Medical Privacy Issues in International Research: Collaborating with U.S. Researchers/Complying with International Guidelines

Critical Research Ethics Issues in the Era of HIV in Tanzania

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Topics For Discussion

- Compliance issues in international research
- FDA standards on international research
- OHRP Federalwide Assurance for domestic and international institutions
- Declaration of Helsinki: CIOMS and ICH/GCP privacy provisions
- HIPAA's application to international research
- HIPAA research authorization in covered international research
- Structuring international trials for compliance

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Compliance Issues Raised by International Research

- May involve populations vulnerable to exploitation
- Foreign institution may lack resources/expertise to handle review of ethical issues
- Sponsoring country and foreign country may have laws, social values and research norms that conflict
- Sponsors or investigators may seek out foreign countries with weaker regulations on human subject research (HHS OIG Report, Sept. 2001)

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Regulation of International Research

- Applicability of FDA Regulations:
  - International studies conducted under an IND (investigational new drug) or IDE (investigational device exemption) must meet the same requirements in FDA regulations that apply to U.S. studies conducted under an IND or IDE
  - 21 CFR Part 50: Informed consent
  - 21 CFR Part 56: IRB oversight
  - 21 CFR Part 312: IND requirements
  - 21 CFR Part 812: IDE requirements

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Regulation of International Research (cont.)

- Applicability of FDA Regulations (cont.):
  - FDA may accept data from foreign studies not conducted under IND or IDE if study conforms with the **more stringent** of:
    - The principles contained in the Declaration of Helsinki; *or*
    - The laws and regulations of the country in which the research was conducted
  - 21 CFR 312.120(c)(4): for non-IND data
    - Applies 1989 version of Declaration of Helsinki
  - 21 CFR 814.15(b): for non-IDE data
    - Applies 1983 version of Declaration of Helsinki

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Regulation of International Research
(cont.)

- Note that FDA has proposed amending these requirements for acceptance of non-U.S. studies to require adherence to GCP guidelines, since these are more specific and more protective of subjects and of data accuracy than Declaration of Helsinki
- 69 Fed. Reg. 32467 (June 10, 2004)

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Regulation of International Research (cont.)

- Applicability of FDA Regulations (cont.):
  - FDA may accept an application for marketing approval based solely on foreign data if:
    - Foreign data applicable to U.S. population and U.S. medical practice
    - Study performed by investigators of recognized competence
    - FDA is able to validate the data through an on-site inspection or other appropriate means, if deemed necessary
  - 21 CFR 314.106(b): IND context
  - 21 CFR 814.15(d): IDE context

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Regulation of International Research (cont.)

- Office for Human Research Protections (OHRP)
  - Jurisdiction of OHRP frequently overlaps with that of FDA (administrative requirements for protection of subjects are comparable)
  - Responsibilities include:
    - Developing and monitoring guidance relative to regulations of the Department of Health and Human Services (HHS)
    - Exercising compliance oversight
    - Establishing criteria for and negotiation of Assurances to protect human subjects submitted by institutions that seek to engage in HHS-conducted or supported research involving human subjects

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Regulation of International Research (cont.)

- Basic OHRP Requirements
  - Assurances to abide by minimal ethical, IRB and consent standards as a prior condition to begin research involving human subjects
  - Reporting of changes in IRB membership as they occur
  - Reasonable provision for IRB reviews to be knowledgeable about the immediate context in which subjects participate
  - That subjects not be involved in research without prior IRB approval
  - Full board convened IRB meetings for initial and continuing reviews of clinical trials

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Regulation of International Research (cont.)

