

Regulatory and Ethical Issues in Research 2017

Boston University

Henry M. Goldman School Of Dental Medicine

Afaf Hourani

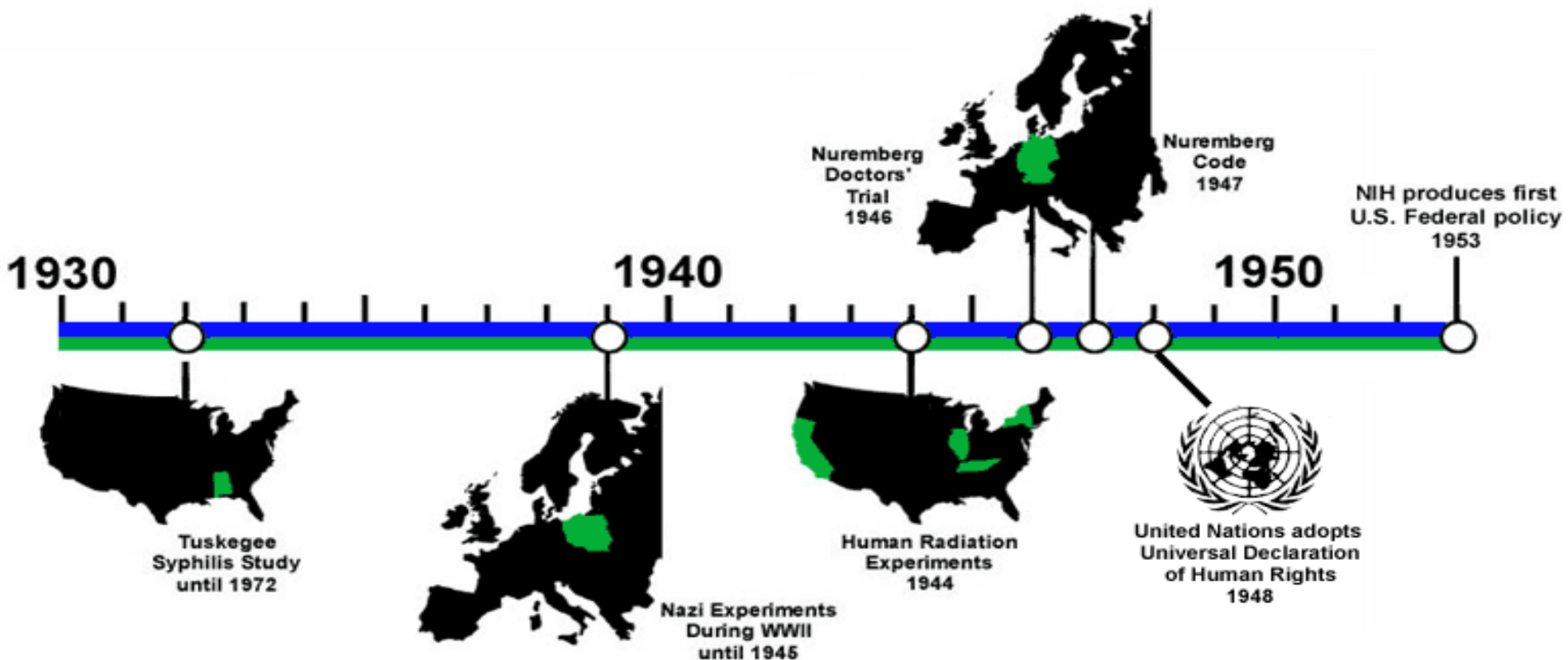


Background and Evolution of Research Ethics

- Clinical research has grown over the last fifty years from an informal activity to one intensely regulated and controlled by the federal government
- Biomedical research requires specialized knowledge, which includes regulatory requirements, good clinical practice (GCP) and medical ethics
- The Nuremberg Code served as the basis for the protection of human subjects since 1950. *“Voluntary consent of the human subject is absolutely essential”*
- The Declaration of Helsinki: the first set of ethics rules was established by the World Medical Association (WMA) in 1964. *“The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins”*
<http://www.wma.net/en/30publications/10policies/b3/index.html>
- The ICH GCP Guideline: The International Conference on Harmonization Good Clinical Practice 2002 version is an international ethical and scientific quality standard. *“A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)”*



Historic Events



Ethical Principles and Guidelines for the Protection of Human Subjects in Research

