# Role of the IRB in Human Subjects Research

Richard D. Stevenson, M.D.

Chair

Institutional Review Board for

Health Sciences Research (IRB-HSR)

**University of Virginia**

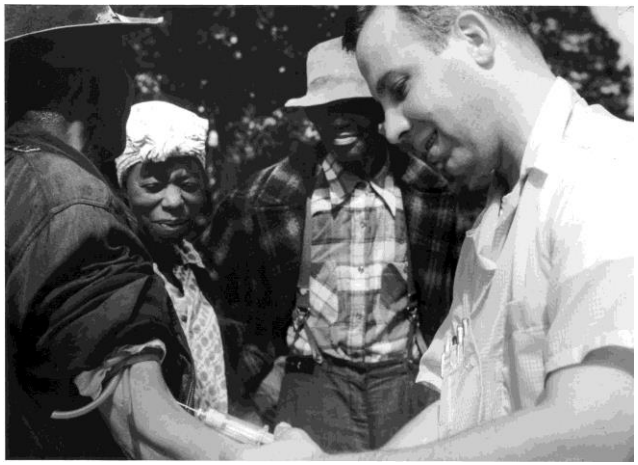
**Office of the Vice President for Research (VPR)**

# Disclosures

- The following speaker indicated that he had no financial relationship with any commercial interest relevant to his presentation:
  - Richard D. Stevenson, M.D.

# PHS Syphilis study: Guatemala

- In 2009 Prof Susan Reverby of Wellesley College discovered archived papers of PHS Medical Officer John Cutler, a Tuskegee investigator
- Unpublished report of studies in 1946-48 involving vulnerable populations intentionally infected with STDs
- Funded by NIH and done with knowledge of Cutler's superiors
- Intent of the study was to look ways to prevent STDs



# Details of Guatemala studies

- Infected female sex workers with gonorrhea or syphilis and arranged “visitation” with soldiers or inmates
- Began direct inoculation of soldiers, prisoners, mental hospital inmates
- ~1,500 subjects; most, but not all, received some treatment
- Institutional officials aware of study; subjects not aware of purpose of study and not consented

# News goes public October 1, 2010

- Secretary of State Hilary Rodham Clinton offer formal apology: “abhorrent,” “unethical”
- President Barack Obama calls Guatemalan President Colon to express his “deep regret”
- Institute of Medicine and President’s Bioethics Commission scheduled to provide reports
- Media coverage frenzied and worldwide
- October 11 JAMA editorial by directors of NIH and CDC: “regrettable and deeply saddening”

# Evolution of Human Subjects Research and Guidelines

**Table.** Evolution of Human Subjects Research and Guidelines

| Year | Event |
|---|---|
| 1932-1972 | Tuskegee Syphilis Study |
| 1939-1944 | Experiments on concentration camp prisoners by Nazi scientists |
| 1944-1974 | Secret human radiation experiments |
| 1946-1948 | Guatemalan STD inoculation studies |
| 1947 | Nuremburg Code |
| 1950 | NIH Clinical Center requires informed consent for its studies |
| 1953-1954 | Sing Sing Prison syphilis inoculation study |
| 1956-1972 | Hepatitis studies at Willowbrook State School for the Retarded |
| 1960 | NIH Clinical Center requires independent ethical review for its studies |
| 1962 | Kefauver-Harris drug amendments |
| 1963 | Jewish Hospital cancer study |
| 1964 | World Medical Association Declaration of Helsinki |
| 1966 | US Surgeon General policy statement on human subjects research (IRB origin) |
| 1971 | NIH Office for Protection from Research Risks established |
| 1974-1978 | National Commission for the Protection of Human Subjects |
| 1974 | HHS regulations for human subjects research |
| 1975 | CDC Office of Human Research Protections established |
| 1978-1983 | President's Commission for the Study of Ethical Problems |
| 1979 | Belmont Report released |
| 1981 | HHS 45 CFR 46 and Food and Drug Administration 21 CFR 50, 56 regulations published |
| 1985 | NIH Clinical Center Bioethics Program founded |
| 1991 | 45 CFR 46 (Common Rule) adopted |
| 1993 | CIOMS guidelines released |
| 1994 | Presidential apology for secret radiation experiments |
| 1995 | World Health Organization Guidelines for Good Clinical Practice |
| 1996- 2001 | National Bioethics Advisory Commission |
| 1996 | Department of Bioethics established at NIH Clinical Center |
| 1997 | Presidential apology for Tuskegee |
| 1998 | NIH support for bioethics training and research expanded |
| 1999 | NIH support for international research and ethics training |
| 2000 | World Health Organization operational guidelines for ethics committees |
| 2001-2009 | President's Council on Bioethics |
| 2002 | Secretary's Advisory Committee on Human Research Protections |
| 2005 | UNESCO Universal Declaration on Bioethics and Human Rights |
| 2009 | Executive order to create Presidential Commission for the Study of Bioethical Issues |