- OHRP Regulated Research
  - All institutions "engaged" in U.S. federally-conducted or supported research must be found by OHRP to comply with *at least equivalent protective procedures* to the basic OHRP requirements, *regardless of national or international location*
  - Much of HHS's international research is conducted or supported by National Institutes of Health (NIH) or the Centers for Disease Control and Prevention (CDC)

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OHRP Regulated Research (cont'd)

- On March 25, 2005, OHRP sought pubic comment on seven criteria recommended by a USG working group for defining "equivalent protections" as:
  - Ethical conduct norms and due diligence in review and performance of research
  - Ensure authority and independence of IRB
  - Protect against biased decision-making in review of research
  - Ensure comprehensiveness of review of research
  - Calibrate degree of review to risks and vulnerability of subjects
  - Protect subjects against unnecessary or unjustified risks
  - Ensure voluntary participation of subjects

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Regulation of International Research (cont.)

- "Engaged" Standard
  - HHS regulations require that each institution (U.S. and international) "engaged" in U.S. federally-supported or conducted human subjects research must submit a FederalWide Assurance (FWA) to OHRP, unless the research is exempt from the requirements of the Common Rule (45 C.F.R. Part 46, Subpart A)
  - Institutions become "engaged" in human subjects research when their employees or agents:
    - Intervene or interact with living individuals for research purposes; *or*
    - Obtain individually identifiable private information for research purposes

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Regulation of International Research (cont.)

- "Engaged" Standard (cont.)
  - Institutions are automatically "engaged" when they receive a direct award to conduct U.S. federally-supported human subject research, even where all activities involving human subjects are carried out by a subcontractor or collaborator
    - The awardee institution is ultimately responsible for protecting human subjects
    - The awardee is also responsible for ensuring that all collaborating institutions engaged in the research hold OHRP-approved Assurances prior to initiation of research
  - Guidance published by OPRR (Office for Protection from Research Risks, the predecessor entity to OHRP) on January 26, 1999 provides examples of situations where research institutions meet and do not meet the "engaged" standard

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Regulation of International Research (cont.)

- Multinational Collaborative Research
  - When a U.S. institution collaborates with a foreign institution on U.S. federally-funded research, *both* entities will likely be considered "engaged" in the research
  - Both institutions will need to submit a FWA to OHRP and comply with its terms
    - U.S. research institutions must comply with Terms of the Federalwide Assurance for Institutions within the United States
    - International research institutions must comply with Terms of the Federalwide Assurance for International (Non U.S.) Institutions
  - Both institutions will need to designate an IRB as part

Regulation of International Research (cont.)

- Multinational Collaborative Research (cont.)
  - Section 46.114 of the Common Rule guides each institution's conduct in this context
    - Each institution is responsible for safeguarding the rights and welfare of human subjects
    - The institutions can discharge these responsibilities by:
      - Dual IRB review (review by both U.S. and foreign IRBs);
      - Review by the U.S. IRB only, so long as it meets the knowledge of the local research context requirement (and the foreign institution designates the U.S. IRB on its FWA); or
      - Review by a central IRB designated as the IRB of record, that meets the knowledge of the local research context requirement

Regulation of International Research (cont.)

- Multinational Collaborative Research (cont.)
  - "*Knowledge of the local research context*" is a principle that guides rules on multinational collaborative research
    - Each IRB designated under an OHRP-approved Assurance must have sufficient knowledge of the local research context and of the research it is reviewing
    - Each IRB's responsibility endures regardless of its geographic location relative to the research institution and the research
    - Responsibility is critical where research involves greater than minimal risk to subjects or vulnerable categories of subjects

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Regulation of International Research (cont.)

- Multinational Collaborative Research (cont.)
  - An institution may designate another Assurance-holding institution's IRB/Independent Ethics Committee (IEC) as the IRB of record on its FWA, so long as the arrangement:
    - Is documented in writing between the two institutions
    - Sets forth the respective responsibilities of the designating institution and IRB organization, and
    - Includes a commitment that the designated IRB/IEC will adhere to the requirements of the Assurance
  - OHRP provides a model agreement at: http://www.hhs.gov/ohrp/humansubjects/assurance/iprotsup.rtf
  - The agreement does not need to be submitted to OHRP, but must be kept on file at the sites, available for review by OHRP upon request

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Regulation of International Research (cont.)

