Research Compliance Professional's Handbook, Third Edition
15 Integrating Research Compliance into the Corporate Compliance Program

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Introduction

Defining a research compliance infrastructure and implementing standard operating procedures (SOPs) poses challenges for many institutions and hospitals. Fostering research compliance within the complexity of an Academic Medical Center (AMC), hospital or university system often ends up in silos of effort within the different facilities or institutions and can even result in conflicting SOPs between departments. Small hospital systems struggle with multiplex compliance issues so that research compliance is neither a priority nor an area of domain knowledge for most compliance officers.

Understanding risk assessments while maintaining training and education is often a challenge for the average research enterprise. This chapter will address the key areas of research risk including regulatory, financial and legal aspects of compliance. The discussion will include strategies and models to deal with policies and procedures and to "synchronize" the operations so that the reader is fully aware of the complex issues involving compliance and an informed participant in risk mitigation. Some institutions have a de-centralized process, while others have centralized systems. You will also find some semi-centralized procedures with a mix of resource support. Any way you set up to operationalize compliance, you must include policy, process, education and auditing. Some of the topics discussed may be covered in other chapters of the manual; however, this chapter will link interrelated principles with policy, procedures, and the operational relativity to highlight critical components of a research compliance strategy within a corporate compliance infrastructure.

Functional Areas of a Research Compliance Program

Human Subject Protection

As demonstrated by the evolution of laws and regulations, research and the quest for scientific discovery must never be more important than the safety and welfare of human subjects. Regulatory agencies have established and codified standards for the conduct of ethical research including specific instructions to committees charged with ensuring the rights of human subjects participating in research. We know these committees as Institutional or Independent Review Boards. The IRB reviews research protocols to assess the risks of the study to subjects and ensure those risks are not greater than the potential contribution to science, and to ensure subjects are adequately informed of those risks and have appropriate study information important to their decision to participate.

To accommodate growth and diversity in research—variations in study design (observational and cohort studies), social and behavioral research, analytics and biospecimens, electronic health and digital data records, mobile technology, etc. HHS published revisions to the Common Rule[2] on January 19, 2017. By an interim final rule published on January 22, 2018, the effective and general compliance dates were delayed for a 6-month period, until July 19, 2018.[3] On June 19, 2018, a final rule was published to delay the general compliance date

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until January 21, 2019.[4] The revised Common Rule, including technical amendments made by the January 22, 2018 interim final rule and the June 19, 2018 final rule, is referred to as the "2018 Requirements." FDA intends to undertake rule-making to harmonize FDA regulations 21 C.F.R. Part 50 (human subject protection) and 21 C.F.R. Part 56 (IRBs) with the 2018 Requirements. The FDA issued guidance to Sponsors, Investigators and IRBs in October 2018 to explain the impact of the revised Common Rule on FDA-regulated clinical investigations.

Institutional Review Boards (IRB)

An IRB is an administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activity. Although conceptually modeled for local IRB review, the regulations allow review of research by IRBs in locations other than where the research is performed. Whether the IRB of record is a function within or external to the organization, institutions conducting research involving human subjects must ensure the protection of those subjects, and in the case of FDA-regulated research, provide assurance of regulatory compliance to the sponsor. In addition, the institution must certify to the sponsor that each research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with the assurance given by the institution to the sponsor.

Research involving human subjects conducted or supported by federal departments or agencies should be reviewed by an IRB with a Federal Wide Assurance (FWA) on file with the Office for Human Research Protection (OHRP). FDA and HHS regulations define the scope of the IRB in terms of applicable types of studies—research involving FDA regulated products and research funded by PHS respectively. Yet, many research protocols reviewed by an IRB involve data collection from living individuals and are neither of these "types." Several reform proposals have recommended application of the Common Rule to apply to all research, yet there is controversy as to whether or not Congress should have the authority to regulate research that is not funded by the government and does not involve an FDA regulated product. Currently, many institutions (in their FWA) agree to protect the welfare of all human subjects involved in research, whether or not the research is regulated by FDA or federally funded (Titles 21, 42 and 45 may not be enforceable) and as such their policies require all human subjects research be reviewed by the IRB. In these and in most circumstances, the IRB has jurisdiction over all human subjects research —a scope broader than the regulations, and their authority to approve, require modifications in, or disapprove research is based on both law and institutional policy.

Currently, the NCI Central IRB offers a hybrid option for facilitated IRB review suggesting its use as key to reduce time, cost, redundancy, and variability, and to increase oversight and safety. The 2018 Requirements make federally funded research involving more than one institution reliant on a single IRB for that portion of the research conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research. Exceptions are 1) cooperative research for which more than a single IRB is required by law (such as tribal law), and 2) research deemed inappropriate for single IRB review. In addition, studies that involve multiple sites have new requirements with earlier compliance dates: For grant applications with due dates on or after January 25, 2018, and contract solicitations published on or after January 25, 2018, NIH expects that all sites participating in multi-site studies, which involve non-exempt human subjects research funded by the NIH, will use a single Institutional Review Board (sIRB) to conduct the ethical review required for the protection of human subjects. The NCI CIRB becomes the IRB of record and is responsible for initial and continuing reviews of studies including amendments, and group distributed documents such as safety reports (adverse events or AEs) and recruitment materials, while the local IRB retains oversight for consideration of local context, performance, and locally occurring AEs.[5] Examples of the active and effective exercise of this oversight would include:

- Establishment of appropriate institution policies and procedures to ensure research is conducted in

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accordance with all applicable laws, rules, and regulations

- Establishment of appropriate IRB(s) to approve and monitor all research involving human subjects
- Oversight of the IRB(s)' activities to ensure they are functioning as intended
- Ensure equitable and enforceable consequences for non-compliance with policies and procedures and IRB actions.

The activities of a local IRB should be considered a part of an active institutional compliance program where complying with federal regulations is of extreme importance. While an institution may have only one or multiple IRBs, each must satisfy certain requirements and implement common functions. The discussion of the IRB is divided into the following sections:

- IRB membership and responsibilities
- Types of reviews
- Human subject informed consent
- Adverse events and protocol deviations.

An IRB often acts as a privacy board for research-related requests to approve a waiver or an alteration of the Privacy Rule's Authorization requirements when protected health information is being used for research (HIPAA). The 2018 Requirements, in the definition of a human subject, include identifiable biospecimens. HHS is expected to provide guidance documents on identifiability, privacy and confidentiality, and broad consent.

IRB Membership and Responsibilities. Each IRB must have at least five (5) members with the appropriate diversity of backgrounds to ensure complete and adequate review of research activities normally conducted by the institution. This diversity includes experience, expertise, race, gender, and cultural backgrounds. In addition, members should possess the professional competence necessary to review specific research activities from the viewpoint of institutional commitments and regulations, applicable laws, and applicable standards of professional conduct and practice. For those institutions that conduct research using vulnerable categories of subjects, consideration should be given to including at least one member on the IRB who has experience with those subjects. Vulnerable categories of subjects include children, prisoners, pregnant women, and people with physical or mental disabilities.

In addition to these general requirements, there are a series of very specific requirements for IRB composition, including:

- The IRB membership cannot be all members of one profession
- Gender cannot be a factor in selecting members, which would indicate that an IRB with all male or all female members would probably be challenged
- At least one member must be active primarily in scientific areas
- At least one member must be active primarily in non-scientific areas
- At least one member must have no affiliation with the institution or be a part of the immediate family of someone affiliated with the institution
- A majority of the members must be present to take action on all matters except expedited reviews and at

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least one of the members present must have primary activities in a non-scientific area.

