverse events, serious adverse events, and abnormal lab results were followed; and for evidence of IRB and sponsor interaction.

When the FDA usually calls to inform you of an inspection and they will probably want to come right away. You have the right to ask for a week to make sure your PI will be available.

Immediately after you end that call, notify the sponsor, the IRB, the PI, the research pharmacist, and your research department to inform them of the inspection and the agreed upon date.

### **IDENTIFY THE FOLLOWING BEFORE THE INSPECTION:**

- Who will serve as escort to the FDA inspector and who will take notes during the inspection
- Who has authority to speak for the site (FDA liaison)
- How will access to computerized or paper records be handled
- Who will make copies for FDA (including one copy for sponsor and site)
- Daily debriefing (time and attendees)
- Dedicated room to use as base for FDA free of unrelated documents in plain sight
- Quiet and adequate work area for FDA with access to phone, fax, power source for laptop

### **THE FDA INSPECTOR ARRIVES: OPENING INTERVIEW**

- Make sure you ask to see the inspector's badge
- Be businesslike and friendly but do not offer information if not requested.
- The PI should be present.
- The inspector will present you with a Form FDA 482, Notice of Inspection.
- Do not offer anything to the inspector except for water, coffee, or tea. Provide them with directions to sites for breakfast/lunch, etc.
- Ask the inspector how long they plan to be at your site.

### **DURING THE INSPECTION:**

- If the inspector requests copies of CRF pages or source, have the designated copier make two sets.
- If asked a question you don't know the answer to, say you will find out, do not try to make up an answer.
- Make sure you understand the question.
- Make sure you are qualified to answer.

- Do not answer a question that is not asked.
- Do not offer information that isn't requested unless it is in your interest.
- Be careful not to "fill the silence" by chatting...you may say something you regret.
- Assist with all requests for information except for financial data or personal data.
- Remember that once on-site, the inspector can request to review ANY studies the site has performed if they are studies regulated by the FDA. They may also visit the IRB, pharmacy, or other study-related facilities if involved in regulated studies.

#### INTERACTIONS WITH INSPECTOR:

- Smile
- Be a self-confident professional
- Show the inspector a measured amount of respect
- Don't admit an error if you don't agree
- Avoid being argumentative
- Listen and try to acknowledge concerns
- Build trust
- Be honest, honest, honest

#### EXHIBITS:

- An exhibit is a specific collection of documents that is described in the inspector's EIR: Establishment Inspection Report.
- Some exhibits are routine, such as a version of the protocol.
- Some exhibits document violations. A progress note listing an AE and a CRF that does not list the AE is an example.

#### ASK FOR A DAILY WRAP-UP:

- Don't make it an hour long argument
- Try to understand concerns
- Try to determine if there are observations that might be listed on the Form FDA 483, Inspectional Observations
- Try to offer explanations or corrections

#### AFTER THE INSPECTION:

- Once the inspector completes his inspection, he meets with the investigator to discuss the findings.
- He issues a Form FDA 483 that lists any problems and deviations he found during his visit.
- The investigator may respond to the Form 483 verbally during the exit interview and in writing thereafter.

Upon his return to the agency, the investigator writes an Establishment Inspection Report (EIR) and forwards it to headquarters for evaluation. When the evaluation is completed, the FDA classifies the inspection and sends a letter to the site.

The FDA could send one of these letters:

- NAI – No action indicated. Approximately 20% of inspections have this result.
- VAI - Voluntary action indicated, it is the most common result, with 70% of cases being requested by the FDA.
- OAI - Official action indicated. 10% have this result.

## **Types of Research Studies**

All research studies that involve human subjects must be reviewed by the HIC. Please refer to the HIC website for the definition of human subject related research and the SOP for initial submissions requirements. <http://www.hic.wayne.edu/hicpol.html>

The types of research studies being summarized in this chapter include:

- Behavioral and Social Science Research
- Case Studies
- Clinical Trials
- Database Studies
- Focus Groups
- Medical Record Reviews
- Oral Histories
- Pilot Studies
- Specimen Banks
- Survey Research

### **Behavioral / Social Science Research**

Behavioral and Social Sciences research investigates behavioral and social factors and the role that they play in health and illness in order to advance the understanding, treatment, and prevention of disease. This research encompasses many disciplines such as, psychology, sociology, anthropology, public health, nursing, and social work as well as methods of study (laboratory and field experiments, randomized clinical trials, surveys and questionnaires, interviews and direct observation, physiological manipulations and recordings, statistical modeling, economic analyses, standardized tests, ethnography, evaluation). Office of Behavioral and Social Science Research. NIH. 5 March 2007 <<http://obssr.od.nih.gov/content>>

#### Resources

The following link(s) provide additional information regarding Behavioral/Social Science Research:

<http://obssr.od.nih.gov/content>

### **Case Studies**

A case study is a research strategy, sometimes likened to an experiment, a history, or a simulation, though not linked to any particular type of evidence or method of data collection.

Rather than using large samples and following a rigid protocol to examine a limited number of variables, case study methods involve an in-depth, longitudinal examination of a single instance or event: a case. They provide a systematic way of looking at events, collecting data, analyzing information, and reporting the results. As a result the researcher may gain a sharpened understanding of why the instance happened as it did, and what might become important to look at more extensively in future research. Case studies lend themselves to both generating and testing hypotheses. In terms with medical case reviews, one or two reported cases is not considered research and HIC approval is not required until there are three cases.

Case study research means single and multiple case studies, can include quantitative evidence, relies on multiple sources of evidence and benefits from the prior development of

theoretical propositions. Case studies should not be confused with qualitative research and can be based on any mix of quantitative and qualitative evidence

### **Clinical Trials**

A clinical trial is a type of interventional research study which investigates the safety and effectiveness of new methods of treatment, screening, prevention, and diagnosis of a disease in a group of human volunteers under controlled environments prior to expanding use in a wider population. Examples of treatments or therapies (interventions) investigated in clinical trials include new drugs, medical devices, biologics, and surgical approaches. Clinical trials conducted in the United States are closely regulated by the U.S. Food and Drug Administration (FDA).

There are many critical aspects to a clinical trial, a few of which are as follows:

**Protocol** - Clinical trials are conducted according to a rigorous protocol. Research staff must adhere to the protocol at all times. The protocol describes details such as: specific aims, research design and methods (design of intervention to be used, inclusion/exclusion criteria, informed consent process, recruitment, retention, follow-up, duration of study), data management, data analysis, and protection of human subjects (Data & Safety Monitoring Plan and reporting of serious adverse events to regulatory agencies).

**Informed consent** - Informed consent is the vehicle for protection of human research subjects. The process for obtaining informed consent for research participants must meet all IRB and Federal requirements (Common Rule, 45 CFR 46).

**Case Report Form (CRF)** - CRFs are used to collect data regarding research participants, to include questionnaires as well as forms to report adverse and unexpected events. It is important to develop CRFs that will ask the right questions pertaining to the protocol objectives.

Stringent standards and obligations pertain to any individual or organization that takes responsibility for and initiates (sponsors) a clinical trial. Examples are as follows:

**Sponsor-Initiated Clinical Trial** - The clinical trial is conducted by an investigator in response to a request from an external entity to explore an idea or question. In this case the external entity acts as the sponsor. Sponsor responsibilities include writing the protocol, designing the CRF documents, FDA safety reporting requirements, and compliance with all applicable FDA regulations. The sponsor is also responsible for registering the clinical trial with [clinicaltrials.gov](http://clinicaltrials.gov) and Investigational New Drug (IND), Investigational Device Exemption (IDE) filing with the FDA, if required.

**PI Initiated Clinical Trial** - The clinical trial investigates an idea or question that an investigator has defined. In this case, the investigator acts as the sponsor and assumes all sponsor responsibilities.

**Commercial/Industrial Clinical Trials** - The clinical trial is conducted by a pharmaceutical or other for-profit company.

Cooperative Group - A cooperative group is a team of researchers, medical centers, and community doctors that plan, implement, conduct, analyze, and disseminate results of high priority clinical trial research.

A contract between the research department and the sponsor or external funding organization must be negotiated and established to include delineation of responsibilities and cost reimbursement. The contract process is explored in greater detail in other sections of this manual.

Study specific questions should be directed to individual department contacts.

#### Resources

The following links provide additional information regarding clinical trials:

<http://www.fda.gov/oc/gcp/regulations.html>

<http://www.clinicaltrials.gov>

<http://www.nih.gov>

#### **Database Studies**

There are 2 types of databases commonly used in research studies. There are public-use databases that are made available by government and non-profit agencies. These databases are either readily available or may require a data use agreement to be put in place. The other type of databases are databases created and maintained by researchers for internal use only.

#### Resources:

Here are some lists of public health databases.

[http://www.ohsu.edu/public-health/education/mph/thesis\\_datasets.shtml](http://www.ohsu.edu/public-health/education/mph/thesis_datasets.shtml)

<http://www.lib.umich.edu/govdocs/sthealth.html#disease>

#### **Focus Groups**

A focus group is a method of collecting information by observing a small group selected from a wider population that is brought together to discuss a particular topic or question. A benefit to the information collected from a focus group is that it provides insight into the group members' opinions and emotional responses to the topic or question.

Special Considerations - It is important to include a trained moderator to lead the group and keep the discussion on track.

#### Resources

The following links provide additional information regarding focus groups:

<http://www.managementhelp.org/evaluatn/focusgrp.htm>

[http://www.usaid.gov/pubs/usaid\\_eval/ascii/pnaby233.txt](http://www.usaid.gov/pubs/usaid_eval/ascii/pnaby233.txt)

[http://ctb.ku.edu/tools/EN/section\\_1018.htm](http://ctb.ku.edu/tools/EN/section_1018.htm)

## **Medical Record Reviews**

A chart review consists of systematically gathering information from the medical record for research purposes. It is recommended that any identifying information be limited and great care is taken to maintain the confidentiality of the records being reviewed.

Resources:

A brief overview on this study methodology can be found at the following website.

[http://www.research.ucsf.edu/chr/Guide/chr12F\\_MedRec.asp](http://www.research.ucsf.edu/chr/Guide/chr12F_MedRec.asp)

Additional information on quality improvement:

[http://www.ajmc.com/files/articlefiles/AJMC2002sepCassidy787\\_793.pdf](http://www.ajmc.com/files/articlefiles/AJMC2002sepCassidy787_793.pdf)

<http://aje.oxfordjournals.org/cgi/content/full/161/10/974>

## **Oral Histories**

Oral history is a method of historical documentation, using interviews with living survivors of the time being investigated.

Most oral history interviewing projects are not subject to the federal oversight because they do not involve research as defined by the HHS regulations. These regulations define research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.”

It is primarily on the grounds that oral history interviews, in general, are not designed to contribute to “generalizable knowledge” that they are not subject to the requirements of the HHS regulations. Historians explain a particular past; they do not create general explanations about all that has happened in the past, nor do they predict the future. Moreover, oral history narrators are not anonymous individuals, selected as part of a random sample for the purposes of a survey. Nor are they asked to respond to a standard questionnaire administered to a broad swath of the population. Those interviewed are specific individuals selected because of their often unique relationship to the topic at hand

Resources

The following links provide additional information regarding oral history:

[http://dohistory.org/on\\_your\\_own/toolkit/oralHistory.html](http://dohistory.org/on_your_own/toolkit/oralHistory.html)

[http://alpha.dickinson.edu/oha/org\\_irb.html](http://alpha.dickinson.edu/oha/org_irb.html)

## **Pilot Studies**

Pilot studies are smaller versions of a larger scale study conducted to test and refine research methodologies. Pilot studies allow for potential methodological problems to be identified and corrected prior to the implementation of the larger study. They also allow an investigator to verify that they are collecting the data they intended to. Often these studies are conducted to enhance proposals to fund the larger study.

Resources:

Here is a website that lists the many reasons for conducting pilot studies.

<http://sru.soc.surrey.ac.uk/SRU35.html>

### **Specimen Bank Research**

Specimen bank or specimen repository research involves storing biological specimens for future research use. Information on this type of research can be found on HIC's policies and procedures website (<http://www.hic.wayne.edu/hicpol.html>) under the "Biological Specimens" link. All specimen banks that are designed to be used for research must be reviewed and approved by the IRB prior to their use for research purposes.

### **Survey Research**

The use of surveys or questionnaires is one of the most common research methodologies used in social science and medical research. A survey is used to gather information from a selected group of people. These surveys can be in the form of a written document, an online questionnaire, a face-to-face interview, or a telephone interview. These surveys can be designed to collect both qualitative and quantitative information. Survey research alone tends to be observational, but questionnaires are often incorporated into clinical trials and intervention studies.

Special Considerations – There are many validated questionnaires available and this may a good starting point when designing a survey.

Resources:

A brief overview on this study methodology can be found at the following websites.