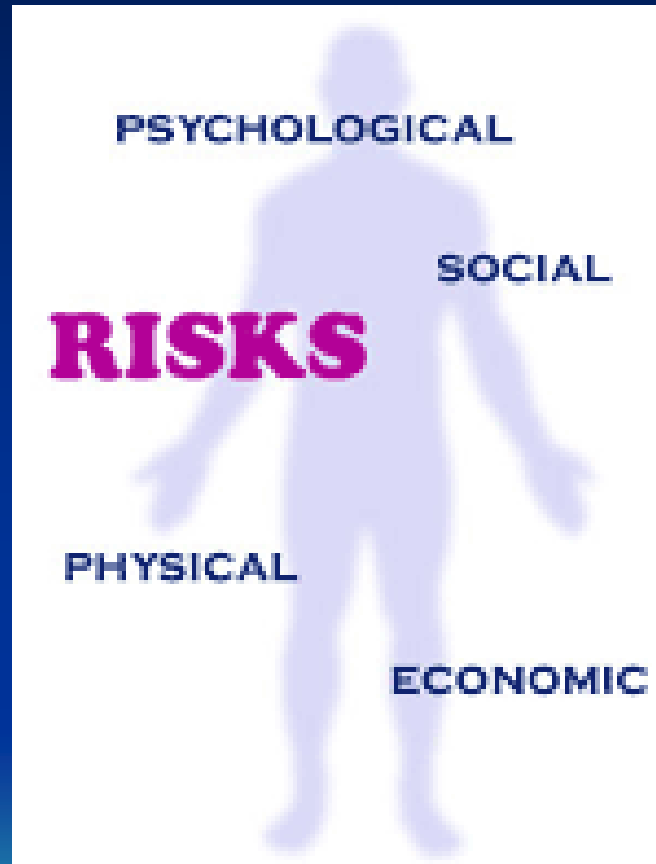
<http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>

The Belmont Report served since 1979 as the cornerstone of ethical principles upon which Federal regulations for the protection of human participants are based. “Scientific research has produced substantial social benefits. It has also posed some troubling ethical problems.” The following principles are the basis for all regulatory criteria applied by IRBs in assessing protocols and informed consents:

- Autonomy: Respecting Rights and self-determination of people that allows people make their own decision about research participation
- Beneficence: Ensuring physical, mental and social risks to potential subjects are minimized and are reasonable to potential benefits
- Justice: Ensuring that the distribution of risks and benefits are equitable through subject selection and recruitment of research participants



Assessment of Risks and Benefits



Minimal Risk



Minimal risk (45 CFR 46.102) is defined by the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The concept of minimal risk is used in the Federal policy:

- to determine if the proposed research should be reviewed by the entire Board or if it may qualify for expedited review
- to determine what research can proceed without consent
- to decide when documentation of subject consent may be waived

What Is Research?



Research is a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge (HHS, FDA, HIPAA)

- Systematic investigation means that there is a research question that you are trying to answer
- Generalizable knowledge means that the results are applied to other populations, published and disseminated

You must determine if the study is:

- Human subjects research
- Using already existing data
- Using coded data with a deciphering key

PERSPECTIVE

REGULATORY SCIENCE

Unmet needs: Research helps regulators do their jobs

Rees H. Brown,* Natalie Elvén, Marc LaRo,* Kathleen M. Glusman*****

A portfolio of innovations is making a positive impact on the nation's regulatory science. A number of these innovations are being used to improve the regulatory process. These innovations are being used to improve the regulatory process. These innovations are being used to improve the regulatory process.

Traditional biomedical science has emerged as a critical research focus over the past decade and a half. The scientific community has been focused on identifying the molecular mechanisms of disease. This focus has led to a number of breakthroughs in the treatment of disease. However, the regulatory process has not kept pace with these advances. The regulatory process is still largely based on the results of animal studies. This is a problem because animal studies are often not predictive of human outcomes. The regulatory process needs to be updated to reflect the advances in biomedical science.

Unmet needs are the areas where the regulatory process is currently lacking. These needs include the need for better data, the need for better tools, and the need for better processes. The regulatory process needs to be updated to reflect the advances in biomedical science. The regulatory process needs to be updated to reflect the advances in biomedical science.

Table 1. Strategic areas of regulatory science research. Information in the table is based on the findings of the National Academies of Sciences, Engineering, and Medicine (NASEM) report, "Regulatory Science: Opportunities and Challenges." The table is organized into three columns: Strategic area, Key challenges, and Key opportunities.

Strategic area	Key challenges	Key opportunities
Biotechnology	Complexity of biological systems, limited data, and limited tools.	Advances in genomics, proteomics, and metabolomics; improved data analysis tools; and improved regulatory processes.
Chemicals	Complexity of chemical systems, limited data, and limited tools.	Advances in toxicology, pharmacology, and other fields; improved data analysis tools; and improved regulatory processes.
Drugs	Complexity of drug systems, limited data, and limited tools.	Advances in clinical trials, pharmacokinetics, and other fields; improved data analysis tools; and improved regulatory processes.
Medical devices	Complexity of medical device systems, limited data, and limited tools.	Advances in engineering, materials science, and other fields; improved data analysis tools; and improved regulatory processes.
Food and drugs	Complexity of food and drug systems, limited data, and limited tools.	Advances in food safety, drug safety, and other fields; improved data analysis tools; and improved regulatory processes.

