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SOP 21 – CONFLICT OF INTEREST REQUIREMENTS FOR RESEARCHERS AND RESEARCH STAFF

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SOP 21 CONFLICT OF INTEREST (COI) REQUIREMENTS FOR RESEARCHERS AND RESEARCH STAFF

21.1 PURPOSE

This SOP and the attached "Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH," (referred to hereinafter as "the Guide) (**Appendix A**) describe how financial and non-financial conflicts of interest in the conduct of clinical research, involving NIH researchers, will be disclosed, resolved or effectively managed.

This SOP specifically addresses four common COI situations, involving NIH employees and collaborators, as also summarized in **Appendix B** to this SOP. The four situations are:

1. Management of COI when an NIH employee is the PI of an NIH intramural protocol and an NIH IRB reviews and has oversight of a protocol within the NIH Intramural Program. The applicable COI policies are found in Part I, **section 21.4**., of this SOP.

2. Management of COI when a non-NIH IRB reviews and has oversight of a single site protocol. In this situation, there is usually a PI at a non-NIH institution and an NIH AI is engaged in human subjects research for that protocol, either at the non-NIH institution or analyzing identifiable data/specimens at the NIH. The subjects are usually at the non-NIH institution. The applicable COI policies are found in Part II, **section 21.5** of this SOP.

3. Management of COI when an NIH intramural IRB is the central IRB for a multi-site protocol. In this situation, there is an NIH PI for the NIH intramural site, however other PIs lead the same protocol at other institutions. Subjects are enrolled both at the NIH Intramural Program and other institutions. The applicable policies are found in Part III, **section 21.6** of this SOP.

4. Management of COI when a non-NIH IRB serves as the central IRB in a multi-site protocol and the NIH Intramural Program is enrolling subjects. In this situation, there is an NIH PI for the NIH Intramural Program, however other PIs lead the same protocol at other institutions. Subjects are located at multiple sites. The applicable policies are found in Part IV, **section 21.7** of this SOP.

This first four sections of this SOP address the four different scenarios described above. If NIH researchers participate in a collaboration that is not identified in

this SOP, OHSRP staff will provide guidance about management of COI issues. This SOP also addresses other issues, including management of protocols involving NIH patents, NIH management of institutional COIs, financial interests of senior NIH administrators, and FDA requirements for financial disclosures.

21.2. POLICY

It is the Federal Government's policy to eliminate or minimize actual or perceived conflict of interest in the conduct of clinical research. The NIH is guided by applicable criminal statutes (18 USC §§ 203, 205, and 207-209), government-wide ethical conduct regulations (5 CFR Parts 2634-2641), and the Supplemental Standards of Ethical Conduct for Employees of the Department of Health and Human Services (5 CFR Parts 5501-5502). These rules, which must be followed by NIH employees, promote objectivity in research, maintain the public's trust, and help to avoid adverse impacts in clinical research arising from conflicts of interest.

Assessment of financial conflict of interest is required for all clinical research protocols that may lead to the financial benefit or loss of any individual or entity.

21.3 DEFINITIONS

A. **Appearance of Conflict of Interest:** An appearance of COI occurs when an individual's impartiality in clinical research, particularly clinical research involving commercial interests, might reasonably be questioned because the interests of a member of the individual's household would be affected by the matter, or because certain persons or entities are involved in or will be affected by the research, including close relatives or household members of the individual or others with whom the individual has or recently had (within the past year) certain personal or business relationships, or with whom the individual's spouse, parent or dependent child has certain personal or business relationships (5 CFR § 2635.502).

B. **Conflict of Interest**: A conflict of interest (COI) occurs when a government matter, including clinical research, will have a direct and predictable effect on the financial interests of an individual or the individual's spouse, minor children, general partner(s), or certain other organizations the individual serves as officer, director, trustee, general partner or employee, and entities with which the individual is negotiating for or has an agreement regarding prospective employment (18 USC § 208, 5 CFR Part 2640).

C. **Covered Individuals:** For purposes of SOP 21**,** covered individuals are personnel who have independent decisional roles in conducting a specific covered research protocol. These individuals are influential in the design,

direction, or conduct of a covered research protocol, or engaged in the analysis or interpretation of data. Individuals who participate only through isolated tasks that are incidental to the research (for example, scheduling patient tests), and those individuals who support research of many protocols through the performance of routine patient care tasks are not covered individuals. Covered Individuals include the principal investigator, personnel whose resume or CV is provided to a sponsor, personnel listed on a FDA 1572 Form, and personnel engaged in human subjects research, including but not limited to individuals who obtain informed consent or who make decisions about research eligibility. Others who have decisional responsibilities that meet the definition of a covered individual, e.g. as co-investigator, research nurse, associate investigators, or an individual who interprets or analyzes research data, are also covered individuals. The PI determines which individuals are "covered individuals" under this SOP. When protocols contain sub-studies that ask a research question about a product, it is possible that only those individuals involved in decisional roles in the sub-study are "covered individuals."

D. **Covered research protocols:** For purposes of SOP 21, covered research protocols include: (1) studies of investigational drugs and devices, (2) studies with a research question about a commercially available drug or device, (3) studies involving collaborations with a substantially affected organization (SAO) or other for-profit entities when the entity is receiving data or specimens from the NIH for the purpose of developing a product, or (4) studies involving a technology/product not developed in an NIH lab which is evaluating the technology/product or comparing the technology/product to another technology/product or treatment. NIH research protocols that are categorized as Teaching and Training, or Natural History studies are not covered research protocols, unless they meet the criteria listed above. Most interventional protocols will be covered protocols unless the intervention does not involve the criteria listed above (e.g. a behavioral intervention might not meet the criteria for a covered research protocol).

E. **Data analysis/interpretation:** In this SOP, the words "data analysis/interpretation" mean the process of assigning meaning to the complete, collected information from the protocol. Although there are many steps involved in data collection and interim analysis is often required, for the purposes of this policy, individuals are only viewed as "covered individuals" if they are involved in determining broad conclusions, significance and implications, based on data analysis or interpretation of "covered" protocols. Individuals who are analyzing aggregate data assigned to a treatment group (even if the name of the treatment group is not given) may be able to influence the results in a way that might lead to financial loss or gain and are therefore considered "covered individuals," if the protocol is a "covered protocol.

F. **Disqualifying Financial Interests (for NIH Employees)** include:

1. Ownership and other financial interests in publicly-traded SAOs involved in or that will be affected by the research unless the values are within regulatory *de minimis* levels (see 5 CFR Part 2640). At present, the *de minimis* exemptions provide there is no conflict where:

   i. The aggregate value of the interest of an investigator and his/her spouse and minor child(ren) in the SAO(s) whose products are being/may be evaluated in the research does not exceed $15,000;

   ii. The aggregate value of the interests of an investigator and his/her spouse and minor child(ren) in all SAOs that may be directly or indirectly affected by the research (including those whose products are being/may be evaluated) does not exceed $25,000;

   iii. The aggregate value of the interest of an investigator and his/her spouse and minor child(ren) in health-related sector funds does not exceed $50,000; and/or

   iv. The otherwise disqualifying financial interest arises from ownership of shares in a widely-diversified mutual fund.