<http://writing.colostate.edu/guides/research/survey/>

<http://www.socialresearchmethods.net/kb/survey.php>

Additional information on survey design:

<http://www.surveysystem.com/sdesign.htm>

## Resources for Patients

There are many resources available for patients who are interested in participating in clinical research trials. Some of the resources are listed below:

- Human Investigation Committee-Wayne State University  
Contact: Linda Herskovitz, Community Liaison  
Office number: 313-57-1628  
\*Ms. Herskovitz gives presentations about research-related topics to the general public
- FDA published brochure entitled, "Why Participate"  
\*available through our IRB office  
Office number: 313-577-1628
- There are MANY websites which contain research-related information for use by the general public. Here are some examples:

[www.centerwatch.com/patient](http://www.centerwatch.com/patient)

- trial listings
- about clinical research
- drug directories
- patient bookstore
- health associations
- notification services

[www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)

- trials listed by condition, sponsor, status of the trials (enrolling vs. closed to enrollment)
- easy to navigate (just enter disease and city where participant lives)

[www.health.nih.gov](http://www.health.nih.gov)

- health databases
- clinical trials
- studies conducted by the National Institutes of Health (NIH)
- studies from around the country
- definitions of research-related terminology

[www.ncrr.nih.gov/](http://www.ncrr.nih.gov/) \*\*more scientifically oriented\*\*

- biotechnology
- clinical research
- comparative medicine
- research infrastructure
- National Center for Research Resources at the NIH

[www.nlm.nih.gov/databases](http://www.nlm.nih.gov/databases)

- National Library of Medicine Databases & Electronic Resources
- publications
- Medline (references for journals)

## **Education and Training Resources for the Research Coordinator**

Welcome to clinical research at Wayne State University. Clinical research differs from clinical care and is governed by specific guidelines and regulations, depending on the types of studies in which you are involved.

One of the primary responsibilities of the study coordinator is to ensure that the studies are compliant with these regulations and guidelines. In order to do that, the coordinator must be knowledgeable about the applicable regulations. These include, but are not limited to the Human Investigation Committee (HIC) at Wayne State University, the Common Rule, the FDA, the NIH, ICH (International Conference on Harmonization), Good Clinical Practice, and the regulations for all VA and Department of Defense regulations.

## Resource List

The following resources have been found helpful by other coordinators and will give you a place to start.

The education and compliance coordinators at the HIC are available to assist and provide guidance for regulatory and compliance questions. Emails with updates and important information are sent periodically. Please provide the Educator at the HIC with your contact information to be included in this distribution. [ddecamillo@wayne.edu](mailto:ddecamillo@wayne.edu)

AAHRPP (Association for the Accreditation of Human Research Protection Programs) is an organization formed to protect the rights and welfare of research participants while promoting scientifically meritorious and ethically sound research through the use of a voluntary accreditation process. Wayne State University was recently awarded full accreditation from this organization. <http://www.aahrpp.org>

Two professional organizations provide educational programs and certification for research professionals:

ACRP (Association of Clinical Research Professionals) [www.acrpnet.org](http://www.acrpnet.org)  
 SOCRA (Society of Clinical Research Associates) [www.socra.org](http://www.socra.org)

The WSU Human Investigation Committee requires mandatory training for all investigators and key personnel involved in research being conducted at WSU and its affiliate institutions. A research project will not be approved to start until all persons engaged in the research activities have completed the training. **(sentence being updated by Debbie)WSU requires the CITI will soon be adopting CITI training to take the place of the human research protection modules that are currently found on the HIC web site:**

Human Investigation Committee (HIC) [www.hic.wayne.edu](http://www.hic.wayne.edu)

The National Cancer Institute (NCI) has developed a course that meets the NIH educational requirement for education in human participant protection for clinical trials:

NCI Human Participant Protections training [www.nci.gov](http://www.nci.gov)

There are also commercial sites that offer courses and educational materials. Some of these include:

Centerwatch <http://www.centerwatch.com/>  
 Barnett Educational Services [www.barnettinternational.com](http://www.barnettinternational.com)  
 Medical Research Management [www.cra-training.com](http://www.cra-training.com)

### Acronyms and Abbreviations

398	NIH Application for Public Health Service Grant (used for new application)
482	FDA Form – Notice of Inspection
483	FDA Form – List of Inspectional Observations
1572	FDA Form – Statement of Principal Investigator Obligations
2590	NIH Non-Competing Grant Progress Report (used for continuing funding)
AAHRPP	Association for the Accreditation of Human Research Protections Programs
ACRP	Association of Clinical Research Professionals
AE	Adverse Event
AR	Adverse Reaction
ARENA	Applied Research Ethics Committee
BIC	Behavioral Review Board (B3) @ WSU
c.c.	Cubic Centimeter
CAT	Computer Axial Tomography
CBC	Complete Blood Cell Count
CBER	Center for Biologics and Research
CBO	Community Based Organization
CCG	Community Constituency Group
CCG	Children's Cooperative/Cancer Group
CCRC	Certified Clinical Research Coordinator (Certification issued to coordinators by ACRP)
CCRA	Certified Clinical Research Associate (ACRP Certification of monitors)
CCRP	Certified Clinical Research Professional (SoCRA certification of coordinators, monitors, and other research professionals)
CDC	Center for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations (usually cited by title and part, eg-Title 21, Part 211 is shown as 21 CFR 211)
CIHR	Canadian Institute for Health Research
CIM	Certified IRB Manager
CIP	Certified IRB Professional
CIRB	Certified Institutional Review Board of the NCI
CLIA	Clinical Laboratory Improvement Act
CMHS	Center for Mental Health Services/Community Mental Health Services
COC	Certificate of Confidentiality
COG	Cooperative Oncology Groups funded by NCI (see also CCG, COG, ECOG, GOG, RTOG, POG, CALGB and NABTC)
COG	Children's Oncology Group
COGR	Council on Government Relations
COI	Conflict of Interests
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRO	Contract Research Organization
CRO	Clinical Research Organization/Contract Research Organization
DHHS	Department of Health and Human Services (see HHS)

DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
EBM	Evidence-Based Medicine
ECG/EKG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
ECRI	Emergency Care Research Institute
ER	Emergency Room
FDA	Food and Drug Administration
FDLI	Food and Drug Law Institute
FERPA	Family Educational Rights and Privacy Act
FHCRC	Fred Hutchinson Cancer Research Center
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GOG	Gynecologic Oncology Group
HDE	Humanitarian Device Exemption
HHS	Health and Human Services (see DHHS)
HIC	Human Investigation Committee (name of WSU's IRB)
HIPAA	Health Insurance Probability and Accountability Act
HMO	Health Maintenance Organization
HRP	Human Research Protections
HUD	Humanitarian Use Device
IACUC	Institutional Animal Care and Use Committee
IB	Investigator's Brochure
IBC	Institutional Biohazard Committee
IC	Informed Consent
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH-GCP	International Conference on Harmonization – Good Clinical Practice
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IEC	Institutional Ethics Committee/Independent Ethics Committee
IND	Investigational New Drug,
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LTF	Long-Term Facilitation/Fellowship
LTF	Lost to Follow Up Subjects
LTFU	Lost to Follow Up
MOOP	Manual of Operations
MRI	Magnetic Resonance Imaging
NAIM	National Association of IRB Managers
NBAC	National Bioethics Advisory Committee
NCCTG	North Central Cancer Treatment Group
NCHGR	National Center for Human Genome Research (NIH)
NCI	National Cancer Institute
NCIC CTG	National Cancer Institute of Canada Clinical Trial Group

NCNR	National Center for Nursing Research (NIH)
NCPHSB BR	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
NCQA	National Committee for Quality Assurance
NCRR	National Center for Research Resources (NIH)
NCVDG	National Cooperative Vaccine Development Group (NIH)
NDA	New Drug Application
NEI	National Eye Institute (NIH)
NHLBI	National Heart, Lungs and Blood Institute (NIH)
NHRPAC	National Human Research Protections Advisory Committee
NIA	National Institute of Aging (NIH)
NIAAA	National Institute of Alcohol Abuse and Alcoholism (NIH)
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH)
NICHD	National Institute of Child Health and Human Development (NIH)
NICU	Neonatal Intensive Care Unit
NIDA	National Institute of Drug Abuse (NIH)
NIDCD	National Institute of Deafness and Other Communication Disorders (NIH)
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases (NIH)
NIDR	National Institute of Dental Research (NIH)
NIEHS	National Institute of Environmental Health Sciences (NIH)
NIGMS	National Institute of General Medical Sciences (NIH)
NIH	National Institute of Health
NIMH	National Institute of Mental Health (NIH)
NINDS	National Institute of Neurological Disorders and Stroke (NIH)
NK	Natural Killer Cells
NLM	National Library of Medicine (NIH)
NSABP	National Surgical Adjuvant Breast and Bowel Project
OAR	Office of AIDS Research (NIH)
OARAC	Office of AIDS Research Advisory Committee
OBA	Office of Biotechnology Activities
OC	Office of Communications (NIAID)
OCR	Office of Civil Liberties/Office of Civil Rights
OHRP	Office of Human Research Protections (formerly Office for Protection of Research Risks – OPRR)
ORA	Office of Regulatory Affairs/Office of Research Administration
ORCA	Office of Research Compliance and Assurance
ORI	Office of Research Integrity
P&P	Policies and Procedures
PACTG	Pediatric AIDS Clinical Trials Group (DAIDS)
PCP	Primary Care Physician
PCP	Pneumocystis Carinii Pneumonia
PHI	Private Healthcare Information/Public/Protected Health Information
PHS	Public Health Services
PI	Principal Investigator
PID	Patient Identification
PMA	PreMarket Approval
POA	Power of Attorney

POG	Pediatric Oncology Group
PPD	Pharmaceutical Product Development, Inc.
PRAB	Pharmaceutical and Regulatory Affairs Branch (DAIDS)
PRIM&R	Public Responsibility in Medicine and Research
PSF	Protocol Summary Form (HIC Submission Form)
QA	Quality Assurance
QC	Quality Control
QI	Quality Improvement
QIC	Quality Improvement Committee
QIP	Quality Improvement Program
QOL	Quality of Life
RA	Regulatory Affairs
RAPS	Regulatory Affairs Professionals Society
RCR	Responsible Conduct of Research
RCT	Randomized Control Trial
REB	Research Ethics Board
ROC	Regulatory Operations Center
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
Rx	The first word on a prescription, therapy
SAE	Serious Adverse Events
SAP	Suspect Adverse Reaction
SBIR	Small Business Innovative Research
SC	Study Coordinator
SMC	Site monitoring Committee
SMO	Site Management Organization
SoCRA	Society of Clinical Research Associates
SOP	Standard Operating Procedure
SR	Safety Report/Significant Risk
SRO	Sponsored Research Office
SWOG	South West Oncology Group
Tx	Treatment
UE	Unexpected Event
URI	Upper Respiratory Infection
VA	Veterans' Affairs
VPR	Vice President for Research
WHI	Women's Health Initiative
WHO	World Health Organization
WMA	World Medical Association

## How to Make Your Site Attractive to Sponsors\*

**This chapter describes steps that can be taken to help your site prepare for the conduct of clinical trials. The content in this section does not apply to the protection of human subjects in research and is not related to the functions and responsibilities of the HIC or its individual institutional review boards at WSU and its affiliate institutions. This section represents the views of the author and not the HIC or WSU.**

### Objectives

- Discuss characteristics that attract Sponsors to a clinical research site.
- Review sponsor requirements of research sites and personnel.
- Discuss ideas for improving site visibility and improving trial volume.

### Research Has Become Competitive

In 1992, industry grants to U.S. Investigators totaled \$1.9 billion. By 1996, total grants to U.S. Investigators had risen to nearly 3 billion. In 2002, the figure approached \$5 billion and continues to grow annually.

Ginsberg, D. (2002). The Investigator's Guide to Clinical Research. Centerwatch: a Division of Thomson Healthcare, Inc.

### Question: Who's getting the grants and how are they getting them?

- Experienced Investigator and support staff.
- Research team knowledgeable about research regulations and guidelines.
- Work environment adequate to support study demands.
- Patient population adequate to fulfill study requirements for enrollment.
- Site Standard Operating Procedures (SOP) specific to research.
- Research team responsive to Sponsor requests and accommodating of their needs.

### Experienced Investigator and Support Staff

- When Sponsors select a site for participation in their study, they put a premium on the Investigator's experience and expertise.
- When Sponsors select a site for participation in their study, they will often choose a less experienced Investigator who has a coordinator over an experienced one who does not.

### Principal Investigator

- Have previous experience in clinical trials and/or expertise in therapeutic area of study.
- Are knowledgeable about GCP/ICH/FDA guidelines.
- Are committed to the time and work required of the clinical trial.
- Are willing to participate in continuing education specific to research.
- Have certification as Principal Investigator (ACRP) optimal.

### Principal Investigator with Previous Clinical Trial Experience

- Previous experience in clinical trials as either a Principal OR Sub-investigator.
- Previous experience in trials in the same therapeutic area i.e. pelvic adhesions, osteoporosis, endometriosis, etc.
- Experience in treating patients of target population and a large patient population in which to recruit participants.

\*\*It is suggested that research experience and/or previous clinical trial participation be well documented in Curriculum Vitae OR create a separate research CV.

### “Who is your Study Coordinator?”

One of the most important decisions made by an Investigator is the selection of an appropriate study coordinator. The coordinator runs the trial and in most cases can manage all aspects of the trial business including marketing your site, negotiating grants and contracts, assisting in accounting, etc. AND will usually do these things in addition to performing their primary coordinating responsibilities.

### Support Staff

- Dedicated staff member to assist in day-to-day operation of conducting the trial.
- Should be able to dedicate the necessary time to tasks specific to the study.
- Should NOT be someone in the office who “needs extra work to do.”
- Experienced in the care of patients in the “target population”. (Endometriosis, postoperative, etc.)
- Previous experience and/or training in clinical research. Certification in clinical research coordination (ACRP, SoCRA) optimal.
- Participation in annual training specific to clinical research.

