Lessons from the Trenches: Avoiding Common Legal Pitfalls in International Research

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  - North America’s premier provider of IRB, IBC and global research compliance services
- Leverage mutual strengths in technology, regulatory expertise and customer service to serve increasingly complex research needs
About Advarra

- Combined 50+ years of experience
- Access to over 2,000 unique institutional research sites
- Global consulting services
- The industry’s most comprehensive and efficient technology
About Today’s Presenters

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- Previously served as senior legal counsel for human research matters at Partners HealthCare in Boston
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About Today’s Presenters

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- Advises institutional and industry clients on the conduct of human subjects research and the implementation of clinical trials, both domestically and internationally, and on related legal issues
- Graduate of University of Pennsylvania Law School; Master of Bioethics from the University of Pennsylvania Department of Medical Ethics and Health Policy
Objectives

- Review select common issues arising in international research studies under U.S. and ex-U.S. research and privacy laws and regulations
- Illustrate how failure to appreciate the potential applicability of these laws and regulations to international research can create legal and practical risk for organizations
- Discuss ways that organizations can identify and address these legal issues for an international study or studies
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➢ The views and opinions expressed in this presentation are the presenters’ alone and do not necessarily reflect the views and opinions of Verrill Dana or any of its clients.

➢ This presentation does not constitute legal advice.
Agenda

- Expansion of international research – focus today is clinical trials
- Application of select U.S. laws and regulations
  - Research: DHHS human subjects regulations; FDA regulations
  - Privacy: HIPAA
- Application of select ex-U.S. laws and regulations
  - Research: sponsorship and approval of clinical trials; human subjects oversight; collection, use, and transfer of biospecimens
  - Privacy: collection, use, and transfer of data (e.g., GDPR)
- Other potentially relevant laws and considerations
- Risks of failure to attend to applicable laws/regulations
- Strategies for identifying legal issues and managing risks and compliance
Growth in International Clinical Trials

- U.S. companies and institutions have increasingly been conducting or engaging in trials on a global scale
- From the Department of Health and Human Services, Office of Inspector General, “Challenges to FDA’s Ability to Monitor and Inspect Foreign Clinical Trials” (June 2010):
  
  “Sources have estimated that between 40% and 65% of clinical trials investigating FDA-regulated products are conducted outside the U.S.”
  “80% of approved applications for drugs and biologics in fiscal year 2008 contained data from foreign clinical trials.”
Map of Trials Registered on ClinicalTrials.gov

Data as of March 26, 2018
Source: https://clinicaltrials.gov/ct2/search/map
Drivers

- Economic incentives (lower per-subject costs)
- Accelerated recruitment
- Availability of desired/unique patient population (treatment-naïve populations or disease incidence)
- Avoidance of bureaucratic and highly regulated environments
- Foreign government incentives
- Foster positive relationships among clinician investigators globally
- Improve global health
Proceed with Caution!

Source: pixabay.com
Select U.S. Laws and Regulations

Source: pixabay.com
DHHS Human Subjects Regulations

➢ Establish human subjects protections for U.S. Department of Health and Human Services (DHHS)-funded research (45 C.F.R. 46)

➢ Apply to such research – and to all organizations “engaged” in such research – even when the research is conducted outside the U.S.

  • U.S. and non-U.S. organizations must comply
  • Note that a prime awardee is generally considered engaged even if not performing human subjects activities itself
  • Other activities that constitute engagement: obtaining data through interventions or interactions with individuals; obtaining individually identifiable private information; obtaining informed consent
Broad Applicability

➢ All Subparts apply:
  • Subpart A: Common Rule
  • Subparts B, C, D: vulnerable populations
  • Subpart E: registration of IRBs with DHHS

➢ Goal is to ensure all human subjects in DHHS-funded research receive the same level of protections no matter where the research is conducted or by whom
If Applicable, Little Flexibility in Practice

A non-U.S. organization’s compliance with recognized international or other standards (e.g., ICH E-6 Guidelines for Good Clinical Practice) does not obviate the need to comply with DHHS regulations.