2. Ownership and other financial interests, regardless of value, in privately-held companies whose products are/may be evaluated by the research and/or that might be indirectly affected by the research.

3. Proprietary interests and royalty sharing rights derived from work done outside NIH that are related to or may be affected by research performed at the NIH including, but not limited to, a patent, trademark, copyright or licensing agreement. (Note: under federal law, neither royalty payments received nor the right to receive such payments from the Federal Government based on work done as a federal employee constitutes a disqualifying financial interest.)

4. A Board or other fiduciary relationship to a commercial sponsor of the research, regardless of compensation. (Note: NIH employees are subject to legal and policy limitations on such activities and need prior approval consistent with NIH and IC procedure(s); such activities with commercial entities are prohibited.)

NOTE: Compensation for performance of clinical research is prohibited by Federal law, e.g. pharmaceutical sponsors cannot compensate NIH or NIH researchers for enrolling subjects in research, as occurs in the private sector. Federal law prohibits NIH employees from receiving payments or

other things of value from any payer other than the US Government for work done as part of official duties.

G. **Diversified mutual fund:** A mutual fund, trust or plan that does not have a stated policy of concentrating its investments in any industry, business, single country other than the United States, or bonds of a single State within the United States and, in the case of an employee benefit plan, means that the plan's trustee has a written policy of varying plan investments. (5 CFR 2640.102(a))

H. **Mutual fund** means an entity which is registered as a management company under the Investment Company Act of 1940, as amended (15 U.S.C. 80a-1 et seq.) (See References below). For purposes of this part, the term mutual fund includes open-end and closed-end mutual funds and registered money market funds (5 CFR § 2640.102 (k)).

I. **NIH Federal employees**: NIH Federal employees include those NIH staff with an appointment to the federal government pursuant to, for example, Title 5, 38 or 42, or the Commissioned Corps, and may include some fellows. These individuals are considered NIH employees. Personnel appointed at NIH through an Intergovernmental Personnel Act (IPA) agreement and special government employees (SGE) working at NIH are considered NIH federal employees for the purposes of this SOP.

J. **Sector fund**: A mutual fund whose objective is to invest in a particular industry or sector of the economy to capitalize on returns. The fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States (5 CFR § 2640.102(q)).

K. **Securities**: Security means common stock, preferred stock, corporate bond, municipal security, long-term Federal Government security, and limited partnership interest. The term also includes “mutual fund” for purposes of 5 CFR §§ 2640.202(e) and (f) and 2640.203(a) (5 CFR § 2640.102(r)).

L. **Substantially Affected Organization (SAO)**: A biotechnology or pharmaceutical company, a medical device manufacturer; or a corporation, partnership, or other enterprise or entity significantly involved, directly or through subsidiaries, in the research, development, or manufacture of biotechnological, biostatistical, pharmaceutical, or medical devices, equipment, preparations, treatments, or products (5 CFR § 5501.109(b)(10)).

21.4 PART I: AN NIH EMPLOYEE IS THE PI FOR NIH INTRAMURAL PROTOCOL AND AN NIH IRB REVIEWS AND HAS OVERSIGHT OF THAT PROTOCOL

21.4.1 FINANCIAL DISCLOSURES AND CERTIFICATIONS FOR COVERED INDIVIDUALS

All Covered individuals must review and follow the "Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH" ("The Guide") (**Appendix A**). The NIH considers that the potential for COI must be considered for all covered individuals participating in covered protocols. **Appendix C** is an algorithm that outlines pertinent questions to consider when deciding whether financial disclosures are required.

21.4.2 NIH EMPLOYEE, SGE AND IPA INVESTIGATOR FINANCIAL DISCLOSURE AND CERTIFICATION[1]

A. NIH employees notified by the agency, and all SGEs, and IPAs who meet the definition of "covered individuals" must make annual financial disclosures consistent with the government-wide regulatory requirements (see 5 CFR Part 2634).[2] In addition, all NIH employees who are Principal Investigators (PIs), accountable investigators, medical advisory investigators, associate investigators (AIs), or other sub-investigators, such as Lead Associate Investigators, are required to disclose the value of all interests in SAOs held or acquired personally or by their spouses or minor children. This is done by filing Form 717-1, Confidential Report of Financial Interests in Substantially Affected Organizations for Employees of the National Institutes of Health and/or a Public or Confidential Financial Disclosure Report (Form OGE-278 or OGE-450) (These forms are available on the NIH Ethics Program website, see **References** below).

B. NIH employees who are covered individuals but who do not make financial disclosures as listed above (**21.4.2.A**), are required to sign a Conflict of Interest (COI) Certification for NIH Employees Who Do Not File a Financial Disclosure Report (Form 450 or 717-1) (**Appendix E**).

[1] Employees of other federal agencies are subject to the government-wide rules regarding conflicts of interest as well as any agency-specific rules established by their employing agencies, and are required as a matter of law and as a condition of federal employment to comply with the directives of their agency ethics program.

[2] Special Government Employees and those appointed or on detail under the Intergovernmental Personnel Act are Federal financial disclosure filers.

Examples might include an employee who routinely screens possible subjects for a covered protocol.

21.4.3 CERTIFICATION FOR COVERED INDIVIDUALS WHO ARE NOT FEDERAL EMPLOYEES

A. Non-federal employees are exempt from the U.S. Government ethical conduct statutes and regulations and the financial disclosure requirements. However, the NIH expects that all covered individuals be aware of real and potential conflicts and provides the "Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH" ("Guide") (**Appendix A**) to assist their understanding.

B. Covered individuals who are not Federal employees are required to sign a Conflict of Interest (COI) Certification for Non-Federal Employees (**Appendix F**). Through this certification, covered individuals certify that they will abide by the Guide, and indicate whether their home institution has a COI policy, and whether they are in compliance with the COI requirements of their home institution.

C. Non-federal employees (e.g. some contractors) whose employers do not have a COI policy, will indicate this on the COI Certification.

D. The PI will submit the completed form to the Institute Ethics Office as part of the process for Deputy Ethics Counselor (DEC) clearance. The Institute Ethics Office will ensure that all required forms, when applicable, have been completed, prior to providing DEC clearance for the particular protocol.

E. If the individual is unable to meet the requirements of the certification and cannot sign this certification, the individual cannot participate in the protocol, unless the NIH Deputy Director for Intramural Research (the NIH DDIR), or his delegate, grants an exception.

Exceptions may be granted in cases involving unusual or extraordinary circumstances. In addition to anything deemed by the NIH DDIR or his delegate to be relevant to the question, the following will be taken into consideration in the case of each request for an exception:

1. The nature of the individual's financial interest or other relationship involved, if known;

2. The potential impact the protocol may have on the financial interest or other relationship, if known;

3. The potential risk or hazard the protocol poses for study participants;

4. The nature and importance of the individual's anticipated role in the research protocol, including the extent to which the individual may be called upon to exercise discretion during the course of the protocol; and

5. Adjustments that may be made in the individual's anticipated responsibilities/duties/role that would reduce or eliminate any potential bias that might result from the real or apparent conflict of interest.