The IRB is responsible for following documented procedures for:

- Conducting initial and continuing reviews of research
- Reporting findings and actions to both the investigator and the institution
- Determining which projects need review more often than annually
- Determining if projects with no material changes require verification from sources other than the investigator since the previous IRB review
- Ensuring that proposed changes in a research activity are promptly submitted to the IRB and are approved by the IRB before such changes are made, except when such changes are for the immediate safety of the subjects
- Maintaining appropriate records of all activities
- Ensuring prompt reporting to institutional officials and/or sponsor:
    - Unanticipated problems involving risks to subjects
    - Serious or continuing non-compliance with requirements or determinations of the IRB
    - Suspension or termination of IRB approval by the institution.

There are several non-compliance risks associated with IRB membership and responsibilities; namely:

- Insufficient diversity of IRB membership for types of research
- Insufficient expertise or training of members
- Failure to have required members; *i.e.*, outsider, non-scientific, vulnerable subject expert
- Failure to disclose conflict of interest
- Insufficient resources to support IRB operations, mainly recordkeeping, space, and staff
- Failure to identify high-risk projects that need frequent oversight and review
- Unusual number of expedited reviews to avoid a quorum for reviewing proposals and changes
- Failure to follow documentation procedures
- Lack of documented procedures for research projects that do not involve human subjects
- Lack of documented procedures for the operation of the IRB
- Lack of documented procedures for research involving human subjects.

There are many mitigation strategies that can be applied to reduce the probability of non-compliance in the IRB operations. Among the most common and most effective are:

- Documented and current policies and procedures for the conduct of research involving humans

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- Documented and current policies and procedures for the composition and operation of the IRB(s)
- Appropriate training curriculum for IRB members and staff
- Appropriate training curriculum for investigators and their staff
- Web-based use of IRB agenda
- Oversight review by the research responsible party for the institution (such as, VP of Research) of IRB actions and operations including:
    - Meeting attendance
    - Qualifications of members
    - Quality of meeting minutes
    - Excessive or unwarranted use of expedited review
    - Quality and frequency of continuation reviews
    - Prompt reporting of adverse events and deviations from protocols
    - Completeness of documentation requirements.

Types of Reviews. A **full-board review** of a proposal for research involving human subjects is one that is conducted at a convened meeting of the IRB in which a majority of the IRB members are present, including at least one whose primary concerns are in nonscientific areas. In order for research to be approved in a full board review, it must receive the approval of a majority of those members present at the meeting. An **expedited review** of a proposal for research involving human subjects is one that is performed by only one member of the IRB, usually the chairperson or another member of the IRB designated by the chairperson. The single reviewer may exercise all of the authorities of the IRB except to disapprove the research. A research activity can only be disapproved in accordance with the full review process. To qualify for an expedited review, the research proposal must meet either of the following requirements:

> (1) Inclusion on the list of categories published in the Federal Register that may be reviewed through an expedited review procedure and (2) found by the reviewer(s) to involve no more than minimal risk (minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater... than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests); or minor changes in previously approved research during the period (of one year or less) for which approval was authorized.

The IRB that uses expedited reviews must establish a formal method for keeping all members advised of proposals which have been approved under the procedure.

The review criteria for both full reviews and expedited reviews are the same; namely,

- Risks to subjects are minimized
- Risks to subjects are reasonable in relation to anticipated benefits

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- Selection of subjects is equitable
- Informed consent is sought from all subjects
- Informed consent is documented
- When appropriate, provision is made to monitor data collected to ensure safety of subjects
- When appropriate, there are adequate provisions to protect privacy of subjects and to maintain confidentiality of data
- When vulnerable categories of subjects are involved, additional safeguards are included.

The 2018 Requirements establish new **exempt** categories of research based on level of risk so that IRBs can focus on higher risk reviews. Examples and criteria for an exempt determination include:

- educational testing, survey procedures where 1) identity of the subjects is not readily ascertained, 2) no identifying information will be recorded that can link subjects to the data, 3) disclosure of the data could not reasonably place the subjects at risk of civil or criminal liability or be damaging to the subjects' financial standing, employability, or reputation, and 4) an IRB makes the exempt determination
- benign behavioral interventions (brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing) if the subject prospectively agrees and at least one of the following criteria are met: 1) identity of the subjects is not readily ascertained, 2) no identifying information will be recorded that can link subjects to the data, 3) disclosure of the data could not reasonably place the subjects at risk of civil or criminal liability or be damaging to the subjects' financial standing, employability, or reputation, and 4) an IRB makes the exempt determination
- secondary research for which consent is not required if at least one of the following criteria are met: 1) identifiable private information or biospecimens are publicly available, 2) information including information about biospecimens is recorded in a way that identify is not readily ascertained or linked with identifiers, and the investigator will not re-identify or contact the subjects, 3) research use of information for health care operations covered by HIPAA, or 4) federal agency (identifiable private information) data collection for non-research that is maintained in systems of records in compliance with HIPAA
- storage or maintenance for secondary research for which broad consent (for future research) is required (storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use) if an IRB makes an exempt determination
- secondary research for which broad consent is required (identifiable biospecimens for secondary research) if the following criteria are met: 1) broad consent was obtained in accordance with regulatory requirements, 2) documentation of informed consent (or waiver of documentation) was obtained, and 3) an IRB determines the research is within the scope of the broad consent and makes an exempt determination and the investigator does not include returning individual research results to subjects as part of the study plan
- federal research and demonstration projects
- taste and food quality evaluation and consumer acceptance studies.

It is the responsibility of the IRB to ensure that there is appropriate documentation to make determinations on

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all of these criteria and that the documentation is maintained in accordance with the recordkeeping requirements. The primary recordkeeping requirements are:

1. Copies of all proposals reviewed including scientific evaluations, if any, approved sample consent documents, progress reports from the investigators, and reports of injuries to subjects
2. Minutes of IRB meetings in sufficient detail to show:
    a. AttendanceActions taken
    b. Vote on each action including number for, number against, and abstentions
    c. Basis for requiring changes in or disapproving a proposal
    d. Written summary of the discussion of controversial issues and their resolution
3. Copies of all correspondence between the IRB and the investigators.

A **continuation review** is the annual (or more frequent) follow-up for each approved research project. The IRB has authority to observe both the consent and research process and to determine that approved protocols are being followed. This continuation review may include correspondence with and reports from the investigators, use of IRB staff to verify protocol adherence, and/or use of third-party verification on the conduct of the research. The 2018 Requirements now permit an exception to the continuing review requirement if 1) the research is eligible for expedited review, or 2) the research has progressed to the point that it involves only data analysis of identifiable private information or identifiable biospecimens and/or follow up is limited to data collection from procedures that subjects would undergo as routine care. HHS is expected to provide additional guidance documents on continuing review. The IRB is required to maintain records of continuing review activities. Common non-compliance issues in the review process include:

- Incomplete protocols
- Incorrect determination of risk/benefit ratio
- Incomplete maintenance of research files:
    - Protocols
    - Documentation of expedited reviews
    - IRB meeting minutes
    - Documentation of continuation reviews
- Protocols and/or consent forms not followed in practice
- Misuse or over-use of expedited review
- Failure to perform continuation reviews within specified time period
- Failure to properly record minutes of the IRB meetings to allow determination of compliance with requirement.

