INTEGRIS System Institution Review Board

Goals and Objectives for Identifying and Resolving Conflicts of Interest in Clinical Research Activities and Providing Appeals of IRB Decisions

System Goals

1. **Protect human subjects based upon respect, beneficence and justice**

   Objectives

   Recognition of conflict of interest disclosure and evaluation as primary method of providing protection

   Create incentives to prioritize human subject protection in clinical research throughout system

   Maintain and enhance integrity of institutional protections

   Foster transparency throughout process

2. **System Risk Management**

   Objectives

   Ensure compliance with state and federal laws and regulations and accreditation requirements

   Foster a culture of transparency within the community of clinical investigators, support staff and reviewers

3. **Establish expectation and practice of sufficient disclosure and evaluation of competing interests of reviewers and researchers**

   Objectives

   Avoid rote, superficial responses on forms

   Achieve common level of reviewer and researcher response

   Consider impact of sponsor payments on investigators

4. System revisions to facilitate and encourage full disclosure of actual, perceived and potential conflicts of interest by reviewers and researchers

Objectives

Education and sensitization of participants that financial rewards for researchers are not intrinsically inappropriate except for appearance of bias in face of significant financial holdings

System definition of "significant financial holdings" in context of clinical research

5. Establish organizational infrastructure for performance of conflict of interest analyses and reviews by identified persons

Objectives

Engage in analyses that focus on situation rather than character

Balance private interests with professional obligations

Establish group of trained analysts to engage in analyses (e.g., FMV analysis) and to select issues for consideration by select group in specific forum (e.g., Governance Committee)

6. Create rules for resolution of identified conflicts in specific forum

Objectives

Create process to facilitate resolution

Select standards to be applied

Create confidence in and acceptance of process through application of rules to facts

7. Create Appeal/Resolution Processes

Objectives

Provide Mechanism for Appeal from IRB Decisions on Expedited or Exempt Review

Provide Mechanism for Appeal from IRB Decisions on New Applications

Provide Mechanism for Resolution of Conflicts of Interest Issues Relating to IRB Members, Clinical Investigators and others involved in Research

INTRODUCTION

This plan represents an effort to bring the system IRB process in compliance with existing regulations and guidelines. It requires creating some new process and refining existing ones. Although the IRB review process has a solid foundation the conflict of interest resolution component requires not only establishing rules, but selecting the standards to be applied and identifying an entity capable of applying those rules and standards to the facts in cases of possible conflicts of interest. In all components of the INTEGRIS appeal and conflicts resolution system for clinical research reviewers and decision makers must avoid a didactic response that discourages research.

The components of the process are the INTEGRIS system Institutional Review Board ("IRB"), the Conflict of Interest Committee* ("COIC") and the Governance Committee of the INTEGRIS Health, Inc. Board. The COIC is made up of individuals not currently on the IRB who represent myriad necessary skill sets such as accounting, risk management, medicine, ethics and law. Its members are appointed by the Chief Executive Officer of the INTEGRIS system. The COIC is charged with providing a safe place for disclosing potential conflicts and the expertise to ask the right questions and gather the right information. The COIC will review the disclosures made by Clinical Investigators on initial applications and make requests through the Office of Research and Grants Administration ("ORGA") staff for additional information. It will consider conflicts that do not pose an actual threat to safety and integrity because the definition of "conflict of interest" includes the appearance of potential impropriety in any aspect of clinical research. In effect, the COIC acts in an expert, advisory capacity. This bifurcation of human subject protection review and conflict of clinical investigators' interests review is encouraged by both The Food and Drug administration and the Department of Health and Human Services. Because of the revitalization of the conflict review process, including communicating clearer expectations and offering a revised form, it is likely that a conflict will be identified at this early stage and referred to the Governance Committee for resolution. The COIC will also gather and provide information to the Governance Committee regarding other conflicts, make conclusions about potential conflicts, and make recommendations to the Governance Committee about responding to and resolving potential conflicts. Decisions concerning responses to conflicts of interest, such as modifications or management plans, are made by the Governance Committee.