21.4.4 EVALUATION OF COI BY THE IC ETHICS OFFICE

A. Responsibilities of the PI. The PI is responsible for determining whether a protocol meets the definition of a "covered protocol" and whether an individual meets the definition of a "covered individual." Questions or disagreements regarding the identification of an individual or a protocol as "covered" will be referred to OHSRP, which will consult with others as needed, for final determination. When protocols contain sub-studies that ask a research question about a product, it is possible that only those individuals involved in decisional roles in the sub-study are "covered individuals." The PI is required to submit a Personal Financial Holdings (PFH) form (**Appendix D** - Clearance of NIH Investigator Personal Financial Holdings by IC Ethics Office) to his/her Institute Ethics Office for its review, both at the time of initial and continuing review of the research protocol and for amendments involving the addition of any covered individuals to a protocol. The form also must be submitted if the protocol changes from "uncovered" to "covered" status; when there are any changes related to the use of commercial products, or if there are additions or changes to an IND/IDE through modification or amendment.

   1. The PFH form lists categories of covered protocols, all investigators, and any additional covered individuals on the protocol.

   2. The PI will indicate the employment status (NIH, non-NIH Federal, Non-Federal) of each covered individual on the PFH form.

B. Evaluation by the Ethics Office.

   1. The Ethics office reviews the PFH for all covered protocols to ensure that all covered individuals have submitted a COI certification form or financial holdings disclosure, or are non-NIH Federal employees.

   2. The DEC will review the forms submitted by financial disclosure filers against their ethics records prior to providing DEC clearance for the

protocol. The office obtains updated information regarding the SAO holdings of each NIH employee, SGE or IPA who is a covered individual on the protocol and evaluates whether any individual's holding(s) constitutes a financial conflict of interest.

a. In instances where a holding could be perceived as a conflict of interest, the PI of the study is consulted regarding whether this holding(s) constitutes a COI in relation to the protocol.

b. If any holding is determined to be a conflict, the PI, the PI's DEC, the conflicted covered individual and the his/her DEC will confer regarding an appropriate remedy:

i. Disqualification of the conflicted party from participation in the research;

ii. Complete divestiture of the conflicting financial interest(s)s or partial divestiture to below the *de minimis* level; and/or

iii. Waiver, with approval of the NIH Director, following consultation with the HHS Designated Agency Ethics Official, to permit participation in all or a portion of the research project.

Questions or disagreements about the identification of any interest or relationship as COI in relation to the protocol will be referred to the Director, NIH Ethics Office, who will consult with others as needed, for final determination.

C. Reporting the COI evaluation to the IRB

1. After review by the Ethics Office, the DEC will sign the PFH (**Appendix D**) form indicating that all covered individuals have submitted a COI certification form or financial holdings disclosure, or are non-NIH Federal employees.

2. Additionally, for NIH Federal employees, SGEs, and IPAs, the DEC will certify via the PFH form that:
   a. No conflict(s) was identified;

   b. One or more NIH Federal employees, SGEs, or IPAs have an over the *de minimis* holding in a SAO(s) which has been reviewed and determined not to constitute a COI;

   c. Conflicts have been resolved through divestiture; and/or

d. A waiver has been granted by the NIH Director.

3. The form is sent to the IRB which accepts the statement by the DEC as sufficient evidence that there is no financial conflict associated with covered individuals on the protocol, or that the NIH Director granted a waiver. Final approval by the IRB is not granted until the DEC signature is obtained on the PFH form (**Appendix D**) and is received by the IRB, and is on record in the Office of Protocol Services (OPS).

21.5 PART II: A NON-NIH IRB REVIEWS AND PROVIDES OVERSIGHT FOR A SINGLE SITE PROTOCOL AND AN NIH COLLABORATOR IS PARTICIPATING IN THAT NON-NIH PROTOCOL

When an NIH employee is a collaborator on a protocol that is led by a non-NIH PI and reviewed by a non-NIH IRB, the lead NIH collaborator should determine whether the outside protocol is "covered" using the definition in this SOP. If "covered," the lead NIH collaborator should obtain DEC clearance for this protocol following Part I of this SOP, before beginning research activities. In this situation, the lead NIH collaborator takes on the role of an NIH PI for the purpose of DEC clearance, under Part I of this SOP. The lead NIH collaborator should maintain the DEC clearance in the NIH research files for the protocol and provide a statement to the non-NIH IRB that DEC clearance has occurred. The NIH PI may not provide the DEC clearance form, or any information about any employee's financial or other interests, even if such information is requested, to the non-NIH IRB.

21.6 PART III: AN NIH INTRAMURAL IRB IS THE CENTRAL IRB FOR A MULTI-SITE PROTOCOL; THERE IS USUALLY A PI AT THE NIH AND PI(S) AT OTHER INSTITUTIONS WHERE THE PROTOCOL IS ALSO IMPLEMENTED

When an NIH Intramural IRB is the central IRB for a multi-site protocol there usually an NIH PI for the NIH Intramural Program, and PIs at other institutions where the protocol is also implemented. In this type of collaboration, the NIH PI follows the COI requirements in Part I of this SOP. The non-NIH PI(s) follows the COI requirements of his/her home institution. The non-NIH PI (or non-NIH Institutional Official) should provide documentation to the NIH IRB that: 1) the outside institution has a COI policy, and 2) the applicable COI policy was, and will be, followed for the protocol in question, during the entire time period (initial review, continuing review, amendments) that an NIH central IRB is the IRB of record.

21.7 PART IV: A NON-NIH IRB IS SERVING AS THE CENTRAL IRB IN A MULTI-SITE PROTOCOL AND THE NIH IS ONE OF THE INSTITUTIONS

When an NIH PI conducts a protocol involving human subjects in the NIH Intramural Program, but there is a central IRB at another institution, all of the provisions in Part I apply to the NIH researchers for those protocols.

If the protocol is "covered," (see **Section 21.3** above), evaluation of COI by the IC Ethics Office is required, and the protocol should have DEC clearance before subjects are enrolled. The NIH PI should maintain the DEC clearance form in the NIH research records. Documentation from the PI that DEC clearance has occurred must be provided to the non-NIH central IRBs, or non-NIH institution, if requested, but the NIH PI may not provide a copy of the DEC clearance document, and may not disclose any information about any employee's financial or other interests.

The NIH will have no involvement with the COI requirements pertaining to the PIs and AIs at other sites. Those individuals should follow the COI requirements of their home institutions.

21.8 PATENTS HELD BY THE NIH

NIH clinical research protocols may evaluate or potentially advance product(s) in which the NIH (i.e., the Federal government) owns patents, a license for technology, or has received invention reports as detailed in the Federal Technology Transfer Act of 1986, 15 USC §1501-1634.

In such cases:

A. An NIH investigator may participate in the clinical trial, even if he/she is listed on the patent or invention report and/or may receive royalty payments from the NIH for the product(s) being tested.

B. When such an investigator participates in a trial, there will be full disclosure of the relationship to the IRB and to the research subjects (i.e., information will appear in the consent form) with review and approval by the IRB. This is to ensure the quality and integrity of the data collected.

C. In the case of continuing review of current protocols where NIH has a new or amended intellectual property interest in the invention, investigators should provide a new human subjects consent form or

correspondence outlining the relationship, for review and approval by the IRB.

D. An independent entity or individual must review the integrity/accuracy of the results/quality of data to assure the safety of human subjects and to assess whether there is a change in the risk benefit ratio or introduction of possible bias.