Once again, there are a wide variety of mitigation strategies that will work to reduce non-compliance in this area. Those that are most common and usually have an impact upon multiple risks when applied include:

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- Provide multiple avenues for informing potential investigators of the requirements for proposal acceptance including:
    - Newsletters
    - Focus groups
    - Websites
    - Training sessions
- Provide checklists of required information for a proposal to be considered
- Provide detailed guidance for cost/benefit and risk/benefit determination including discussion on Medicare Advantage issues within clinical trials coverage
- Refuse to accept proposals for IRB action that are incomplete
- Perform oversight review of IRB activities (either by research management or internal audit) to ensure:
    - Proper use of expedited reviews
    - Proper documentation of waivers and alterations
    - Proper continuation reviews in accordance with initial approval time table
    - Adequacy of meeting minutes
    - Completeness of project files
    - Adequacy of resources to support the IRB operations.

Informed Consent

Informed consent is the foundation of all research involving human subjects. The 2018 Requirements emphasize the need to provide essential information a reasonable person would want to know before providing other supplemental information to the subject. As such, the informed consent form (ICF) format may change so that study details are organized in a way that highlights the critical information potential subjects will process in their voluntary decision to participate in the study. Additionally, within 60 days of a trial being closed to recruitment, Common Rule agencies will be required to post a final consent and contact information on a publicly available website. HHS is expected to provide guidance documents on the new consent requirement as well as the clinical trial consent form posting location. Requirements of informed consent will be covered under the following headings:

- General requirements
- Essential elements
- Additional elements
- Alterations and waivers
- Vulnerable categories of subjects

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- Documentation of informed consent.

The general requirements for legally effective informed consent establish the conditions which must be present for a subject to even be presented with the required consent forms and information sheets. If these conditions do not exist, there is no legally effective informed consent, even though the documents signed by the subject or the subject's representative may contain all the necessary information. As of the 2018 Requirements, broad consent for the storage, maintenance and secondary research use of identifiable private information or biospecimens is permitted as an alternative to the informed consent requirements. The essential elements of broad consent are noted parenthetically below.

The general requirements are:

1. The informed consent is obtained under circumstances that provide the subject or the subject's legal representative with sufficient opportunity to consider freely and without coercion or undue influence whether or not to participate in the research project.
2. The informed consent is in the language understandable by the subject or the subject's legal representative.
3. The informed consent does not include any language (written or oral) that waives or appears to waive the subject's legal rights.
4. The informed consent does not include any language (written or oral) that releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

For an informed consent to be considered legally effective, it must contain at least the following essential elements (unless applicable exceptions apply; see Alterations and Exemptions below). The essential elements are:

1. statement about the project that indicates:
    a. it is a research project
    b. an explanation of the purpose of the research
    c. expected duration of the subject's participation
    d. description of the procedures to be followed
    e. identification of any procedures that are experimental
2. description of any reasonably foreseeable risks or discomforts to the subject (required for Broad Consent)
3. description of any benefits to the subject or to others which may be reasonably expected (required for Broad Consent)
4. disclosure of appropriate alternative procedures or treatments, if any, that may be advantageous to the subject
5. statement describing the extent, if any, by which confidentiality of records identifying the subject will be maintained (required for Broad Consent)
6. for research that involves more than a minimal risk, an explanation as to:

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a. whether any compensation and any medical treatment are available if injury occurs

b. what those elements consist of

c. where further information may be obtained

7. explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject

8. statement that (required for Broad Consent):

    a. participation is voluntary

    b. refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled

    c. the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

9. (New 2018 Requirement) One of the following statements about any research involving identifiable data or specimens:

10. statement that identifiers may be removed from the identifiable private information or biospecimen and after such removal, the information or biospecimen can be used for future research or distributed to another investigator for future research, or

11. statement that the subject's information or biospecimen collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

12. statement that biospecimens, even if identifiers are removed may be used for commercial profit,

Additional elements that may be provided to each subject are:

1. A statement that the particular treatment or procedure may involve risks to the subject that are not currently foreseeable

2. Anticipated circumstances under which the subject's participation in the research may be terminated by the investigator without regard to the subject's consent

3. Any additional cost to the subject that may result from participating in the research

4. Procedures for the orderly voluntary termination of the subject from the research and any consequences to the subject because of that termination

5. A statement that any new findings developed during the research project that might relate to the subject's willingness to participate in the research will be provided to the subject

6. The approximate number of subjects in the research project

7. (New 2018 Requirement) A statement that biospecimens may be used for commercial profit and whether or not the subject will benefit from such profit (required for Broad Consent)

8. (New 2018 Requirement) A statement about whether or not research involving biospecimens, including individual research results, will be disclosed to subjects, and if so, under what conditions

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9. (New 2018 Requirement) A statement whether the research will (if known) or might include whole genome sequencing (*i.e.*, sequencing a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen) (required for Broad Consent).

Additional elements required for **Broad Consent** are:

1. Description of research using identifiable data or specimens including enough information to permit the type of research
2. Description of the identifiable data or specimen used for the research, whether or not it will be shared and the types of institutions or researchers that will use the identifiable data or specimens
3. The time periods that the identifiable data or specimens will be used for research and/or stored (could be indefinite)
4. A statement that the subject will not be informed of the details of the research (including purposes they may have consented to)
5. A statement regarding the disclosure of clinically relevant research results
6. An explanation of who to contact for questions regarding the use and storage of identifiable data and specimens.

Generally, the essential and additional elements that are to be transmitted to each subject will be documented in an information sheet which is included in the proposal package submitted to the IRB for approval. Once approved it is then the responsibility of the investigator to provide each subject with this sheet and obtain the signed consent form under the conditions specified in the general requirements.

Alterations and/or waivers to the requirement to obtain informed consent may be approved by the IRB when it finds and documents one of the following conditions:

- That the project is to be conducted by or is subject to the approval of state or local government officials and is designed to study, evaluate or examine the delivery, procedures, or benefits of a public benefit or service program and the research could not be carried out without the alterations or waiver; or
- that the project:
    - involves no more than minimal risk to the subjects, and
    - the waiver or alterations will not adversely affect the rights and welfare of the subjects, and
    - the research could not be practically carried out without the waiver or alterations, and
    - if the research involves identifiable data or specimens, the research could not be practically carried out without the use of such data or specimens in an identifiable format, and
    - when appropriate, subjects will be provided additional pertinent information after participation.

Furthermore, the secondary research use of identifiable private information or biospecimens would not require informed consent if at least one of the following criteria are met:

- the information or specimens are publicly available

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- information is recorded by the investigator in such a way that the identity of the human subjects cannot be readily ascertained directly or indirectly through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects
- the research only involves information collection and analysis involving the investigator's use of identifiable information for the purposes of treatment, payment and operations (as defined by HIPAA), or for public health activities and purposes
- research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch.

There are several vulnerable categories of human subjects that may be involved in research projects. Because of the unique nature of each category, there are specific elements that must be included in the informed consent procedure for the category. The following references will provide the details required for each category when needed:

- Title 46.200 Pregnant Women, Human Fetus, and Neonates Involved in Research
- Title 46.300 Biomedical and Behavioral Research Involving Prisoners as Subjects
- Title 46.400 Children Involved as Subjects in Research.

