HRPP STANDARD OPERATING PROCEDURE/POLICY APPROVAL & IMPLEMENTATION

OFFICE OF HUMAN SUBJECTS RESEARCH PROTECTIONS

SOP Number: 23

SOP Title: QUALITY MANAGEMENT SYSTEM FOR THE NIH HUMAN RESEARCH PROTECTION PROGRAM (HRPP)

Distribution: Scientific Directors; Clinical Directors; Clinical Investigators, IRB Chairs, IRB Administrators, Protocol Navigators

Approval: _____ 2/24/16
Deputy Director for Intramural Research **Date**

Date of Implementation: 2-24-2016

Materials Superseded: **SOP 23 (ver. 2), dated 2-26-2014**
SOP 23 (ver. 1), dated 6-28-2013

SOP 23: QUALITY MANAGEMENT SYSTEM FOR THE NIH HUMAN RESEARCH PROTECTION PROGRAM (HRPP)

TABLE OF CONTENTS

SOP 23: QUALITY MANAGEMENT SYSTEM FOR THE NIH HUMAN RESEARCH PROTECTION PROGRAM (HRPP)

23.1 PURPOSE

NIH is committed to ongoing evaluation and improvement of the Human Research Protection Program (HRPP). This policy describes roles and responsibilities of entities involved in the NIH HRPP. It delineates procedures to identify the strengths and weaknesses of the HRPP and make improvements as needed.

23.2 POLICY

The DDIR, NIH Quality Officer, Institutes and Centers (ICs), Office of Human Subjects Research Protections (OHSRP), investigators and the IRBs work to carry out the NIH HRPP. These activities are divided among the entities (as described in **23.5**) and include the following:

A. Establish and implement NIH-wide assessment of compliance with federal regulations (45 CFR 46 and, as applicable, 21 CFR parts 50, 56, 312 and 812, see **References**) and NIH policies, and the quality, effectiveness and efficiency of HRPP activities;

B. Establish Quality Improvement (QI) efforts to address deficiencies in compliance and to improve the quality, effectiveness and efficiency of HRPP activities;

C. Evaluate effectiveness of IC QI efforts;

D. Ensure ongoing monitoring of individual research protocols within ICs;

E. Educate NIH personnel about Federal regulations (45 CFR 46 and, as applicable, 21 CFR parts 50, 56, 312 and 812, and **References** below) and guidance and NIH policies that ensure protection of human research subjects;

F. Continuously review regulatory developments and guidance and incorporate these as appropriate into the HRPP;

G. Develop policies to support the HRPP.

23.3 DEFINITIONS

For purposes of this SOP, some definitions comport with those of the FDA Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance (FDA GCP) (April 1996), see **References** below.

A. **Audit:** A systematic and independent examination of trial-related activities and documents to determine whether a particular HRPP research activity was conducted and the data were recorded, analyzed, and accurately reported according to specified requirements, such as protocol requirements, NIH IRB standard operating procedures (SOPs), FDA GCP (when applicable) and applicable regulatory requirements. For example, there may be questions about whether IRBs or researchers complied with specific regulatory requirements, or whether researchers and/or IRB members successfully completed the required HRPP training programs.

B. **Good Clinical Practice (GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. The NIH follows the FDA Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance (April 1996).

C. **The Human Research Protection Program (HRPP):** is the integrated means by which the NIH safeguards and promotes the health and welfare of human research subjects by ensuring that their rights, safety and well-being are protected, by providing timely and high quality education for investigators and research staff, by reviewing and monitoring human research projects, and by facilitating excellence in human subjects research. The objective of this system is to direct and oversee the organization in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

D. **The Human Subjects Research Advisory Committee (HSRAC):** This committee advises the DDIR on policies and procedures regarding the conduct of human subjects research in the NIH IRP. Members of the committee include all of the NIH IRB Chairs, the Director of the Clinical Center, the Deputy Director for Clinical Research, the Chief of the Clinical Center Department of Clinical Bioethics, the Director of OHSRP and representatives of the IRB Professional Administrators Committee and the NIH Fellows Committee (see **References**-Links to Websites.)