21.9 RECRUITMENT INCENTIVES

Payment arrangements among sponsors, organizations, investigators, and those referring research participants may place participants at risk of coercion or undue influence or cause inequitable selection. Payment in exchange for referrals of prospective participants from physicians ("finder's fees") is not permitted in connection with research at NIH. Similarly, payments designed to accelerate recruitment that is tied to the rate or timing of enrollment ("bonus payments") also are not permitted in connection with research at NIH.

21.10 NIH REQUIREMENTS TO PREVENT INSTITUTIONAL CONFLICTS OF INTEREST

The Federal government has enacted laws, regulations, and policies to ensure that Institutional Conflicts of Interest (ICOI) involving human subjects research do not occur at the NIH. The following sections describe Federal laws and NIH policies that address this issue:

21.10.1 GIFTS

The NIH is authorized receive gifts to supplement appropriated funds, to support its research efforts. The NIH Policy Manual 1135 (Gifts Administration) outlines policy and procedures concerning the acceptance, acknowledgment, and administration of gifts (including bequests, devises of real property, legacies, grants, and donations from living donors) to the National Institutes of Health (NIH) or to support its activities or components. This manual chapter applies to the receipt of gifts, both monetary and non-monetary that are accepted under the authority established in Sections 231, 405(b)(1)(H), and 497 of the Public Health Service (PHS) Act, as amended (42 U.S.C. §§238, 284(b)(1)(H), and 289f). Gifts intended for supporting or supplementing a current permanent employee's salary are not permitted (see References below).

21.10.2 ACTIVITIES MANAGED BY THE NIH OFFICE OF TECHNOLOGY TRANSFER (OTT)

The NIH Office of Technology Transfer (OTT) evaluates, protects, markets, licenses, monitors, and manages the wide range of NIH discoveries, inventions, and other intellectual property as mandated by the Federal Technology Transfer Act and related legislation. The following sections provide information about the responsibilities of the OTT (see References below).

21.10.2.1. Licensing Agreements and Royalties

A. Several acts of Congress have deemed technology transfer functions an incentive to the advancement of public health and exempt from individual and institutional conflict of interest [Bayh-Dole Act (35 USC §200 et al.) and Federal Technology Transfer Act (15 USC §3701 et al)]. All royalty monies resulting from patents or licensing are received and distributed by the Federal Government to the NIH employee and the Institute which oversees that employee. Royalty income is also distributed to the Institute(s) of the inventor(s) listed on the patent and may be used for purposes consistent with the overall mission of the NIH. Public disclosure is required in all consent forms where NIH patents, licensing agreements or CRADAs are involved. Annual compensation to NIH employees is limited to $150,000. (USPHS Technology Transfer Manual 311, NIH Royalty Policy).

B. For protocols where technology licenses are involved, NIH policy (See **Appendix A** "Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Clinical Research at NIH") requires that these arrangements are disclosed to all participants. Below is an example of the kind of information related to drug/device development that the PI should include in the consent document:

> The National Institutes of Health and the research team for this study have developed (a drug, imaging agent, device) being used in this study. This means it is possible that the results of this study could lead to payments to NIH. By law, the government is required to share such payments with the employee inventors. You will not receive any money from the development of _____ (drug, imaging agent, device).

21.10.2.2 Cooperative Research and Development Agreements (CRADAs)

A. Research protocols may be conducted under a Cooperative Research and Development Agreement (CRADA) jointly between the NIH and an outside entity, such as a pharmaceutical company. These agreements carefully lay out the obligations of the CRADA partner to provide specific materials and financial support (if any), and the deliverables by the specific investigator, usually related to basic research and/or clinical trials. These instruments are carefully evaluated by the Office of Technology Transfer and all financial interests of the PI named on the agreement are cleared by the IC Ethics Office.

B. For protocols that are associated with a CRADA, these arrangements are disclosed to all participants. The following is an example of language that should be included in the consent document as applicable:

> The NIH and the research team for this study are using (a drug, imaging agent, device) developed by (company name) through a joint study with your researchers and the company. The company also provides financial support for this study.

21.10.3 CLINICAL TRIAL AGREEMENTS

Clinical Trial Agreements (CTAs) between the pharmaceutical industry and NIH Institutes for the clinical development of new methods of therapy are part of the NIH mission to improve treatment of specific diseases. These agreements focus on a specific experimental drug and a targeted disease. In some cases, representatives from the collaborating company may participate on the protocol as Associate Investigators or Medical Monitors for purposes of gathering information for New Drug Applications or a Biological License Application with the FDA.

A. For protocols for which there is a CTA, the existence of these arrangements is disclosed to all participants. The following is an example of language that will be included in the consent document:

> (Company name) is providing (the drug/device) for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from (Company).

B. If there are non-NIH investigators and no identified conflicts with NIH investigators, the following is an example of language that will be included in the consent document:

No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested. However, there are some non-NIH collaborators on this study who may receive payments or benefits, limited by the rules of their workplace.

21.11 FINANCIAL INTERESTS OF SENIOR NIH ADMINISTRATORS

NIH institutional leaders who have direct authority over faculty appointments, promotions, allocation of institutional resources, funding or space, including the NIH Director and Deputy Directors, Institute Directors and Deputy Directors; Scientific Directors, and Clinical Directors, are subject to increased scrutiny and regulation.

Generally individuals with this greater authority are not permitted to hold more than the *de minimis* value ($15,000) in any SAO, except in certain limited circumstances (5 CFR § 5501.110). Individuals holding Presidential appointments are subject to even more stringent requirements. As appropriate and required by regulation, all financial holdings are evaluated by the Office of the General Counsel, Ethics Division, the NIH Ethics Office (NEO), the IC Ethics Office and/or by the NIH Deputy Ethics Counselor, the Deputy Director of the NIH. Financial conflicts are managed through the NEO and Office of General Counsel by divestiture, recusal and, on very rare occasion, by waiver.

21.12 FDA REQUIREMENTS FOR FINANCIAL DISCLOSURES BY CLINICAL INVESTIGATORS

Under FDA regulations[3] when an applicant submits a marketing application for a drug, biological product or device, is required to submit to the FDA a list of all clinical investigators who conducted covered clinical studies and to identify those who are full-time or part-time employees of the sponsor of each covered study (21 CFR § 54.4). For each clinical investigator who was not a full time or part time employee of a sponsor of the clinical study, the applicant must provide either a certification, using Form FDA 3455 (**Appendix G**) , that none of the financial interests or arrangements described in 21 CFR § 54.4(a)(3) exists, or completely and accurately disclose, using Form FDA 3454 (**Appendix H**), the nature of those interests and arrangements to the agency and describe any steps taken to minimize the potential for bias resulting from those interests and arrangements (21 CFR § 54.4(a)). If the applicant acts with due diligence to obtain the required information but is unable to do so, the applicant may certify that it acted with due diligence but was unable to obtain the information and include the reason the information could not be obtained (21 CFR § 54.4).