July 7, 2006 DHHS Notice on Interpretation of Assurance Requirements (71 F.R. 38645)
“[A]ll institutions ... engaged in [DHHS-supported] research must comply with the requirements of 45 CFR part 46 ... regardless of whether the institution marked one or more other procedural standards on the FWA form for international (non-U.S.) institutions as a standard to which the institution committed itself to comply.”

- DHHS can allow substitution of foreign procedures if it finds they provide “equivalent” protections, but it has not (to date) so found.
- Non-compliance may result in study suspension or termination, loss of authority to conduct DHHS-funded research.
Key Implications for U.S. & Non-U.S. Engaged Organizations Subject to DHHS Regulations

➢ Threshold implications:
  • Must have/obtain a Federalwide Assurance (FWA)
  • Must obtain an ethics review by a registered IRB that meets DHHS composition requirements and applies DHHS approval criteria

➢ Other implications include:
  • Informed consent
  • Continuing review at least annually
  • Reporting of unanticipated problems and serious/continuing non-compliance
  • Maintenance of research and IRB records
Challenges for the U.S. IRB

➢ The U.S. IRB must “be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice” (and many other aspects of local context)
  • Local ethics rules and norms: *e.g.*, recruitment, coercion, access to standard of care, therapeutic misconception, literacy, LARs
  • Local laws/regulations: *e.g.*, biospecimens, genetic information

➢ Utilize local ethics committee approval, consultation with experts, other strategies
Impact of Revised Common Rule

- Revised Common Rule (effective July 19, 2018) does not change regulations’ applicability.
- Single IRB mandate in Revised Common Rule (and in NIH Single IRB Policy) only apply to the portion of the research conducted in the U.S.
- Thus, it remains an option – but not a requirement – for non-U.S. organizations to rely on a U.S. IRB to review DHHS-funded research on their behalf.
  - Non-U.S. organizations will still need to obtain review of the research under their own human subjects protection laws, which generally means review by their local ethics committees.
FDA Human Subjects and Drug/Device Regulations

➢ Establish informed consent and IRB review requirements for FDA-regulated clinical investigations and investigations supporting applications for research or marketing permits for FDA-regulated products (21 C.F.R. 50; 21 C.F.R. 56)

➢ Establish requirements for use of investigational drugs and devices under INDs/IDEs (21 C.F.R. 312; 21 C.F.R. 812)

➢ Apply to all investigations conducted under an IND or IDE, even if the investigation is conducted outside the U.S.
  • Sponsor and all investigators (U.S. and non-U.S) must comply
  • Non-compliance may result in withdrawal of trial approval, disqualification of investigators, debarment, civil monetary penalties, even criminal prosecution

➢ But note that investigations conducted outside the U.S. are not required to have an IND/IDE
Key Implications for Sponsors and U.S. & Non-U.S. Investigators for Investigations Conducted Under an IND/IDE

**Sponsors must:**
- Select qualified investigators and obtain signed investigator statements (in IND trials, these are Form 1572s)
- Ensure proper monitoring of the investigation
- Review and report safety information to FDA and investigators

**Investigators must:**
- Obtain compliant IRB review and approval (unless waived by FDA)
- Obtain compliant informed consent
- Report adverse events to sponsor
- Report unanticipated problems and serious/continuing non-compliance to IRB
- Maintain compliant records and allow inspection by FDA
FDA will accept data from ex-U.S. trials not conducted under INDs/IDEs in certain circumstances (21 C.F.R. 312.120; new 21 C.F.R. 812.28 effective February 21, 2019)

• If the trial was conducted in accordance with Good Clinical Practice (GCP) (includes initial and continuing review and approval by an independent ethics committee, and informed consent); and
• If FDA can validate the data from the trial through onsite inspection
  - Such inspections are increasing and should be addressed in contracts with non-U.S. organizations