“Clinical trials should be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).” - Guideline for Good Clinical Practice

### Knowledgeable about Research Guidelines and Regulations

- Food and Drug Administration (FDA)
- Information Sheets
- Code of Federal Regulations (CFR)
- Title 45 CFR 46 Common Rule
- Title 21-Food and Drugs
  - Part 50-Protection of Human Subjects
  - Part 54-Financial Disclosure by Investigators
  - Part 56-Institutional Review Boards
  - Part 312-Investigational New Drug Application
  - Part 800-Medical Devices
- International Conference of Harmonisation (1997) (“ICH Guidelines”)
- Contains Guideline for Good Clinical Practice (GCP) which was formally adopted by the FDA in May 1997.

- Belmont Report
- World Medical Association-Declaration of Helsinki (Oct 2002)
- Paragraph 29 regarding the use of placebos in clinical trials considered “controversial” by some.

### Pretty as a Picture

Packaging matters. A clean, well organized facility, that is conducive to conducting a trial; tells the Sponsor that you are serious about research and reassures them that you are the right choice for a study site. Remember: The Sponsor’s viewpoint is that you are representing them during the conduct of the trial.

### Facility and Equipment

Does the site have...?

- Adequate exam rooms/clinic space to conduct the study.
  - Comfortable reception area, waiting room, and exam rooms.
  - Adequate space to accommodate monitoring visits.
- Necessary equipment for study specific procedures.
  - May need to contract some services or purchase additional equipment.
  - Sponsor may assist in equipment needs.
- Laboratory area for specimen handling.
  - Area for obtaining, processing, and shipping lab specimens.
  - Equipment for specimen storage.
  - Appropriate safety equipment in place; current CAP/CLIA certifications.
- Adequate and secure storage space.
  - Area for archiving study related documents once the study is completed.
  - Fire, water, and theft proof. Sponsor will want to record the address where records will be archived.
  - Easily assessable in case of audit.
- Dedicated study area.
  - Shows dedication to research and the Sponsor’s study. May be coordinator’s office.
  - Houses study related supplies and documentation (Case Report Forms, regulatory documentation, study drug and supplies).
  - “Double lock” rule for study drug.
  - Optimal to have at least one dedicated phone line, fax line, and data port.

### Where Are All the Patients?

Sponsors will choose sites that they believe can effectively recruit participants for their study but some important points to remember are:

- Sites should be realistic about recruiting potential and not overestimate to the Sponsor their ability to contribute a certain number of participants to the study.

- It is preferable to underestimate recruitment and fill the study in order to establish a good track record with Sponsors. You can always revise the contract to enroll additional participants later.
- It is better to decline participation in a study that you do not have the patient population for than to take on a study and not enroll any participants.

### Locating Potential Patients

- Database searches (by ICD 9 codes) can give sites a realistic idea of the number of patients available for participation in a given study.
- Patient referrals from partners or community physicians may boost enrollment capabilities.
- New efficacious therapies may have been recently approved that would “compete” with study treatment.
- Protocol inclusion-exclusion criteria may be too narrow for recruiting participants.
- Seasonal recruitment of participants or recruitment over holidays may impact enrollment.
- Competing trials being conducted with the same target population may affect ability to enroll.
- Study procedures may be too far removed from “real world” clinical practice and thus too burdensome for the site and/or participants.

### Standard Operating Procedures (SOP)

- Today more than ever, sites are expected to have Standard Operating Procedures that govern the way they conduct their research.
- A site’s SOPs will standardize the way common research procedures are conducted for all studies and increase the quality of data collected.
- During site audits, the FDA will usually ask if SOPs are available for review.
- Key Points Regarding SOPs
- SOPs should be reviewed annually and updated as appropriate.
- SOPs should be reviewed and signed by all members of the research team.
- New SOPs should be discussed at staff meetings and approved by the entire research team.
- SOPs should be specific but not so specific that they are unable to be followed.
- Development of SOPs should be an ongoing process with contributions from the entire research team.
- SOPs HAVE NO VALUE IF THEY ARE NOT FOLLOWED.

### SOPs: How Do I Get Them?

- Network with other sites to create and/or share SOP templates.
- Contract with a consultant to create SOPs specific to your site.
- Purchase SOP templates and customize to your particular site.
- Develop your own SOPs that reflect how your site operates.

## **Committee needs to discuss this section**

### Sponsor Needs

- Sponsors bring “repeat business” to sites that have been responsive to their needs in the past.

### Time is Money

- Sponsors place great emphasis on shortening study start-up time and as a result those sites that can accomplish this will be selected to participate in clinical trials.
- Historically, Investigators in academic settings have taken longer to get a study up and going than those in the private setting, therefore improving communication with the IRBs in your institution and becoming knowledgeable in what your institution requires is very important in decreasing the time it takes to get a protocol submitted and approved.

### What’s the Holdup?

- Academic Setting - 2 to 5 month timeframe to complete budget/contract negotiations and obtain IRB approval
- Community Setting - 1 to 4 week timeframe to complete budget/contract negotiations and obtain IRB approval

### Why Such a Difference?

- Administrative process of academic centers often more diverse and complicated.
  - Budget and contract negotiations may impact multiple departments of the institution and as a result may require input from several different parties.
  - IRB process may be lengthy due to application requirements, meeting frequency, etc.
  - Academic institution affected as a whole by research.
- Community based sites are often able to utilize a commercial (“central”) IRB which predominately means faster turnaround time for IRB approval.
  - Usually meet weekly or bi-weekly.
  - Application process may involve less red tape than academic setting.
  - Sponsor may submit Investigators/sites in bulk for initial review.
  -

### Competition

The competitive nature of clinical research has made it essential for sites to streamline processes and have administrative machinery in place to start a trial within a few weeks.

- An experienced site in the community setting should aim to complete start-up tasks in 7 to 10 days.
- An academic site should aim to complete start-up tasks in one to two months.

## Sample Site Qualification Information Questionnaire

**INDICATION: Ovulatory menorrhagia (heavy menstrual bleeding)**

### A. PRINCIPAL INVESTIGATOR

1. Please provide the Principal Investigator's name and office address.

Investigator Name John Doe, MD

Organization Wayne State University

Street Address 1234 Woodward Ave, Ste. 200-D

City Detroit State MI Zip Code 48201

Phone Number 313-993-1234 Fax Number 313-993-4321

E-mail Address mdiamond@med.wayne.edu

2. Please provide the address of the study site, **i.e.** where the study will be conducted, if different than question number 1.

Name Clinical Research Center

Institution Wayne State University

Street Address 3750 Woodward Ave.

City Detroit State MI Zip Code 48201

Phone Number 313-993-1234 Fax Number 313-745-1234

E-mail Address jdoe@wayne.edu

3. Please indicate which category(ies) best describe your practice:

_____ Private Practice	_____ Hospital Based
_____ Multi-specialty Group Practice	XX Academic Medical Center
_____ Site Management Organization (SMO)	_____ Government/Military

4. If the practice is part of an SMO, please note the type of SMO model: Owned model  Affiliated model

Please provide the following SMO contact information:

Contact Name \_\_\_\_\_

Organization \_\_\_\_\_

Street Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip Code \_\_\_\_\_

Phone Number \_\_\_\_\_ Fax Number \_\_\_\_\_

E-mail Address \_\_\_\_\_

Board Certified

5. Principal Investigator's medical specialty(ies):

Obstetrics & Gynecology

Yes  No

Repro. Endocrinology & Infertility

Yes  No

\_\_\_\_\_

Yes  No

6. How many years of experience does the Principal Investigator have in conducting clinical research? 20+ years

7. List the most recent studies conducted by this investigator and any study involving treatment of study participants with heavy menstrual bleeding

	Study Indication	# of Subjects Enrolled/ # of Subjects Expected to be Enrolled	Length of Enrollment Period	Number Screened	Study Status Ongoing/Active
1	<u>PCOS</u>	<u>94 enrolled</u> <u>50 expected</u>	<u>15 months</u>	<u>Approx. 150</u>	<u>Active/ Closing soon</u>
2	<u>Infertility</u>	<u>15 enrolled</u> <u>10 expected</u>	<u>6 months</u>	<u>Approx. 30</u>	<u>Active/Ongoing</u>
3	<u>Male Infertility</u>	<u>245 enrolled</u> <u>600 expected</u>	<u>2 months</u>	<u>Approx. 250</u>	<u>Active/Ongoing</u>
4	<u>Male Fertility</u>	<u>20 enrolled</u> <u>40 expected</u>	<u>2 months</u>	<u>Approx. 22</u>	<u>Active/Ongoing</u>
5	<u>Uterine Fibroid</u>	<u>3 enrolled</u> <u>5 expected</u>	<u>2 years</u>	<u>8 screened</u>	<u>Follow-up period</u>

8. Has the PI and/or study site been inspected by the FDA or other regulatory agency?

Yes \_\_\_\_\_ No XX

If Yes, please explain and include name of the regulatory agency:

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9. Has the Principal Investigator and/or study site received a form FDA 483 (Inspectional Observations) and/or warning letter from the FDA or other regulatory agency?

Yes

No

If Yes, please attach the form FDA 483 and responses.

## B. PATIENT POPULATION / DEMOGRAPHIC

1. List anticipated source of subjects for this study.

A. Own practice 20 % B. Advertising 70 %

C. Referrals 5 % If using referrals, specify the number of physicians in your referral network: 10

D. Hospital Unit 5 %

2. Please provide **the total number of patients at your practice or institution** that were diagnosed and treated for menorrhagia in the previous year. 500+

3. How many patients were diagnosed and treated **last month**? 50+

4. What criteria do you use to diagnose menorrhagia?

menstrual history, CBC, ultrasound, etc..

5. After review of the protocol summary, how many subjects does the Principal Investigator estimate can be enrolled into this study in a **6-month** enrollment period? 50+

6. After review of the protocol summary, how many subjects does the Principal Investigator estimate can be enrolled into this study in a **9-month** enrollment period? 75+

7. Are you currently involved in a competing clinical trial with this same subject population?  
Yes  No  If Yes, when is enrollment scheduled to end?

## C. IRB / ETHICS COMMITTEE

1. Can you utilize a **central IRB/Ethics Committee** for this study? Yes  No

2. If no, how often does **your local** IRB/Ethics Committee meet? 3X per month

3. How far in advance of the meeting must the application be submitted? 2 weeks

4. List the next 3 meeting dates for your local IRB / Ethics Committee and the deadlines for consent to the IRB/ Ethics Committee.

Submission Date	IRB/ Ethics Committee Meeting Date
October 6	October 20
October 13	October 27
October 20	November 3

5. What is the length of time required to obtain approval after the IRB/ Ethics Committee meeting date? 1-2 weeks

6. If your site uses a local IRB, please provide the name and address::

Name	Human Investigation Committee		
Institution	Wayne State University		
Street Address	101 East Alexandrine		
City	Detroit	State	MI Zip Code 48201
Phone Number	313-577-1628	Fax Number	313-993-7122
Email Address	www.hic.wayne.edu		

7. What is the typical length of time required for CSA and budget approval? 1 month

### G. STUDY-SPECIFIC INFORMATION

1. Will a full-time study coordinator be dedicated to this study?

Yes  No

If no, how many studies will he/she be responsible for? \_\_\_\_\_ [number]

What stage are these studies in? \_\_\_\_\_ [closed enrollment, enrolling, etc.]

2. This study will require you to be able to store sanitary products (multiple cartons) in addition to the standard study-related materials. Do you have adequate storage space?

Yes  No

3a. This protocol requires a dilated eye exam. Will you have any problem obtaining an ophthalmology group that can do dilated fundoscopic exams with or without capabilities of photo of retina to participate? Yes  No

3b. How far would your subjects have to drive from your office for the eye exam?

1 block

4. The subjects will return the used sanitary products to your office at the end of their menstrual flow. These products will be stored in non-see through plastic bags. Specifically, your responsibility will only be to 1.) check that the bags have proper identification on the outside; 2.) ship to central lab for analysis. Do you see any problems with collecting these bags and shipping them to the central lab for analysis?

Yes  No  If yes, please explain \_\_\_\_\_

5. Do you anticipate the requirement for the subject to use the brand of sanitary products (P&G and Kimberly Clark) supplied by the sponsor to have any negative impact on subject recruitment? Yes  No

6. You will be required to complete CRF Tracking/Transmittal Forms and Screen Failure Logs in order to receive your investigator payments. Are you willing to do this?

Yes  No

7. Do you have experience in using ECG equipment supplied by a central ECG lab and transmitting the information to the central ECG for reads?