OHRP sample text for an Institution with a Federalwide Assurance (FWA) to rely on an IRB outside their institution (institutions may use this sample as a guide to develop their own agreement).

IRB Authorization Agreement

Name of Institution or Organization Providing IRB Review (Institution A):

_____

IRB Registration #: _____ Federalwide Assurance (FWA) #, if any: _____

Name of Institution Relying on the Designated IRB (Institution B):

_____

OHRP Federalwide Assurance (FWA) #: _____

The Officials signing below agree that ___(*name of Institution B)*___ may rely on the designated IRB for review and continuing oversight of its human subject research described below: (*check one*)

(___) This agreement applies to all human subject research covered by Institution B's FWA.

(___) This agreement is limited to the following specific protocol(s):

Name of Research Project:

Name of Principal Investigator:

Sponsor or Funding Agency: _____ Award Number, if any: _____

(___) Other (*describe*):

The review and continuing oversight performed by the designated IRB will meet the human subjects protection requirements of Institution B's OHRP-approved FWA. The IRB at Institution A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the terms of its OHRP-approved Assurance. This document must be kept on file at both institutions and provided to OHRP upon request.

Signature of Signatory Official (Institution A): _____ Date: _____

Print Full Name: _____ Institutional Title: _____

Signature of Signatory Official (Institution B): _____ Date: _____

Print Full Name: _____ Institutional Title: _____

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Regulation of International Research (cont.)

- Multinational Collaborative Research (cont.)
  - The institution relying on the other institution's IRB remains ultimately responsible for protecting human research subjects for all research covered by its FWA, including:
    - Safeguarding the rights and welfare of human subjects within its local research context
    - Educating the members of its research community in order to establish and maintain a culture of compliance with federal regulations and institutional policies relevant to the protection of human subjects
    - Implementing, within the local research context, appropriate oversight mechanisms to ensure compliance with the determinations of the reviewing IRB

Regulation of International Research (cont.)

- Multinational Collaborative Research (cont.)
  - Review by a Central IRB
    - It may be efficient to use one central IRB where U.S. federally-funded research involves multiple foreign sites, and each site has designated the central IRB (which has sufficient knowledge of the local research context)
    - The U.S. institution could also designate the central IRB to avoid duplication of effort
    - Many U.S. institutions, however, prefer dual review in this context
      - Dual review is not a regulatory requirement, this is merely a preference

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Regulation of International Research (cont.)

- Multinational Collaborative Research (cont.)
  - When international research is supported by the U.S. federal government, the foreign institution(s), in addition to the U.S. collaborating institution, must:
    - Submit a FWA to OHRP, and
    - Comply with the FWA's terms

Regulation of International Research (cont.)

- FWA for International Institutions
  - Must comply with terms for International FWA
    - Human subject research guided by ethical principles
    - Compliance with procedural standards
    - IRB/IEC written procedures
    - Responsibilities and scope of IRB(s)/IEC(s)
    - Informed consent
    - Considerations for special class of subjects
    - Assurances for collaborating institutions/investigators
    - Written agreements with non-affiliated investigators
    - Institutional support for the IRB(s)/IEC(s)
    - IRB(s)/IEC(s) compliance with the Terms of Assurance
    - Assurance training
    - Educational training
    - Renewal of Assurance

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Regulation of International Research (cont.)

- FWA for International Institutions (cont.)
  - Ethical Principles: International human subjects research must be guided by *ethical principles*
    - The FWA for international institutions requires the applicant to provide assurance that *all* of the institution's human subject research, *regardless of funding source*, is guided by one of the following:
      - The Declaration of Helsinki (as adopted in 1996 or 2000);
      - The Belmont Report; or
      - Other appropriate international ethical standards recognized by Federal Departments and Agencies that have adopted the U.S. Federal Policy for the Protection of Human Subjects

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Regulation of International Research (cont.)