Abbreviations: CDC, Centers for Disease Control and Prevention; CFR, Code of Federal Regulations; CIOMS, Council for International Organizations of Medical Sciences; HHS, Department of Health & Human Services; IRB, institutional review board; NIH, National Institutes of Health; STD, sexually transmitted disease; UNESCO, United Nations Educational, Scientific and Cultural Organization.

**Frieden, TR and Collins, FS. JAMA 2010;0:jama.2010.1554v1-2.**



JAMA

# Is the public safe?

- Ethical violations in Guatemala studies
  - Study subjects vulnerable populations
  - Intentional infection of subjects with serious pathogens
  - Deception used
- Could such ethical violations occur today?
  - "… the answer is no. All federally funded research projects … must be reviewed by an institutional review board (IRB) before proceeding,…"
- "…continued scrutiny of guidelines governing research involving human subjects remains critical."

**Frieden, TR and Collins, FS. JAMA 2010;0:jama.2010.1554v1-2.**

# IRB: An Alternate Reality?

# Learning Objectives

- Discuss the differences between clinical research, clinical care, practice improvement
- Describe some principles of ethical human search
- Describe the role of the IRB in clinical research
- Highlight some changes coming soon
- Discuss how to work with your IRB

# Take Home Points

- Research with human subjects is not easy; it is complicated and changing
- Major changes will be implemented soon
- IRB is PRO-research…intended to help, not hinder (may not seem like it)
- IRB staff are highly skilled and knowledgeable and service oriented

# Start at the beginning…training

- Institutional Training
- CITI = Collaborative Instructional Training Initiative
  - Web-based training for investigators
- PRIM&R = Public Responsibility in Medicine and Research
  - Regional and national programs
  - Online training for IRB members

# Distinction between clinical practice & clinical research

- Clinical practice, defined:
  - interventions that are designed solely to enhance the well-being of an individual patient and that have a reasonable expectation of success
- Clinical research, defined:
  - activity designed to test a hypothesis, permit conclusions to be drawn, and thereby develop or contribute to generalizable knowledge; usually described in a formal protocol that sets forth an objective and a set of procedures
- What about Quality Improvement or Public Health?

# Quality Improvement

- Implementation of accepted practice to improve the delivery or quality of care and data collection is to evaluate the effects of the change in practice
- Data collection (including biospecimen) and analysis for an institution's own internal operational monitoring and program improvement processes
- In general this means:
  - No interaction with patients for data collection beyond what is done for clinical care and/or data gathered from medical records and
  - No sharing of data from project outside UVA then project is QI and ***no review by the IRB is required***

# Quality Improvement vs Research

- Some projects may not be so clear to determine, if involve interaction with patient and so IRB offers help: Determination of Human Subjects Research Form
- Some examples may not need IRB review:
  - Implementation of practices with sufficient published evidence that make it standard of care/best practice
  - Practices unique to UVA not likely of interest to anyone else
  - Increasing compliance with an intervention that is already standard of care