Source: National Academies of Sciences, Engineering, and Medicine (NASEM). "Regulatory Science: Opportunities and Challenges." Washington, DC: National Academies Press; 2017.

Regulatory Definitions of Human Subject and Research

- According to HHS, (45 CFR 46.102(f)), Human Subject means a living individual about whom an investigator (whether professional or student) conducting research obtains
 - (1) data through intervention or interaction with the individual, or
 - (2) identifiable private information
- According to FDA, a Human Subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control (21 CFR 50.3(g))



The Institutional Review Board (IRB)

In the United States, regulations protecting human subjects first became effective on May 30, 1974. Congress passed the National Research Act which required the establishment of IRB to protect the rights, safety, and welfare of human research subjects

Any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of research involving human subjects

BUMC IRB Policies and Procedures



IRB at BUMC

<http://www.bumc.bu.edu/irb/bumcirb/>

The IRB conforms with the requirements set forth in 45 CFR Part 46 and 21 CFR Parts 50 and 56. In addition to these mandates, the Board safeguards the rights and welfare of human subjects by making determinations regarding ethical standards and by evaluating the risk/benefit ratio of all studies

IRB at BUMC is comprised of review panels (blue, green, red and orange). IRB panels Blue and Green meet as determined by a schedule set at the beginning of the academic year.

Protocols approved by any of the three boards are covered by a Federal Wide Assurance number (FWA)

- <http://www.bumc.bu.edu/irb/bumcirb/irbassurancenumber/>



Human Research Protection Program (HRPP)

Boston Medical Center and Boston University Medical Campus Institutional Review Board (IRB) and the Office of Clinical Research (OCR) have been consolidated into a single entity called, the “Office of Human Research Affairs (OHRA)”.

OHRA is responsible for the oversight of the human subjects research conducted at BMC and the three schools on the BU Medical Campus, and is committed to ensuring that this research is conducted according to the highest ethical standards and in compliance with all regulatory requirements. This is accomplished through an effective and collaborative Human Research Protection Program (HRPP).



Criteria for IRB approval

<http://www.hhs.gov/ohrp/humansubjects/guidance/>

- Risks to participants are minimized – *research design*
- Risks are reasonable to anticipated benefits
- Selection of participants is equitable
- Informed consent is sought and appropriately documented
- Research plan – monitoring data collection and protecting the privacy of participants – *confidentiality*
- Protection of the rights and welfare of vulnerable population (*children, prisoners, pregnant women, mentally disabled, economically disadvantaged, or educationally disadvantaged*)
- Subjects must be protected from coercion



Clinical Research with Children.mht



Need for IRB Approval

- if you are reviewing medical records and you see the patient names and/or medical record numbers, even if you don't record them in your dataset, you are "obtaining" identifiable private information, so this, in fact, constitutes human subjects research
- If you are researching your own clinical database, then you have access to all data and any key to any codes; therefore, this requires IRB approval
- You can not reuse data without IRB approval



Types of IRB Review

- Full Board Review - approval of a majority of voting members
- Expedited Review
- Exempt Category

IRB Review Times and User Satisfaction

<http://www.bumc.bu.edu/irb/bumcirb/irb-review-time/>

Check with IRB regarding rules for international research



Exempt low-risk research

<http://www.hhs.gov/ohrp/policy/exmpt-pb.html>

What is “Exempt” Human Subject Research, And What Does It Mean?

Research does constitute human subjects and meets the requirements of a defined low-risk category exempt from some but not all requirements governing human subjects research.



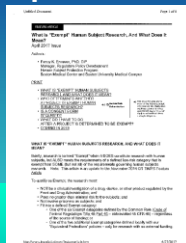
6 Federally exempt research categories

CRRO-Exempt-4-Tool.pdf

- Research in educational settings: instructional strategies, comparison of instructional techniques; Use of educational tests, surveys when information is recorded; Other educational tests, surveys where confidentiality is maintained, public observations (that do not involve children), studies of public officials; Studies of existing data, anonymous; public benefit or service program; consumer acceptance, taste and food quality studies

5 new additional categories: Equivalent protections - the study does not have external funding and fits into one or more of the equivalent protections Exempt categories.