There are two forms of documentation of informed consent. One of the two is required unless the IRB waives the requirement for the investigator to obtain a signed consent form from some or all subjects.

They are:

- The long form written consent document that includes each of the essential and additional and vulnerable category of subject requirements appropriate to the research project. The investigator may read the material in the document to the subject or subject's representative, but must give the subject or subject's representative adequate opportunity to read it personally before it is signed; or
- The short form written consent document which states that the elements which would have been included in the long form above have been presented orally to the subject or the subject's representative. When the short form written consent document is used, the following requirements must be met:
    - A witness must be present for the oral presentation
    - The IRB must approve a written summary of what is to be orally presented to the subject or subject's representative
    - The subject or subject's representative will sign only the short form
    - The witness will sign both the short form and a copy of the summary
    - The person obtaining the consent will sign a copy of the summary
    - The subject or the subject's representative will be given a copy of the signed short form and the signed summary.

HHS and FDA regulations permit the flexibility of using electronic and paper informed consent methods independently or in combination throughout the course of the research study. The FDA and the Department of Health and Human Services' Office for Human Research Protections (OHRP) issued joint guidance on the use of

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electronic informed consent (eIC). The final guidance replaces a draft FDA-only question and answer guidance released in March 2015.

The IRB may waive the requirement to obtain a signed consent if it finds either of the following:

- That the research presents no more than a minimal risk of harm to subjects and involves no procedure for which written consent is normally required, or
- That the only record linking the subject with the research would be the consent form and the principal risk would be potential harm from breach of confidentiality, and the subject chooses not to be so linked to the research. In cases where the IRB waives the documentation of informed consent requirement, they may require the investigator to provide the subject with a written statement regarding the research.

Likewise, access to a study's data or biospecimens may be approved by an IRB without signed consent for the purposes of screening, recruiting or determining eligibility. The appropriate procedures for this consideration are:

- The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
- The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.
- Non-compliance common to the obtaining of informed consent forms includes:
- Lack of required elements
- Use of inappropriate language
- Inadequate protection of vulnerable populations
- Failure to submit research projects for IRB consideration for approval, waiver, or exemption
- Inadequate explanation of pertinent aspects of the research to subjects before obtaining consent
- Inadequate research subject confidentiality mechanisms
- Inadequate or incorrect translation into subject's native language.

Mitigation strategies addressing non-compliance in the obtaining and maintenance of informed consents include the use of:

- a consent form template for a normal project and for each vulnerable category of subject that is appropriate to the institution
- training modules (online, written, and face-to-face) for all aspects of the informed consent procedure
- review of each consent form in a proposal for research by an IRB member or IRB support staff
- auditing of research project files to ensure that informed consent forms have been completed where needed or that other required documentation is present.

Adverse Events and Protocol Deviations/Violations

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Adverse events and unanticipated problems must be reported to the IRB, institution officials and the sponsor, and in certain cases to other specified government oversight bodies. Unanticipated problems that are adverse events should be reported within a very short time period. Other unanticipated problems may be reported within a longer time period.

Depending on the level of detail in a research institution's Policies and Standard Operating Procedures, it may identify and define adverse events in sub-categories with more specific criteria. These have different reporting obligations depending on 21 C.F.R. Part 812 (devices) and 21 C.F.R. Part 312 (drugs) .

Adverse Event (AE): any untoward or unfavorable medical occurrence, although not necessarily unexpected, whether or not considered to be related to investigational product.

Serious Adverse Event or Serious Suspected Adverse Reaction (SAE): An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction (SAR): Any adverse event for which there is a reasonable possibility the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unanticipated Adverse Device Effect (UADE): any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol, instructions for use, or consent form, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Problem (UP): An adverse event that is unexpected (specificity and/or severity is not consistent with the protocol or the investigator brochure (IB), informed consent form (ICF), product labeling, package insert or any other protocol related documents; or is not an expected natural progression of any underlying disease or condition), and related or possibly related to participation in the research, and places subjects or others at a greater risk of harm than previously known or recognized; *e.g.*, results in death, is life-threatening, results in hospitalization or prolonged hospital stay, results in persistent disability/incapacity, results in congenital anomaly/birth defect, or may require medical or surgical intervention to prevent these outcomes.

Unexpected Adverse Event or Unexpected Suspected Adverse Reaction: any adverse drug/biologic experience for which the specificity or severity is not consistent with any of the following:

a. Investigator brochure

b. Protocol

c. Risk information in the consent form

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the

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investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents.

Protocol deviations will be defined by the institution with criteria to determine reporting obligations. A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB. Some institutions differentiate among minor protocol deviations, that can be "voluntarily" reported, and major protocol deviations, which must be reported:

Minor Protocol Deviation:

a. has no substantive effect on the risks to research subjects

b. has no substantive effect on the value of the data collected (*i.e.*, the deviation does not confound the scientific analysis of the results)

c. did not result from willful or knowing misconduct on the part of the Investigator(s)

d. did not result in or require any substantive action to be taken or result in any change to the subject's condition or status (*i.e.*, did not affect the subject's participation in any way, did not result in a change to the subject's emotional or clinical condition, did not cause an adverse experience or require a change to the clinical care of the subject, etc.)

Major Protocol Deviation:

a. resulted in or required a substantive action to be taken or resulted in a change to the subject's condition or status

b. caused harm or posed a significant risk of substantive harm to research subjects

c. damaged the scientific integrity of the data collected for the study

d. is evidence of willful or knowing misconduct on the part of the Investigator(s)

e. involves serious or continuing noncompliance with federal, state or local research regulations

f. repeated minor protocol deviations

g. failure to follow action ordered to correct minor protocol deviations

h. failure to follow action ordered in accordance with the emergency action section of this policy

Additional Guidance:

a. Minor protocol deviations should be reported to the IRB at the time of continuing review.

b. Major protocol deviations that affect subject safety, increases risk or results in a serious adverse event must be reported to the IRB within 24 hours of discovery of the deviation. All other major protocol deviations must be reported within 10 working days of discovery of the deviation.

c. Major protocol deviations and their administrative resolutions must also be tabulated and reported to the IRB at the time of continuing review.

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d. Investigators who also serve as the sponsor of an investigational drug, biologic or device study, must report adverse events to the appropriate federal agency within the time frame specified in the applicable regulations.

Research Project Personnel and Training

The following areas relate to the role of those staff members involved in the conduct of a research project (study). The structure of how staffing and training is established is extremely important to a solid compliance program.

Areas reviewed are:

- Principal Investigator Responsibilities
- Policies and Standard Operating Procedures (P&P)
- Research Integrity and Misconduct.

Principal Investigator Responsibilities

The principal investigator (PI) on a research study is the individual who is ultimately responsible and accountable for all aspects of the study, including scientific, financial, operational, and informational.