The task of establishing guidelines for Governance Committee evaluation of financial and non-financial conflicts along the continuum of acceptable to unacceptable risk rests with a multi-disciplinary group as the COIC with extensive knowledge of the unique nature of the INTEGRIS system and support provided by HHS and FDA regulations, IRB/clinical research industry standards, Medicare Conditions of Participation, Joint Commission standards and the like. It is anticipated that the COIC will relieve the board and ORGA staff of pressure while providing a safe venue for disclosure by researchers and ultimately both support the growth of research activities throughout the INTEGRIS system and minimize risks for the system.

*Term derived from federal regulations

INTEGRIS Health, Inc. Institutional Review Board

Review, Appeal and Resolution Processes

I. Process for Appeal of IRB Decisions that Do Not Present Conflict of Interest Issues

A. Appeal to Governance Committee of IRB Decision on Initial Application That Received Full Review

1. Bases for Appeal

a. IRB approvals, disapprovals and recommendations are subject to review within the institution and its decisions give rise to the right to appeal

b. ORGA to establish guidelines for submission of appeals including bases for appeal and review standards

c. ORGA determines completeness of appeal

2. Appeal Process

a. Appeal by Clinical Investigator ("CI") for denial of initial application by IRB

b. Appeal by IRB Member concerning approval or denial of an application for failure to comply with regulatory requirements or for substantive reasons provided in guidelines established by ORGA

c. ORGA to create appeal form and guidelines for mandatory and permissive submission of materials

d. Materials may include complete application, IRB Minutes (including vote) and summary of discussion

3. Substantive Standard for Review of IRB Decision

a. Failure to follow IRB procedures

b. Failure by reviewer or other IRB member to disclose conflict of interest

c. Significant Financial Interest ("SFI") as conflict of interest

(I.) SFI reasonably appears to be affected by research at issue

(II.) SFI is in an entity that reasonably appears to be impacted by the research

(III.) Disclosure required

d. Failure by reviewer or other IRB member to recuse himself or herself (See II.C. below.)

4. The matter proceeds to Governance Committee because full IRB has previously considered and voted upon the matter.

B. Appeal Process for Exempt and Expedited Reviews

1. Reviewer

In the case of an exempt or expedited review, staff or IRB may require certain changes to secure approval. In an appeal process for exempt and expedited reviews the Reviewer first works with the CI to resolve the identified issues (e.g. reason for denial, required revisions, etc.) "Reviewer" refers to the IRB Member assigned to review the application for the clinical study.

2. IRB

If the attempts at resolution are unsuccessful, the issue is referred to the full IRB for formal discussion and deliberation. Note that, although the IRB Member/Reviewer has been working on this limited application, the IRB as a whole is now seeing it for the first time. The CI may attend the IRB meeting to respond to questions from IRB Members. S/he shall step out for the vote and all discussion that does not require his or her responses but shall return for verbal notice of the vote and an explanation of the board's decision.

3. Governance Committee

If the CI continues to be dissatisfied with the outcome, s/he can appeal to the Governance Committee within a period of time and in a format specified in guidelines established by ORGA.

4. Conflict of Interest Committee

If such an appeal includes a conflict of interest issue, the process involves the COIC as is described above.

C. Appeal Process for Full Board Reviews (for matters which have received expedited or full review)

1. IRB

In the case of a full IRB review and resulting decision deemed unsatisfactory by the CI: Where a protocol is tabled or disapproved by the IRB, the CI works with reviewer(s) or staff to resolve the identified issues. Although this has rarely occurred in INTEGRIS facilities, federal regulations do require a written notice of the reasons for the decisions along with the opportunity to respond in person or in writing. Note that this appeal can also be initiated by an IRB member dissatisfied with the IRB decision on an application. The IRB Member's right of appeal is limited to failure to follow IRB procedure or for substantive reasons, such as failure to properly evaluate risks to the subject population. Once s/he appeals, the CI may attend the appropriate subsequent IRB meeting to answer questions and provision clarification regarding the revised and resubmitted protocol. The CI steps out for the vote but returns for verbal notice of the vote and an explanation of the IRB decision; a written notice will follow.