Exemption does not apply to research involving prisoners, fetuses, pregnant women or newborn



Expedited

<http://www.hhs.gov/ohrp/policy/exprev.html>

- Research involving materials (*data, documents, records, or specimens*) that have been collected, or will be collected solely for non-research purposes (*such as medical treatment or diagnosis*);
- no more than minimal risk
- minor changes in approved research

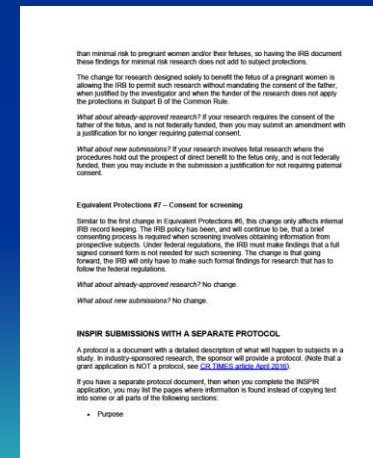
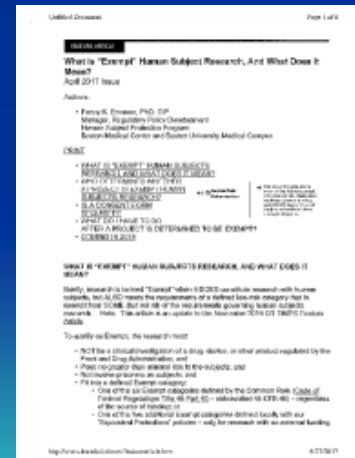
IRB chair or a designated member reviews the protocol



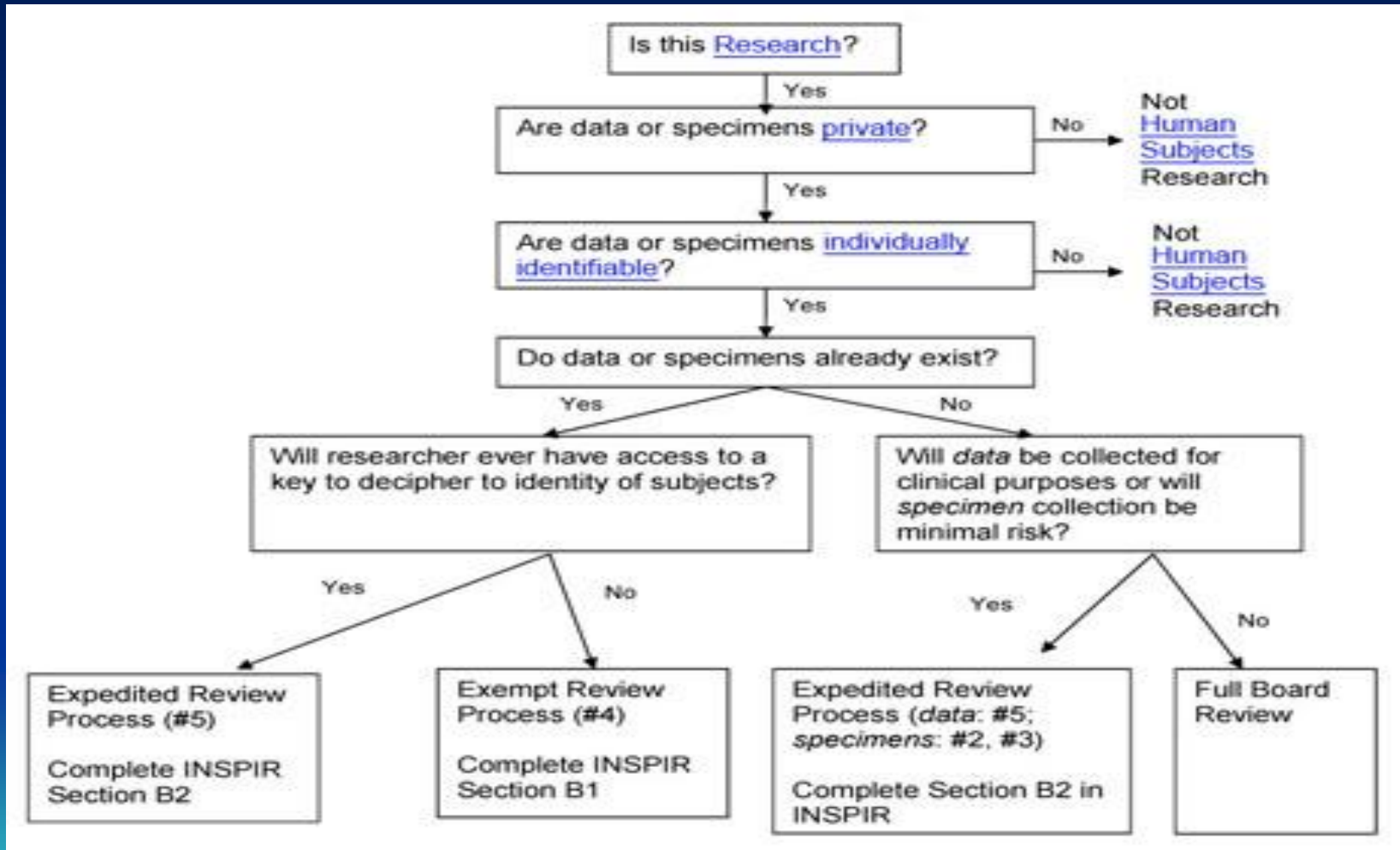
Altered IRB Requirements – Low-Risk Research