Yes  No

8. Based on your review of the study summary and schedule of visits, do you foresee any specific problems with subject recruitment? Yes  No

Explain: \_\_\_\_\_  
\_\_\_\_\_

9. Based on your review of the study summary and schedule of visits, do you foresee any specific problems with subject compliance with the collection and/or counting of used sanitary supplies? Yes  No  Explain: \_\_\_\_\_

\_\_\_\_\_

10. Do you foresee any problems with subjects contacting your site when their menstrual period stops to schedule the next visit within 1-4 days after the end of their menstrual period? Yes  No  If so, please explain: \_\_\_\_\_

\_\_\_\_\_

11. Have you conducted trials in which subjects have been required to collect used sanitary products? Yes  No

If yes, do you have any suggestions for retaining subjects? \_\_\_\_\_

\_\_\_\_\_

If yes, please list what the subject compensation should be A) for visits during which used sanitary products are collected? \$\_\_\_\_\_ to \$\_\_\_\_\_

and B) for other visits during the study? \$\_\_\_\_\_ to \$\_\_\_\_\_

## **Budgeting: Sponsor studies (such as pharmaceutical)**

### Should You Accept the Sponsor's Summary of Events and Payment?

Often sponsor's will provide a basic template budget that is missing many of the items that will cost your department money. If your budget is not prepared wisely, your department will lose money and subsidize the pharmaceutical industry. Before you accept a sponsor's initial budget, carefully count the cost.

- **Carefully review the protocol.** Examine budget activities proposed by sponsor
- **Identify if any discrepancies exist between protocol and sponsor's budget**
- **Does the contract match the protocol?**

### Identify Your Expenses

- Who will be conducting the activity? (coordinator, physician, PA, Etc)
- How often will the activity occur? (ECG, laboratory testing, etc...)
- What do you have to pay for the test?
- How many patients are needed?
- Which activities will they participate in?
- Have you included the WSU Indirect costs to each item?
- Will you have legal expenses that need to be included?
- Is the CRF (case report form) consistent with the protocol and how much time will be needed to complete these forms?
- Is it Electronic Data Capture? If so, will they provide a computer for your use?

### Reimbursement Issues

When do you get paid?

- For services?
- Out of pocket costs?
- Additional procedures?

What subjects do you get paid for?

- Only completed subjects?
- What about drop-outs?
- What about screen failures?
- What about pre-phone screening time?

Who pays for unanticipated expenses? (and who will invoice for these items?)

- Repeat laboratory tests?
- Emergency procedures?
- An amended protocol without an amended contract that requires additional work for staff?

Are all services included?

- Advertising expenses?
- IRB charges?
- Long-term storage of records?

- PI assessment time?
- Phone & fax expenses?
- Subject reimbursement?
- Reimbursement for travel for subjects?

#### Tracking Activities & Reimbursements

- Compilation of services provided
- Reporting by sponsors of what activities/visits they have paid for
- Is your site or department able to use the integrated CFS system to handle reimbursements?

#### Negotiation Topics

- Per subject reimbursement – completed subjects
- Reimbursement issues
- Publication rights
- Subject payments

#### Protocol Review

- Can you do all that is required?
- What will you have to outsource?
- Will you need to buy equipment?
- Do you have sufficient staff, or will you need to hire more?

#### Budgeting

Did you remember to include fees for:

- FedEx/DHL Express/etc. overnight shipping
- Long distance phone calls
- Copying
- Subject travel and parking reimbursement
- Long-term record storage
- Advertising (posters, pamphlets, radio, newspaper)
- Postage (stamps)
- Stationary
- Certified letters
- Etc...

Did you remember to include fees for supplies:

- Video tapes
- CD's
- Speculums
- Gown
- Exam table paper
- Gloves
- Pipettes
- Etc...

### CFS (Clinical Financial Services)

This is a tracking service provided by SPA to assist in reimbursement. Currently, not all departments are using this service.

If your site uses the service, CFS should email the coordinator or financial assistant in your group a monthly spreadsheet per study to be filled out. This spreadsheet will itemize all procedures or study expenses that need to be invoiced. CFS will track the invoices and the payments. A monthly report will be provided to the site of incoming payments. If you have further questions, you may contact the CFS group at [sgustafson@clinicalfinancialservices.com](mailto:sgustafson@clinicalfinancialservices.com).

### **Budgeting: Grant Studies (NIH)**

For assistance with budgeting for grant related studies with the federal government, WSU SPA (Sponsored Program Administration) can help. The SPA website can provide the necessary forms and assistance for completing a grant budget. [www.spa.wayne.edu](http://www.spa.wayne.edu)

**Budget Template**

WSU – Clinical Research Center

<b>Department</b>	<input type="text"/>	<b>IRB No.</b>	<input type="text"/>	<b>Sponsor:</b>	<input type="text"/>
<b>P. Investigator</b>	<input type="text"/>	<b>Dept. Phone:</b>	<input type="text"/>	<b>Dept. Contact:</b>	<input type="text"/>
<b>Study Name</b>	<input type="text"/>			<b>Begin Date:</b>	<input type="text"/>
<b>No. of Subjects</b>	<input type="text"/>	<b>Coordinator:</b>	<input type="text"/>		

	<b>Procedures/Tests Description</b>	<b>Charge Price</b>	<b>Indirects (26.5%)</b>	<b># of times</b>	<b>Total Sponsor Charge</b>
<b>Screening</b>					
	Consent				
	Medical History/demographics				
	Con meds				
	Physical exam				
	Blood draw				
	Screening - inclusion/exclusion				
	Coordinator fee				
	(list all procedures/tests)				
	Subject reimbursement				
<b>Subtotal Screening</b>					
<b>Study visits</b>					
Visit 1	Randomization				
	(list all procedures/tests)				
	subject reimbursement				
	storage fees				
<b>Subtotal Study Visits</b>					
		<b>Total</b>	<b>Total # of subjects</b>	<b>Total Sponsor</b>	
<b>Subtotal Screening</b>					
<b>Subtotal Study Visits</b>					
<b>Total Patient Care Costs</b>					

<b>IRB Fees</b>	<b>WSU IRB</b>	<b>Dept. Fees</b>
<b>Initial Submission</b>	1800	1500
<b>Full Board amendments</b>		250
<b>Expedited amendments</b>		50
<b>AE's</b>		100
<b>Yearly Continuations</b>		250



CFS is a service retained by Wayne State University (WSU) to assist in Receivable Management for industry sponsored clinical trials. It provides tracking, billing, collection, reconciliation, and detailed monthly financial reporting on clinical trial accounts receivable and revenue.

#### How does it work?

- Once contract is executed at WSU the contract along with the study flow sheet is given to CFS by your grants officer.
- CFS creates subject visit logs that are completed by the coordinator. (access to this is provided by your department manager)
- CFS creates and maintains invoices based on these logs.
- CFS bills for pass through cost based on contract and completion of logs (pharmacy, IRB, amendments).
- CFS will act as a liaison between WSU and the sponsor to provide collection and reconciliation.
- CFS applies payments received from the sponsor to the study.
- CFS provides online access to all the study visit logs as well as invoices and payments and monthly reports.

For more information about whether or not CFS is an available resource in your department you can contact your grants and contract officer at Sponsored Program or your department manger.

## Contract Process at WSU

When there is a contract between a study sponsor and the research department, there is a process of review, negotiation and approval. In your department the research coordinator may be expected to be part of that process, or it may fall to a supervisor or business manager. Whether you are responsible for this or not, it is helpful to be aware of what goes on in the contract negotiation process. Speak with your supervisor and find out what part, if any, you are expected to play in the contract work. Work closely with a designated person to learn the process in greater detail, particularly when real contract work begins.

Typically a sponsor will send a contract for that study to the research department, which may be quite specific, or may be more general and in the form of a template. The contract contains language discussing subjects such as payment schedules and/or amounts, publishing privileges, liability, and so on. Usually the department conducting the proposed study reviews in greater detail the payment/budget-related pieces. This is often part of the budget negotiation as well, and should be considered carefully by whoever is working with the sponsor on reimbursement issues.

When ready, the contract is submitted to the department responsible for next-level review, along with other required documents. In WSU's Internal Medicine Department, these papers go to the Research Administration office. A typical list of requested documents to be turned in to Research Administration include Form for External Support (FES), cost sharing/in-kind documentation (if applicable), internal budget, internal budget justification, protocol or research plan, two copies of contract including all attachments (ie-per-patient budget spreadsheet) and exhibits (if available), Affirmation Memo (if contract is included), sponsor contact information, Time and Events Schedule (if applicable), blank or completed W9, HIC-AIC form for "Human or Animal Research Information" (signed by Department Chief). The Research Administration office reviews the internal budget and other items briefly. They may request changes or clarification from the research department, and usually have completed their review within 2-3 days.

Once satisfied, they send the entire packet to the Sponsored Programs Administration (SPA) office. The SPA reviews everything in greater detail, and then begins direct communication with the sponsor to discuss and adjust language in the contract. Not uncommonly, there may be several changes made back and forth, with both WSU's and the sponsor's legal departments are involved in review of original and subsequent versions. Depending on the changes required by both sides, and how rapidly changes and reviews are made, this entire process may well last several weeks. It is recommended that you check in periodically with the SPA to find out the status of your study's contract, especially if the study is on a tight timeline (e.g., as with a limited enrollment period).

Some departments and/or facilities that do research guided by WSU's HIC have different procedures. For example, the VA Medical Center uses a Cooperative Research and Development Agreement (CRADA) and does not use Clinical Trial Agreements at all.

Once a contract has been fully agreed upon in its language by both WSU and the sponsor, "clean copies" are printed, usually two, that allows for signatures by the Principal Investigator of the study, the sponsor's legal representative, and WSU's representative. Sometimes the sponsor prefers the final printed document be routed through their departments for signatures first, and then both copies are sent to WSU for the P.I. and University signatures. Some sponsors allow WSU to sign first and send to them. Either way, once all signatures have

been obtained and verified by both sides, each gets a fully-signed original. At that time, typically, the sponsor will notify the monitor and/or the study site that a contract is approved and study procedures may commence. WSU will also notify the department that the contract is fully “executed”, as well as the assigned index (account) number, and that activity may begin. NOTE: it is important to receive permission from BOTH the sponsor and WSU before beginning, as there may be other pre-study visits, procedures, paperwork, and approvals that need to be completed as well before you start.

WSU will also notify Clinical Financial Services (CFS) that a study contract has been executed. CFS has been contracted by Internal Medicine to help facilitate billing and payment for study activities. CFS will use the protocol, Time and Events Schedule, budget, and contract to develop a spreadsheet to be used by the study coordinators. These spreadsheets will list the sponsor, WSU department, P.I., index number, and other identifying information, as well as study events/visits and the associated fees. The spreadsheet is sent to the study coordinator or person designated by the department, and as visits/procedures are completed, dates are simply filled in the appropriate places. CFS puts out a call for updated spreadsheets monthly, which they use to base billing to the sponsors, and follow-up for payment.

Below are some miscellaneous hints, suggestions, tips, and FYI's for completing some of the paperwork that gets submitted with the contract to the University for further review, compiled from the experience of those who've done the work!

- Read sponsor's budget, contract and protocol (especially time and events schedule) IN DETAIL.
- Look at expenses to do study and proposed revenue from sponsor, numbers of patients to be enrolled, number of visits, internal costs (labs, personnel time, materials/supplies needed, equipment to be purchased, etc.) Compare: IS IT WORTH DOING IT for the money?
- Work with sponsor for missing items on their proposed budget. Keep negotiating until both you and sponsor are satisfied. Sponsor will send you a new, revised budget and contract to include the items that were agreed upon.
- Prepare internal department budget and internal justification (see samples), Affirmation Memo, FES (get signed by PI and Department Chief), list of sponsor's financial/budget contact info.
- When preparing budget and justification for department, be sure to put full protocol title, protocol number, protocol short name, & Investigator's name on each page
- On FES form: put “Sponsors Deadline” date as about 3-4 weeks after the date FES will be submitted to Research Administration.
- Put together a folder to keep all items to be submitted clean and together. Research Administration will review, sign, and forward to SPA. They will call you to get it after their review if you have requested them to do so, without automatically sending to SPA.
- About 1-2 weeks after submitting packet to Research Administration, check in personally with the SPA about status (e.g., has it gone to legal yet?)

#### Misc. Resources/Facts

- Index number = account number assigned by SPA after there is a fully-executed contract between WSU and sponsor. This number should be referred to when corresponding with SPA about the protocol.
- SPA web page: [www.spa.wayne.edu](http://www.spa.wayne.edu)

- “Proof” of Indirect Cost (IDC) rates for WSU, plus actual ICD document, found on SPA web if sponsors need to see it.
- FES form is on SPA web, “forms” pg
- PI Access ID is their banner access number
- A “letter of intent” will be needed for subcontracts with other sites who will participate with you on a study.
- SPA proposal requirements at <http://www.spa.wayne.edu/forms/proposalpaperwork.pdf>  
Pharmaceutical requirement on page 2
- If PI is not available to sign the FES and Affirmation Memo when ready to submit all budget/contract info, it is acceptable to sign PI’s name/your initials
- At WSU, an FTE = 1957 hours/year
- All line items on internal budget must be listed and justified in internal justification.
- For Internal Medicine Department studies, checks to be paid to Univ. info:

Tax ID: 38-6028429

Carole Bach

Institution: Wayne State University

Sponsored Programs Administration

5057 Woodward Avenue, 6th Floor

Detroit, Michigan 48202

Phone 313-577-1445

fax 313-577-1348

orspsmail@wayne.edu

#### Study Budget and Contract Work

- Time and % effort can be personnel specific, ie-5% time for PI for 1 month, or 7% effort for RA for 6 months, etc.
- Look at total \$ amount, calculating number of patients to be anticipated for enrollment, subtract out PI salary (based on % effort and time), RA salary, PD salary, lab tech time, etc. Compare balance with costs and what net profit to dept would be. IS IT WORTH IT?
- The Department Administration at 5% cost on Internal budget is calculated on total direct costs.
- The F & A (Facilities and Administration = overhead = indirect costs [IDC]) of 26% is calculated on total direct costs.