[3] 21 CFR parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860

FDA generally expects that applicants will be able to provide this information. Under 21 CFR §§ 312.53(c), 812.20(b)(5) and 812.43(c), a sponsor is required to obtain clinical investigator financial information before allowing the clinical investigator to participate in a covered clinical study. Under 21 CFR § 54.4(b), each clinical investigator who is not a full-time or part-time employee of the sponsor of the covered clinical study is required to provide the sponsor with sufficient accurate financial information to allow for complete disclosure or certification and to update this information if any relevant changes occur during the study and for one year following its completion.

REFERENCES

A. Public Health Service (PHS) Act, as amended (42 U.S.C. §§238, 284(b)(1)(H), and 289f): http://oma1.od.nih.gov/manualchapters/management/1135/

B. Investment Company Act of 1940, as amended (15 U.S.C. 80a-1 et seq.): http://www.law.cornell.edu/uscode/text/15/80a-1

C. NIH Ethics Program: http://ethics.od.nih.gov

D. Office of Technology Transfer (OTT): http://www.ott.nih.gov/

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APPENDIX A: A GUIDE TO AVOIDING FINANCIAL AND NON-FINANCIAL CONFLICTS OR PERCEIVED CONFLICTS OF INTEREST IN CLINICAL RESEARCH AT NIH

September 2015

Avoiding financial and other conflicts of interests is important for NIH, where the trust and protection of research participants is vital to our mission to improve the public health. The number and complexity of laws and regulations in this area makes it difficult to know when there is a conflict or perceived conflict and what to do. This guide is intended to assist those engaged in clinical research and NIH IRB members in avoiding real or perceived financial and non-financial conflicts of interest.

I. What are potential conflicts of interest for those engaged in clinical research?

All NIH employees, including clinical researchers, when engaged in their NIH duties have an interest in advancing the public's health. For clinical researchers, these interests may include obtaining knowledge that will promote health and health care, and helping to ensure the safety and health of research participants. Employees often have other personal interests that could be affected by their NIH work such as a spouse's job, stock holdings and/or outside positions at universities and professional organizations. These outside interests are generally permissible, but in some circumstances they have the potential to compromise, or appear to compromise, the judgment of employees with respect to their NIH duties. When these outside interests have the potential to compromise the integrity of an employee's NIH work, a conflict of interests occurs between the employee's interest in his or her government work and his or her outside interests. Under the government rules, this conflict must be resolved before the employee can proceed to work on his or her NIH project.

This guide provides information to identify and prevent or mitigate financial and other conflicts, thereby helping to ensure both the integrity of our research and the safety of participants.

II. To whom does the guide apply?

The restrictions discussed in this guide are based on the laws that apply to NIH employees[1]. These financial disclosure rules apply to those NIH employees, Special Government Employees (SGEs), and individuals at NIH under an Intergovernmental Personnel Act (IPA) agreement who have key decisional roles in protocols that may lead to financial benefit, termed "covered individuals"[2] and

"covered protocols"[3]. These rules also apply to NIH employees who serve on NIH Institutional Review Boards (IRBs) and Data and Safety Monitoring Boards (DSMBs).

It is expected that non-NIH employees[4] who are covered individuals or IRB or DSMB members[5] will review this guide and adhere to the rules set out. Covered individuals who are not NIH employees should be mindful of real and potential conflicts and discuss such conflicts with the protocol's PI and their home institution, as applicable. Non-federal employees must certify that they have received this guide and will comply with its tenets. Please note that the National Institutes of Health expects that all non-NIH investigators will comply with the ethics and conflict of interest policies and procedures set forth by their institution or employer.

III. Examples of investigator, covered individual, and IRB and DSMB member financial conflicts of interest

As noted below, some of these examples of financial conflicts of interest are prohibited by regulation for NIH employees. We list them, however, as guidance for non-NIH employee investigators, covered individuals, and IRB and DSMB members who are reviewing this guide. It should be noted that in addition to his or her own financial interests and outside interests, *an NIH employee's financial interests also include the financial interests of others, such as his or her spouse, dependent children, or household members.* Examples of such interests are:

- Serving as a director, officer or other decision-maker for a commercial sponsor of clinical research (prohibited activity for NIH employees);
- Holding stock or stock options in a commercial sponsor of clinical research (unless below the applicable de minimis amount or held within a diversified, independently managed mutual fund);
- Receiving compensation for service as consultant or advisor to a commercial sponsor of clinical research (excluding expenses) (prohibited activity for NIH employees);
- Receiving honoraria from a commercial sponsor of clinical research (prohibited activity for NIH employees);
- Personally accepting payment from the clinical research sponsor for non-research travel or other gifts (for NIH employees, government receipt of in-kind, research-related travel is not included and other exceptions may apply);
- Obtaining royalties or being personally named as an inventor on patents (or invention reports) for the product(s) being evaluated in the clinical research or products that could benefit from the clinical research (special rules apply in this case when NIH holds the patent – see **Section VII** below);

- Receiving payments based on the research recruitment or outcomes (prohibited activity for NIH employees);
- Having other personal or outside relationships with the commercial sponsor of the clinical research (prohibited activity for NIH employees);
- Having financial interest above the applicable de minimis in companies with similar products known to the investigator to be competing with the product under study (prohibited activity for NIH employees); or
- Participating in an IRB or DSMB decision that has the potential to affect your spouse's employer (prohibited activity for NIH employees).

IV. Examples of non-financial real or apparent conflicts of interest for IRB and DSMB members

- Voting on a protocol when the member of the IRB is the protocol's Principal Investigator, Associate Investigator or study coordinator;
- Voting on a protocol when the member of the IRB or DSMB is or has a spouse, child, household member or any other individual with whom the protocol's Principal Investigator, Associate Investigator or study coordinator has the appearance of a conflict of interest; or
- Voting on a protocol when the protocol's Principal Investigator is the IRB member's supervisor (up the chain of command to the Clinical Director).

As noted in Section II - The National Institutes of Health expects that all non-NIH investigators are in compliance with their institutional/employer's conflict of interest policies.

CLEARANCE OF NIH EMPLOYEES ONLY – PERSONAL FINANCIAL HOLDINGS

V. NIH's system to assist in identifying and preventing personal financial conflicts for investigators in covered clinical research protocols

The Principal Investigator of a covered protocol is responsible for assuring that each covered individual receives a copy of this guide. The guide should be distributed to any new covered individual added to a protocol while the protocol is active. All NIH employees, and individuals who are not federal employees, who are covered individuals shall acknowledge receipt of this guide via a written or electronic statement. Certain NIH employees (those who are Principal Investigators (PIs), accountable investigators, medical advisory investigators, associate investigators (AIs), or other subinvestigators, such as Lead Associate Investigators) on covered protocols are required to disclose the value of all interests in Substantially Affected Organizations[6] (SAOs) held or acquired personally or by their spouses or minor children. This is done by filing Form **717-1**, Confidential Report of

Financial Interests in Substantially Affected Organizations for Employees of the National Institutes of Health (available at http://ethics.od.nih.gov), and/or a *Confidential Financial Disclosure Report (Form OGE-450)*. Non-federal employees, and NIH employees who do not file an OGE-450 or 717-1 form will provide the PI with a Conflict of Interest (COI) Certification form.