# The blurred line…

- Confusion between research and care
  - Distribution of possible risks & benefits is different in research versus therapy
- Therapeutic misconception
  - Misunderstanding by patients that they will benefit, even after informed consent
- Blurred roles of clinician and researcher
  - Potential conflict of interest
  - Potentially conflicting role is difficult for patients to understand
  - Often research is combined with clinical care

# Why does the IRB exist?

- Involves first identifying what is research and distinguishing from clinical care, public health, and quality improvement initiatives
- The IRB exists to protect research participants by reviewing human subject research from the standpoint of its ethical conduct

# How are subjects protected?

- Ethical Codes
  - Nuremberg Code
  - Declaration of Helsinki
  - Belmont Report
- Federal Regulations
  - Regarding Informed Consent
  - Regarding IRB's
- Guidance documents
- IRB Standard Operating Procedures
  - Internal policies governing how your IRB does business

# Ethical Principles in Belmont Report

- Respect for Persons
  - Informed consent, privacy and confidentiality, special protections for vulnerable populations
- Beneficence
  - Do good; do no harm
  - Minimize risks, balance risks and benefits
- Justice
  - Select research participants equitably
  - Share the risk; share the benefit

# DHHS Regulations: OHRP

- 45 CFR 46, Subpart A: Adopted in 1981
  - Became known as Common Rule in 1991
- Subpart B- Protections pertaining to research, development, and related activities involving fetuses, pregnant women and human in vitro fertilization
- Subpart C- Protections pertaining to biomedical and behavioral research involving prisoners as subjects
- Subpart D- Protections for children involved as subjects in research

# Food & Drug Administration

- Separate regulations
  - 21 CFR 56 – IRBs
  - 21 CFR 50 – Informed consent

Based primarily on use of FDA regulated products: drugs, devices, or biologics

# FDA & DHHS Regulations

- Basic requirements for IRBs and for Informed Consent are similar

- Differences in applicability
  - DHHS based on federal funding
  - FDA regulations based on FDA-regulated products ( study involves a drug, device or biologic)

# Ethics *versus* Regulations

- Both intend to protect human subjects
- Belmont report does not mention how human subjects are to be protected
- Federal regulations scarcely mention ethics nor the function of ethics in protecting human subjects
- IRBs must “put a hand in each glove”

# Basic Protections in Action for Subjects in Human Research

- Institutional Assurances
- IRB Review
- Informed Consent

# What is an institutional assurance?

- Called an FWA ( Federal Wide Assurance)
- The documentation of an institutional commitment to comply with Federal regulations and maintain adequate programs and procedures for the protection of human subjects
- The principle mechanism for compliance oversight by OHRP

# IRB Review

- The IRB review must review and oversee all research projects
- The IRB has authority to approve, require modifications or conditions in, or disapprove all research activities, including proposed changes in previously approved human research

# Requirements for approving human subjects research

- Risks to subjects are minimized
- Risks to subjects balanced by anticipated benefits to subjects and/or society
- Equitable selection of subjects
- Informed consent appropriately obtained
- Informed consent appropriately documented
- Adequate procedures in place to monitor subject safety
- Adequate procedures in place to protect privacy and confidentiality

Per federal regulations 45 CFR Part 46.111 (DHHS) and 21 CFR Part 56.111 (FDA)

# Informed Consent

- Unless authorized by IRB, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative
- Informed consent document
- Informed consent process

# Assessing Risk: What is "minimal risk"?

- Minimal risk is only risk defined
- Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(h)(i))

# In addition to IRB full board review…

- If applicable to your research, you might need approvals from other committees
  - Protocol Review Committee (PRC)
  - Radiation Safety Committee (RSC)
  - Institutional Biosafety Committee (IBC)
  - Materials Support Services (Device Studies)
  - Information Security, Policy, and Records Office (ISPRO)
  - SOM Clinical Trials Office (Physician sponsored IND or IDE or physician-sponsored multi-site trials)
- Contact information found in Protocol Builder