## How and Why to Submit to the Human Investigation Committee (HIC)/Institutional Review Board (IRB)

The terms Human Investigation Committee (HIC) and Institutional Review Board (IRB) are used interchangeably to refer to a specially constituted review board established to protect the welfare of human participants (subjects) recruited to participate in biomedical or behavioral research in accordance with federal regulations. All research that involves human participants must be reviewed and approved by the Wayne State University (WSU) HIC prior to the implementation of research.

Principal investigators (PI), Co-Investigators and “key personnel” conducting research at WSU are required to complete the on-line training program before protocol submission. The link to this training can be found on the HIC website [www.hic.wayne.edu](http://www.hic.wayne.edu).

The protocol provided by the company (sponsor), granting agency or written by the investigator must be submitted to the HIC for review. The types of IRB review include: 1) exemption from review, 2) expedited review, and 3) full board review.

- **Exempt Review:** Exempt review can be requested for research where the entire project falls within one or more of the six specific regulatory categories set forth in 45 CFR 46.101(b) and satisfies all Institutional policies and procedures. An investigator cannot exempt his/her research project from HIC review and concurrence. Instead, the HIC chairperson or his/her designee must determine that a project is eligible for exemption. (See HIC Policy/Procedure “Exempt Procedures”) Any study that the HIC chairperson or his/her designee believes is not exempt must be reviewed by either an expedited or full board review process. A research project meeting the criteria for exemption cannot start until after the HIC chairperson or his/her designee has given “concurrence” of exemption. Retroactive “concurrence” or review cannot occur. Approval of research under an exemption is given for an indefinite time period. Re-review is not required unless the investigator proposes changes to the exempt research project
- **Expedited Review:** Expedited review can be requested for project activities that: (1) present no more than minimal risk to human participants, and (2) involve only procedures listed in one or more of the regulatory categories set forth in 45 CFR 46.110 and satisfies all Institutional policies and procedures. (See HIC Policy/Procedure “Expedited Review Procedures”)
- **Full Board Review:** A research proposal that does not meet the criteria for review by exempt or expedited process, must be reviewed by a WSU IRB. The HIC currently has four IRB’s that review initial submissions; they include:
  - M1 which reviews adult medical protocols,
  - MP2 and MP4 review adult and pediatric medical protocols, and
  - B3 which reviews behavioral research only
  - CTS1 which provides rapid review for specified projects

Criteria for initial IRB review and approval of research protocols are set forth by federal regulations and include: determining the level of risk to the participant, potential benefits, informed consent process and documentation, and safeguarding the participant’s rights and welfare (i.e., safety monitoring, equitable selection, protection of privacy and confidentiality and special protections for vulnerable populations)

## Scientific Review

Before the HIC can review a protocol involving the use of human participants in research, the protocol must be reviewed for scientific merit by the Principal Investigator's (PI) department. Various departments conduct this scientific review in different ways and the IRB will accept any of these methods as long as the Chair and/or his/her designee certifies on the Protocol Summary Form that the scientific review has been completed and that the research has scientific merit and ensures that appropriate support and resources will be provided to conduct the study. Research initiated by an investigator without a designated department must obtain certification from a department with the expertise to determine the scientific merit of the study. (See HIC Policy/Procedure "Investigator Initiated Research")

All research involving cancer and human participants must be reviewed by the Protocol Review Committee of the Karmanos Cancer Institute (PRMC). The approval letter must accompany the protocol submission.

All research involving human participants at the John D. Dingell VA Medical Center (JDD VAMC) must be reviewed by the JDD VAMC Clinical Investigation Committee (CIC) before the protocol can be reviewed by the HIC. If the VA research involves cancer, an approval from the PRC (see above) should be obtained before submission for review by the CIC. The approval letter(s) must accompany the protocol submission.

Research involving human participants in the Department of Psychiatry and Behavioral Neuroscience, the protocol must first be reviewed by the Department Review Board. That approval must accompany the protocol submission.

While not a scientific review, the Detroit Medical Center (CMC) conducts a mandatory pre-review on all protocols to be conducted in their institutions. This process involves a review for liability and privacy issues. This review can occur concurrently with the IRB review process. A study cannot start until both the HIC and DMC reviews have been completed and official notice of both have been received.

### Materials for submission of a new protocol to the HIC must include:

- A completed Medical Exemption Form or a Medical/Behavioral Protocol Summary Form and required Appendices (as applicable)
- A full research protocol/grant proposal
- The following items, as applicable:
  - If accessing WSU medical records, a completed HIPAA Summary Form and, if applicable, a HIPAA Authorization Form attached to Informed Consent
  - Informed Consent/ Assent /Information Sheet documents
  - An Investigator's Drug Brochure
  - Surveys, questionnaires, data collection instruments or other measurement tools
  - Advertisements, notices, flyers
  - Recruitment Material
  - Educational materials that will be distributed to participants
  - Data and Safety Monitoring plan if applicable

### Possible IRB Actions

After an in-depth review of the range of the research study, possible actions by the Institutional Review Board include: (See HIC Policy/Procedure “Outcome of Proposal Reviews by the IRB”)

- Approved, the study can begin
- Specific minor revisions required,
  - Response can be review by the IRB chairperson (no deadlines)
- Tabled, the submission did not provide enough information to allow the risk/benefit ratio
  - Response must be reviewed at a full board meeting of the original committee
- Disapproved, protocol lacking science or major components.
  - Must re-write to resubmit. Can be reviewed by any committee qualified to review the study

## **Research Team Responsibilities**

### Principal Investigator - Background

The individual who accepts responsibility to conduct research with human subjects must possess the experience, facilities, resources, and professional qualifications to ensure that the rights and welfare of these human subjects are protected. This individual is identified in research documents as the Principal Investigator.

The title "Principal Investigator" is defined by the Office of Human Research Protection (OHRP) Guidebook as "the scientist or scholar with primary, responsibility for the design and conduct of a research project".

FDA regulations [21 CFR 56.102(h)] state that "investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team."

### Principal Investigator - HIC Procedure

The WSU IRB defines "Principal Investigator" as the one individual, (i.e., scientist or scholar), who accepts responsibility for the design and conduct of a research project. He/she is responsible for complying with all IRB decisions, conditions and requirements. These requirements include reporting all modifications to the project, the prompt reporting of unanticipated risks, and the progress of the research at intervals appropriate to the degree of risk but not less than once a year [45 CFR 46.109(e)]. Therefore, for purposes of the submission of research proposals, the IRB recognizes only one individual as principal investigator.

### Investigator Responsibilities:

- The one individual who accepts responsibility for conduct of the study
- The primary responsibility is the protection of the human research participants
- The PI must adhere to sound scientific & ethical principles
- Compliance with FDA, GCP, ICH, and state regulations and guidelines
- Complete over-site of the study
- Provide training to research staff
- Provide supervision to research staff
- Communicate regularly with study staff
- Review all materials prior to them being submitted to the IRB
- Confirm that IRB approval before initiating a project
- Confirm that informed consent has been appropriately reviewed and signed by study participant prior to commencing any study-related procedures
- Maintain all required records and provide necessary access to office charts
- Adhere to all standards and procedures outlined in the protocol
- Notify research staff if a study patient has an interim visit or non-study related visit
- Sign and date all required documents and labs as required by the study in a timely manner
- Complete all contracted procedures as outlined in study contract

- Attend the investigator meeting
- Meet with sponsor representatives at site initiation visit and monitoring visits as necessary
- Review data on a regular basis for reliability and completeness
- Maintain appropriate licensure and liability insurance

### Coordinator Responsibilities

#### Research Study Management

- Review protocols and informed consents
- Assist with development of study budgets
- Manage clinical data throughout course of study
- Inventory control of all supplies including CRFs, lab kits, and investigational medications
- Submit IRB submissions, progress, and closure reports
- Consult with PI's on all submission materials and reports to the HIC
- Educate ancillary personnel as required by study
- Coordinate personnel and resources for initiation of study
- Attend study initiation meetings
- Provide accurate information for weekly enrollment logs
- Meet with the study monitor to review and correct CRFs
- Complete CRFs from appropriate source documentation
- Assist with development of source documents
- Collect all necessary source documentation
- Review study documents for quality assurance
- Review information for regulatory binders with Regulatory Management
- Schedule patients to meet protocol required visits
- Maintain accurate financial tracking logs of all visits and procedures
- Prepare study documents for archiving at conclusion of study
- Complete monthly study tracking forms
- Attend regularly scheduled staff meetings

#### Investigational Medications

- Dispense investigational medications to study subjects, if licensed to do so
- Maintain drug accountability records
- Check refrigeration and proper drug storage for medications
- Maintain daily temperature log of medications
- Maintain security and confidentiality
- Dispense medications to a physician's office or hospital as required by study
- Demonstrate knowledge of effects and side effects of medications
- Demonstrate understanding of blinding procedure and un-blinding procedure

#### Patient Evaluation

- Perform patient assessments as required by studies
- Document medical history
- Review medical records and gather information for source document and CRF
- Document and chart study procedures

- Demonstrate knowledge of steps to take if a study subject experiences and AE/SAE

#### Laboratory Testing

- Record laboratory data as required
- Process laboratory specimens and send to appropriate laboratory
- Read laboratory values and report abnormal values to investigator
- Follow directions in protocol for required laboratory sampling
- Follow approved laboratory safety precautions

#### Communication

- Write memos, send faxes, and other documents as required
- Contact sponsors, investigators, staff members, nursing personnel in a professional and polite manner
- Handle phone calls from study subjects with concern, confidentiality, and efficiency
- Acquire basic computer skills for documentation of visits and logs

## Data and Safety Monitoring

In order to ensure the safety of human participants throughout research studies a data and safety monitoring board (DSMB) and/or safety monitoring plan may be necessary for a protocol under IRB review.

The criteria that may be used to determine if a data and safety monitoring plan/board would be required include:

- A large study population is being studied and there is the potential for many participants to be harmed before problems are recognized;
- The study is blinded, includes vulnerable participants or employs high risk interventions;
- Multi-site studies where no one Principal Investigator (PI) studies more than a few participants and it is more difficult to recognize a pattern of increased or unusual problems;
- Where the research involves highly toxic therapies or dangerous procedures;
- When the study population is such that high morbidity and mortality rates are expected and where that could mask adverse reactions and unexpected events that occur from a research intervention;
- There is a high likelihood that the study may be terminated for reasons of safety, efficacy, or futility; and
- A data and safety monitoring plan is required by the NIH or FDA

For non-clinical trials or studies that do not meet any of the criteria cited above, the IRB will determine if the submission of a data safety and monitoring plan is required on a case-by-case basis.

DSMB is an independent committee set up specifically to monitor data throughout the duration of a study to determine if continuation of the study is appropriate scientifically and ethically. Many of the large sponsored clinical trials often have a DSMB already in place. The board is typically comprised of experts including scientists, physicians, statisticians, bio-ethicists, and others, which meet periodically throughout the course of a research study. This committee will monitor: (1) the disease, drug, device, procedure or outcome measures of the research; and (2) methodological issues including design, data management and statistical analysis. The groups are usually external to the research team. Its primary functions are to monitor outcomes to assure the safety of participants and the scientific integrity of the research study. The results of their reviews determine whether or not a study must continue or be closed. At each meeting, the group reviews summary reports of related studies, adverse events, cumulative toxic summaries, interim data, major protocol amendments, safety and efficacy outcomes, and other compliance issues. The PI should receive a written report from the DSMB regarding the significant findings or concerns for safety.

The DSMB is not specifically required to communicate with the IRB, but the intent is clear that the important information get to the IRB. The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators that must be shared with the IRB.

Data and Safety Monitoring Plan is a written description of the PI's plan to monitor the data and safety of participants enrolled during the course of a study. This should include:

- Who will be involved in the monitoring (PI, medical monitor, independent committee, etc.) and the composition of the committee/board;
- At what intervals during the research will data monitoring occur (specified intervals and when harm is first identified);
- If appropriate, how many persons will be enrolled prior to interim analyses;
- Plan for collection and storage of data and security measures for the data;
- What type of monitoring will be done;
- How will the data be analyzed and by whom (comparing character, incidence and actual harm to that expected, comparing the magnitude and probability of benefits to that expected, or determining causality of unexpected harm);
- Who will be responsible for monitoring and reporting the occurrence of adverse reactions and unexpected events throughout the study; and
- Outcomes that will be used to stop the study.

A description of the data and safety monitoring plan, if required for research study, must be submitted to the IRB for review. It may be a formal board that is required and organized by a sponsor, a local independent board organized by the PI, or a plan for monitoring the data and safety by the PI and his/her research staff.

## Maintaining Regulatory Files for Clinical Trials

The terms “regulatory files” and “regulatory documents” refer to documents required by the study sponsor and/or the FDA for research. A few examples of such documents are the consent form, the study proposal or protocol, and IRB submission forms and approvals. Maintaining these files carefully is a crucial part of successful study participation, and understanding what some of the documents are can help you.