2. Governance Committee

Where the CI and IRB cannot reach an agreement the CI can request an appeal to the Governance Committee as described below. The Governance Committee is experienced in considering and deciding upon such matters within INTEGRIS.

II. Process for Review of Conflicts of Interest of IRB Members and Researchers

A. Characterize Conflicts of Interest

1. Financial. This descriptor relates to research and products associated with research, financial interests of IRB Members, consultants and immediate family, and payments to CIs and Subjects.

2. Non-Financial. This descriptor relates to involvement in design and conduct of research, similar involvement of immediate family, and professional and organizational goals and pressure.

3. Payments or interests generally with low potential for significant financial conflict of interest rarely require conflict resolution or management but are proper for review.

B. Disclosure Requirement

1. Process

The process ideally begins with disclosure by the CI of a CFI or other conflict followed by review by the COIC. If satisfied, the COIC so indicates to ORGA staff member who is processing the application so that it may move forward. If not, the matter goes to the Governance Committee for Resolution. The application for approval of a protocol requires that the CI indicate if there is a conflict of interest, if it has been properly disclosed, and if there is a management plan in place regarding the conflict. Education and clear expectations adequately communicated to CIs are necessary to standardize the disclosure which currently varies significantly in terms of fully identifying entities with which the CI is involved and divulging the financial significance of that involvement.

2. Threshold for Disclosure

HHS guidelines recommend that, where appropriate, the CI consider including in the informed consent document disclosure of the source of funding, funding arrangements, and the manner in which a relevant financial arrangement is being managed. The CI may identify the appearance of a conflict and choose at the outset to modify the informed consent process to ameliorate at the onset the impact of the conflict. Examples include independent monitoring of the research and having another individual who does not have the potential or actual conflict involved in the consent process. The COI process will, in most circumstances, have been resolved when the application reaches the IRB.

C. Guidelines for Review and Resolution

1. Disclosure

The IRB and the ORGA will assist the COIC in establishing guidelines as to the detailed nature of information required of its Members and CIs and that must be provided to research Subjects regarding the funding arrangements, source of funding and financial interest of those involved in the research.

2. Identify Conflict

It will also provide guidelines (ranges of acceptable involvement) that the CIs and the COIC will follow in identifying potential conflicts, so educating the appropriate persons, and selecting remediation alternatives.

3. Standards

a. The IRB can require that appropriate financial interest management techniques be applied in the interest of protecting human subjects and avoiding the fact or appearance of impropriety. This material will also be provided to the Governance Committee for the matters to be resolved at that level. The COIC, using the guidelines established by the IRB, will develop standards by which to evaluate and resolve conflicts of interest.

b. Suggested guideline private or personal interest, conflict of private interest

c. "Significant Financial Interests" Standards

i. Belmont Report guidelines of "respect for persons, beneficence and justice" should not be compromised by financial relationships

ii. The 2010 Public Health Service proposed regulations expand the scope of and narrow the exclusions from "significant financial interests" and also expand institutional responsibilities to detect, report, ensure disclosure and manage conflicts. Note that these will apply only to PHS-funded entities but do not provide insight into future health policies and regulations. For example, the U.S. Public Health Service defines "significant" as $10,000 or 5% ownership in sponsor's enterprise

iii. Do any reported financial interests reasonably appear to be directly and significantly affected by project? "Direct" impact occurs when the project results would be directly relevant to the technology or product in which the CI (or other involved in the design, conduct or reporting of the research or project) has a financial interest. "Significant" impact materially affects the value of technology or of the entity (sales, earnings or market position). Review is of a "reasonable basis" for drawing such conclusions.