New Protocols

For any covered protocol, at the earliest point possible, the PI is responsible for providing his or her IC Deputy Ethics Counselor (DEC) with a completed copy of the "Clearance of NIH Investigator Personal Financial Holdings" *(PFH Clearance)* (see Appendix 1), which lists all covered individuals. Alternatively, an electronic equivalent could be used to provide this information. If applicable, the PI also will provide copies of the signed Conflict of Interest (COI) Certification for Non-Federal Employees, or the Conflict of Interest (COI) Certification for NIH Employees Who Do Not File form 450 or 717-1.

For each protocol:

1) The DEC will verify that all covered individuals have submitted a form 450 or 717-1 or one of the two COI certification forms, if appropriate. The DEC will verify that the personal investment information on the form 450 or 717-1 is current (within 6 months) as of the date on the PFH Clearance. The IC DEC will then review file copies of the 450 or 717-1 forms that enumerate stock holdings in Substantially Affected Organizations (SAOs).

2) If SAO holdings are above the de minimis values, the DEC will provide the PI with an anonymous list of the covered individual's holdings in SAOs as reported on these forms so the PI can determine if any pose a conflict of interest for the protocol in question. Any covered individual who has a potential conflict will be contacted by his or her DEC to determine how to resolve any actual or apparent conflict. The employee's supervisor and/or the Clinical Director will be consulted as necessary if a conflict exists. The conflicts review will occur in parallel to the IRB submission process.

At the completion of the personal financial holdings review, the IC DEC will return a signed copy of the Protocol PFH Clearance to the PI. The PI will then note the date of DEC clearance on the *Protocol Application* and ensure that the Protocol PFH Clearance is included in the protocol packet.

The DEC clearance form will become part of the protocol packet forwarded to the IRB Chair for final approval. The IRB chair may not provide final approval by signing a protocol until the completed Protocol PFH Clearance is included in the protocol packet.

The PFH form may be submitted, reviewed and returned using electronic systems for protocol submission.

Continuing Review

A COI analysis will take place at the time of continuing review using the same process as described above. The Protocol PFH Clearance will be used for this process. For the conflicts analysis, the IC DEC will evaluate the addition of new covered individuals, any changes related to the use of commercial products (as part of the scientific hypothesis) or any change to an IND/IDE.

Amendment

A COI analysis will take place for amendments involving the addition of covered individuals to a protocol, any changes related to the use of commercial products (as part of the scientific hypothesis), or any addition of an IND/IDE. The Protocol PFH Clearance will be used for this process following the procedure above. If just adding a new covered individual, only that individual needs to be cleared.

Although government-wide regulations allow NIH employees to hold de minimis amounts of publicly-traded stock without triggering conflict of interest restrictions, there may be other factors to consider with respect to stock ownership. If a publication should result from the protocol, most journals require the authors to disclose individual financial holdings within the text of the published paper. Such disclosures could raise at least the appearance of the conflict of interest. Thus, all investigators should consider these outside factors when making personal financial investments.

VI. IRB and DSMB Clearance for COI

Before beginning protocol review activities, the Chair asks whether any member is aware of any real or apparent conflict of interest. The minutes will reflect which individual(s) has a real or apparent conflict of interest. No IRB or DSMB may have a member participate in the initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB or DSMB.

When the Principal Investigator or Associate Investigator is the Institute Director, or Scientific Director, the protocol will be reviewed by an IRB not affiliated with that institute. The Deputy Director for Intramural Research may waive this requirement.

When the Principal Investigator is the Clinical Director (CD) it shall be the prerogative of an IRB either to review such protocols or refer them to another Institute's IRB. IRBs reviewing protocols in which their CD is the PI must have a majority of voting members present at the meeting who are not employed by the CD's Institute, otherwise an alternative plan must have prior approval by the Clinical Center Director and the Deputy Director for Intramural Research.

VII. NIH Intellectual Property and Royalties

In some instances, NIH clinical research protocols will evaluate or potentially advance product(s) in which NIH (i.e., the government) owns patents or has received invention reports. In such cases:

An NIH investigator may participate in the clinical trial, even if the investigator is listed on the patent or invention report and/or may receive royalty payments from the NIH for the product(s) being tested.

When such an investigator participates in a trial, there will be full disclosure of the relationship to the IRB and to the research subjects (i.e., information should appear in the consent form) with review and approval by the IRB. This is to ensure the quality and integrity of the data collected.
In the case of continuing review of current protocols where NIH has a new or amended intellectual property interest in the invention, the Principal Investigator should provide a new human subjects consent form or correspondence outlining the relationship, for review and approval by the IRB.

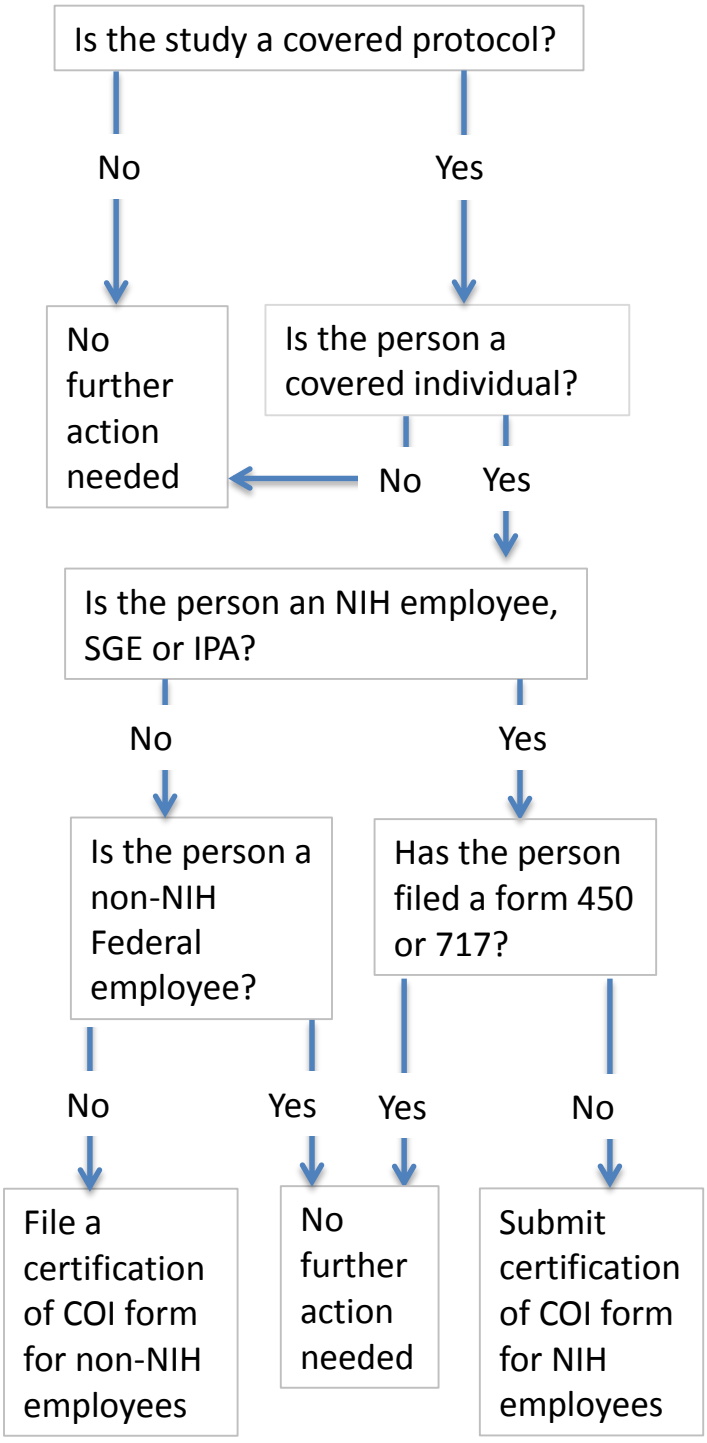
An independent entity or individual must review the integrity/accuracy of the results/quality of data to assure the safety of human subjects and to assess whether there is a change in the risk benefit ratio or introduction of possible bias.