Human Research Protection Program HRPP

- Seven Equivalent Protections – Research must:
 - Not supported by federal funds (even a training grant)
 - Not be clinical investigation of a drug, device or other regulated by FDA
 - Not be required by sponsor or funder to follow federal regulations
 - Not use any clinical services (if billed to federal program)
 - Initially approved after Feb 14, 2011.
- Extended Approval Period Minimal Risk Research
- New Exempt Categories
- New Expedited Categories
- Children
- Prisoners
- Pregnant Women
- Consent for Screening



Type of Review Determination



Informed Consent Process

<http://www.hhs.gov/ohrp/policy/consentckls.html>

Informed Consent is a process, not a document. All research protocols that require Expedited or Full Board review are required to have a consent process and consent forms that contain all of the elements of consent Research Description; Risks; Benefits; Alternatives; Confidentiality; Compensation; Contacts; Voluntary Participation unless

- The IRB approves a waiver of consent for the protocol
- The IRB approves the waiver of certain elements of consent (including the requirement for documentation of consent)

Key Issues: clear and balanced description of potential risks and benefits, understandable information with regards to literacy level and language

IRB can waive the requirement for informed consent if :

- The research involves no more than minimal risk to the subjects
- The waiver or alteration will not adversely affect the rights and welfare of the subjects
- The research could not practicably be carried out without the waiver or alteration

[BUMC IRB Policies and Procedures](#)



Adverse Event Reporting

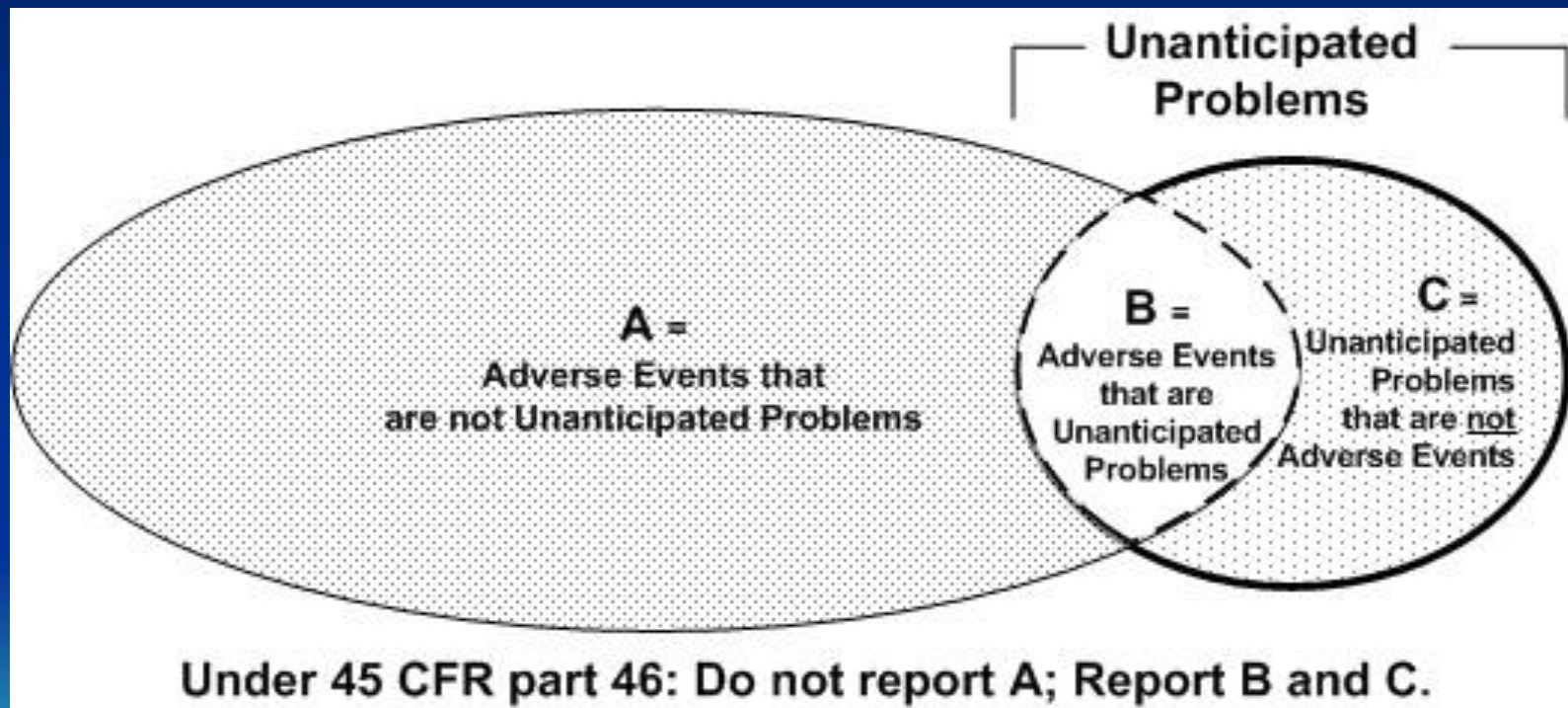
- The researcher and team should be familiar with the IRB policies, adhere to the policies, and maintain a copy of the policies in the research study file
- The researcher is responsible for accurate documentation, investigation and follow-up of all possible study-related adverse events
- The IRB must be notified of any unanticipated problem involving risks to participants or others, including physical or psychological injury to participants, improper disclosure of private information, economic loss, or other potentially harmful occurrences
- OHRP and the FDA regulations require prompt reporting of events that meet ALL of the following three criteria:
 - Be unexpected (*in terms of nature, severity, or frequency*)
 - Be related or possibly related to participation in research
 - Subjects or others at a greater risk of harm due to research
- ONLY events (internal or external) that meet all three criteria should be reported to the IRB within TWO business days of the investigators learning of the event:
 - Internal events if subject is enrolled by BUMC investigators
 - External events if subject is enrolled at other sites (non-BUMC)