While not exhaustive, the following is a list of those responsibilities:

- The preparation of the proposal for the research study in conformance with the institution's Policies and Standard Operating Procedures for Research
- Obtaining written approval from the Institutional Review Board (IRB) for the conduct of the study before beginning research activities
- Obtaining Human Subject Protections and HIPAA Researcher Training (personally and for all appropriate study personnel) before performing any human subject research and maintaining certifications of that training in the study's regulatory files
- Obtaining all required informed consent forms and filing the signed forms in a secured area with limited and documented access during the term of the research and for a period of 6 years after the termination of the study
- The conduct and/or supervision of all study procedures and activities including scientific, financial, operational and informational
- Obtaining prior written approval of the IRB for any amendment or modification to the protocol or supporting materials, including (but not limited to) changes to:
    - inclusion/exclusion criteria
    - procedures
    - sub-investigators
    - sponsor funding agencies
    - informed consent documentation or procedures

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    - recruiting materials
    - patient education materials unless immediately required for the protection of study subjects
- Obtaining yearly updated, documented, signed, and dated conflict of interest statements on all human subject investigators involved in the study and maintaining them in the study files
- Promptly reporting (in accordance with the P&P) any serious adverse events, unanticipated problems, or significant new findings that arise throughout the course of the study
- Complying with all IRB requests to report on the status of the study including annual reviews
- Maintaining an active IRB approval through proper submission of request for annual continuation of the study
- Complying with all requirements of the sponsor (funding organization) of the study
- Maintaining accurate and complete regulatory records of all study activities
- Filing a final report to the IRB upon conclusion of the study.

Sponsor-Investigator Responsibilities

A sponsor-investigator is an individual who both initiates and conducts an investigation, and under whose immediate direction the test article is administered, dispensed, deployed or implanted. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor. Sponsor-investigators must develop the study plan (including the protocol, statistical analysis plan, risk analysis, description and labeling of test article(s), monitoring procedures, and consent materials with document version control. Sponsor-investigators define and standardize data elements, manage data collection (CRFs or electronic data collection, spreadsheets, etc.), keep an audit trail of data edits, and verify and protect data integrity according to the data management plan. The following is a list of responsibilities for an investigator-initiated study funded by the public health system (PHS), intended to support an FDA submission, or for scientific and scholarly contributions to generalizable knowledge:

- Conduct in accordance with all institutional policies, applicable laws and regulations for HSP, IRB review, and Financial Disclosure
- Comply with all terms, conditions, reporting, and financial management requirements of the funding award (PHS) (the PHS sponsor role may be limited to funding with specific conditions so that the investigator becomes responsible for HSP safety, and the proper conduct and monitoring of PHS funded research)
- Comply with all FDA IND, IDE requirements such that it may be necessary for the investigator to obtain an IND or IDE for the research
- Comply with all requirements applicable to both an investigator and a sponsor
- Include a DSMP (data safety monitoring plan) reviewed by the IRB and in compliance with the funding agency policies (PHS); or if the research involves treatment with unknown or significant risk, or a vulnerable population (FDA and scholarly activity)
- Report adverse events to the appropriate federal agency within the time frame specified in the applicable

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regulations.

Policies and Standard Operating Procedures

Policies and Standard Operating Procedures (P&P), while similar for all research institutions, will vary because of the culture and operating model of each organization. Consequently, in this section we will review the types of material that should be in the P&P for a research organization rather than the particular wording of the material. A generic P&P might include the following:

- Policy statement that indicates what is covered and who has authority over the process
- A set of Standard Operating Procedures to effectuate the policy statement
- Practice aids or guidelines for critical steps in a research study
- Forms and templates to aid the IRB and PIs in carrying out their responsibilities.

The policy statement should indicate that the IRB is the authoritative body for authorizing and overseeing research studies. In addition, it will usually specify:

- The exact authority or charter of the IRB, including whether or not it will act as the privacy board
- The proposals for research that are covered by this authority
- The criteria for acceptance of proposals as research studies
- The pre-conditions for performing research, such as training and certifications.

The Standard Operating Procedures table of contents should include at least the following categories:

- Review and approval of studies
    - Full review
    - Expedited review
    - Exempt
- Criteria for the acceptance of studies
    - Required documentation
- Training of research personnel
    - Initial
    - Refresher
- Ongoing monitoring and reporting
    - Changes
    - Adverse events
- Continuation reviews

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- Special situations
    - Sabbaticals and leaves of absence
    - Research at collaborating institutions
    - Research contracts and pricing
    - Research integrity and misconduct
    - Use and disclosure of PHI in research
    - Research conflict of interest
- Documentation and records retention
    - Informed consent forms
    - Scientific information
    - Financial information
    - Reports.

Practice aids or guidelines should be prepared for any activity that has special and unique requirements. This will enable consistency of treatment across many researchers and make review by the IRB and other oversight organizations easier. Usually these aids or guidelines fall into two categories: study procedures and study populations. A sample list of each follows:

- Study procedures
    - Surveys/questionnaires/interviews
    - Oral history activities
    - Private data, human specimens and cells
    - Data protection
    - Audio taping/videotaping
    - Research involving deception
    - Research that may affect privacy of healthcare information
    - Payments/costs involving subjects
- Study guidelines
    - Students as subjects
    - Students as investigators
    - Minors as subjects
    - Subjects with limited comprehension

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- Subjects with limited ability to read, hear, or see
- Non-English speaking subjects
- Other vulnerable subjects.

One of the most effective ways to ensure that all forms needed to approve and conduct research are properly constructed and contain the required information is to develop a set of standard forms and templates to be used by all PIs. This tactic reduces the time required of the IRB to review and approve both individual document content and the proposal to conduct research. For the PI, it provides a simple solution to what is required. A list of possible standard forms and templates follows:

- Application for Approval to Use Humans as Experimental Subjects (exempt)
- Application for Approval to Use Humans as Subjects (standard)
- Checklist for Standard Application Form
- Continuing Review Questionnaire
- Application for Changes to an Approved Protocol
- Consent to Participate in Biomedical Research
- Consent to Participate in Non-Biomedical Research
- Consent to Participate in Interview
- Assent to Participate in Research (for minors)
- Authorization for Release of Protected Health Information (PHI).

Examples of actual policies, procedures, guidelines and forms and templates may be found on the web page of most institutions conducting research.

Research Integrity and Misconduct

Research integrity includes both the avoidance of misconduct and the performance of the hallmarks of good scholarship, namely rigor, carefulness and accountability. Integrity in research is the responsibility of every faculty member, staff member and student involved in the research enterprise. It is supported and nurtured by a strong organizational ethical culture. Specific activities that foster intellectual honesty and integrity in research are:

- Open publication and discussion
- Institutional and departmental emphasis on quality of research
- Appropriate supervision at all levels of the research enterprise
- Maintenance of accurate and detailed research procedures and results
- Appropriate assignment of credit and responsibility for research and publications
- Clear and documented policies and procedures for the conduct of research, including pre-defined

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consequences for non-compliance

- Appropriate avenues for all stakeholders to report misconduct in research
- An established procedure to respond to allegations of misconduct.

It is clearly the responsibility of the institution conducting the research to ensure the presence of research integrity and to take appropriate action on all allegations of misconduct in research. As noted above, research integrity is much broader than the avoidance of misconduct. Consequently, an institution can have many policies that deal with integrity. These will be unique to each institution.

Misconduct generally means fabrication, falsification, plagiarism or other practices that seriously deviate from those that are commonly accepted within the scholarly and scientific community for proposing, conducting and reporting research. Misconduct does not include honest errors or differences of judgments or interpretations of data.