E. **The Intramural Clinical Research Steering Committee (ICRSC):** The ICRSC, Chaired by the Deputy Director for Intramural Clinical Research (DDICR), is advisory to the DDIR and is a forum for trans-NIH governance and policy development in the area of human subjects research. It is charged with providing guidance for the development, review and implementation of human subjects protocols; IRB operations, support and accountability; the scientific review of protocols, and Boards of Scientific Counselors' review of clinical programs.

F. **The IRB Professional Administrators Committee (IPAC):** This committee is composed of IRB administrative staff members, and representation from Institute/Center protocol navigators and the Clinical Center's Office of Protocol Services. It is dedicated to ensuring compliance with regulatory standards governing human subjects research by developing and promoting effective and consistent procedures and practices across the NIH Intramural Research Program.

G. **The Medical Executive Committee (MEC):** The MEC, comprised of the Clinical Directors of the NIH intramural clinical research programs and other senior medical and administrative staff, advises the Clinical Center Director and develops policies governing standards of medical care in the Clinical Center. The Committee represents and acts for the Medical Staff and other clinical professionals in the Clinical Center, and enforces the rules and policies of the Clinical Center.

H. **Inspection:** An official review and evaluation by a regulatory agency such as the FDA or OHRP of facilities, records, and any other resources that are deemed by the authority(ies) to be related to a specific aspect of clinical research.

I. **Monitoring:** The act of overseeing the progress of a specific research study and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, NIH HRPP policies, standard operating procedures (SOPs), FDA GCP (when applicable), and the applicable regulatory requirement(s). This is a continuous process throughout the life of a research protocol. Monitoring activities are the responsibility of each IC. The entity/individual responsible for the monitoring should be documented in writing or in IC policy (ies).

J. **Quality Assurance (QA):** A systematic evaluation of program functions to maximize the probability that quality standards are being attained. In the context of clinical research this means auditing NIH organizational systems to determine

whether they are effectively meeting established NIH HRPP policies and regulatory requirements. QA includes a systematic and independent examination of study related activities and documents, including IRB operations. Audits are used to implement QA work.

K. **The Quality Assurance Professionals Advisory Committee (QAPAC)**: QAPAC is an NIH-wide committee consisting of QC/QA/QI representatives from each IC. The committee meets once a quarter for the purpose of sharing best practices and concerns about specific QC/QA/QI issues.

L. **Quality Control (QC):** A process by which entities review the quality of work products. In the context of clinical research, this means continuously monitoring the progress of a specific clinical research protocol to verify that the protocol is being conducted and data are being generated, collected, recorded, analyzed and reported according to federal regulations and NIH policy. This requirement has been a long-standing component of the NIH Standards for Clinical Research.

M. **Quality Improvement (QI):** A series of actions taken to correct or improve the conduct of human subjects research by comparing the outcomes of monitoring and auditing activities that show the difference in the actual performance of research teams or IRBs compared with the established HRPP policies.

23.4 QC/QA/QI INTERACTIONS

A. QC, QA and QI activities intersect with other HRPP activities, particularly IRB activities. As permitted by law and policy, information should be exchanged between components of the HRPP. For example, if results of QC or QA activities indicate an unanticipated problem such as non-compliance with regulations, protocol requirements or NIH HRPP policies, this information must be reported to the relevant IRB as required by SOP 16 - Reporting Requirements for Unanticipated Problems, Adverse Events, and Protocol Deviations and SOP 16A **-** Allegations of Non-Compliance with Requirements of the NIH Human Research Protection Program (HRPP).

B. Compliance problems that are identified during the course of quality assurance activities should be addressed following the processes outlined in SOP 16A **-** Allegations of Non-Compliance with Requirements of the NIH Human Research Protection Program (HRPP).

23.5 ROLES AND RESPONSIBILITIES

23.5.1. RESPONSIBILITIES OF THE INSTITUTIONAL OFFICIAL (IO) AND NIH-WIDE REQUIREMENTS

The Institutional Official (IO) for NIH is the Deputy Director for Intramural Research (DDIR) who is responsible for oversight of the NIH HRPP QC, QA and QI activities. Some of these responsibilities are delegated to the Institutes, the QI Officer, OHSRP and IRBs, as delineated in this policy.