- FWA for International Institutions (cont.)
  - Must comply with *one or more* of the following procedural standards for all U.S. federally-supported research:
    - 45 CFR 46 and all of its subparts A through D;
    - 45 CFR 46, subpart A (Common Rule);
    - 21 CFR 50 and 21 CFR 56;
    - The May 1, 1996 International Conference on Harmonization Guidelines for Good Clinical Practice (ICH-GCP-E6, Sections 1-4);
    - The 1993 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects;
    - The 1998 Medical Research Council of Canada Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans;
    - The 2000 Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human Subjects; or
    - Other standard(s) for the protection of human subjects recognized by U.S. Federal Departments and Agencies which have adopted the U.S. Federal Policy for the Protection of Human Subjects

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Regulation of International Research (cont.)

- FWA for International Institutions (cont.)
  - IRBs/IECs
    - The applicant must designate at least one (or more) IRB/IEC as the IRB/IEC of record for research conducted under the FWA (the IRB/IEC must also register with HHS)
    - Except for exempted research, U.S. federally-supported research should be:
      - Reviewed
      - Prospectively approved, and
      - Subject to continuing oversight and review at least annually by the designated IRB(s)/IEC(s)
    - The IRB(s)/IEC(s) should have authority to approve, require modifications in, or disapprove the covered human subject research

Regulation of International Research (cont.)

- FWA for International Institutions (cont.)
  - IRBs/IECs (cont.)
    - The applicant institution is responsible for ensuring that:
      - The designated IRB(s)/IEC(s) agree to comply with the terms of the Assurance
      - The IRB(s)/IEC(s) possess appropriate knowledge of the local research context for all research covered under the Assurance

Regulation of International Research (cont.)

- FWA for International Institutions (cont.)
  - Required written procedures:
    - Ensuring prompt reporting to the IRB/IEC, appropriate institutional officials, the relevant Department or Agency Head, any applicable regulatory body and OHRP of any:
      - Unanticipated problems involving risks to subjects or others
      - Serious or continuing noncompliance with the Federal regulations or IRB requirements, and
      - Suspension or termination of IRB approval
    - Verifying, by a qualified person(s) *other than* the investigator or research team, whether proposed human subject research activities qualify for exemption from the requirements of the U.S. Common Rule

Regulation of International Research (cont.)

- FWA for International Institutions (cont.)
  - Required written procedures (cont.):
    - Conducting IRB/IEC initial and continuing review (not less than once per year), approving research, and reporting IRB/IEC findings to the investigator and the Institution
    - Determining which projects require review more often than annually, and which projects need verification from sources other than the investigator that no material changes have occurred since the previous IRB/IEC review
    - Ensuring that changes in approved research protocols are reported promptly and are not initiated without IRB/IEC review and approval (except when necessary)

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Regulation of International Research (cont.)

- FWA for International Institutions (cont.)
  - Requirements for Special Classes of Subjects
    - For all HHS-supported human subjects research involving pregnant women or fetuses, prisoners or children, the institution must comply with 45 C.F.R. Part 46, Subparts B, C or D, respectively
    - For non-HHS U.S. federally-supported human subject research, the institution must comply with any human subject regulations and/or policies of the supporting Department or Agency for these classes of subjects
    - *These requirements for special classes of subjects apply regardless of which procedural standard the institution has chosen to comply with under the terms of its FWA*

Clinical Research Outside U.S. (but to be used for FDA submissions)

- Must comply with more stringent of Declaration of Helsinki, or national research subjects protection standards
- If Declaration of Helsinki, interpretations are offered by:
  - CIOMS
  - ICH/GCP
- Declaration of Helsinki restrictions, and those of CIOMS and ICH/GCP, not clearly limited to investigators only; sponsors covered also?

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Declaration of Helsinki (1989)

- The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

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Council for International Organizations of Medical Sciences (CIOMS) Guidelines

- 2002 Guidelines supersede 1993 Guidelines
- Intended to define "national policies on the ethics of biomedical research involving human subjects, applying ethical standards in local circumstances, and establishing or improving ethical review mechanisms."
- Set forth standards consistent with Declaration of Helsinki

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CIOMS Guidelines (cont.)