Sponsoring organizations would expect institutions performing research to bear primary responsibility for prevention and detection of research misconduct including the following:

- Developing and maintaining procedures to respond to allegations of research misconduct to include:
    - Appropriate separation of responsibilities for inquiry and investigation and for adjudication
    - Maintenance of objectivity
    - Due process
    - Whistleblower protection
    - Confidentiality
    - Timely resolution
- Initiating prompt inquiries into allegations of misconduct
- Conducting investigations, if warranted
- Taking action(s) necessary to ensure the integrity of research, to protect the rights and interests of research subjects and the public, to ensure the observance of legal and contractual requirements
- Providing appropriate safeguards of the subject of allegations and the informants.

In addition, sponsoring organizations would also expect prompt notification should the institution become aware during an inquiry or investigation that:

- Public health or safety was at risk
- The sponsor's resources, reputation or other interests needed protecting
- There is reasonable indication of possible violations of civil or criminal laws
- Research activities should be suspended
- External action may be necessary to protect the interests of a subject of the investigation or someone else

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potentially affected

- The scientific community or the public should be informed.

Research Finance

Billing

The Office of Inspector General (OIG) has exercised enforcement of research billing compliance, giving researchers a new incentive to look closely at cost calculations for clinical research, time and effort reporting for grants, budget negotiations and third-party billing practices. In addition, there is arguably some obligation to manage the business aspects of research activity to the extent that organizations establish financial reporting controls and maximize their potential investment return by making informed research enterprise decisions.

The Federal government holds a person or entity liable for knowingly submitting a false claim for payment or using a false record or statement to obtain payment or causing a third party to do the same, and can result in monetary penalties of $5,000–$11,000 (discretionarily adjustable) per false claim plus three times the damages sustained by the government.[6] In addition, a person or entity that knowingly and willfully makes or causes to be made a false statement or representation on any claim with the intent to fraudulently secure overpayment can be subject to 5 years imprisonment and/or a $25,000 fine.[7] Suspension and disqualification from participation in government-sponsored programs such as Medicare or Medicaid is also a possible adverse outcome.

The liability and risks associated with clinical trial billing were highlighted with the first false claims settlement related to billing for routine services provided during clinical trials announced in December of 2005. The one million dollar settlement acknowledged overbilling Medicare for services already paid by another entity and under billing Medicare for services assuming that there was an alternative primary payor. In addition, "the U.S. attorney also (said) that some or all of the physician and hospital inpatient and outpatient services charged to Medicare and Medicaid were not reimbursable because they were not considered routine care associated with clinical trials."[8] This case of false claims submissions is a key area of financial risk in clinical research and suggests that clinical trial sites should become increasingly more familiar with billing statutes, regulations and guidelines. (See also, Chapter 11 Clinical Research Billing Compliance.)

The Federal False Claims Act applies also to recipients of federal research grants who contractually agree to perform the stated project activities in exchange for a government commitment to pay for the expenses attested to in the grant application. "When (a government agency) awards a grant, the grantee institution has the responsibility to ensure that grant funds are expended only for allowable costs under the award as budgeted. When a grantee requests payment for costs not budgeted, even though incurred, it is submitting a false claim in violation of the False Claims Act."[9] (See also, Chapter 12, Grant Management.)

Private insurers may have policies and coverage criteria for clinical trial services that must also be adhered to. Obtaining payment from a commercial payor by means of false presentations is fraud and could also result in imprisonment and fines.[10] Medicare is, however, the largest single payor for medical services in the United States, and CMS (Centers for Medicare and Medicaid Services) provides the most detailed clinical trial billing guidance and enforces the most severe penalties for fraud and abuse. For these reasons, research billing determinations are often based on Medicare guidance:

Key areas of financial risk in clinical research include:

- **Overcharging.** Receiving payments from pharmaceutical/medical device sponsors that significantly exceed

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the costs of the research, especially for Phase 4 marketing studies, could be construed as a violation of the anti-kickback law.

- **Undercharging.** Conducting clinical studies without receiving adequate reimbursement for the costs of the study. This is primarily a financial (business) risk but may be a concern for not-for-profits if the under-recovery of costs could be viewed as a subsidization of a for-profit enterprise such as a pharmaceutical or medical device company.
- **Mischarging.** Billing patients or their insurance carriers for the costs of research, especially where those costs have already been covered by the sponsor of the study.[11]

Overcharging. The Office of Inspector General (OIG) has indicated in their guidance to pharmaceutical manufacturers that, "Payments for research services should be fair market value for legitimate, reasonable, and necessary services" and must support bona fide research activity.[12] Sites should scrutinize studies generated by sales departments for clinical or statistical merit to validate that payments are not associated with sham "research" designed to encourage product use. An analysis of study expenses should provide detailed support for study payments consistent with fair market value for the work performed. Excessive industry sponsor payments could be a compliance risk if there is a perception that an individual or entity is receiving remuneration in exchange for purchases or referral.[13] Thus, it is important to document legitimate reasons for accepting enrollment incentives, recruitment bonuses, finders' fees and excessive or disproportionate benchmark payments. Sponsor benefits such as meals, honoraria, conference travel or educational funding should also be considered with caution.

Flowing sponsor payments through to investigators must be in accordance with fair market value compensation for investigator services. Excessive investigator payments can otherwise be perceived as a kickback to induce physician referrals. In addition, sponsor payments should not be used to support subject deductibles or co-insurance to the extent that providing this form of remuneration to the subject could be perceived as an inducement for study participation.

Overcharging a federal agency can occur as a result of false certifications in grant applications, budgeting unallowable costs or submitting overstated time and effort reports and is a violation of the False Claims Act. Violating certain federal laws and regulations can result in civil monetary penalties, criminal fines and/or imprisonment, loss of licensure, special considerations in the form of integrity agreements and possibly exclusion from participation in federal programs including Medicare, Medicaid and federal granting opportunities.

Undercharging and Fiscal Accountability. Analyzing a research study for an accurate assessment of cost establishes an expense justification to support and develop a budget for a grant application as well as negotiate sponsor payment contracts. It is important to define and communicate business tolerance in reference to clinical trial funding and to establish consistent and accurate cost calculation and funding thresholds that force business decisions. While a project may be financially underfunded, studies that align with a specific mission or service line may have merit or value that compensates for the monetary shortfall. As a matter of compliance, undercharging for clinical services and labor required in conducting clinical research must be considered within the context of tax laws. Tax exempt organizations cannot take on clinical research activity at a financial loss resulting in a substantial private benefit to another individual or entity. Documenting a value statement supporting equal consideration or benefit comparable to the financial loss may be a strategy to avoid jeopardizing tax exempt status.

Institutions should develop pricing standards to support standardization in budget development as well as a

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minimum level of payment expectation. Budget negotiations with a sponsor are then based on verifiable and consistent costing principles with logic that provides added leverage to the funding requests. This type of process and strategy facilitates responsible and fiscally sound research decisions.