Sponsors of FDA-regulated research are required to report SAEs to the sponsor, who reports them to the FDA

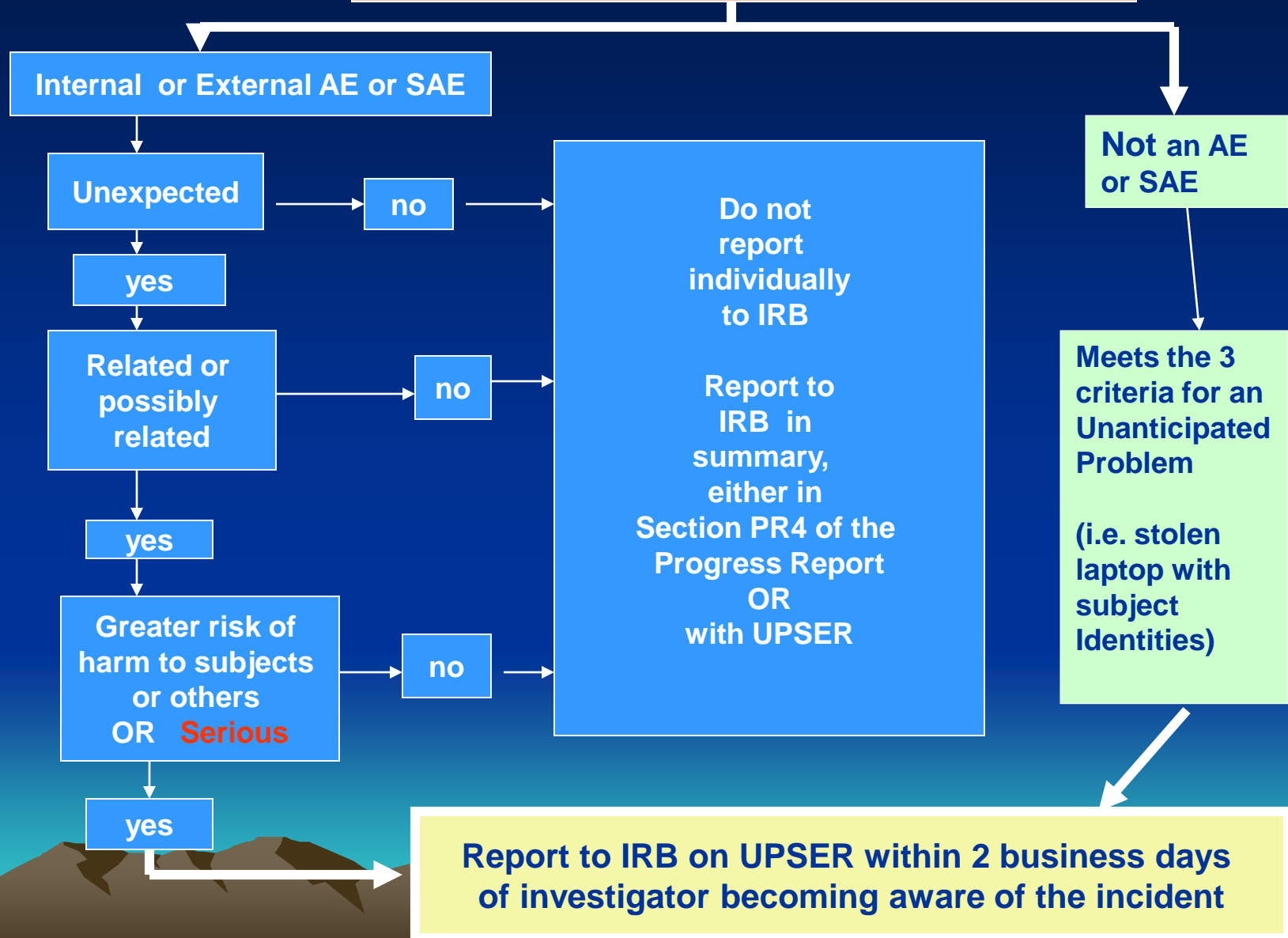


Reporting Unanticipated Problems

ONLY B and C should be reported to the IRB



Incident, experience, or outcome



Data Safety Monitoring Plans (DSMPs)

