RESEARCH INVOLVING MULTIPLE SITES

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The purpose of this policy is to provide guidance to DUHS investigators who conduct research at multiple sites. This guidance also applies to DUHS researchers who receive federal awards, grants, and contracts to support human subjects research, even if all human subjects activities are conducted at other sites.

1) A DUHS INVESTIGATOR CONDUCTS RESEARCH EXTERNAL TO DUHS

When a DUHS investigator plans to conduct research at a site or sites external to DUHS, and the site(s) will be engaged in research according to OHRP guidance*, the investigator must submit the following information to the DUHS IRB prior to any sites engaging in research:

In iRIS section 600:

- An Outside Key Personnel list to reflect the key personnel at the external site(s), in addition to a list of Key Personnel at Duke.

In section 1200, Multi-Site Research:

- Contact information for the site(s);
- Documentation that the site(s) has granted permission for the research to be conducted there;
- Documentation of whether the site(s) has an IRB and if so, whether it has approved the research or will rely upon the DUHS IRB;

The Research Summary (now embedded in the iRIS application) should include the following information:

- A description of the specific research activities to be conducted at the site;
- A description of the research activities to be conducted by the Outside Key Personnel listed in section 600.

<u>No research activities at the site, including ascertainment and recruitment, may begin until approval has been obtained from the DUHS IRB.</u>

The DUHS IRB will not act as IRB-of-Record for an institution located outside of the U.S. That institution must independently obtain IRB or Ethics Committee (EC) approval and forward a copy of the site IRB/EC approval to the Duke investigator.

A. Reliance on the DUHS IRB

If the site plans to rely on the DUHS IRB and regularly engages in research, and therefore possesses a Federal Wide Assurance (FWA), a reliance agreement such as the SMART IRB Agreement or IRB Authorization Agreement (IAA) between the site and DUHS must be established prior to the initiation of study activities at the site. The investigator will be responsible for consulting with the Director of Extramural IRB Programs who will oversee the completion of the applicable reliance agreement. If the IAA is used, any changes to the IAA that are requested by the external site will be reviewed and approved by the IRB Executive Director in conjunction with the Director of Extramural IRB Programs. If there are changes to the insurance/indemnification, the IAA will need to be reviewed by the Office of Research Contracts (ORC) as well. The site and the DUHS IRB will each maintain one fully executed copy of the agreement for inspection by OHRP, as requested.

If an external investigator plans to rely on the DUHS IRB, an Individual Investigator Agreement (IIA) between the external investigator and DUHS must be established prior to the initiation of any research activities. The investigator will be responsible for consulting with the Director of Extramural IRB Programs who will oversee the completion of the DUHS template IIA. Any changes to the IIA that are requested by the external investigator will be reviewed and approved by the IRB Executive Director in conjunction with the Director of Extramural IRB Programs. If there are changes to the insurance/indemnification, the IIA will need to be reviewed by the Office of Research Contracts (ORC) as well. The external investigator and the DUHS IRB will each maintain one fully executed copy of the agreement for inspection by OHRP, as requested.

If the site plans to rely on the DUHS IRB, the Outside Key Personnel list must reflect all personnel at the site who satisfy the DUHS IRB's definition of Key Personnel. These individuals will be required to complete ethics training as required by the external site. Individuals not already affiliated with an IRB (e.g., private physician's practice) with whom an IIA is executed are required to complete the Duke Health CITI modules and provide documentation of completion to the DUHS IRB.

B. Reliance on the Site's IRB

If the site has an IRB (or plans to use an independent IRB), and does not plan to rely on the DUHS IRB, the DUHS investigator is responsible for providing documentation of that site's IRB initial and continuing approval of the investigator's research at that site. In addition, the investigator is responsible for ensuring that the site's IRB approval is current, and for providing documentation of that approval to the DUHS IRB or assurance

that such current approval is on file with the Duke investigator's team. When the site is using an IRB other than the DUHS IRB, only the site's Principal Investigator must be named on the Outside Key Personnel list provided to the DUHS IRB.

C. Disseminating Protocol Information to Sites

At the time of initial and continuing review, the DUHS IRB will assess the procedures for promptly disseminating protocol information to all participating sites. Such protocol information includes unanticipated problems involving risks to participants or others, protocol modifications and interim findings, or for a specific site, a finding of serious or continuing non-compliance, or the suspension or termination of IRB approval. Any unanticipated problems occurring at the external site(s) that are related to the study must be reported to the DUHS IRB according to the Prompt Reporting policy.

D. Reporting to Federal Agencies

The DUHS IRB will follow its policy on Reporting IRB Findings to DUHS Officials and Federal Regulatory Agencies for instances of unanticipated problems involving risks to participants, serious or continuing non-compliance, or suspension or termination of IRB approval.