- Twenty One (21) Guidelines addressing:
  1. Ethical justifications and scientific validity of biomedical research involving human beings
  2. Ethical review committees
  3. Ethical review of externally sponsored research
  4. Individual informed consent
  5. Obtaining informed consent: essential information for prospective research subjects
  6. Obtaining informed consent: obligations of sponsors and investigators
  7. Inducement to participate

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CIOMS Guidelines (cont.)

- Benefits and risks of study participation
- Special limitations on risk when research involves individuals who are not capable of giving informed consent
- Research in populations and communities with limited resources
- Choice of control in clinical trials
- Equitable distribution of burdens and benefits in the selection of groups of subjects in research
- Research involving vulnerable persons
- Research involving children

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CIOMS Guidelines (cont.)

- Research involving individuals who by reason of mental or behavioral disorders are not capable of giving adequate informed consent
- Women as research subjects
- Pregnant women as research subjects
- Safeguarding confidentiality
- Right of injured subjects to treatment and compensation
- Strengthening capacity for ethical and scientific review and biomedical research
- Ethical obligations of external sponsors to provide health-care services

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CIOMS Guidelines Relevant to Subject Privacy

- Individual Informed Consent
  - Requires separate section relating to consent for use of specimens
  - Medical records and specimens taken during clinical care can only be used for research if minimal risk is involved, privacy protected, research designed to answer "important" questions, and impracticability of consent
  - Secondary uses of research data or specimens constrained by original consent, which should describe future secondary uses, plans to gain consent, plans for anonymization, rights of subjects to withdraw data/specimens

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CIOMS Guidelines Relevant to Subject Privacy (cont.)

- Obtaining informed consent: contents of informed consent

Subsections:

- Subjects' right of access to research data on demand, unless limited beforehand by research ethics committee
- Privacy protections for data
- Limits on investigators' ability to safeguard privacy of data
- Possible research uses, direct and secondary, of data and specimens taken during clinical care
- Planned/possible future uses of specimens taken during research

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CIOMS Guidelines Relevant to Subject Privacy (cont.)

- Investigator must establish secure safeguards of confidentiality of subjects' data
  - Limit access of third parties to identified information
  - Coding/anonymizing data
  - Disclose sponsor and government access to identified data

International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP)

- An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve human subjects
- Compliance with GCP provides public assurance that subjects' rights, safety and well-being are protected and data are credible
- GCP consistent with Declaration of Helsinki principles
- FDA has endorsed GCP as guidelines (62 Fed. Reg. 25,692)

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ICH Guideline for GCP (cont.)

Thirteen (13) ICH GCP Principles:

- Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
- Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interest of science and society.

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ICH Guideline for GCP (cont.)

- The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
- A trial should be conducted in compliance with the protocol that has been received prior to institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.
- The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

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ICH Guideline for GCP (cont.)

- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

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ICH Guideline for GCP (cont.)

- **The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).**
- Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
- Systems with procedures that assure the quality of every aspect of the trial should be implemented.

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ICH Guideline for GCP (cont.)

Guidelines:

- 4.8.10(n): Content of informed consent includes reference to monitor, auditor, IRB/IEC, government to subjects' data
- 4.8.10(o): Records kept confidential; publication only without identifying information
- 4.9.7: Direct access to identified records for monitors, auditors, IRB/IEC, government
- 5.5.3(d), 5.5.3(e) and 5.5.5: Sponsor's duties re: security of subjects' data

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ICH Guideline for GCP (cont.)

Guidelines:

- 5.15.1: Sponsor must ensure its access to original data as specified in protocol or CTA
- 6.10: Sponsor must ensure direct access of monitors, auditors, IRB/IEC and government, by protocol or CTA

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HIPAA vs. Declaration of Helsinki/CIOMS/ICH/GCP

- If HIPAA applies to the international study, and Declaration or other regimes apply, which is more stringent?
- If HIPAA does not apply to the international study, what rules regarding privacy do apply?