APPENDIX B: COI PROCEDURES FOR FOUR DIFFERENT, BUT COMMON SITUATIONS AT THE NIH, INVOLVING RESEARCH COLLABORATORS

IRB location and type of protocol (single site vs. multi-site)	Institution of PI or AI	Role of collaborator	Research subjects	COI requirement
An NIH Intramural IRB is reviewing and providing oversight for a single site protocol.	An NIH employee is the PI and the protocol is implemented within the NIH Intramural Program. There is an AI on the protocol who may be an employee of another institution,	Non-NIH collaborators are usually AIs on the NIH protocol, doing human subjects research (HSR) at the NIH or at the collaborator's home institution e.g. reviewing identifiable data.	In most cases, the research subjects are enrolled in the NIH Intramural Program	SOP 21 Part I: The NIH PI and AIs have NIH DEC review, if the protocol is "covered" and the non-NIH collaborator signs an SOP 21 certification form for non-NIH employees.
A non-NIH IRB is reviewing and providing oversight for a single site protocol.	There is a non-NIH PI at a non-NIH institution working with NIH collaborators who are engaged in HSR.	The NIH collaborator(s) is/are engaged in HSR at the non-NIH institution; or the NIH collaborator(s) is/are engaged in HSR (such as analysis of identifiable data) at the NIH.	Research subjects are usually at the non-NIH institution where the IRB is located.	SOP 21, Part II: The NIH collaborator(s) should obtain NIH DEC clearance if the protocol is "covered" under NIH SOP 21, before starting research. In this situation, the lead NIH collaborator makes the decision about whether the protocol is "covered." The DEC clearance must be kept by the lead NIH researcher in the research files for the protocol.
An NIH Intramural IRB is the central IRB	The NIH Intramural Program is participating as	Collaborators are normally other PIs and their research	Subjects may be participating in the protocol at the NIH	SOP 21, Part III: The NIH PI and AIs have NIH DEC review, if NIH is a

for a multi-site protocol.	a study site, however the NIH IRB also has oversight for HSR at non-NIH institutions, where the protocol is also being implemented by the PIs at those institutions.	teams at non-NIH institutions, and the entire protocol is also being implemented at those institutions.	Intramural Program, and subjects are also participating in the same protocol at non-NIH institutions.	study site and the protocol is "covered." PIs at the non-NIH institution/s follow their home COI policies and provide documentation to the NIH IRB that the institution has a COI policy and that the applicable home institutional policy was followed. Any problems should be discussed with OHSRP.
A non-NIH IRB is serving as the central IRB in a multi-site protocol and the NIH Intramural Program is participating in the protocol, or an NIH lead researcher is engaged in HSR in another capacity e.g. receiving identifiable data.	An NIH lead researcher (PI) is enrolling subjects in the NIH Intramural Program, and non-NIH PIs are leading the same protocol at non-NIH institutions.	Collaborators are usually other PIs leading the same protocol at other institutions	Subjects may be enrolled at the NIH or at other institutions.	SOP 21 Part IV: The NIH researchers must have NIH DEC review, if the protocol is "covered" but the PIs leading the same protocol at other institutions follow their home institution COI requirements. The DEC clearance must be kept by the NIH researcher in the research files for the protocol.

APPENDIX C: ALGORITHM FOR DECISIONS REGARDING FINANCIAL DISCLOSURE



Covered research protocols: Covered research protocols: For purposes of SOP 21, covered research protocols include: (1) studies of investigational drugs and devices, (2) studies with a research question about a commercially available drug or device, (3) studies involving collaborations with a substantially affected organization (SAO) or other for-profit entities when the entity is receiving data or specimens from the NIH for the purpose of developing a product, or (4) studies involving a technology/product not developed in an NIH lab which is evaluating the technology/product or comparing the technology/product to another technology/product or treatment. NIH research protocols that are categorized as Teaching and Training, or Natural History studies are not covered research protocols, unless they meet the criteria listed above. Most interventional protocols will be covered protocols unless the intervention does not involve the criteria listed above (e.g. a behavioral intervention might not meet the criteria for a covered research protocol).

Covered Individuals: Covered individuals are personnel who have independent decisional roles in conducting a specific covered research protocol. These individuals are influential in the design, direction, or conduct of a covered research protocol, or engaged in the analysis or interpretation of data. Individuals who participate only through isolated tasks that are incidental to the research (for example, scheduling patient tests), and those individuals who support research of many protocols through the performance of routine patient care tasks are not covered individuals. Covered Individuals include the principal investigator, personnel whose resume or CV is provided to a sponsor, personnel listed on a FDA 1572 Form, and personnel engaged in human subjects research, including but not limited to individuals who obtain informed consent or who make decisions about research eligibility. Others who have decisional responsibilities that meet the definition of a covered individual, e.g. as co-investigator, research nurse, associate investigators, or an individual who interprets or analyzes research data, are also covered individuals. The PI determines which individuals are “covered individuals” under this SOP. When protocols contain sub-studies that ask a research question about a product, it is possible that only those individuals involved in decisional roles in the sub-study are “covered individuals.”

APPENDIX D – CLEARANCE OF NIH INVESTIGATOR PERSONAL FINANCIAL HOLDINGS BY IC ETHICS OFFICE (PFH)

Instructions: Email the completed document to the IC DEC for your Institute and include the protocol précis for ALL protocols. To facilitate this process, ensure that the list of covered individuals is current; the DECs can provide information on whether NIH employees have filed financial disclosure.

[1]**Date Received by Ethics Office:**

[2]**Date of Memo:**

[3]**Date of IRB Meeting:**

[4]**Date Protocol Expires:**

☐ [5]New Protocol

☐ [6]Continuing Review

☐ [7]Amendment: check all that apply:

- ☐ Investigator Added
- ☐ Product Added or Changed
- ☐ Change in role—new covered investigator
- ☐ Change in status—new covered protocol

[8]**To:** _____

I.C. Deputy Ethics Counselor

[9]**From:** _____

Principal Investigator

cc:

[10]**Protocol #:**

[11]This protocol involves (check all pertinent boxes):

- ☐ Investigational biologic, drug and/or device (IND/IDE)
- ☐ Clinical Trials or CRADA agreement
- ☐ An issued or pending patent
- ☐ A research question that evaluates a commercially available drug or device
- ☐ Clinical Trial: Phase: ☐ 0 ☐ 1 ☐ 1-2 ☐ 2 ☐ 3 ☐ 4 ☐ PK/PD ☐ Expanded access
- ☐ Collaboration with an SAO