2) A DUHS INVESTIGATOR IS THE PRINCIPAL INVESTIGATOR ON A MULTI-SITE RESEARCH PROJECT

When a DUHS investigator is responsible for the overall conduct of a multi-site study that is federally funded, both the investigator and DUHS are engaged in research according to OHRP guidance*, *regardless of whether human subjects are enrolled at DUHS or identifiable private information is used for research by the investigator or others within DUHS*. To satisfy those responsibilities, the investigator must:

- Submit a blanket (administrative) protocol if the scope of human research will involve multiple separate research questions and therefore multiple separate IRB protocols;
- Submit a coordinating center protocol (see 3 below) if DUHS will also be the site of the coordinating center for this multi-site research;
- Submit a statistical center protocol (see 4 below) if DUHS will also be the site of the statistical center for this multi-site research;
- Submit separate IRB protocols to cover each aspect of the multi-site research involving human subjects that will not occur at DUHS in order for the DUHS IRB to:

    - Evaluate whether the management of information that is relevant to the protection of participants is adequate, including:
        - Reporting of unanticipated problems involving risks to participants or others;
        - Interim results;
        - Protocol modifications;
- Submit separate IRB protocols to cover each aspect of the research involving human subjects that will occur at DUHS;
- Submit a database and/or repository protocol if maintained at DUHS.

These IRB protocols will be reviewed initially and at the time of periodic continuing review according to the DUHS IRB policies and procedures that apply to them.

Federally Funded Multi-Site Research

If the research is federally funded, the Duke Principal Investigator will either: (i) at the time of initial review, provide an appropriate monitoring plan to the DUHS IRB describing how the Duke study team will ensure that external sites maintain current IRB approval and a current FWA for the duration of the study; or (ii) at each continuing review, provide copies of current IRB approval and current FWA number to the IRB. The IRB will follow its policy on Reporting IRB Findings to DUHS Officials and Federal Regulatory Agencies for instances of unanticipated problems involving risks to participants, serious or continuing non-compliance, or suspension or termination of IRB approval.

A DUHS investigator who wishes to add sites to his/her federally funded, multi-site study must do so via an amendment and follow the procedures described in section (1) above.

3) A DUHS INVESTIGATOR OVERSEES AN OPERATIONS OR COORDINATING CENTER FOR MULTI-SITE RESEARCH

When an operations or coordinating center for a multi-site research project is based at DUHS, both the leadership and staff of the center and DUHS as an institution will be engaged in research with humans according to OHRP guidance*. To satisfy the responsibilities of an operations or coordinating center, where activities at DUHS involve no interaction or intervention with subjects, the IRB will not review each collaborative protocol. However, the IRB will determine and document that the operations or coordinating center has sufficient mechanisms in place to ensure that (i) management, data analysis, and data safety and monitoring (DSM) systems are adequate, given the nature of the research involved; (ii) sample protocols and informed consent documents are developed and distributed to each collaborating institution; (iii) each collaborating institution holds an applicable OHRP-approved Assurance; (iv) each protocol is reviewed and approved by the IRB at the collaborating institution prior to the

enrollment of subjects; (v) any substantive modification by the collaborating institution of sample consent information related to risks or alternative procedures is appropriately justified; and (vi) informed consent is obtained from each subject in compliance with HHS regulations.

The IRB will initially receive from the operations or coordinating center lead investigator an IRB protocol submission containing documentation of how the center will ensure that the above six activities will be performed appropriately, and a listing of active sites and contact information for each site where research participation is to occur. At the time of initial review, the IRB will assess the procedures for prompt dissemination of protocol information to all participating sites. Such protocol information includes unanticipated problems involving risks to participants, protocol modifications and interim findings. At the time of each periodic continuing review, the investigator will provide the IRB with updated information about each of these items, including the six items noted above.

If during the course of the study, the DUHS Coordinating Center takes on the duties of the local investigator at one or more of the sites, then Duke will be considered to be conducting site-based research, exceeding the normal role of the Coordinating Center. In this case the Duke study team must promptly notify the IRB (via an amendment), and the IRB will review the study to reflect the new shift to site-based research (with Duke as a site).

4) A DUHS INVESTIGATOR OVERSEES A STATISTICAL CENTER FOR MULTI-SITE RESEARCH

When a statistical center for a multi-site research project is to be based at DUHS, both the leadership and the staff of the center and DUHS as an institution will be engaged in research with humans according to OHRP guidance*. To satisfy the responsibilities of a statistical center, where institutional activities involve no interaction or intervention with subjects, and the principal risk associated with institutional activities is limited to the potential harm resulting from breach of confidentiality, the IRB need not review each collaborative protocol. However, the IRB will determine and document that the statistical center has sufficient mechanisms in place to ensure that (i) the privacy of subjects and the confidentiality of data are adequately maintained, given the sensitivity of the data involved; (ii) each collaborating institution holds an applicable OHRP-approved Assurance; (iii) each protocol is reviewed and approved by the IRB at the collaborating institution prior to the enrollment of subjects; and (iv) informed consent is obtained from each subject in compliance with DHHS regulations.

The IRB will initially receive from the statistical center lead investigator an IRB protocol submission containing documentation of how the center will ensure that the above four activities will be performed appropriately, and a listing of active sites and contact information for each site where research participation is to occur. At the time of initial review, the IRB will assess the procedures for prompt

dissemination of protocol information to all participating sites. Such protocol information includes reports of unanticipated problems involving risks to participants, protocol modifications and interim findings. At the time of each periodic continuing review, the investigator will provide the IRB with updated information about each of these items, including the four items noted above.

Reference*

October 16, 2008 OHRP Guidance: Engagement of Institutions in Human Subjects Research

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