HIPAA Issues with International Research

- HIPAA applies to all United States "Covered Entities:"
  - Health plans
  - Health care clearinghouses
  - Health care providers who transmit any health information in electronic form in connection with one of the transactions covered by HIPAA

HIPAA Issues with International Research (cont.)

- Under HIPAA "'research' means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." (45 C.F.R. § 164.501).
- *Same definition as Common Rule, but no "exemptions" available. Understanding this is essential to HIPAA compliance in research.*

HIPAA Issues with International Research (cont.)

- Under HIPAA, individual authorization is needed before a Covered Entity may use or disclose PHI for research purposes *unless*:
  1. An IRB or Privacy Board waives or alters the authorization requirement
  2. The use or disclosure is for a "review preparatory to research" and the recipient of the PHI has given the Covered Entity certain representations
  3. The use or disclosure is for research on decedents' information and the recipient of the PHI has given the Covered Entity certain representations

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HIPAA Issues with International Research (cont.)

4. The PHI disclosed is part of a "limited data set" and the recipient of the PHI has executed a Data Use Agreement with the Covered Entity; *or*
5. The data disclosed are "de-identified" under HIPAA's standards, in which case HIPAA does not apply to the use or disclosure of the data

HIPAA Issues with International Research (cont.)

- HIPAA's requirements for research are applicable regardless of source of funding
  - Even if FDA and/or HHS regulations are *not* applicable to the clinical study at issue, Covered Entity is still bound by HIPAA Privacy Regulations

HIPAA Issues with International Research (cont.)

- What activities are subject to HIPAA?
  - Health or mental health information created or received by Covered Entity is PHI subject to HIPAA
  - Covered Entity medical staff/professional staff receives PHI from abroad, then PHI is subject to HIPAA
  - Covered Entity or its agent collects PHI abroad, then PHI is subject to HIPAA
- Mistaken impression that HIPAA has no applicability to many international trials if conducted by U.S. Covered Entities, and their staff, and overseen by Covered Entity's IRB

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International Trials on "Foreign" PHI: HHS Commentary

- **Comment**: A few comments expressed concern that the proposed definition of "individual" excluded foreign military and diplomatic personnel and their dependents, as well as overseas foreign national beneficiaries.

International Trials on "Foreign" PHI: HHS Commentary (cont.)

- **Response**: We agree with the general principle that privacy protections should protect every person, regardless of nationality. As noted in the discussion of the definition of "individual," the final regulation's definition does not exclude foreign military and diplomatic personnel, their dependents, or overseas foreign national beneficiaries from the definition of individual. As described in the discussion of § 164.512 below, the final rule applies to foreign diplomatic personnel and their dependents like all other individuals. Foreign military personnel receive the same treatment under the final rule as U.S. military personnel do, as discussed with regard to § 164.512 below. Overseas foreign national beneficiaries to the extent they receive care for the Department of Defense or a source acting on behalf of the Department of Defense remain generally excluded from the final rule protections. For a more detailed explanation, see § 164.500.

65 Fed. Reg. 82594 (Dec. 28, 2000)

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Examples of HIPAA's Impact on International Trials

- Research Authorization
  - *Problem*: U.S. investigators receive health information from other investigators abroad, it becomes PHI, and U.S. investigators cannot use/disclose it absent authorization from the foreign research subject or IRB waiver or alteration of the authorization requirement

Examples of HIPAA's Impact on International Trials (cont.)

- Research Authorization (cont.):
  - *Solution*: In order to use data in compliance with HIPAA authorization requirement, must obtain:
    - Written HIPAA-compliant authorization from subjects at foreign sites; or
    - IRB or Privacy Board approval of a waiver of authorization; or
    - IRB or Privacy Board approval for an alteration of authorization form

Examples of HIPAA's Impact on International Trials (cont.)