d. Fair Market Value Analysis

i. This includes payments to CIs (sign-up fees, payments per Subject, etc.)

ii. The analysis must also consider payments to Subjects with the perspective of avoiding coercion or the appearance of coercion.

iii. The analysis will include an outside assessment of fair market value in the context of research or other market data where considered necessary to ensure compliance, protection of human subjects and avoiding the appearance of impropriety.

iv. Other ties to Sponsor are considered—board or other advisory position, paid lecturer/educator, royalties, licenses, investments, etc. as discussed below.

D. Options for Managing COI

1. Public Disclosure

2. Modification

3. Disqualification of individuals

4. Monitoring

5. Divestiture

6. Severance of relationships

7. Rebuttable Presumption establishing compelling reason to continue with project or relationship in face of conflict

8. Reports to regulatory bodies

E. Recusal of IRB Board Member

1. Common Rule. In the Common Rule the only circumstance specifically addressing recusal is conflict of interest. Conflicted members are excluded from voting, must leave the room for discussion and voting and are not counted toward a quorum. Further, consultants who are conflicted must disclose the conflict and cannot provide information to the IRB.

2. Recusal Implied. Although not defined in the regulations, recusal is implied in 45 CFR 46.107 stating that a member cannot participate in initial or continuing review where conflict exists.

3. OHRP focuses entirely on financial conflicts.

4. Recusal required for the following IRB members:

a. Members who are CIs for project under review or whose spouse or child is an investigator

b. Members who have any financial interests

(I.) That would reasonably appear to be affected by the research; or

(II.) In entities whose financial interests would reasonably appear to be affected by the research

c. Members who believe existing circumstances may directly affected their objectivity

d. Certain ownership interest, stock, stock options, or other financial interest related to research

e. Certain compensation related to the research including salary, consultant payments, honoraria, royalty payments, dividends, loans, other payments/considerations of value

f. Members involved in a potential competing research program or activity

g. Members with access to funding or intellectual information that may create an unfair competitive advantage

h. Members with personal biases that may interfere with his or her impartial judgment

5. A Board member's failure to recuse himself or herself can be appealed to the COIC by another board member or CI.

III. Conflict of Interest Committee

A. Make up of Committee

1. This COIC will be comprised of a minimum of three (3) members appointed by the CEO who will represent at the minimum medicine and ethics.

2. There shall always be an odd number of members of the COIC.

3. Every effort shall be made to identify and select members who are knowledgeable of various aspects of research but not involved in current practice or research in such a way as to bring bias into the review process.

B. Role of Committee

The COIC brings together expertise for evaluating potential and actual conflicts of interest concerning IRB members, CIs and sponsors. It provides for safe and confidential disclosure thereby encouraging disclosure. The COIC, following its reviews, makes recommendations for resolution of management of actual or potential conflicts to the Governance Committee.

C. COIC Review of All Initial Applications

1. The COIC will standardize disclosure by all CIs listed on the Protocol of potential conflicts of interest beginning with recommendations of revisions to the COI form included in the application for IRB approval

2. Includes consideration of the following: CIs plans to manage, reduce, eliminate conflicts, appearance of impropriety, potential coercion affecting Subject consent, design of study, and integrity of data

3. Information collected on financial relationships Sponsor to CI will be available for COIC review

4. Information collected of financial relationships Sponsor to Subject will be available for COIC review

5. Information collected on financial relationships CI to Subject will be available for COIC review.

6. COIC may determine to create an exception to the full disclosure requirement for preclinical research based upon the concept that research studies do not involve patients or patient materials (medical records or biospecimens) represent lesser potential for conflict.

D. Review competing holdings and interests

1. Identify "significant financial holdings" and ascertain which financial interests reasonably appear to be directly or significantly affected by the activities and outcome of the clinical trial.