Mischarging. The overriding statute governing Medicare billing for patient care items and services performed in the context of clinical research is the Social Security Act. Title XVIII of this statute specifically states that such services must be "reasonable and medically necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."[14] A section of the act is specific to research, stating, "Notwithstanding any other provision of this title, **no payment may be made** under Part A (hospital and skilled nursing services) or part B (doctor's services and outpatient care) **for any expenses incurred for items and services**—in the case of research conducted pursuant to section 1142, **which is not reasonable and necessary** to carry out the purposes of that section...."[15] The Social Security Act requires that specific coverage decisions include input from the Agency for Healthcare Research and Quality (AHRQ) to recommend the standards and processes that would be most likely to ensure that the requirements of the Social Security Act would be met. Whether externally or internally generated, National Coverage Decisions, or NCDs help ensure that access to advances in health technologies that may result in improved healthcare are available to Medicare beneficiaries when those items and services are reasonable and necessary. NCDs may also be used to bar payment for specific items or services that are not reasonable and necessary as described in the Medicare Act. The NCD process facilitates the rapid and uniform diffusion of beneficial technologies, items, and services.

Billing Compliance. On June 7, 2000, the President of the United States issued an executive memorandum directing the Secretary of Health and Human Services to explicitly authorize [Medicare] payment for routine patient care costs... and costs due to medical complications associated with participation in clinical trials. The Health Care Financing Administration (now the Centers for Medicare & Medicaid Services, or CMS) responded to the executive order with the clinical trial policy NCD issued on September 19, 2000. The NCD for routine costs in clinical trials was implemented through the CMS NCD process and determined the circumstances under which certain items and services would be reasonable and necessary when provided to Medicare beneficiaries in clinical trials. The Clinical Trials Policy (CTP) NCD was reopened for revision July 10, 2006. On April 10th, 2007, CMS issued the first proposed decision memo outlining recommended policy revisions followed by an additional public comment period. In response to the voluminous feedback, CMS issued a second proposed reconsideration memo and issued a final decision memorandum on July 9, 2007 that preserved the status quo of the 2000 CTP with minimal changes. On October 17, 2007, CMS closed the reconsideration with a final decision memorandum that retained the July 9, 2007 policy.[16]

Category B Device Regulations. The Category B Investigational Device Regulations are part of the Federal Register and address the criteria and procedures for extending Medicare coverage to certain devices and related services. Title XVIII prohibits Medicare from providing coverage for the use of devices that are not "reasonable and necessary for the diagnosis and treatment of an injury or illness or to improve the functioning of a malformed body member."[17] Consequently, prior to the category B regulations, Medicare denied any and all reimbursement for experimental devices and associated costs due to the absence of medical necessity that cannot be established when the safety and effectiveness of a device are unknown. A device the Food and Drug Administration (FDA) categorized as investigational was presumed to be experimental, including devices being studied under investigational device exemptions (IDE). An IDE allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA. A medical device required FDA approval for marketing (post marketing approval, also PMA), the device's safety and effectiveness having been established, to qualify for payment consideration.

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There was increasing recognition that there are devices that are refinements of existing technologies or replications of existing technologies that could be viewed as "reasonable and medically necessary" if devices were categorized into those that are "experimental" and those that are "investigational." On November 1, 1995, Congress enacted legislation that now permits coverage of some investigational devices. The resulting interagency agreement established an FDA risk assessment that would assist CMS in determining Medicare coverage for devices. The FDA now places all approved IDEs into one of two categories. Category A devices are typically novel, innovative first-generation products determined to be experimental in addition to investigational, given that the FDA has insufficient evidence to determine whether these device types can be safe and effective. Category B devices are investigational but usually similar to another approved device type for which safety and efficacy has already been established. CMS acknowledges this FDA risk assessment and has indicated that category B devices may be eligible for coverage consideration. The final coverage decision is made by Medicare and their contractors, who must authorize billing for these devices (and related patient services) prior to any claims submissions. Medicare payment may also be made for patient care services related to the use of a Category B device as well as services required to treat complications related to the device.

While not explicitly stated in the category B regulations, the underlying principle and federal intent would indicate that investigational devices provided free of charge by the sponsor are not considered a billable item or service because the cost of the device has already been covered by the sponsor of the study. When the study sponsor intends to charge the investigator or facility for the device, the final decision to reimburse for an investigational device and related services is not based on the FDA category B status, but rather, on the Medicare contractor review of the claim. The category B regulations state, "Medicare coverage of a non-experimental/investigational (Category B) device will be subject to the same process and criteria used by Medicare contractors when making coverage decisions for legally marketed devices. Coverage of the device is dependent on it meeting all other Medicare coverage requirements contained in the statute, regulations, and instructions issued by HCFA."[18] In addition, the charge "should not exceed an amount necessary to recover the costs of manufacture, research, development, and handling of the investigational device."[19] CMS updated the IDE regulations so that effective January 1, 2015, coverage of devices and related clinical trial items and services are subject to centralized review. An approval of a Category A device study permits coverage for routine care, but the Category A device itself remains statutorily excluded from coverage. Study sponsors may request coverage by submitting a letter describing the scope of the IDE study and a dossier (FDA category A or B letter, NCT registration number, IDE protocol, etc.) to facilitate CMS review. Claims for IDE clinical trial services should not be submitted until the study is identified on the CMS website as approved.[20]

Medicare may cover those FDA-approved devices with modifications (developed after marketing approval) determined by an Institutional Review Board (IRB) to pose a "non-significant risk" (NSR) to patients. Effective January 1, 2015 (revision to the Medicare Benefit Policy Manual chapter 14) Medicare contractors are to "apply the same coverage criteria…to these devices as are applied to FDA-approved Category A and B IDE devices."[21] This revision to the Medicare Benefit Policy Manual chapter 14 also imposed IDE study criteria very much like the "qualifying trial" criteria cited in NCD 310.1 (clinical trials policy NCD). The purpose of the study must test for improved health or therapeutic outcomes, the study is to be scientifically rigorous (appropriate methodology and N value) and registered on clinicaltrials.gov; should not duplicate existing knowledge; and have a protocol description of the method and timing of release of results and how those results impact Medicare beneficiaries. Non-significant risk devices are billable only if they are "reasonable and medically necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."[22] More often, non-significant risk devices are typical diagnostic tools and would not meet these "treatment" criteria.

The current Medicare CTP established as an NCD in 2000 evolved out of an executive memo issued by former

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President Clinton directing Medicare to pay for "routine costs" in certain clinical trials. The CTP, as it applies to investigational drug studies, states that "routine costs" of "qualifying" clinical trials are billable so long as those costs are reasonable and medically necessary, they are generally available to Medicare beneficiaries, they are not statutorily excluded and there is no national noncoverage decision.

When a clinical trial meets the criteria of a "qualifying trial" as defined by the CTP, it means that routine care services delivered in the course of the study may be considered for Medicare coverage. The CTP states that the subject or purpose of the trial must be supported within a Medicare benefit category, the trial must have therapeutic intent, and trials of therapeutic interventions must involve diseased subject populations and trials of diagnostic interventions may include healthy subjects as a control group. In addition, the trial should test an intervention that potentially improves subjects' health outcomes, be well supported by medical information, should not duplicate existing studies, should have scientific merit and design, and should be sponsored by a credible organization with the capacity to execute the trial in compliance with federal human subject protection regulations. The CTP specifically identifies some trials as automatically "qualified." They include studies funded by specified federal granting agencies such as the NIH and any cooperative groups supported by such federal agencies, trials conducted under an IND application and drug studies determined to meet the criteria for IND exemption.