There are additional criteria for marketing approval based solely on foreign data (21 C.F.R. 314.106; new 21 C.F.R. 814.15(b) [currently (d)]; new 21 C.F.R. 812.28)
FDA Guidance provides recommendations for submission of supporting information re: conformance to GCP

- Drug trials: “FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions” (March 2012)
- Device trials: “Acceptance of Clinical Data to Support Medical Device Applications and Submissions and Frequently Asked Questions” (February 2018)

“FDA encourages sponsors and applicants to discuss any questions or concerns they may have about the format and content of the required information during pre-submission meetings with FDA ... .”
HIPAA – General

- General principle: applies to the Use and Disclosure of Protected Health Information (PHI) by a Covered Entity or Business Associate

- In the context of an ex-U.S. clinical trial: only relevant if a Covered Entity or Business Associate uses or discloses PHI
  
  - Particularly relevant to U.S. institutions and investigators conducting studies abroad or receiving data from outside the U.S.
  
  - Pharma and device companies are not typically subject to HIPAA
    - Should be mindful when using U.S. institutions as data coordinating centers
Debate exists regarding the application of HIPAA in the context of ex-U.S. research studies

- Clear that HIPAA applies to PHI of ex-U.S. research subjects once it is held by a Covered Entity or Business Associate in the U.S.
- Less clear is the application of HIPAA to uses and disclosures of PHI of ex-U.S. research subjects outside of the U.S.
HIPAA – Strategies for Compliance

➤ PHI of **ex-U.S. research subjects** – use and disclosure **in the U.S.**
  • Need to ensure use and disclosure are permitted under HIPAA, through a HIPAA-compliant authorization or otherwise
  • Consider obtaining an alteration of HIPAA’s authorization requirements for ex-U.S. research subjects

➤ PHI of **ex-U.S. research subjects** – use and disclosure **outside of the U.S.** (if determined that HIPAA applies)
  • May be challenging to satisfy privacy rule and security rule requirements, particularly regarding security standards and Business Associates
Other Potentially Relevant Laws and Considerations – U.S.

- Federal grants requirements
- PHS Policies on Research Misconduct *(42 C.F.R. Part 93)*
- PHS financial conflict of interest regulations *(42 C.F.R. Part 50, Subpart F)*
- Foreign Corrupt Practices Act and other fraud and abuse laws
- Anti-boycott laws
  - 1977 amendments to the Export Administration Act and the Ribicoff Amendment to the Tax Reform Act of 1976
Other Potentially Relevant Laws and Considerations – U.S. (cont’d)

➢ Import and export control laws
  • FDA’s requirements for export of investigational drugs and devices
  • Department of Commerce Export Administration Regulations
  • Department of State International Traffic in Arms Regulations
  • Department of Treasury Office of Foreign Asset Control’s Specially
    Designated Nationals list

➢ AAHRPP Accreditation Standard I-3

➢ State laws (privacy, genetic information, etc.)

➢ Many others depending on specifics of the study ...
Select Ex-U.S. Laws and Regulations

Source: pixabay.com
Human Subjects Protections and Oversight

- Most countries have their own framework for ethical and/or scientific oversight
- U.S. human subjects regulations (where applicable) do not override local requirements: research must comply with both
  - E.g., Review by independent ethics committees, informed consent
  - May even be a requirement for local government approval (e.g., Botswana)
- May require coordination with U.S. IRB – some U.S. IRBs require approval from the local ethics committee before granting final approval
Sponsor Status

Who is the “sponsor” of the research for regulatory purposes in the ex-U.S. country(ies)?

- Sponsor status typically comes with significant responsibilities and often explicit financial responsibility/liability for participant injuries.
- Applicable definition of “sponsor” may be very broad:
  - For example, under new EU Clinical Trial Regulation applicable in 2019: Sponsor = “an individual, institution, company or organization which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial” (need not be an entity in the EU).