2. Analyze reasonableness or fair market value of payments including those made to CIs, institutions and Subjects

3. Analyze significant financial holdings of Clinical Investigators that pose risks for creation of conflicts according to conflict of interest disclosure guidelines established by ORGA

   a. significant effect on design of study

   b. significant effect on conduct of study

   c. significant effect on results of study

   d. significant effect on recruitment of patients in study

E. Approve Conflict of Interest Disclosure Guidelines Submitted by ORGA

1. Disclosure to appropriate state and federal officials, research Sponsors and other funding entities, publication editors, personnel listed as key personnel (researchers, students, trainees), human subjects participating in research

2. Situations exist that suggest impropriety such as where CI earns annual consulting fees from a commercial entity for personal gain or who has a contractual relationship whereby such fees are received. Policies are required to guide the committee in analyzing the facts for the preceding twelve months. A percentage of annual salary may be applied as a benchmark.

3. The same type of substantive rules will apply to licensing fees and royalties. A percentage of annual salary is frequently applied as a benchmark.

4. Suggest disclosure policies to Governance Committee and ORGA

F. Establish guidelines and standards regarding types of financial relationship that may exist between parties involved in research studies and circumstances under which those financial relationships and interests may or may not be properly held.

G. Consult with CI to develop management strategies to define special conditions or restrictions to manage, reduce, eliminate conflicts of interest, such as the following:

1. Modification research or project plan

2. Monitor by independent reviewers or oversight committee

3. Disqualification from participation in all/part of project

4. Divestiture of significant financial interest by CI where no other alternative appears to exist

5. Rebuttable presumption analysis

   a. A project deemed to meet rebuttable presumption due to compelling reasons, despite individual and institutional conflict of interest will be approved to proceed with appropriate management strategies for period of one year.

   b. Certain developments trigger additional review, i.e., technology patented or licensed in the interim subject to certain payments based on research and/or royalties in excess of $10,000 for the individual and institution annually.

6. Remedial disclosure policies

a. Verbal disclosure to patient with documentation (Some IRBs require maintenance of documentation in the Subject's medical record.)

b. Collegial collaboration when ordering medication involving conflict or even transfer patient to another practitioner

c. Collegial corroboration of patients recruited for studies

d. Some policies are expansive and include all forms of public communication including press releases, posters, web posting, communications to shareholders

e. Disclosure in patient information materials acknowledging relationship between, e.g., Clinical Investigator and commercial entity (sponsor or other) includes language that patient may ask physician or other care given or contact IRB for information regarding the relationship.

f. Appointment separate oversight committee

g. COIC will provide information/materials to Governance Committee

IV. Governance Committee

A. Acts on COIC Recommendations

B. Substance

1. Responsibilities and experience provide foundation

2. Review COIC recommendations

3. Review of Rebuttable Presumption Analysis to be prepared by Legal Services as requested by COIC

4. Standards as established by COIC

C. Process

1. Meetings Regular Quarterly or Special

2. GC to specify materials and format to be provided with COIC recommendation

D. Evaluative Guidelines to be selected

1. COIC standards

2. Foundation of GC Rebuttable Presumption experience in INTEGRIS system

3. Options discussed below in Sections E. and F.

E. Guidelines options address following situations:

1. Research Decisions

a. Holders of equity in a company sponsoring research excluding investments in mutual funds

b. Recipients within the preceding 12 months of license fees, royalties or contractual rights to receive future royalties per year where the research is directly related to the licensed technology interest to the individual

c. Recipients of fees for consulting, honoraria, salary, gifts or other emoluments or remuneration or other in-kind compensation in the preceding12 months (can be evaluated as % of salary)

d. Recipients of unrestricted research or education grants within preceding 12 months

e. Recipients of research or education grants within the preceding 12 months that provide funds in excess of those required for reasonable expenses incurred in the performance of the research or educational activity