- All studies that are greater than minimal risk must have Data Safety Monitoring Plans (DSMPs)
- The IRB reviews these plans for confirmation that appropriate data monitoring is being done to ensure the safety of subjects
- Depending on the risks or complexities of the study, the IRB may require outside monitoring by a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC), as part of the DSMP
- The DSMP is part of the protocol, so when the protocol is approved so is the DSMP. The DSMP must be followed as written and modifications cannot be made without prior approval by the IRB. Failure to comply with the approved DSMP is considered to be serious non-compliance



IRB Applications / INSPIR II

<http://www.bumc.bu.edu/irb/>

<http://www.bumc.bu.edu/irb/inspir-ii/>

<http://www.bumc.bu.edu/irb/inspir-ii-instructions-for-investigators/>

<http://www.bumc.bu.edu/inspir/request/>

complete the information and submit the form. It takes 1-3 days to get a response in order for you to work on the protocol

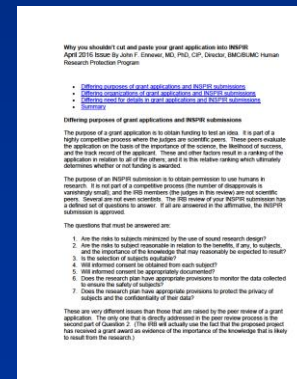
- New investigators with BU user-names & Kerberos passwords can be added to a protocol in INSPIR II (no “INSPIR registration is required)
- The PI can give access privileges to any member of the team by adding the member to the study protocol
- ONLY the Principal Investigator (PI) can initiate new protocols, submit progress reports (CR) and amendments and changes to the approved protocol
- Using submit button = PI's signature
- For amendments: Log on to my Homepage and Select “My Studies”. Locate the study that you wish to amend and click on “open” (red arrow)



INSPIR Submissions and Separate Protocol

- A protocol is a document (Grant application is NOT a protocol)
- In a separate protocol (drug and device clinical trials) list pages where information is found
- Do not copy from a grant and paste in the following parts of the protocol:

- Purpose
- Subjects
- Design/procedures
- Data safety and monitoring
- Screening procedures
- confidentiality



Animal Protocol

IACUC still uses the old INSPIR.

<http://www.bumc.bu.edu/inspir/>

New investigators with BU user-names & Kerberos passwords can be added to a protocol in INSPIR. (INSPIR registration is required)



Health Insurance Portability & Accountability Act



www.bumc.bu.edu/hipaa

- Federal law enacted in 1996 requires that each institution appoint a “Privacy Board” to review and approve research related HIPAA waivers of authorization
- The IRB at BUMC serves as the privacy board that reviews HIPAA as part of the overall IRB review

Principal Investigator (PI)

- PI must be a member of the staff or faculty at one of the institutions affiliated with BUMC
- Assumes responsibility for the conduct of research ensuring that the research is implemented as specified in the approved IRB protocol & reporting progress reports, adverse events, etc
- Must have sufficient expertise in the conduct of research
- Students, residents and fellows are allowed to serve as PIs
The faculty advisor or mentor must be listed as co-PI
- For IRB purposes all individuals who have contact with the subjects or their identifiable data for research purposes must be listed in the protocol



changes to IRB.mht



Initial IRB Approval

Submissions to the IRB After Initial Approval



Training Requirements

- All BUMC investigators and co-investigators having contact with human subjects or their identifiable data are required to be certified in human subjects protection and recertified every two (2) years
- BUMC CITI courses for the protection of human subjects in research and the HIPAA training at <http://www.bumc.bu.edu/ocr/instructions-for-taking-bumc-citi-courses/>
- Login as BU First Time and go to Biomedical Researchers and HIPAA. Completion certificates can be downloaded at the end of each course
- Training from other institutions are honored
- Ongoing training (*recertification - CR Times Articles*)



Ongoing Training - Recertification

www.bumc.bu.edu/ocr/certification

<http://www.bumc.bu.edu/ocr>

<http://bu.edu/crtimes>

- Required for investigators with primary affiliation at BUMC;
- involved in the design of clinical studies
- face-to-face contact with research subjects
- collect their data
- involved in statistical analysis and results interpretation