It may be you (U.S. organization)!
If possible, identify non-U.S. party(ies) in the country(ies) where the research is conducted that agree they are the sponsor(s)

May not always be possible
- May not be a non-U.S. party meeting the definition
- May be a U.S. party that meets the definition but will not agree to serve in the role
  - Example: NIH has declined to be the sponsor of clinical trials in the EU, citing the U.S. Anti-Deficiency Act

If not possible, U.S. organization must decide if it is able/willing to take on sponsor role
- U.S. investigator may be another option, but financial responsibility/liability or other sponsor obligations may preclude or weigh against that outcome
- Joint or co-sponsorship with another party may be an option depending on the country, but U.S. organization will retain at least some liability
Common Sponsor Obligations Under Ex-U.S. Laws

- Obtain regulatory approval for the trial (including use of investigational products) and notify authorities of amendments and trial completion
- Apply for local ethics committee approvals
- Ensure control and compliance with respect to investigational drug/product
- Conduct safety monitoring and reporting
- Provide for clinical trial insurance, indemnification, or other means to cover participant injury and ensure compensation for liability to participants
- Register trial and report results (transparency)
- Identify legal representative(s) in the ex-U.S. country(ies)

Non-compliance may result in: loss of approval, civil and criminal liability
Approval for Use of Investigational Products

➢ Jurisdiction of local regulatory authorities under their applicable regulations may be broader than under FDA regulations – e.g., may extend to research using an approved product within its approved indication

  • Example: under current EU Clinical Trial Directive, investigational medicinal product (IMP) includes products with marketing authorizations “when used to gain further information about the authorised form”

➢ Different local regulatory authorities may reach different conclusions

  • Example: START trial
Many countries regulate any and all of these activities, including transfer outside the country.

Examples:

- **Collection/use:**
  - **Argentina:** consent for collection must include specific information, including statement that samples and derived data will not be sold.
  - **Spain:** special restrictions on “collections” and “biobanks” (e.g., collections can only be used by researcher, cannot be transferred to third parties, and cannot be used for secondary research unless described).
  - **Portugal:** samples cannot be used for any commercial purposes, and commercial entities cannot store or use identified samples.

- **Transfer:**
  - **South Africa:** biospecimens may not be exported without a government permit.
  - **Nigeria, Zambia:** transfer of biospecimens requires a Material Transfer Agreement addressing certain issues (location, ownership).
Ex-U.S. Data Protection Laws – General

➢ U.S. data protection laws are lagging
➢ Other country laws are often:
  • Broader in scope
    - Entities subject to laws
    - Type of data covered
  • More protective of data subjects
    - Consent
    - Rights
Ex-U.S. Data Protection Laws – EU

- EU standard is followed in other ex-U.S. jurisdictions
- EU Data Protection Directive – applies until May 25, 2018
- General Data Protection Regulation (GDPR) – applies on May 25, 2018
  - Broader application to non-EU entities
  - Penalties up to the greater of €20,000,000 or 4% of the total worldwide annual turnover of the preceding financial year
Ex-U.S. Data Protection Laws – EU (cont’d)

**HIPAA**
- Covered Entity
- Business Associate
  - Use
  - Disclosure
- Protected Health Information
- De-identified

**GDPR**
- Controller
- Processor
  - Processing*
- Personal Data
  (including, generally, pseudonymised data)
- Anonymised

*Note that special rules apply to transfers of personal data out of the EU (a particular type of processing).*
Ex-U.S. Data Protection Laws – EU (cont’d)

➢ GDPR applies to non-EU controllers or processors that:
  • Offer goods or services within the EU
  OR
  • Monitor the behavior of individuals within the EU

➢ The GDPR will apply to many U.S. research sponsors

➢ When the GDPR applies, U.S. sponsors will typically be characterized as controllers
If the GDPR applies to a U.S. institution or company as a controller, there are significant obligations that may apply (among others):

- Identify a basis under the GDPR for all processing activities, including transfer of personal data out of the EU into the U.S. (if identifiable)
- Adopt GDPR-compliant privacy and security policies and procedures
- Appoint an EU legal representative
- Appoint a Data Protection Officer and notify relevant EU data protection authorities of his/her identity
- Enter into data processing agreements with vendors and others who receive personal data
Resources for Ex-U.S. Research-/Privacy-Related Laws

DHHS Office for Human Research Protections:
International Compilation of Human Research Standards

- General research laws
- Drugs and devices
- Clinical trial registries
- Research injury
- Privacy/data protection
- Human biological materials
- Genetics
- Embryos, stem cells, and cloning

NIAID: ClinRegs
Other Potentially Relevant Laws and Considerations – Ex-U.S.