2. Individual Clinical Practice/Research

a. Fees, stipends, bonuses paid to or offered to Clinical Investigators above fair market value and/or that encourage recruitment of Subjects or provisions of services above that normally expected within the confines of the Clinical Investigator's practice or the clinical study milieu.

b. Fees paid to Subjects that by virtue of their amount or other attribute coerce or exert undue influence on Subjects

c. Pressure exerted by superiors or supervisors related to job security, promotions and other personal goals of Clinical Investigator

d. Existence of licensing agreements, know-how agreements, consult agreements or board membership involving the Clinical Investigator, INTEGRIS, and the Sponsor or other commercial entity.

e. Other payments including royalties, annual consulting fees for personal gain exceeding specified percentage of annual salary from relationship with commercial entity.

3. Leadership

a. Recipients of Board of Directors' or Trustees' fees annually

b. Recipients with preceding 12 months of license fees, royalties or contractual rights to receive future royalties or contractual rights to receive future royalties annually where the leadership decision is directly related to the licensed technology of interest to the individual

c. Holders of equity in a for-profit company for which Clinical Investigator serves as Director or Trustee in a company excluding investments in mutual funds

d. Recipients within 12 preceding months of consulting fees, honoraria, salary, gifts, or other emolument or other in-kind compensation where the leadership decision is directly related to the licensed technology of interest to the individual

e. Recipients of consulting fees, honoraria, salary, gifts, or other emoluments or other kin-kind compensation per year within preceding 12 months

f. Recipients of unrestricted research or education grants within preceding 12 months

F. Guidelines include recognized exclusions from "significant financial interests"

1. An equity interest that when aggregated for the Clinical Investigator and immediate family meets the following test: Does not exceed $10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a 5% ownership interest in any single entity

2. Salaries, royalties or other payments that when aggregated for the Clinical Investigator and immediate family over the next 12 months are not expected to exceed $10,000 and disclosure from first dollar can be required

3. Including/excluding payments associated with the clinical trial/sponsor at issue; these often exceed $10,000 annually)

4. Income from seminars, lectures or teaching engagements sponsored by public or non-profit entities

5. Income from service on advisory committees or review panels for public or non-profit entities

G. Options for managing, reducing or eliminating conflicts

1. Public disclosure "significant financial interests"

2. Independent reviewers to monitor research

3. Modify research plan

4. Disqualify Clinical Investigator from participation in study/portion of study affected b y the "significant financial interests"

5. Divestiture by Clinical Investigator of "significant financial interests"

6. Discontinuance by Clinical Investigator of relationship that creates conflict

7. Determination that conditions or restrictions will be ineffective or inequitable and that scientific or community health/welfare value of research outweighs concerns regarding conflict

8. Requirement of appropriate monitoring, reporting and enforcement

Attachment A

HHS provided guidelines in 2004 for addressing financial interest issues. The agency suggests asking questions such as the following, among others to identify and manage those concerns:

- **Does research involve financial relationships that could create potential or actual conflicts?**
- Who designed the study?
- How is it financed?
- What interest s do those financial relationships create?
- Is any compensation tied to or affected by study outcome?
- Does institution and/or clinical investigator have proprietary interest in any component of the study—patents, trademarks, copyrights—or have an equity interest in the sponsor?
- Is sponsor a publicly or non-publicly held company?
- Does sponsor also provide significant payments such as honoraria, consultation retainers, equipment?
- Are there per participant incentive payments and, if so, are they reasonable?
- On balance and given the financial relationships involved
- How is it feasible to manage the conflict—disclosure, reduction, separation of responsibilities, elimination of interest, modification of researcher's role, additional oversight or monitoring?

HHS encourages "[e]stablishing the independence of institutional responsibility for research activities from the management of the institution's financial interests" including creation of a COIC to establish the procedural and substantive course for dealing with conflicts of interest and ensuring the protection of human subjects.

69 Fed.Reg. No. 92 Pages 26393-26397 (May 12, 2004) Department of Health and Human Services: "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection."