Most pharmaceutical study sponsors provide some sort of binder or file in which you will keep all of the regulatory documents. Usually there are tabbed dividers already in place with designated categories printed on them such as: Protocol, Form FDA 1572, CV/Medical License, IRB, Informed Consents, Investigator Brochure/Package Inserts, IND Safety Reports, Study Logs, CRF Completion Guidelines, Legal/Financial, and Correspondence. There may be other sections as well, and some of the above may not be there. As you become familiar with the specific documents, you will recognize where to put those that are not obvious. It is also not uncommon for research departments to maintain their own regulatory files, such as in a department cabinet. Setting those files up with similar categories to the sponsor files is helpful, as it provides relatively consistent places to look for required documents.

Depending on the type of study being done (Investigator-initiated, Investigational New Drug [IND], non-IND, observational, interventional), the specific documents required may vary somewhat. For example, the Form FDA 1572 is required for IND studies, but not for non-INDs. Some sponsors may have a non-IND equivalent to the 1572. Some studies do not have informed consent forms per se, but may instead have an assent form, a waiver, an information sheet, or nothing at all. It will be important for you to familiarize yourself with each study that you are responsible for, and what documents pertain to it.

Many documents require periodic updating to ensure that they contain current information. Updates might include changes in address, addition or removal of research personnel, new laboratory being used, and so on. Such documents usually require the signature of the Principal Investigator, and may also require submission to the IRB. Documents requiring updates as they occur include but are not limited to the 1572, the pharmacy plan (if applicable), sponsor/CRO contact sheets, signature logs, and CVs. Usually it is prudent, even required, to keep old versions as well as current ones. Check with the sponsor and your department policies for guidance on this. But when in doubt, err on the side of caution and keep everything! When one policy about this conflicts with another, for example the department vs. sponsor policies, always use the most “restrictive” or conservative to use as your guide. To illustrate: if sponsor policy states that you may delete or destroy old versions of the Investigators Brochure once the latest version is IRB-approved and in your regulatory files, but your department policy dictates that you keep all versions, then do keep them.

Because having accurate, up-to-date, organized files is important, you might consider limiting access to them where possible. Just as “too many cooks spoil the soup”, so too do too many hands in the files increase the likelihood of losing or disarranging them! Having one or two designees to access the regulatory files as needed can help keep them in good order, and decrease the need to track down missing documents or getting new copies from the sponsor or the IRB.

Doing a periodic review of your files to ensure that everything is filed appropriately can be helpful, especially as you are preparing for a monitoring visit. If you decide to do this, you might wish to develop a checklist or tool to guide you. At the end of this section is an example of

a tool used by one research department at WSU, based on the NIH grant it functions under, as well as department policies. Feel free to use this tool, and adapt it to fit your needs or the sponsor's requirements.

When monitors from the sponsor come to your site to review the study, almost inevitably they will also be reviewing your regulatory files to ensure that they are in good order. Monitors are there to help you, so ask them for suggestions on how the sponsor prefers the documents be filed, sponsor's policies on keeping or destroying old versions, and also what helpful tips the monitors may have learned through their own experiences. **USE THE MONITORS!** They are there to help you improve all aspects of your study conduct, documentation, and regulatory maintenance. Ultimately the need for having those files well-maintained is so that the FDA, should they ever do an audit on your site (Heaven forbid!), will find that all documents FDA guidelines require are there, accessible, current, and support the actual research you are conducting.

WSU Regulatory File Internal Audit (NIH and WSU-Specific)

Date \_\_\_\_\_ Person Completing Audit \_\_\_\_\_  
 Study name/number \_\_\_\_\_  
 Current active version \_\_\_\_\_ Date of last audit of this study \_\_\_\_\_  
 Audited by \_\_\_\_\_ WSU \_\_\_\_\_ CRO \_\_\_\_\_

Item/Location (See menu)	Yes	No	N/A	Comments/Action
<b>Copy of full initial protocol and each subsequent version (1)</b>				Versions:
<b>Current IRB Members rosters (2)</b>				
<b>Original initial IRB memo of Full Board Approval (2)</b>				Memo Date:
<b>IRB Memo: Investigator was not present at initial protocol approval (Conflict of Interest Memo) OR Memo to file: Investigator was not a member of IRB group approving protocol (2, attached to initial approval memo)</b>				
<b>Memo to file with HIC FWA #/Exp (2)</b>				
<b>Yearly IRB memos of Continuation Approval (2)</b>				Memo Dates:
<b>Other IRB approvals (amendments, etc.) (2)</b>				
<b>Copy of initial protocol summary (3)</b>				
<b>Copies HIC forms submitted to IRB (amendments, Continuations, etc.) (3)</b>				
<b>DSMB Reports (3, attached to HIC submission forms)</b>				
<b>Patient and clinician letters, flyers, recruitment materials, etc, IRB approval-stamped (3, attached to HIC submission form)</b>				
<b>HIPAA Summary Form and HIPAA Authorization Form (4)</b>				
<b>IRB approval-stamped Informed Consents/Assents for initial version and each subsequent version (5)</b>				Versions and approval dates:
<b>Memo to file: PI designated RA's for obtaining informed consent (5)</b>				
<b>Initial and subsequent signed 1572 or IoR Agreement forms (6, includes IoR w/CV available, sites' addresses where study will be conducted, drug dispensing location, laboratories, IRB, sub-investigators all current)</b>				
<b>Copies of local AEs and outside safety reports submitted to IRB(7)</b>				
<b>SAEs (7)</b>				
<b>Safety memos considered not-reportable by WSU HIC policy filed with signed memo stating reason(s) (8)</b>				
<b>HIC memo re: reportability criteria (8)</b>				
<b>Misc. emails, communications, etc. (9)</b>				
<b>Old Screening Logs if study is closed to enrollment (9)</b>				
<b>Off-site documents (10)</b>				
<b>Protocol Registration Checklists, and letter or email approving initial</b>				Sites and date of email:

registration of protocol and each subsequent version (11)				
Item/Location (See menu)	Yes	No	N/A	Comments/Action
Email signifying deregistration of a protocol for a particular site (11)				Site and date of email:
Current copies of CLIA and CAP for all laboratories used for the study (12)				
Dated current Investigators Brochures and IB addendums/revisions (13)				
Dated, current drug package inserts (13)				
Final Study Report (14)				
Final/Close-Out Monitoring Report (14)				
Laboratory Normal Values (16)				
Monitoring Log (16)				
Monitoring Reports (16)				
Protocol Training Records (16)				
CVs for all investigators and other research staff (16, current, signed, dated)				
Signed Agreements (17)				
Financial Disclosures (17)				
Pharmacy Accountability Records (18)				
Record of Retained Body Fluids and/or Tissue Samples (19)				
Screening and Randomization/ Enrollment Logs (20)				
CRF binders (20)				
Signature Key/Log (20)				
Subject Identification Code List (20,21)				
Signed Original Informed Consents (21)				
Source Documents/research files (22)				
All HIC submission forms IRB-stamped "Received" and dated on front page				
Duplicate items confirmed and discarded				
All items in folders arranged in reverse chronological order				
Regulatory cabinet locked when not in use				
Files marked and identifiable, with study numbers on each folder				

**Folders required for each study:**

1. Front folder: Study name and number, and "Protocol"
2. IRB Approvals
3. HIC Submissions
4. HIPAA
5. Informed Consents
6. 1572
7. Adverse Events
8. Safety Memos – Not Reportable
9. Correspondence

**Folders that may possibly be required for each study:**

10. MCO
11. Protocol Registration
12. Lab Certifications

## 15. Others (protocol-specific) \_\_\_\_\_

**Other locations where reg/essential docs may be kept:**

16. Project Director's files/shelves
17. Business Mngr's files or Grants & Contracts Office
18. Investigational Drug Pharmacy
19. Lab Tech Files or Research Lab room (6<sup>th</sup> floor)
20. Designated central shelf/binder
21. Designated locked file cabinets
22. Individual Research Assistants' files

- 13. Investigators Brochure
- 14. Close-Out Information

## Financial Disclosures

It is very common for industry-sponsored trials and other sponsors as well, to ask each research staff member who participates to complete and sign a financial disclosure form. Typically these are very short (one to two pages) and easy to fill out. The purpose is to ensure that all potential financial conflicts of interest have been completely disclosed to the sponsor. The FDA asks that any investigators, sub-investigators, or other key personnel relay all financial interests they may have in the study project, its outcomes, or any sales, patents, or gains that may come to the investigator as a result of the trial. Usually disclosure involves checking boxes "yes/no" as to varying levels or types of income that the investigator may receive from the sponsor. Examples include stock dividends, salaries, honoraria, and so on. It is not uncommon for the financial disclosure forms to also ask about the investigator's immediate family members' potential financial gains as well. Note that disclosure of such income does not usually preclude the investigator's ability to participate in the study...the information just needs to be disclosed.

Wayne State University also has questions about potential conflicts of interest on both the HIC submission forms and the Sponsored Programs Administration forms. Again, full honesty and disclosure are required here. Should there be such potential financial gain, there are additional forms that need to be completed, and there is mandated verbiage that must be added into the informed consent, so that patients are aware of the investigator's potential gain as well. The University Financial Conflict of Interest Committee reviews all disclosures and determines a management plan if deemed necessary. The IRB review may result in additional management of the disclosed COI.

## Standard Operating Procedures

Many research departments at WSU have their own policies and procedures, which may also be known as standard operating procedures, or SOPs. SOPs serve as guidance on the specific steps to follow for given procedures. They provide continuity in those procedures, and decrease the likelihood of errors. It is important that you learn early on whether your department has such SOPs, and where they may be located.

Review your department's list of SOPs briefly. Discuss with a co-worker or supervisor which SOPs are pertinent to your current position and job description, which need to be learned in-depth now, and which can wait until later. Familiarizing yourself with the basics can ease your orientation into your position, decrease errors, and hopefully decrease some anxiety.

Below is a sample SOP from a WSU research department, and a sample list of SOPs that you might see in your department.

### Example of types of SOPS

#### SOP TABLE OF CONTENTS

##### INDEX

##### GEN = GENERAL PROCEDURES

GEN 1.01	Preparation, Review, and Approval of SOPs
GEN 2.01	SOP Orientation and Training
GEN 3.02	Responsibilities of Principal Investigator
GEN 4.02	Responsibilities of Medical Director of Research
GEN 5.02	Responsibilities of Project Director
GEN 6.03	Responsibilities of RAs Who Conduct Study Visits
GEN 7.03	Responsibilities of RA/Social Worker
GEN 8.02	Responsibilities of Research Secretary
GEN 9.02	Responsibilities of RA/Specimen Technician
GEN 10.02	Responsibilities of CPCRA Data Manager
GEN 11.01	Responsibilities of Research Business Manager

##### SS = STUDY START-UP

SS 1.02	Project Feasibility
SS 2.01	Communication With Sponsors/CROs
SS 3.01	Site Qualification Visits
SS 4.03	Interactions With Human Investigation Committee
SS 5.01	Site Initiation Visit
SS 6.02	Project Budgets and Contracts

##### SM = STUDY MANAGEMENT

SM 1.05	Subject Screening
SM 2.03	Patient Recruitment
SM 3.03	Obtaining Informed Consent
SM 4.03	Enrollment Procedures/Protocol Exemptions/Remuneration
SM 5.01	Clinical Assessments

SM	6.03	Specimen Collection
SM	7.01	Early Termination Procedures
SM	8.02	Safety Reporting
SM	9.02	Managing Documentation in Women of Childbearing Potential
SM	10.02	Obtaining and Recording Screening Consent
SM	11.01	Maintaining Current Consent Forms and Re-consenting Patients

DM = DATA MANAGEMENT

DM	1.04	Collecting and Recording Data
DM	2.03	Source Documentation
DM	3.01	Archiving Data
DM	4.03	Certified Copies

QC = QUALITY CONTROL

QC	1.01	Ongoing Monitoring Visits
QC	2.05	Internal Quality Control Procedures
QC	3.01	Preparation for Regulatory and/or General Audits

PM = PROJECT MANAGEMENT

PM	1.01	Project Start-Up
PM	2.01	Communications
PM	3.03	Regulatory Files
PM	4.01	Drug Accountability/Tracking/Storage
PM	5.01	Study Termination

**Example of a SOP****Wayne State University  
HIV/AIDS Research Office****Standard Operating Procedure  
Safety Reporting  
SM 8.03****Purpose:**

The purpose of this SOP is to describe the methods of safety reporting to all clinicians, investigators, subjects and the IRB.

**Other Related Procedures**

GEN and SM SOPs

**Procedure****Who**

Principal Investigator, Physician Subinvestigator(s), Research Assistants, research secretary and Project Director (PD)

**When**

At any time safety information has been made available to the site.

**How**

- The person in receipt of safety information is to pass it to the unit secretary for dissemination among research staff.
- When the PD receives the Monthly Safety Report Distribution List by email, the PD will sort the data by Group (to cluster CPCRA & ESPRIT reports together)., This page is given to the unit secretary, who will ensure that all reports listed therein have already been reported to the IRB, or filed as non-reportable with the appropriate cover memo. The secretary is to report any missing items to the PD so they can be obtained.
- Adverse events are determined according to protocol reporting requirements as well as IRB reporting requirements. The stricter of the two will be followed in the event that the requirements differ.
- All FDA regulations for safety reporting will be followed as outline in GCP.
- All telephone reporting will be done the research assistant coordinating the trial or the research assistant following the subject if the two are different persons.
- Research assistants will complete and submit safety reports to the secretary for submission to the IRB. Safety reports coming from the Division of AIDS will be handled by the PD and given to the secretary to type. A log is kept by the secretary of all DAIDS safety reports and their submission date to the IRB.
- IRB policies will be followed regarding submission to the IRB.