- Fraud and abuse laws (e.g., U.K. Bribery Act 2010)
- Electronic signature laws
- Labor and employment laws
- Immigration laws (e.g., visas for U.S. researchers)
- Registration to conduct business
- Tax laws (e.g., value added taxes)
- Import and export laws
- Medical licensure requirements
- Various others ...
Risks and Compliance Strategies

Source: pixabay.com
Risks of Failure to Attend to Laws/Regulations

- Unexpected delays and financial costs in start-up
- Disruption to or inability to complete the research
- Inability to use the data/results from the research or fulfill product marketing plan
- Reputational harm
- Breach of contractual obligations
- Regulatory/legal penalties and liability
Spectrum of Approaches for Addressing ex-U.S. Laws

What is the approach of your institution or company?

- No Diligence
- Scorched Earth

Source: pixabay.com
Spectrum of Approaches (cont’d)

▷ Determine tolerance for risk
  • 110% compliance?
  • Reasonable, good faith efforts?

▷ Comfort level will vary by study
  • Prominence of study
  • Number of sites
  • Nature of intervention
  • Sensitivity of data involved and protections in place
  • Funding source(s)
  • Other factors ...
Practical Strategies To Identify and Manage Risk of ex-U.S. Laws

Possible approach for ex-U.S. laws

• Step 1 – Assess legal landscape, starting broad and then narrowing down
• Step 2 – Discuss with ex-U.S. site/collaborators
• Step 3 – Assess need for further support (CRO, local counsel, etc.)

100% compliance in every jurisdiction won’t always be possible
Contracts with Non-U.S. Organizations

- Legal structure must be reflected in relevant contracts and consent forms
  - Contract language isn’t dispositive, but it will help frame discussions and demonstrate intent (including good faith efforts) in the event of an inquiry
  - Consent forms must be consistent and reflect legal structure

- Contract hurdles are often study and country-specific
  - For example, who is the “sponsor” under local country laws?
Contracts with Non-U.S. Organizations (cont’d)

- Choice of law, venue, and dispute resolution
  - Generally easier to get an arbitration decision enforced in a non-U.S. jurisdiction than to get a judicial decision enforced
    - U.S. has no bilateral treaty/convention with any other country in which U.S. and the other country have agreed to enforce each other’s judicial decisions
  - But most countries are signatories to the so-called New York Convention and have agreed to recognize and enforce non-U.S. arbitral awards (with limited exceptions)
  - U.S. federal and state law and U.S. venue for arbitration can still govern the contract (if the non-U.S. site will agree to it)

- Consider carefully choice of law and clauses that explicitly disclaim specific U.S. law (e.g., HIPAA)
Contracts with Non-U.S. Organizations (cont’d)

➤ **Intellectual property, inventions, and ownership**
  • May be difficult to obtain rights to intellectual property due to intellectual property frameworks that differ from U.S. (*e.g.*, in Germany)
  • May be difficult to enforce intellectual property rights even once they are theoretically obtained (*e.g.*, in China and India)

➤ **Indemnification**
  • Consider seeking indemnification for non-compliance with local country laws as risk mitigation

➤ **Governing language**
  • Obtain certified translations if English does not govern

➤ **Flow down of requirements under U.S. laws**
  • U.S. federal grants requirements
  • Application of Common Rule or FDA regulations
Closing Thoughts

Source: pixabay.com
Thank you!

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