Pharmaceutical companies sponsoring investigational new drug (IND) studies typically provide the test article free of charge. Often times, the sponsor also provides payment for frequent subject visits that exceed what would be considered "reasonable and medically necessary" for the patient's condition. In these situations, only the services that are not already paid by the sponsor can be billed to Medicare or any other third-party payer. In addition, any item or service provided solely to collect data for the study is also not billable. A specific example mentioned in the CTP is that of serial CT scans required at scheduled intervals or more frequently than would usually be required for the stated condition. Items and services required to administer the test article, monitor for side effects of the test article or treat complications arising from participation in a clinical trial are billable services under the CTP.[23]

Effective July 9, 2007, CMS extended coverage under the current CTP for certain items and services "for which there is some evidence of significant medical benefit, but for which there is insufficient evidence to support a 'reasonable and necessary' determination." This coverage provision is in reference to the Coverage with Evidence Development (CED) standards within CMS's National Coverage Determination (NCD). The purpose of coverage with evidence development is to generate data on the utilization and impact of the item or service evaluated in the NCD, so that Medicare can:

a. document the appropriateness of use of that item or service in Medicare beneficiaries under current coverage

b. consider future changes in coverage for the item or service

c. generate clinical information that will improve the evidence base on which providers base their recommendations to Medicare beneficiaries regarding the item or service.

Adding coverage for items and services furnished to Medicare beneficiaries considered reasonable and medically necessary under CED allows Medicare coverage for services that would have otherwise been non-covered. For example, PET scanning is a billable and covered procedure for specified indications. CMS has determined that the evidence is sufficient to conclude that a PET scan for other cancer indications not previously specified is reasonable and necessary only when the provider is participating in, and patients are enrolled in, either an FDA approved IDE clinical trial or a PET clinical study that is designed to collect additional information at the time of

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the scan to assist in patient management. In the latter case, the CED affords coverage for a PET scan that would have otherwise been a non-covered service. NCDs that require CED are listed on the CMS website.[24]

Affordable Care Act 2014. Beginning January 2014, the Affordable Care Act (ACA), Public Health Service Act section 2709(a) established by the 10103(c) of the Reconciliation Act provides for coverage for Individuals Participating in Approved Clinical Trials. A qualified individual (eligible for the trial and referring clinician is a participating provider or the individual provides medical and scientific information supporting participation) has coverage consistent with the CTP for "routine costs," including all items and services consistent with the coverage provided in the plan that is typically covered if not enrolled in the trial.

Financial Tracking and Reporting

Study sites must have sound financial tracking and reporting mechanisms to validate fiscal stewardship. It is prudent business practice to track earned revenue and reconcile sponsor payments. In addition, the Code of Federal Regulations uniform administrative requirements for federal awards specifically cites minimum grant recipient standards for financial management systems. These include:

- The capacity to relate financial data to performance data
- Accurate, current and complete financial status reporting
- Records that identify the source and application of funds
- Evidence of accountability for all funds, property and assets
- Budgetary control
- Federal cash management procedures
- Written procedures for determining reasonableness, allocability and allowability of costs, and
- Cost accounting records supported by source documentation (*i.e.*, time and effort reports, purchase records.)[25]

An institution should consider the following policies and SOPs as critical to risk management for research finance and billing compliance:

- Research Pricing and Fair Market Value Considerations
    - Discount pricing for physicians
    - Service fees and reimbursement
- Research Budget Negotiation
    - Cost and coverage analysis – Drug studies
    - Cost and coverage analysis – Device studies
    - Device authorization requirements from the Medicare Administrative Contractor (MAC) or Fiscal Intermediary (FI)
- Research Financial Accounting and Reporting

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- Research Subject Registration and Billing
- Grant Processing Authorization
- Time and Effort Reporting.

Clinical Research Legal Considerations

(Note: This discussion is limited to clinical trial agreements with primarily industry sponsors. Refer to Chapter 12, Grants Management for specific legal commentary in reference to grants, cooperative agreements and government contracts.)

It is reckless to employ or contract with debarred individuals or companies. Suspension and debarment actions protect the government from doing business with individuals, companies or recipients who pose a business risk to the government. Before entering into a legal contract to conduct research, institutions should assure by a search that sponsors and key study personnel have not been debarred or excluded from participation in federal programs. Debarment or Exclusion lists are available at:

- **Disqualified/restricted/assurances lists for clinical investigators:**http://www.fda.gov/ICECI/EnforcementActions/ucm321308.htm
- **FDA Debarment List:**http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/
- **Excluded Parties Listing System:**https://www.sam.gov/portal/public/SAM/
- **Exclusions Database, Office of Inspector General–HHS:**http://exclusions.oig.hhs.gov/.

Federal regulations require research sponsors to establish written agreements that ensure that the research will be performed. Three basic questions need to be answered in order to establish the appropriate parties to the contract:

- Who is the sponsor as defined by the regulations and ICH Guidelines for Good Clinical Practices (GCP)?
- Who will own the data?
- Who is the funding source?

Clinical trial agreements are then drafted to define and direct the scope of work and length of term, protect the rights of the engaging parties, protect the confidentiality of proprietary science and subject information, establish payment amounts and schedule, and describe accountability and provisions for errors, research misconduct, and subject injury.

Clinical trial agreements typically include the following sections:

- Recital—identifies the parties to the agreement and assigns roles
- Scope of Work—describes what work will be done, by whom, and special rules and conditions
- Length of Term—effective dates, process for extending or early termination, special procedures for delays, force majeure (uncontrollable events preventing compliance, *i.e.*, war, flood, civil unrest, disputes)
- Payments (most often as an exhibit to the agreement)—per subject, benchmark or milestone amounts; schedule of payments; pass-through payments that require invoice; one-time, startup, administrative and

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IRB fees; contingent charges; close-out payments; refunds; and demographics for payment exchange

- Indemnification—identifies who the sponsor holds harmless (*i.e.*, academic institution, investigator, sub-investigator, and/or IRB); describes exceptions for protocol noncompliance or negligence; assigns scope of indemnification, who controls defense of lawsuits and pays legal fees, insurance requirements and survival of obligation to indemnify. (Research involving a Contract Research Organization or CRO drives the additional considerations to require both the sponsor and the CRO as parties to the agreement with signature lines or a letter of indemnification from or authorizing the CRO to bind the sponsor.)
- Federal exclusion validation
- Publication rights—description of institution/investigator rights to publish or present; access to multi-site data, rights to publish early for reasons of public health, safety, or public welfare; sponsor's right to review and edit within a stated time frame; authorship determinations for publications resulting from multi-site trials
- Confidentiality—identifies parties with access to data and binds them to state and federal privacy laws
- Intellectual Property—defines scope, disclosure, ownership and licensure of data, inventions, discoveries, patents and improvements
- Governing law and termination.

This is not an exhaustive list of legal terms to think about when negotiating clinical trial agreements with industry sponsors. Sites should consider the different types of research activities occurring at their institutions and develop template agreements consistent with their risk tolerance and inclusive of all minimally expected institutional liability protections. As study-specific agreements are negotiated, institutions should frequently assess which terms and conditions prolong negotiations. Understanding the institutional thresholds for legal terms that are ideal, desirable and "deal breakers" can help move discussions forward to an endpoint. Model clinical trial agreements and budget exhibits can be found on Model Agreements and Guidelines International's website.[26] This must be integrated well into a process for compliance, as having the contract process independent will cause problems in many areas for the research team.

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