- *Partial Solution*: If data received from a foreign research site are de-identified or are a limited data set, then no authorization is required for the Covered Entity to use and disclose the information for research purposes, but the PI and IRB, even if at a U.S. Covered Entity, must retain the ability/ authority to inspect original, identified data for accuracy/integrity purposes

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Examples of HIPAA's Impact on International Trials (cont.)

- Adverse Event Reporting:
  - HIPAA allows Covered Entities to disclose PHI without an authorization to a person subject to the jurisdiction of the FDA with respect to an FDA-regulated product or activity for which that person has responsibility, for purposes related to the quality, safety, or effectiveness of the FDA-regulated product or activity

45 CFR § 164.512(b)(1)(iii)

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Examples of HIPAA's Impact on International Trials (cont.)

- Adverse Event Reporting (cont.):
  - Not intended to be a broad exception for all sponsor-related research activities, but permits some information-sharing between Covered Entities, research sponsors and the FDA
  - Examples of permissible disclosure under the FDA exception include, but are not limited to:
    - Adverse event reporting
    - FDA-regulated product tracking
    - Post-marketing surveillance
    - Enabling product recalls, repairs, replacements, or lookback
  - May be used as authority for U.S. sites/U.S. researchers in multi-center studies to use/disclose adverse events-related PHI from foreign sites/investigators

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Examples of HIPAA's Impact on International Trials (cont.)

- Regulatory Record Keeping:
  - HIPAA requires Covered Entities to maintain written or electronic records of:
    - Communications that are required by HIPAA to be in writing
    - Action, activity, or designation that is required by HIPAA to be documented
  - Records must be kept for 6 years from date of creation or date when last in effect
  - For example, research authorization forms, including IRB waivers and alterations, must be kept on file for 6 years.

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Examples of HIPAA's Impact on International Trials (cont.)

- Regulatory Record Keeping (cont.):
  - To waive or alter the authorization requirement, IRB must find and document that there is an adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research unless there is a health or research justification for retaining them, or such retention is required by law

Examples of HIPAA's Impact on International Trials (cont.)

- Concern that HIPAA's requirements are inconsistent with other recordkeeping requirements:
  - FDA recordkeeping requirements are generally 2 years after (i) date on which investigation terminated; or (ii) date records no longer required to support a marketing application (21 CFR 812.140(d); 312.62(c))
  - International Standard Organization (ISO) on control of quality records requires that data be kept for the life of a device (ISO 13483, 4.16)

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Examples of HIPAA's Impact on International Trials (cont.)

- HHS commentary suggests that complying with FDA and ISO requirements are "consistent with the conduct of the research" and identifiers would not need to be destroyed to the extent required for such compliance
- Furthermore, such retention is required by law and therefore permitted

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International Conflicts of Law: General Overview

- Conflicts arise when litigation invokes laws of different jurisdictions (*i.e*, the U.S. and a foreign country)
- Court decides which jurisdiction's laws apply
  - Determination depends on the conflicts of law approach adopted by the jurisdiction in which the court sits
- Under basic international law principles, hosting country should have jurisdiction over research conducted within its borders

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Structuring International Trials for HIPAA Compliance

- On-going debate within industry as to the extent of HIPAA's application to international research activities
- Some research sponsors/government agencies have taken the position that HIPAA does not apply to any international research
- Position not clearly supported by HHS commentary on international research, or by structure of HIPAA Privacy Regulations

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Structuring International Trials for HIPAA Compliance (cont.)

- HIPAA regulates protected health information that is in the hands of Covered Entities
- Conversely, it does not apply to protected health information in the hands of entities that are not covered under HIPAA, and it does not apply to information in the hands of Covered Entities if the information does not qualify as protected health information

Structuring International Trials for HIPAA Compliance (cont.)