- Sponsor requirements will be followed for reporting to the sponsor. Research assistants will perform all sponsor notification of adverse events.
- Source documentation will be done for adverse event reporting for an individual subject in the subject's research chart.
- Distribution of safety letters to the patients will be recorded and a copy filed in the subject's research chart.
- The Principal Investigator of that particular study must sign off on all adverse event reports submitted. This is done either on a sponsor-specific form and/or the IRB form.

Author Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Approval of Med. Dir. of Research: \_\_\_\_\_ Date: \_\_\_\_\_

Approval of PI: \_\_\_\_\_ Date: \_\_\_\_\_

Date of Implementation: \_\_\_\_\_

This version replaces version 8.02 Not applicable: \_\_\_\_\_

**Annual SOP Review**

Principal Investigator: \_\_\_\_\_ Date: \_\_\_\_\_

Medical Director of Research: \_\_\_\_\_ Date: \_\_\_\_\_

Project Director: \_\_\_\_\_ Date: \_\_\_\_\_

**Annual SOP Review**

Principal Investigator: \_\_\_\_\_ Date: \_\_\_\_\_

Medical Director of Research: \_\_\_\_\_ Date: \_\_\_\_\_

Project Director: \_\_\_\_\_ Date: \_\_\_\_\_

## **Clinical Trial Advertising**

At the start of a potential clinical trial, it is important to ask the question “Does our group have the patient population necessary to fulfill the trial enrollment?” If the answer is yes, advertising may not be necessary. If the answer is no, your group may need to pursue advertising to locate the needed study participants.

Before any advertising is done, it is important to read, review, and adhere to Wayne State University’s HIC policies on advertising. See the following website below and go to the Advertising link. This link will address WSU guidelines about advertising. All advertising must be submitted to IRB before it may be utilized to recruit study patients.  
[www.hic.wayne.edu/hicpol.html](http://www.hic.wayne.edu/hicpol.html)

### Common methods to Locating Potential Patients

- It is vital to realize your target population and create a clear profile including age, sex and ethnicity. A careful demographic analysis for the advertisement sources you plan to use is vitally important also.
- Does your clinic or group already have the patient population? If so, the physicians may be able to present the study to each patient or hand the patient a quick brochure or flyer.
- Database searches (by ICD 9 codes) can give sites a realistic idea of the number of patients available for participation in a given study.
- Patient referrals from partners or community physicians may boost enrollment capabilities. It is good to provide them with a brochure about the study and your contact information to assist them in referring potential patients.
- Posting flyers around Wayne State University, DMC, and its’ affiliates. You need special approval to post at the VA hospital. Also, it is better to check with a manager at each location or hospital to make sure you do not violate the rules about advertising. Many hospital and building lobbies around campus will allow you to place a stack of flyers on their lobby counter or hang a flyer on a bulletin board. Cost: paper and ink to print the flyers.
- Newspaper Ads are also a very effective way to recruit potential patients. Before running the ad, make sure you have IRB approval. Also, make sure you have a designated phone line for subjects to call and the necessary staff to handle the phone calls. Newspaper advertisement can cost anywhere between \$200 for a day up to several thousand for a month. It is also good to try to post the advertisement in the health section of the paper.
- Radio Ads are another effective way to reach a large population of potential subjects. To effectively utilize a radio ad, it is important to contact the station and ask them to send the demographics of their listening population. This will allow you to see if the station reaches your target population. Radio advertisement will usually costs between \$3000 and \$4500 for one week of ads. You may negotiate time slots and prices. Also important to know is that some of the stations require payment from WSU up-front to run the ad, which may take about 2-3 weeks.
- TV Ads reach a large population also. The TV marketing personnel will help you to develop a time frame and method to advertise the study. This will cost anywhere from \$3000 to \$6000 depending on the time slots and time of the ad.
- Internet recruitment is another means to reach your target population for a study. The IRB requires the website you intend to use for your advertising. This may be filled out with the protocol summary form at the initiation of a trial or may be submitted by an

amendment later. Currently, you may post clinical trials on the school of medicine prognosis website or on WSU pipeline. Other potential websites to utilize are:  
www.clinicaltrials.gov (an NIH sponsored website)  
www.centerwatch.com (this website requires a fee to become a member which allows you to list your trials, information about your group, and “sell your site” to potential pharmaceutical companies looking for research clinicians to conduct their trials.

Potential problems to overcome in locating your targeted patient population:

- New efficacious therapies may have been recently approved that would “compete” with study treatment.
- Protocol inclusion-exclusion criteria may be too narrow for recruiting participants.
- Seasonal recruitment of participants or recruitment over holidays may impact enrollment.
- Competing trials being conducted with the same target population may affect ability to enroll.
- Study procedures may be too far removed from “real world” clinical practice and thus too burdensome for the site and/or participants.

Paying for the Advertising:

It is often difficult to get through the “red-tape” to pay for an advertisement. To pay for newspaper, radio, or TV, it is important to establish good communication with the company that will run the ad. Have them send you a quote that may be submitted to WSU with your purchase requisition. Attached is a copy of a purchase requisition. (You must submit the quote and a copy of the IRB approved ad with the purchase requisition). You CANNOT use a WSU procurement card (WSU VISA) to pay for advertisement. You may establish a blanket PO that will allow quick payment of advertisement and will help expedite the process. Attached is a copy of that also. With the blanket PO, you will be given by WSU a Purchase Order number (PO#) that may be used quickly to run an ad. You must then submit the invoice to WSU for payment with the established PO# listed.

## **Subject Recruitment**

There are many different types of recruitment strategies to help locate the appropriate subjects for your studies.

### Issues of HIPAA and Recruitment

Initial Recruitment Steps-At WSU the HIPAA Privacy Board requires that a person in a clinical relationship with the participant be the one to introduce the potential participant to the study. If the participant is interested, the research personnel can then be introduced to the participant and start the consent and enrollment processes. This can be done in several ways:

- Face-to-face introductions in the clinical setting.
- Letters, information sheets or other documents generated from the clinician's office that are mailed out or given to patients in the clinical setting. The document can be used to introduce the patient to the research study and inform them that they may be called regarding the research. These contact documents should allow the participant to refuse a contact by the research team member if they choose.
- If the researcher does have a clinical relationship with the potential participant, he/she can provide the initial introduction of the study and proceed with the in-depth consent and enrollment process, with verbal permission from the patient.

Prior to beginning any of these activities, the HIC must approve the introductory phase of the recruitment process.

How can participants be recruited?

- Direct person to person solicitation
- Classroom instructor
- Clinician/Nurse
- Co-Investigator/Collaborator
- Primary Care Provider
- Principal Investigator
- Research Nurse
- Resident/Fellow
- Student/Student assistant
- Advertisement
- Notice/flyers
- Brochures
- Psychology Student Pool
- Internet

## The Consent Process/Informed Consent

Obtaining informed consent is more than a signature on a piece of paper; it is an ongoing process that continues during all phases of research. It begins with recruitment and continues through the completion of the study. This process is interactive in that information, questions and answers are exchanged between the investigators and the research participant. An investigator shall seek such consent only under circumstances that provide the prospective participant or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

The information that is given to the participant or the representative needs to be in language understandable to the participant or the representative. The person consenting should make sure that the participant has sufficient knowledge of the study.

The federal regulations state that no investigator may involve human subjects in research unless the investigator has obtained “legally effective consent” of the subject or the legally authorized representative (LAR).

The federal regulations require the following elements to be included in the consent form, when applicable:

- Statement that it involves research
- Risks/discomforts
- Benefits
- Available alternatives
- Confidentiality of records
- If treatment or compensation is provided if injury occurs
- Contact number for questions
- That participation is voluntary

When applicable, the consent should contain:

- Statement of unforeseeable risks
- Circumstances for termination from research
- Additional costs
- Consequences of early withdrawal and procedures
- New findings given when appropriate
- Approximate number of subjects

The WSU Human Investigator Committee is requiring that the HIC consent templates be used for all consent submissions. If your sponsor sends a template for a study, use the WSU template and cut and paste the required sponsor language into the WSU template. The required language in the WSU template cannot be removed from the consent documents. See <http://www.hic.wayne.edu/hictemplates.html> for specific templates.

Written Informed Consent is the golden standard in research and should be used when possible and practical. The language must be understandable to the targeted population so true informed consent can be given. This document is the blue print for the study.

Written informed consent can be obtained via fax when the consent process takes place in person and participant faxes the signed informed consent document. In addition, when the Legally Authorized Representative (LAR) is not available to sign the informed consent document, the consent process takes place over the phone and then the document is faxed back to the investigator. Notes coinciding with the dates and signatures on the informed consent documents provide the source documentation

Written informed consent obtained via mail is used when there has been a change to the informed consent that may affect the participant and the individual is not scheduled for a study visit. The consent process should take place over the telephone and the signed consent form is mailed back to the investigator. Once the signed informed consent is received it should be signed with the date it is received.

#### Foreign Language Short Form for Consent (must be used when potential participant cannot read or speak English)

- Using the short form to consent a person who speaks a foreign language
- The translator can be a member of the research team
- Family members who are fluent both in English and the native language may serve as the translator
- The process requires a witness fluent in both English and the other language
- The long form (English version) is read to the participant by the translator.

#### Information Sheet

- Contains the elements of consent but does not require a signature.
- Used when the only risk to the participant is loss of identity and involves no procedures for which written consent is normally required outside of the research context
- The participation is considered consent

#### Oral Consent

- A script of the consent must be provided for review
- Generally only allowed doing a phone survey

#### Parental Permission

- Parental Permission must be obtained prior to approaching the child
- May use the appropriate adult template and clarify that “you or your refers to you or your child”
- For studies involving greater than minimal risk and no prospect of benefit to the child, two parent signatures are required

#### Assent for Children

- Must be obtained in non-life threatening studies involving minors
- A parent’s “yes” does not override a child’s “no”
- Must be written assent for children age 13-17
- Can be the same form as the informed consent if written in simple language

- Oral assent is obtained for children ages 7-12

#### Waiver of Consent

- For studies that involving no more than minimal risk, the waiver would not violate participants rights and research could not practically be done without the waiver
- Generally for medical records review and specimens research

#### Federally Mandated Documentation

- A copy of the Informed Consent must be given to the subject or LAR
- Oral consent must have a witness to the process

#### Patient Competency

- It must be determined if the patient is competent to make their own decisions
- If a person has a guardian, permission from the guardian must be received prior to approaching that person
- Always check medical records to see if a guardian is listed
- A note must be included if the person suffers from mental illness to why this person is competent
- Standardized assessment of competency is required for every potential participant if the study involves persons with potential for altered competency

#### Consent Documentation

- More than just the consent form
- Must be noted in the medical record, research record or other source document
- Must address that participant had a chance to ask questions, state participant's understanding of consent and a copy was given to person

#### Documentation Options

- Written note
- Dictated note
- Sticker in chart
- Stamp in chart
- Worksheet
- Others

## Participant Retention

Participant retention begins at recruitment. Explain to individuals why their participation is important, why they will be contacted frequently, how the protocol will be different from standard medical care, and the impact on the study if they are noncompliant or lost to follow-up. "Every participant counts."

Ask participants for phone numbers for work, cell phones, vacation homes, neighbors, children, or another trusted person outside of their home that you may contact if unable to reach them at home. Explain the need for this additional contact information: over the course of the study, people sometimes move, have changes in their health, or changes in their family status that may affect their ability to participate. Ask participants to contact you with updated information if they move or change their phone numbers.

As participants allow, involve support persons (spouse, children, friends, or neighbors) in the decision to participate and in study contact visits. At each contact, thank them for participating, and reinforce the importance of returning for scheduled visits.

Give participants a schedule of all expected follow-up windows. At each contact, schedule the next follow-up visit, if possible.

Provide cab or wheelchair van transportation, mileage, or parking reimbursement when appropriate. Sponsors may include funding for this in the study budget, or may reimburse these expenses if invoiced.

Understand that retention may be easier during the active phase of the study, when participants are returning frequently to receiving study drug or for treatment with study devices. Long-term follow-up, which may include annual visits or phone calls, may make retention more difficult. Explain to participants the information that will be collected at each visit, and ask them to call you and report events that occur in between follow-up visits (hospitalizations, emergency room visits, etc.). It is much easier to collect supporting documentation and report unscheduled events soon after they occur, than it is for participants to remember event details up to a year later.

Send birthday cards or holiday greeting cards. (These must receive HIC review and approval prior to being used). These are a friendly way to remind participants to keep in touch with you. Give participants business reply or self-addressed stamped envelopes to mail information back to you (medical record release forms, etc.). In long-term follow-up, mail a postcard to participants approximately a month before visits are due, to remind them to call and schedule the appointment or to expect a call from their coordinator. Reminder: Make sure you have indicated on your HIPAA Summary and Authorization Forms that you will be "USING" name, address, phone numbers, or fax and e-mail, for study purposes.

As appropriate, update participants on study progress and results. Some sponsors will provide updates that are specifically intended to be distributed to participants for this purpose. (Please evaluate if this information requires IRB approval before distribution to participants.)