In addition to the HRPP SOPs, specific NIH-wide requirements that support the HRPP include:

A. Training in human subjects research protections is required and documented for all individuals engaged in such research so that PIs, CDs, OHSRP and IRBs can ensure that these requirements are met. See SOP 25 - Training Requirements for the NIH Human Research Protection Program (HRPP) for additional information;

B. Potential conflict of interest (COI) is reviewed and addressed, if needed, before a protocol can proceed. For more information, see SOP 21 - Conflict of Interest Requirements for Researchers and Research Staff;

C. All studies must address the need for monitoring;

D. All Cooperative Research and Development Applications (CRADAs) are reviewed to determine whether they require IRB review before approval;

E. All Institutes/Centers conduct an annual audit of aspects of their HRPP responsibilities;

F. HSRAC meets regularly to facilitate consistency and quality improvement within all IRBs, and to set policies on human subjects research protections;

G. The Intramural Clinical Research Steering Committee meets regularly to address issues related to clinical research, including issues related to the NIH HRPP;

H. In conjunction with the DDIR and OHSRP, MEC may develop certain policies related to HRPP and monitors compliance with the “Standards for Clinical Research within the NIH Intramural Research Activities”, see **References** below;

I. All researchers are expected to comply with HRPP SOPs, NIH Medical Administrative Series (MAS) policies (when at the Clinical Center) and the “Standards for Clinical Research within the NIH Intramural Research Activities”, (see **References**) as they pertain to the program of human subjects research protections and See SOP 19 - Investigator Responsibilities;

J. NIH expects that investigators will cooperate with the activities described in this SOP.

23.5.2. RESPONSIBILITIES OF THE AGENCY RESEARCH INTEGRITY OFFICER (RIO)

The NIH RIO reports directly to the DDIR and reviews all allegations of research misconduct and develops training in research ethics. Additional duties include:

A. Consults with IC QA personnel, the DDIR and the OHSRP Director (as applicable) about QA needs related to these responsibilities;

B. Chairs a committee of IC QA/QC personnel, QAPAC, to share best practices and concerns.

23.5.3 RESPONSIBILITIES OF OHSRP

The DDIR delegates many day-to-day responsibilities for QA/QI to OHSRP. Those responsibilities include:

A. Works closely with IC QA personnel to assist when an IC or IRB identifies a need for a QA review;

B. Provides guidance to ICs and to the QA/QI staff on corrective actions;

C. Reviews ICs’ annual reports on QC/QA/QI activities to identify trends and to determine if systemic changes are required to prevent re-occurrence. If so, the Director and other relevant parties such the IO, the IRB Chairs, the Clinical Director, and/or other IC leadership will collaborate in the development of a corrective action plan, its implementation, and evaluation of its effectiveness.

D. Ensures that corrective action is taken as needed;

E. Develops educational programs/announcements for investigators and their research staff, via website, to disseminate formal and informal guidance;

F. Continuously reviews federal regulations and incorporates changes as appropriate into the NIH HRPP education program, SOPs and policies;

G. Provides initial one-on-one education of IRB members and ongoing education of IRBs through retreats and presentations;

H. Works to obtain and maintain the Association for the Accreditation of Human Research Protections Programs (AAHRPP) accreditation. This includes maintenance of applicable documentation representing current policy and procedures; utilization of the AAHRPP Self-Evaluation Instrument; and evaluation of current HRPP practices to ensure appropriate fulfillment of accreditation standards;

I. Reviews reports of unanticipated problems to identify gaps in understanding and conduct;

J. Updates technology within OHSRP to provide data for quality assessment, (e.g., computerization of forms that request a determination of exempt from IRB review);

K. Develops standards and procedures for evaluation of NIH IRB operations as well as the performance of IRB Chairs, members, and IRB staff, as indicated in SOP 26 - Evaluation of NIH IRB Chairs, Vice Chairs and Members, IRB Administrative Staff and IRB Committee Activities;

L. Conducts annual review of IRB and IRB Chair performance (see SOP 26 - Evaluation of NIH IRB Chairs, Vice Chairs and Members, IRB Administrative Staff and IRB Committee Activities);

M. Assists as needed in evaluation of non-compliance as set forth in SOP 16A - Allegations of Non-Compliance with Requirements of the NIH Human Research Protection Program (HRPP).