# Review by IRB-HSR Full Board

23 members on the IRB-HSR full board

- Chair, non-scientists, community reviewers, prisoner advocate, PIs and study coordinators, attorney, cardiology, neuropsychiatric services, oncology, pediatrics, internal medicine, surgical oncology, neurology, pharmacy services, radiology, statistics
- Pediatric representative is John Barcia
- Full Board meets twice monthly on 2nd and 4th Tuesdays of the month at noon in basement conference room of MR-6

# Full board review

- Process
  - Pre-Review and Submission
- Five possible review outcomes:
  - Approvable
  - Approvable with Conditions
  - Deferred
  - Disapproved
- Timeframe from submission to comments back takes about two weeks

# Life after IRB approval…

- Advertisements
- Modifications
- Continuing review
- Protocol violations
- Adverse event reporting
- Post Approval Monitoring (PAM)
- Protocol/grant closure

# Final Common Rule Updates

- 2011 Advance Notice of Proposed Rule-Making
- 2015 Notice of Proposed Rule-Making
  - Robust discussion with 2100 public comments
  - Influential Reports
- 2017 New Rule
  - Announced January 20, 2017
  - Goes into effect January 19, 2018
- Single IRB of Record not required for all research until January 19, 2020

# Final Common Rule- Part A 45CFR46
# Major Revisions: Effective Date 1-19-2018

- Elimination of continuing review requirements for expedited protocols. *Still require annual update from study team- study active or closed?*
- Requires posting of consent documents for certain federally funded trials to a public website.
- Elimination of grant review by the IRB.
- Revised “exempt” categories: chart review collecting retrospective or prospective identifiable health information in which data is protected by HIPAA- now exempt. IRB must also perform a data security review: e.g. Data Security Plan and Privacy Plan required.
- Requires use of a single IRB for most collaborative (multi-site) research. *This point not effective until January 19, 2018 .*

# Consent Changes

- Consent  must begin with a concise and focused presentation of the key info that is most likely to assist a prospective subject in understanding reasons why one might or might not want to participate.
- Required statements if collecting identifiable private info or identifiable specimens
- Statement clarifying if results will be given back to subject
- Notification if future research with biospecimens will involve whole genome sequencing.
- New wording required in Short Forms
- At UVA will be implemented at time of 5 year update for Full Board Protocols.

# NIH Single IRB Review Policy

- The NIH Policy requiring a single IRB to serve as the IRB of Record for all domestic sites on an NIH funded multi-site trial will go into effect on September 25, 2017 (postponed from May 25, 2017).
- This policy will go into effect for any Grant/Proposal submission to the NIH for a new grant/proposal or a competitive renewal of a grant/proposal submitted AFTER September 25, 2017.
- Multi-site studies within ongoing, non-competing awards will be expected to comply with the policy when a competing renewal application is submitted.
- This means that if additional subjects will be enrolled in the federally funded multi-site trial under the new funding, the IRB oversight of the study for all sites will need to be transferred to a single IRB of Record.

# Additional Information: NIH Single IRB Review

- Learning Shot: Single IRB Review for Multi-Site Studies
  - http://www.virginia.edu/vpr/irb/learningshots/Single_IRB_Review_LS_3-17-17/player.html
- NIH Single IRB Policy FAQs for Extramural Community
  - http://osp.od.nih.gov/sites/default/files/sIRB%20Extramural%20%20FAQs%20.pdf
- Scenarios to Illustrate the Use of Direct and Indirect Costs for Single IRB Review under the NIH Policy on the Use of a Single IRB for Multi-site Research
  - https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-109.html
- **UVA** IRB Reliance Agreements- Frequently Asked Questions
  - http://www.virginia.edu/vpr/irb/hsr/IRB_Reliance_Agreements-Frequently_Asked_Questions.docx

# What are the differences in sIRB policies: NIH vs Common Rule

NIH

- Requires a sIRB  for all domestic sites on an NIH funded multi-site trials
- Effective Date: September 25, 2017

Common Rule

- Requires use of a sIRB for most federally funded multi-site clinical trials.
- Effective Date: January 19, 2018

# Upcoming changes at UVA

## Major Updates to Protocol Builder: April 17, 2017

- *Please note:* if you have a protocol built in Protocol Builder that has not yet completed pre-review by the IRB you may have to re-answer the questions in Protocol Builder. You are encouraged to do one of the following things to make this transition easier:
  - Complete submission and pre-review prior to April 17th
  - Hold off on beginning a new protocol in Protocol Builder until after April 17th
  - If neither of the above options will work for you, save the Protocol Cover Sheet as a reminder of how you answered the questions so they may be re-answered if needed.