[12]**Title:**

[13]**Principal Investigator's I.C.:**

[14]**Responsible IRB:**

Name of study product(s) (drug, biologic or device):

[16]**Manufacturer of study product(s) (drug, biologic or device):**

[17]**IND/IDE# (if applicable):** [18]**IND/IDE Sponsor (if applicable):**

[19]**Do you know of competitors for study drug, biologic or device manufacturer(s) for purposes related to this protocol? If yes, please list:**

[20]**: Objective of the study *(one sentence summary)***:

[21] **List individuals serving on the protocol** who are covered individuals, identifying for each their affiliation (i.e., outside entity) and if an NIH Employee or Non-NIH Employee. *Covered individuals are personnel who have independent decisional roles in conducting a specific covered research protocol. These individuals are influential in the design, direction, or conduct of a covered research protocol, or engaged in the analysis or interpretation of data. Individuals who participate only through isolated tasks that are incidental to the research (for example, scheduling patient tests), and those individuals who support research of many protocols through the performance of routine patient care tasks are not covered individuals. Covered Individuals include the principal investigator, personnel whose resume or CV is provided to a sponsor, personnel listed on a FDA 1572 Form, and personnel engaged in human subjects research, including but not limited to individuals who obtain informed consent or who make decisions about research eligibility. Others who have decisional responsibilities that meet the definition of a covered individual, e.g. as co-investigator, research nurse,*

associate investigators, or an individual who interprets or analyzes research data, are also covered individuals. The PI determines which individuals are "covered individuals" under this SOP. When protocols contain sub-studies that ask a research question about a product, it is possible that only those individuals involved in decisional roles in the sub-study are "covered individuals."

Enter Name, Affiliation, Employment Status and for NIH Employees enter Role on the study: (*Enter one person per row)*

Name:	Affiliation:	Employment Status	Role:
		FTE (Full-time Equivalent)	**Principal Investigator (PI)**
		FTE (Full-time Equivalent)	**Principal Investigator (PI)**
		FTE (Full-time Equivalent)	**Principal Investigator (PI)**
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		FTE (Full-time Equivalent)	**Principal Investigator (PI)**
		FTE (Full-time Equivalent)	**Principal Investigator (PI)**
		FTE (Full-time Equivalent)	**Principal Investigator (PI)**

Append a sheet with additional names and information if required.

The information below is for IRB information only and shall not be included on the protocol consent form.

[22] ☐ If applicable, a "Conflict of Interest (COI) Certification for Non-Federal Employees" form has been submitted.

[22] ☐ If applicable, a "Conflict of Interest (COI) Certification form for NIH Employees who do not file financial disclosure form 717-1 or 450" has been submitted

[22] ☐ No conflicts identified for NIH employees, or conflicts have been resolved through divestiture or waiver.

[23] ☐ No conflicts exist however one or more NIH employees have a *de minimis* holding in the manufacturer of the product(s) used in the study. Name of manufacturer(s):

[24] ☐ No conflicts exist however one or more NIH employees have an over the *de minimis* holding in the manufacturer of the product(s) used in the study and has been cleared to participate by waiver. Name of manufacturer(s):

Deputy Ethics Counselor for IC of P.I. Date Signed Date Returned to P.I.

Ethics Office Use Only: DER ☐ 8/3/2015

APPENDIX E: CONFLICT OF INTEREST (COI) CERTIFICATION FOR NIH EMPLOYEES WHO DO NOT FILE FINANCIAL DISCLOSURE FORMS 717 OR 450

This form should be completed by NIH employees who are covered individuals who do not file financial disclosure forms 450 or 717.

Covered individuals are personnel who have independent decisional roles in conducting a specific covered research protocol. These individuals are influential in the design, direction, or conduct of a covered research protocol, or engaged in the analysis or interpretation of data. Individuals who participate only through isolated tasks that are incidental to the research (for example, scheduling patient tests), and those individuals who support research of many protocols through the performance of routine patient care tasks are not covered individuals. Covered Individuals include the principal investigator, personnel whose resume or CV is provided to a sponsor, personnel listed on a FDA 1572 Form, and personnel engaged in human subjects research, including but not limited to individuals who obtain informed consent or who make decisions about research eligibility. Others who have decisional responsibilities that meet the definition of a covered individual, e.g. as co-investigator, research nurse, associate investigators, or an individual who interprets or analyzes research data, are also covered individuals. The PI determines which individuals are "covered individuals" under this SOP. When protocols contain sub-studies that ask a research question about a product, it is possible that only those individuals involved in decisional roles in the sub-study are "covered individuals."

Name:	
Role on Study:	
NIH Institute:	
Name of PI:	
Title of Protocol:	

I certify that I have received and read the NIH ***Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Human Subjects Research at NIH*** and that I will comply with the Policy. I certify I have no conflict of interest with this protocol. In the event I become aware of any potential conflict of interest, I will contact my ethics office.

_____ _____

(Signature) *(Date)*

APPENDIX F: CONFLICT OF INTEREST (COI) CERTIFICATION FOR NON-FEDERAL EMPLOYEES

This form should be completed by the Principal Investigator and signed by covered individuals who are not federal employees.

Covered individuals are personnel who have independent decisional roles in conducting a specific covered research protocol. These individuals are influential in the design, direction, or conduct of a covered research protocol, or engaged in the analysis or interpretation of data. Individuals who participate only through isolated tasks that are incidental to the research (for example, scheduling patient tests), and those individuals who support research of many protocols through the performance of routine patient care tasks are not covered individuals. Covered Individuals include the principal investigator, personnel whose resume or CV is provided to a sponsor, personnel listed on a FDA 1572 Form, and personnel engaged in human subjects research, including but not limited to individuals who obtain informed consent or who make decisions about research eligibility. Others who have decisional responsibilities that meet the definition of a covered individual, e.g. as co-investigator, research nurse, associate investigators, or an individual who interprets or analyzes research data, are also covered individuals. The PI determines which individuals are "covered individuals" under this SOP. When protocols contain sub-studies that ask a research question about a product, it is possible that only those individuals involved in decisional roles in the sub-study are "covered individuals."

Name of Non-NIH Employee:	
Role on Study:	
NIH Institute:	
Home Institution/Employer:	
Name of PI:	
Title of Protocol:	

I certify that I have received and read the NIH ***Guide to Avoiding Financial and Non-Financial Conflicts or Perceived Conflicts of Interest in Human Subjects Research at NIH*** and that I will comply with the Policy.

_____ _____

(Signature) *(Date)*

If applicable, I certify that my home institution/employer has a Conflict of Interest Policy and that I am in compliance with the Conflict of Interest policy of my home institution. I understand and agree that I must promptly inform the PI of this protocol if I am no longer in compliance with the Conflict of Interest policy of my home institution.

_____ _____

(Signature) *(Date)*

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: December 31, 2015

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated
Name of clinical investigator

as a clinical investigator in the submitted study _____
Name of

_____ is submitted in accordance with 21 CFR part 54. The
clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
FIRM/ORGANIZATION	
SIGNATURE	Date *(mm/dd/yyyy)*

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 5 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

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Office of Chief Information Officer
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: December 31, 2015

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
FIRM/ORGANIZATION	
SIGNATURE	DATE *(mm/dd/yyyy)*

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