N. Tracks internal metrics that are informative in considering IRB and Investigator efficiency such as the amount of time from receipt of a submission through pre-review, assignment to the IRB, and final approval and the amount of time it takes investigators to develop and submit responses to pre-review and IRB requirements. IRBs will provide metrics reports to OHSRP annually. OHSRP will collate these and present to the CDs and IRB Chairs.

O. Annually, the Director, in collaboration with other relevant parties, will define Quality Improvement goals for the year. The targeted issues, goals, and means to measure progress are documented in a written QA/QI plan. To evaluate whether the defined goals are being achieved, OHSRP staff collect, record, and provide a written report to the Director for tracking purposes. At the end of each review cycle, the Director and the IO evaluate whether the respective goals were achieved and adjust the affected processes to correct any deficiencies.

23.5.4 RESPONSIBILITIES OF THE INSTITUTES/CENTERS

A. Designate QC/QA/QI functions to a specific individual or individuals.

B. Develop an IC QC/QA/QI plan.

C. Define annual goals for IC QC/QA/QI activities.

D. Oversee data collection using audits, surveys or other tools to implement annual goals and review HRPP performance.

E. Participate in NIH-wide QC/QA/QI activities for sharing information about best practices.

F. Annual reporting to OHSRP of all IC QC/QA/QI activities, including the following:

1. Internal and external audits, reviews and surveys;

2. Actions in response to monitoring reports;

3. Any investigations of non-compliance;

4. Any trends noted in QC/QA/QI activities.

5. Progress with annual QA/QI goals

G. Conducts routine and for-cause audits based on the IC QA plan.

23.5.5 RESPONSIBILITIES OF THE IRBS

A. Ensure that auditing and monitoring plans and potential conflict of interest are addressed in each protocol.

B. Review allegations of non-compliance as set forth in SOP 16A - Allegations of Non-Compliance with Requirements of the NIH Human Research Protection Program (HRPP).

23.5.6 RESPONSIBILITIES OF THE QAPAC

A representative of the DDIR/IO Chairs this committee, which reviews issues related to Quality Assurance at the NIH. The DDIR encourages this committee to make recommendations about goals for NIH-wide QC/QA/QI activities.

25.5.7 SHARED RESPONSIBILITIES

A. The IRBs, Institutes/Centers and/or OHSRP develop corrective plans as needed in response to findings of internal and external investigations and inspections.

B. The Institutes/Centers and OHSRP share responsibility for ensuring appropriate education and training of clinical investigators on their roles and responsibilities.

C. OHSRP and HSRAC determine and annually review requirements for minimal training and for refresher training for research staff.

D. OHSRP and Institutes/Centers implement corrective plans to address performance gaps.

E. OHSRP, IRBs or an institutional official receive, investigate and respond to allegations of non-compliance (see SOP 16A - Allegations of Non-Compliance with Requirements of the NIH Human Research Protection Program (HRPP)).

REFERENCES

A. Human Research Protection Regulations (45 CFR 46):
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

B. FDA regulations - Informed Consent and Children (21 CFR 50):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50

C. FDA regulations – Institutional Review Boards (21 CFR 56):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56

D. FDA IND regulations (21 CFR part 312):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

E. FDA IDE regulations (21 CFR part 812):
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=812

F. FDA Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance (GCP):
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073122.pdf

G. Human Subjects Research Advisory Committee (HSRAC):
https://federation.nih.gov/ohsr/nih/hsrac.php

H. “Standards for Clinical Research within the NIH Intramural Research Program” October 2009: http://www.cc.nih.gov/ccc/clinicalresearch/standards1.html

I. NIH Medical Administrative Series (MAS) Policies:
http://intranet.cc.nih.gov/mec/mas/index.shtml

J. Association for the Accreditation of Human Research Protections Programs (AAHRPP): http://www.aahrpp.org/