## UVA Human Research Protection Program (HRPP) Website ( by June 1st)

- New format- viewable on multiple types of devices
- Will combine common info from IRB-HSR and IRB-SBS Websites.
- Remaining info on IRB-HSR website will be converted to new format

# HRPP Accreditation

- Accreditation of the UVA Human Research Protection Program (HRPP) by the Association for the Accreditation of Human Research Protection Programs (AAHRPP)
- Application to be submitted summer of 2017
- Estimated site visit early 2018
  - Will interview researchers, staff of UVA compliance offices ( VPR, SOM G&C, SOM CTO, IRB etc.) and IRB members.
- Estimated review of application before AAHRPP Council- June or September 2018.

# IRB-HSR Submission Process

- IRB-HSR website
  - http://www.virginia.edu/vpr/irb
- Protocol Builder: Major Updates April 17, 2017
  - First time using Protocol Builder or just need help?
  - Please contact Eileen Sembrowich, IRB Associate Director, ecs3b@virginia.edu (3-6542) or Margaret Ball, IRB Coordinator, at mnw2h@virginia.edu (3-0639)

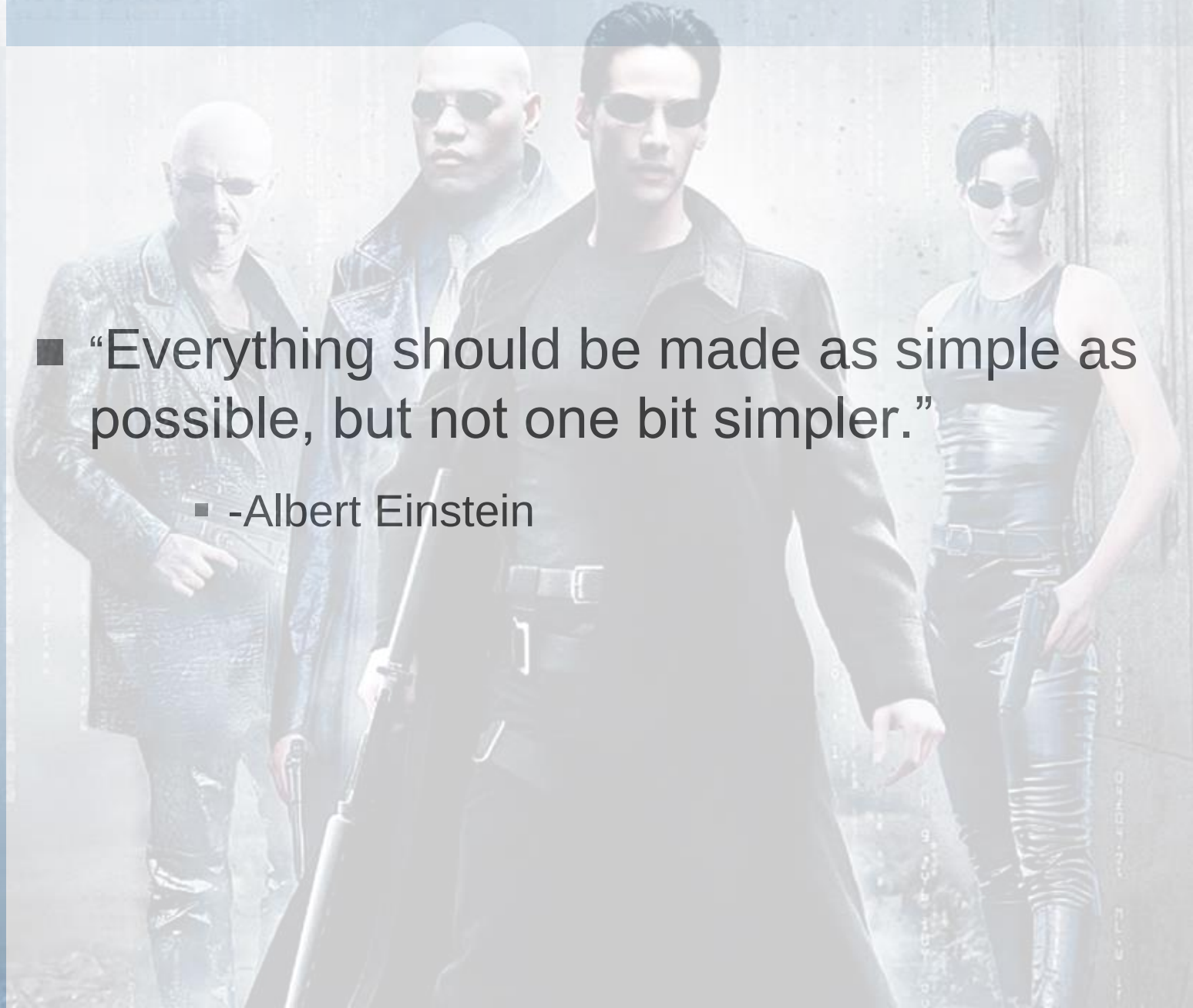
# Summary and Conclusions

- Research with human subjects is not easy; it is complicated and changing
- Major changes are coming soon
- IRB is PRO-research…intended to help, not hinder
- IRB staff are highly skilled and knowledgeable and service oriented

# Recommendations

- Get your basic training as required by the institution
- Regulations are on a need to know basis
- Get a certified research coordinator if you can
- Work with a biostatistician
- Get to know your IRB
  - Call them up on the phone
  - Go to the IRB meeting
  - Ask questions, try to understand
- If appropriate, push back (professionally)
- Volunteer to serve on the IRB

# Time for discussion



- “Everything should be made as simple as possible, but not one bit simpler.”
  - -Albert Einstein

# IRB-HSR Chair

**Richard Stevenson, M.D.**

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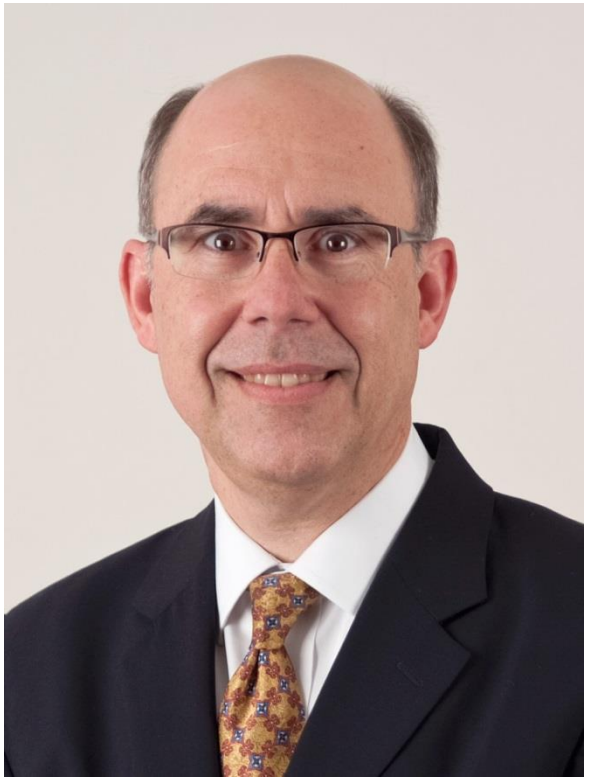