If unable to contact participants by telephone after three calls on three different days and times, send a registered letter. However, sending an additional copy of the letter by regular mail might speed the contact process up by a few days. If participants have moved, standard mail

may be forwarded faster than registered mail. If participants are not home during mail delivery times, they may not be able to pick up registered mail for several days.

Finally, if you are still unable to contact participants, try an online search, such as Yahoo! People Search (<http://people.yahoo.com>) to find contact information, or a search of the Social Security Death Index (<http://ssdi.rootsweb.com>) to determine vital status.

## Research Documentation

Data is the cornerstone of any clinical trial. Data is collected, and then analyzed to determine the results of the trial. Information is obtained from a study participant's clinical record and then transcribed onto specific forms, CRF's or case report forms. This prepares the data for evaluation. Investigators or Biostatisticians determine in advance what data is relevant to the endpoints of the study. The nature of the study determines the complexity of the forms. Forms need to be completed in a timely manner, accurately and legibly to ensure success of the study.

## Source Documents

Source documents are documents that support any information collected on a clinical trial. Source documents can include history and physicals, lab reports, radiology reports, operative and pathology reports, progress notes, treatment records, or any pertinent notes that may have been written on scrap paper, not just formalized, it also may include any other information obtained from a study participant's medical record. All source documentation needs to be saved. It is important for the validity of the study. It is the only proof that the data that is collected is accurate.

There are different ways to organize source documents. Please see attachment on next page. One way is to flag each source with a specific colored post it flag. Keep all succeeding flags of the same color, matched in the same spot on the page so there are not numerous flags scattered all over. For example all information related to history and physicals and progress notes will get tagged with a purple flag, all radiology with a blue flag etc. The documents are then put in chronological order under each different heading. This makes it easy to do eligibility quickly and accurately with all source documents attached.

### Color Code References for Source Documents

<b>1</b>	<b>Purple</b> – History & Physical, Weight, Performance Status, Demographics, Checklists
<b>2</b>	<b>White</b> – Operative and Pathology Reports
<b>3</b>	<b>Blue</b> – Diagnostic Imaging - X-rays and Scans, PFT
<b>4</b>	<b>Red</b> - Laboratory Tests
<b>5</b>	<b>Yellow</b> – Toxicity Evaluations
<b>6</b>	<b>Green</b> - Tumor Measurements - Disease Status @ BMT
<b>7</b>	<b>Orange</b> – Treatment Records

**Case Report**

**Forms**

Case report forms are data collection tools. Case report forms (CRFs) are used to record protocol specific required data for each study subject. Case report forms can be either electronic or paper and are used to standardize the collection of study data and to help assure that all the needs of the study are met. This includes statistical, regulatory, data management and medical.

Data is abstracted from source documents and filled into appropriate areas of the CRF. When errors are made on paper CRFs a correction can be done. Corrections are made by drawing one line through the incorrect entry, making the correct entry and dating and initialing it. It is never acceptable to write-over an entry, use white-out or erase the entry without properly correcting it. All documentation should be completed in ink, not pencil. There always needs to be a paper trail. Anyone reviewing the CRF needs to be able to see what was corrected, when and why.

When filling out CRFs, it is important to check for completeness, legibility, and are the answers pertaining to the proper or requested time frame. When data collected in the CRF is in agreement with data collected in source documents it is a good indicator of the quality of the data.

#### **Note to File**

There are times when source documentation located in a patients record is missing pertinent information required by the study parameters, in those instances a patient note to file can be constructed to document any of the missing pertinent data. The note to file helps to fill in the gaps and make the information more complete and understandable. Important information to include in the note to file is the date of the event, the subject study accrual ID number, subject initials, and a detailed description of the missing data. Signatures of involved personnel are required including the CRA to validate the missing data.

## **Study Articles (Drug/Device) Accountability**

If this is the first time working with an investigational drug or device, please know that a complete and accurate final accounting of all clinical trial drugs and clinical trial devices is the ultimate responsibility of the Site Investigator at each of the participating sites.

The participating pharmacy also has a responsibility to keep complete and accurate records of all clinical trial drugs received and dispensed by the site. A problem can arise, however, with the devices. Each protocol is different and so, these can be sent to the PI, the research department or even the OR. In cases like this, it is very easy to lose accountability. Depending on how your department is set up, you may have better control if you have the device sent to your attention. This will make it easier for you to keep copies of all shipping documents that accompany the devices and a log of when and to whom the devices were dispensed. It is important to keep a record of when the initial drug/device shipment arrives after IRB approval.

### Storage

Each protocol is different but in general, storage of research drugs/devices should be the responsibility of the research pharmacy. They probably have their own accountability form but it is a good idea for you to keep your own. If the study drug is stored for any amount of time in your area, you may need to keep a daily temperature log of the study refrigerator.

### Dispensing

Research drugs will be dispensed according to the protocol and your site's regulations. The PI will probably write the order, the pharmacist will then label the drug and the coordinator will then give to the patient. As coordinator, you must double check to make sure the correct drug is being given to the participant and that the study drug has not expired. Whatever the policy is you are to follow, make sure you document what was given to whom, when it was given and with what instructions.

### Returns/Disposal

Unless your participants are given the exact number of pills to take, there will probably be unused drug returned to you. The returned pills will need to be counted and documented. This is very important if you need to report to the sponsor regarding participant compliance. The unused drug will also need to be returned to the sponsor or the manufacturer for destruction depending on the protocol. There will be a specific procedure for you to follow in the operations manual. Make sure you keep copies of all shipping notices and return forms for your regulatory binder. The research pharmacy may also need copies of these documents.

Devices may have to be returned due to breakage or receipt of a faulty device. The sponsor will issue you a Returned Goods Number before you can return the device for repair or exchange. This may be the only way you have to keep track of the device and is important to keep all documents safe.

The typical steps in the life of a research drug are as follows:

- The drug is shipped out from the manufacturer to the Study Coordinator or Research Pharmacist at the site soon after approval.
- Coordinator receives drug, signs and faxes required form acknowledging receipt to sponsor and keeps a copy of all documents pertaining to the shipment and its receipt. (This step may be completed by the Research Pharmacist, if so, ask for copies of shipping documents.)
- The drug is logged in for storage at the pharmacy and placed on a shelf.
- Soon, the drug is assigned to a patient and the order is written by the PI.
- The Research Pharmacist prints out a label, dispenses the drug and gives to the Coordinator.
- The Coordinator gives the drug to the participant with instructions and documents this information.
- The Coordinator may need to let the sponsor know (paper form faxed or use of a website) that the drug was dispensed to the participant.
- The participant will return the unused portion of the drug depending on the protocol and this will be returned to the manufacturer for destruction. (This step will differ according to the protocol)
- Please see the HIC policies and procedures on drug and device studies for further information.

The next page is an example of a spreadsheet that could be used to keep track of research drugs and/or devices. It can be modified to fit your protocol and is an excellent tool for accountability.

## IND – Investigational New Drug

### What is an IND?

An IND is an Investigational New Drug Application. It is a detailed document submitted to the FDA requesting the use of a drug/biologic that is new or not approved to be administered in the population, dosage, formulation or indication the clinical trial requires. Once applied for and approved it will generate an IND number that will apply to the existing study and all additional studies the applicant wishes to run using the drug.

There are three types of INDs that can be applied for:

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
- Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

### Do I need an IND?

To determine if you require an IND ask yourself the following 6 questions. If all six of the conditions are met you DO NOT NEED AN IND. If any of the 6 are not met you WILL REQUIRE AN IND.

- (1) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
- (2) it is not intended to support a significant change in the advertising for the product;
- (3) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- (4) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
- (5) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
- (6) it does not intend to invoke 21 CFR 50.24.

LOG ON TO [www.fda.gov](http://www.fda.gov) for more detailed information on the topic of IND's

### How do I compile an IND Application?

The FDA has a specific format to follow for completing an IND application. The necessary documents are:

- Cover letter
- FDA Form 1571

- FDA Form 1572
- Study protocol
- CV's
- Preclinical and manufacturing data (if the drug/biologic is commercially available you will require a letter from the manufacturer allowing the IND applicant to cross reference their IND).

#### How long is the approval process?

Once submitted the FDA will respond within 30 days with an acknowledgement letter and IND number. This does not mean they have approved your protocol unless the letter states the study can begin. The FDA will usually send a supplemental letter letting you know either a) the protocol requires modifications before it can begin or b) the study is exempt and does not require an IND. **Remember the study cannot start unless all FDA concerns are addressed**

#### What do I do once I am approved?

Once approved the applicant is ultimately responsible for all aspects of the clinical trial conduct and is bound by the Code of Federal Regulations and Good Clinical Practice.

- must maintain a regulatory binder with all FDA communication
- must have IRB approved consents and protocol
- must conduct the study according to the most current approved protocol
- must notify the FDA of all protocol/consent changes
- must submit protocol/consent changes to the IRB
- must promptly notify FDA all serious adverse events (use medwatch form)
- must submit an annual report
- must maintain drug accountability log
- must maintain data collection forms
- must label all drug with the investigational drug label
- must have your study monitored
- must have a data safety monitoring plan (if applicable)
- once the study is completed notify the FDA

The following web site will give more detail on completion, submission and maintenance of an IND application:

[http://www.fda.gov/cder/regulatory/applications/ind\\_page\\_1.htm](http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm)

**If unsure always contact the FDA directly at CDER or CBER before starting your project.**

**Investigation Device Exemption**

\*Under Construction\*

## **Packaging and Shipping : Biological Specimens, Category B, UN3373**

Many clinical research studies require patient specimens be sent to a sponsor-designated lab. The shipping of these hazardous materials is regulated by the U.S Department of Transportation (D.O.T.) and the International Air Transport Association (IATA). The IATA regulations are always equal to or more stringent than the D.O.T. regulations. The IATA regulations govern air transport not only in the US, but worldwide as well.

The shipping of hazardous materials can pose a serious threat to anyone who might come in contact with the contents. Therefore, it is important that the rules be followed so that any possible unsafe condition is minimized.

Before you can ship blood specimens to the lab you will have to complete the training required by IATA. Most facilities have the training on a disc and a certificate will be available to print when completed. This training will need to be repeated every two years.

Patient specimens are those collected directly from humans or animals, including, but not limited to, excreta, secreta, blood and its components, tissue and tissue fluid swabs, and body parts being transported for purposes such as research, diagnosis, investigational activities, disease treatment and prevention.

The specimen may need to be refrigerated or frozen before shipment. It will be your responsibility to keep a daily log of the refrigerator and/or freezer temperature.

Requirements regarding the shipping and handling of these substances were developed in coordination with experts from the World Health Organization (WHO) and other technical experts in the field of transport, packaging and health.

Patient specimens are classified as Category B Infectious Substances and are assigned the shipping name of Biological Substance, Category B and the UN (United Nations) number UN3373 (Category A being those infectious substances that are life-threatening). They are to be package according to Packing Instructions 650 (you will learn about this during the training).

Most research labs will send the necessary packing supplies and instructions to you at your site and it will be your responsibility to reorder these supplies as needed. Examine their packaging carefully to be sure it meets the requirements of IATA since it is ultimately your responsibility to package the specimens safely. And for that reason, anyone who is responsible for the shipment of patient specimens is required to be trained and certified as required by IATA.

Some labs will send you a gel "cold" pack that you refrigerate before shipping and then put in the box with the specimen. Some specimens require being packed with Dry Ice to maintain samples at low temperature during shipment.

The U.S. Department of Transportation (DOT) and the International Air Transport Association (IATA) regulate shipments of dry ice because it is a hazardous material. As a result, specific procedures must be followed when packaging and shipping materials refrigerated with dry ice and a record of training must be kept.

Dry ice is classified by DOT and IATA as a "miscellaneous" hazard, class 9. Dry ice is considered hazardous during transportation for three reasons:

- Explosion hazard: dry ice releases a large volume of carbon dioxide gas as it sublimates. If packaged in a container that does not allow for release of the gas, it may explode, causing personal injury or property damage.
- Suffocation hazard: a large volume of carbon dioxide gas emitted in a confined space may create an oxygen deficient atmosphere.
- Contact hazard: dry ice is a cryogenic material that causes severe frostbite upon contact with skin.

Packaging dry ice properly will minimize the risk to personnel transporting the material. The explosion hazard will be eliminated with a package designed to vent gaseous carbon dioxide. Suffocation and contact hazards will be greatly reduced by labeling the package correctly, so those who come in contact with it will be aware of the contents. The package requires a Dry Ice diamond label. Be sure the sponsor provides them for you.

Here are some suggestions on how to obtain Dry Ice:

- At the VA Medical Center, we call the Research Office and ask if there is any available (the labs on the 4th floor often stock it) and we can take from their supply
- The HIV/AIDS Research Dept. in the UHC, orders their dry ice weekly and as needed from Hav-a-Bar (at \$15/shipment) and stores in their research lab in a large cooler
- Cardiovascular Development--9 Webber Core picks up dry ice in the Send-out department at DMC University Laboratories, 3rd floor, University Health Center. However, this must be pre-arranged with Chip Brown, DMCUL dispatch supervisor, tel. 313-993-0974, to ensure that enough dry ice is available and that it is charged to the correct cost center

However a group may need to purchase their own dry ice and it may not be readily available in some departments. Some grocery stores provide dry ice but it can easily be purchased from a company called "Hav-A-Bar Inc." that will delivery directly to your office. Their phone number is 800-875-2227.

## **Unexpected Problem Reporting**