Attachment B

EXCLUSIONS FROM "SIGNIFICANT FINANCIAL INTERESTS"

Not included in SFI for Public Health Service-funded research:

1. A salary, royalty or other payment of any amount from the institution applying for the PHS grant to the investigator;

2. Any ownership interest in the institution, if the institution is an applicant under the Small Business Innovation Research Program (SBIRP);

3. Income from seminars, lectures, or advisory committees for public or nonprofit entities;

4. Income from services on advisory committees or review panels for public or nonprofit entities;

5. Equity interests of less than $10,000.00 that do not constitute greater than five per cent ownership interest in any single for profit entity; or

6. Salaries, royalties, or other payments that when aggregated for the investigator are not expected to exceed $10,000.00 over the next twelve months.

Source: 42 C.F.R. §50.603

Attachment C

Sources

21CFR 50.20 IRB is responsible for, among other things, determining that the possibility of coercion and undue influence is minimized.

21 CFR Part 54. FDA disclosure regulations

21 CFR 54.2(b) definition significant equity interest, significant payments and proprietary interest

21 CFR 56.107(e) This FDA regulation prohibits IRB member from participating in the Initial or Continuing Review of an application with which s/he has a conflict except to provide information and answer questions.

42 CFR 56.109(b): Currently there is no FDA requirement to disclose financial relationships in informed consent forms but the FDA acknowledges that IRBs may so require. There is increased emphasis on the clinical site assuring prompt and accurate disclosure and updates of financial interests to sponsors. Future may include language regarding the financial relationship on the consent form, and in this case the language will need to be meaningful to subject and stated objectively.

45 CFR 46.107(e) also prohibits IRB member from participating in the Initial or Continuing Review of an application with which s/he has a conflict except to provide information and answer questions.

45 CFR 46.108 concerns IRB function and operations.

45 CFR 46.124 HHS, as funding agency, may impose additional conditions as necessary for protection of human subjects.

45 CFR 46.109(d) Regulations effecting HHS policies regarding IRB review of research

45 CFR 46.116 Elements of Informed Consent require that the clinical investigator minimize coercion and undue influence.

69 Fed.Reg. No. 92 Pages 26393-26397 (May 12, 2004) Department of Health and Human Services: "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection." HHS has issued this guidance document raising points to consider in determining if specific financial interests could affect the rights and welfare of human subjects and, if so, the actions that could be taken to protect affected subjects. As a guidance document it is not binding and alternative approaches may be used by IRBs.

60 Fed.Reg. No. 132 Pages 35820-35823 (July 11, 1995) National Science Foundation: "Notice of technical changes to investigator financial disclosure policy." NSF requires designation of a person to ask questions regarding the nature, value and impact of the relationship upon the clinical investigator in the study at issue.

FDA Forms 3454 "Certification: Financial Interests and Arrangehments of Clinical Investigators" and 3455 "Disclosure: Financial Interests and Arrangements of Clinical Investigators"

Mayo Clinic IRB Handbook "Managing Conflict of Interest" and "Individual or Institutional Recruitment Incentives"

McDonald, Michael, Ethics and Conflict of Interest, W. Maurice Young Centre for Applied Ethics, University of British Columbia, quoted in Yale Interdisciplinary center for Bioethics, Re: IRB Members and Personal Conflicts of Interest. http://www.yale.edu/bioethics/irbcse2.htm.

FDA "Establishment Inspection Report" INTEGRIS Southwest Medical Center IRB 2009 "Summary of Findings"

Notes changes presented by PPACA and coverage for patients in clinical trials by TPPs.

Attachment D

Disclosure by Sponsor of Research

FDA Form 3454

By completing this form the sponsor attests to the FDA its lack of certain financial interests and arrangements. The sponsor may append a list of researchers without such financial arrangements.

FDA Form 3455

By completing this form the researcher describes his or her financial interest and explains the steps taken to mitigate potential bias.