- Contact Regarding:
  - Subject Safety Concerns

# IRB-HSR Vice Chair

**J. Stephen Huff M.D.**

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**Contact Regarding:**

- Subject Safety Concerns

# IRB-HSR Director

**Susie Hoffman,** RN, BSN, CIP

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- **Contact Regarding:**
  - Policy Issues
  - Template Issues
  - IRB Reliance Agreements
  - Emergency Use
  - Compassionate or Treatment Use

# IRB-HSR Assistant Director

**Eileen Sembrowich** BS, BA, CCRP, CIP

243-6542

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- **Contact Regarding:**
  - Pre-Review of Full Board Submissions
  - Five Year Updates-Full Board Studies

# IRB-HSR Compliance Coordinator

**Karen Mimms,** RN,

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- Contact Regarding:
  - IRB Reliance Agreements

# IRB-HSR Compliance Coordinator

- **Margaret Ball**
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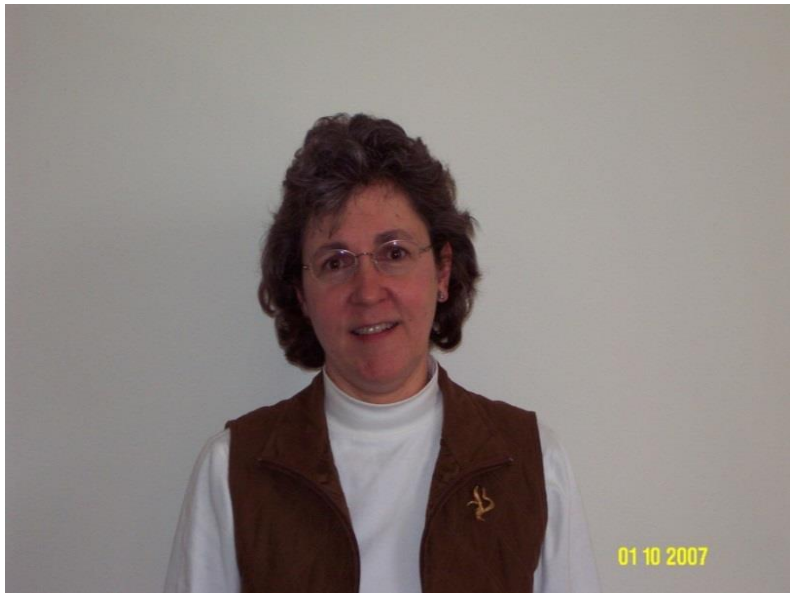
- Contact Regarding:
  - New Protocol Issues
  - Expedited Protocols



# IRB Compliance Coordinator

**Helena Estes-Johnson,**


- 243-0734
- hve5r@virginia.edu
- Contact Regarding:
  - Agenda Development
  - FU of new Full Board Submissions following IRB meeting

# IRB Compliance Coordinator

**Medard Ng, PhD CIP**

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- **Contact Regarding:**
  - Modifications
  - NCI Cancer Center CIRB Submissions

# IRB Compliance Coordinator

**Amy Blackman MSN, RN,**

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- Contact Regarding:
  - New Expedited Submissions
  - Adverse Events
  - Protocol Violations
  - Unanticipated Problems

# IRB-HSR Compliance Coordinator

- Andrea Ruhsam BS
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**Contact Regarding:**

- Full Board
  Modifications

# IRB Compliance Coordinator

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Contact Regarding:

- Continuations
- Closures
- Advertisements

# IRB-HSR Compliance Coordinator

**Joanna Faulconer**

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- Contact Regarding:
  - Human Subject Research Determinations
  - Exempt, Non-engaged
- Continuations
- Closures
- New Grants

# IRB Administrative Specialist

**Robert Banks- “Rob”**

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- Contact Regarding:
  - Personnel Changes
  - CITI Training

# IRB-HSR Administrative Specialist

**Florence Thoms**

243-7039

fgt@virginia.edu


- Contact Regarding:
  - General Information

Note: Florence works part-time

# Please note!

- Personnel may change at any time
- Please go to IRB-HSR website to obtain most current contact info