(Investigators, research coordinators, other study staff, study statisticians and data managers)



Responsible Conduct of Research Using Animals

<http://www.bu.edu/orc/training/animal-care/iacuc-training/>

Students working with animals, mentor needs to add the trainee to the protocol.
The animal requirements are :

- Institutional Animal Care and Use Committee (IACUC) Orientation
- Laboratory Animal Science Center (LASC) New Researcher Orientation
- Medical Surveillance Clearance by Research Occupational Health Program (ROHP) rohp@bu.edu 617-414-7647 <http://www.bu.edu/rohp/forms/>

To register for RIMS to take IACUC Orientation and Lab Safety

<http://www.bu.edu/rims/>

New Research Orientation, please see the list of upcoming dates:

<http://www.bu.edu/animalcare/calendar/> then sign up at:

<http://www.bu.edu/orc/training/animal-care/buasc-training-course-sign-up/>



Responsible Conduct of Research (RCR)

<http://www.bu.edu/orc/programs-committees/rcr/>

- RCR is defined as “the practice of scientific investigation with integrity. It involves the awareness and application of established professional norms and ethical principles in the performance of all activities related to scientific research.
- All members of the BU community are expected to adhere to the highest ethical and professional standards as they pursue research and scholarly activities.
- BU requires the vigilance of all members engaged in research and scholarly endeavors to comply with the legal, regulatory, and ethical requirements established by the University, regulatory agencies, funding sources and professional organizations.
- [Training Programs](#)



NIH-Funded Awards – Conflict of Interest (COI)

<http://grants.nih.gov/grants/policy/coi/index.htm>

- Research Conflicts of Interest Policy Changes. The federal policy promulgating this change is here –

<http://www.gpo.gov/fdsys/pkg/FR-2011-08-25/pdf/2011-21633.pdf>

BU and BMC faculty, staff and students that may be engaged in research will be asked to complete an annual financial interest disclosure, including all outside interests related to institutional responsibilities in the past 12 months and an online training module on new policy responsibilities

<http://www.bu.edu/orc/training/conflicts-of-interest/>



Summary of Research Requirements prior to starting

- CITI Courses Human Subjects Protection Training and Hipaa training at <http://www.bumc.bu.edu/ocr/instructions-for-taking-bumc-citi-courses/>
Required training - Human Subjects Protection Training – Initial Certification
 - 1) HUMAN SUBJECTS PROTECTION TRAINING CERTIFICATES
 - 2) BUMC HIPAA MODULE. Download a completion certificate for each course
- Laboratory safety training for lab settings. Information on classroom or online courses [Register via RIMS](#) take the online course then test and download or print a certificate at: <http://www.bu.edu/orc/training/environmental-health-safety/lab-safety-training/> OR go to a scheduled session and sign the log at: <http://www.bu.edu/orc/training/environmental-health-safety/lab-safety-training/lab-safety-training-schedule/>
- Animal training for students working with animals. Mentor needs to add the trainee to the protocol. The animal requirements <http://www.bu.edu/orc/training/animal-care/iacuc-training/>
 - Institutional Animal Care IACUC Training
 - Laboratory Animal Science Center (LASC) New Researcher Orientation
 - Laboratory Safety Training (shown above)
 - Medical Surveillance Clearance by Occupational Health Program. To schedule an appointment (ROHP) 617-414-7647 or rohp@bu.edu
 - 670 Barrier Orientation to schedule call 617-638-0192 or poggaggon@bu.edu
- Students who will be working in direct contact with the subjects and/or identifiable data must be added to the IRB protocol
- Students who will be handling Human-Derived samples (including cell lines) or recombinant DNA, PI needs to file an amendment to add the student's name to the form found at www.bumc.bu.edu/Dept/Home.aspx?DepartmentID=357
- Additional requirements as per individual mentor

Additional Information

- Regulatory Support & Education Program at BUMC CRRO:
<http://www.bumc.bu.edu/crrro/investigators-and-research-staff/regulatory/>
- Office of Research Integrity ORI
US Department of Health and Human Services
Introduction to the Responsible Conduct of Research
<http://www.ori.hhs.gov/education/products/RCRintro/>
- Research
Boston University
Henry M. Goldman School of Dental Medicine
650 Albany St. X343D
Ms. Sarah Sohm, Grant / Research Coordinator
Sohm, Sarahanne (sasohm@bu.edu) or 8-4707



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Further Information

Afaf Hourani MS, MPH

Asst Director of Predoctoral Research
Research

Boston University

Henry M. Goldman School of Dental Medicine

650 Albany St. X344A

Boston, MA 02118-2393

Tel: (617) 414-1048

Fax: (617) 638-4974

ahourani@bu.edu

<http://www.bu.edu/dental/research/predoctoral/>

<http://www.bu.edu/dental-research>

Thank you!