- Covered Entities and research sponsors must comply with HIPAA's individual authorization requirements in their international research activities if the research involves the collection, storage, receipt or use of PHI by a Covered Entity
- Several options exist for structuring international research to avoid and/or facilitate compliance with HIPAA

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Structuring International Trials for HIPAA Compliance (cont.)

- Option #1: Obtain Authorization as Required by HIPAA
  - Obtain individual authorization that meets the core elements of HIPAA from all foreign subjects at the time of enrollment
  - Requires coordination with international sites and sufficient explanation to foreign subjects
  - Applies HIPAA recordkeeping requirements to information gathered through authorization process
  - Translation required

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Structuring International Trials for HIPAA Compliance (cont.)

- Option #2: Obtain Short Form Authorization
  - Obtain modified HIPAA authorization (which can be incorporated into international research informed consent)
  - Investigators must obtain IRB alteration of HIPAA's authorization requirement (in order to permit the use of an authorization that fails to meet HIPAA's required core elements)
  - Translation required

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Structuring International Trials for HIPAA Compliance (cont.)

- Option #3: Sponsor Use Non Covered Entity as Data Coordinating Center
  - Sponsors of international research may elect to use a non Covered Entity to act as the data coordinating center for data collected at international research sites (e.g., international research sites report directly to sponsor or to CRO, not to U.S. based research sites)
  - Neither sponsor nor CRO is a Covered Entity; therefore the collection of PHI is not governed by HIPAA so long as investigator at international research site is not subject to HIPAA's requirements (since not affiliated with Covered Entity)

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Structuring International Trials for HIPAA Compliance (cont.)

- Option #3 (cont.): Sponsor Use Non Covered Entity as Data Coordinating Center
  - *Problem*: Danger to Covered Entity's business interest in clinical trials
    - If Covered Entities want to coordinate multi-national trials for industry sponsors and insist that HIPAA apply across the board, sponsors will be incentivized to cut Covered Entity out of the picture to avoid HIPAA's application (assume the role itself or contract with a non-HIPAA-covered CRO)

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Structuring International Trials for HIPAA Compliance (cont.)

- Option #4: Carving Research Activities Out of the Covered Component of a Hybrid Entity
  - "Hybrid" entities are Covered Entities that conduct both covered and non covered activities
  - For hybrid entities, research that is conducted through a non covered component will be exempt from HIPAA's requirements so long as the covered component(s) does not collect, store, receive or use PHI from the research, and does not provide treatment in the course of research
  - Investigators affiliated with a covered entity may also be "hybrid" or "split" persons for purposes of HIPAA compliance

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Structuring International Trials for HIPAA Compliance (cont.)

- Option #4 (cont.): Carving Research Activities Out of the Covered Component of a Hybrid Entity
  - Impact on IRB as Health Care Component
    - On-going debate regarding whether affiliated IRBs should be included in the covered component of a hybrid entity, excluded, or "split"
    - If hybrid entity uses Option #4 to carve-out certain international research from HIPAA's requirements but submits PHI from those research studies to an IRB that is within the covered component, the research arguably becomes subject to HIPAA's requirements

Structuring International Trials for HIPAA Compliance (cont.)

- Option #4 (cont.): Carving Research Activities Out of the Covered Component of a Hybrid Entity
  - Solution to Impact on IRB as Health Care Component
    - Keep IRB outside the covered component
    - Maintain two affiliated IRBs; one within and one outside of the covered component
    - "Split" the IRB into covered and non-covered activities

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The Compliance "Bottom Line" for International Clinical Trails

Sponsors and researchers must determine:

1. Is any research entity covered under HIPAA?
   - If so, compliance required
   - If not, does any HIPAA Covered Entity receive identified data during the study and its analysis?
     - If so, compliance required
2. If not conducted under IND or IDE requirements, what applies?
   - Applicable national research standards and privacy laws
   - Declaration of Helsinki: CIOMS and ICH/GCP
3. Site of research: national laws must <u>always</u> be obeyed

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