

Laws, Regulations and Clinical Trial Agreements

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Abstract: As clinical research increasingly becomes a global enterprise, investigators and sponsors must deal with multiple legal jurisdictions, with differing laws, regulations and other rules. A mutual understanding of the legal environment will streamline the clinical trial agreement negotiation process and avoid contracts that are legally unenforceable. A sampling of laws and other rules that impact clinical trial agreements is provided. The objective of this paper is to elicit contributions to a comprehensive and detailed compilation of rules that impact clinical study agreements.

The Legal Environment

As clinical research increasingly becomes a global enterprise, investigators and sponsors must deal with multiple legal jurisdictions, with differing laws, regulations and other rules. (The term “law,” as used in this paper, includes both laws and regulations.) These rules establish expectations based on each party’s locale. Public and non-profit entities also have various legal constraints. These rules limit the flexibility of investigators (i.e., research sites) when negotiating clinical trial agreements (CTAs). The objective of this paper is to elicit contributions to a comprehensive and detailed compilation of rules that impact clinical study agreements.

Because the rules may be numerous, obscure or subject to change and differing interpretations, it is often difficult even for contract specialists in the affected organizations to understand their application in specific circumstances and to intricate language drafted by sponsors. A mutual understanding of these regional and institutional differences by both sponsors and investigators will streamline the clinical trial agreement negotiation process.

Investigators are subject to rules on multiple levels:

- International
- Multinational
- National
- State or Province
- Ethics Committee
- Institutional
- Societal

International. Various international bodies that define rules for clinical research such as the Nuremberg Code, Declaration of Helinski, and the International Conference on Harmonization ICH E6 Guideline for Good Clinical Practice. However, they do not enforce their rules; they leave that to governments. (There may, someday, be an exception to this generalization: The World Trade Organization theoretically could adjudicate accusations of unfair clinical research trade practices.) In addition, some industry associations publish ethical codes that require member compliance with international rules.

Multinational. Multinational laws may apply. The European Union (EU) and Mercosur (Uruguay, Paraguay, Argentina and Brazil) have published extensive laws for their member states. Member states may or may not be required to enforce these laws as their own. Adoption of the EU Clinical Trials

Directive by member states is required, and an arduous process of “approximation” is now in progress. Of the Mercosur members, only Uruguay legally enforces Mercosur laws as its own.

National. Nations in the developed world, and many in the developing world, have laws that govern the conduct of clinical research within their borders, and sometimes outside their borders. These laws are generally variations on a theme, although the variations can be quite significant, and rules that some countries consider important may be absent in other countries. In practice, levels of reporting, auditing and enforcement vary widely, with none at all apparent in some countries.

State and Province. States and provinces may have their own laws that specifically or incidentally govern clinical research. This generality applies to every state in the United States, but with different specifics. The author is unaware of any county, city or parish laws specific to clinical research, although they may exist, perhaps in countries without states or provinces.

Ethics Committees. Ethics committees may have rules that do not have legal force but, for practical purposes, are strictly required. Ethics committees may review CTAs as part of their normal review process; anything that potentially impinges on subject welfare (or anything else they consider within their jurisdiction) may receive their attention.

Institutional. Institutional laws place requirements on specific types of entities such as federal, state, non-profit, or those that receive funding from those sources. Non-negotiable rules of the entity that are not legal requirements are not addressed in this paper. Such rules may originate from the entity’s idiosyncratic interpretation of the laws, which have been known to be ambiguous.

Societal. The customs of a society may prohibit contract terms that are otherwise legal. Concepts of personal privacy, for example, may be problematic in societies where the individual is subordinate to the extended family.

A study may be subject to conflicting laws, even if the sponsor and investigator are in the same legal jurisdictions. These conflicts are normally resolved by priority of law, e.g., national laws override state laws, but it may not always be straightforward to untangle (or remember) overlapping conditional requirements, authorizations and prohibitions. For example, if HIPAA requires a disclosure and a state law prohibits it, which prevails? Some laws may apply to one party to an agreement, but not to the other party, e.g., if they are in different jurisdictions or are different types of entities. The parties to the agreement may be unaware of the conflicts of law, unaware of a law at all, or may interpret differently the laws or to whom they apply.

When the sponsor and investigator have knowledge of the entire legal environment, time need not be wasted attempting to negotiate terms that are clearly illegal. Negotiation of the law’s interpretation and implementation will provide adequate stimulation for the parties. Of course, there may be circumstances when the conflict between laws, regulations, and legally or self-imposed institutional restrictions make an agreement impossible, but it’s better to find out sooner rather than later if the conflicts are insurmountable.

Forces for Change

Unlike most other global industries, clinical research has an intense regulatory component. Increasing globalization of both the medical products and clinical research industries will encourage legal convergence to enable data collected anywhere in the world to support marketing applications anywhere in the world. As developing countries with low costs and ready availability of subjects gain market share, they will come under increasing pressure to adopt and enforce the legal standards of developed countries, e.g., ICH GCP guidelines. This pressure will come from sponsors in developed countries as well as competition between developing countries.

Technology will drive evolution in the legal environment. For example, the impossibility of maintaining anonymity of biological samples containing DNA or RNA, which intrinsically identify their source, eventually will be addressed.

A broader understanding of the complex terrain of the legal landscape may also encourage regulatory simplification and rationalization.

Clinical Trial Agreement Content

Because clinical trial agreements are legal documents, much of their content necessarily has a legal flavor to it. Sponsors, however, are often tempted to include great detail in CTAs about the investigator's regulatory (e.g., GCP) responsibilities. This practice places the burden on the sponsor to understand the investigator's full legal and regulatory environment and make relevant laws accessible to the investigator. An incorrect definition of a term that has a legal definition is obviously asking for trouble. Describing the requirements for informed consent is a minefield, as illustrated in Table 1 below.

Clinical trial agreements should include suitable citations and accommodate investigators who do not have easy access to these laws (in their native language). Sponsor personnel should have the means to monitor investigator compliance and advise investigators when they stray. Current compliance with this requirement is easily tested: Randomly select three CRAs who monitor ICH trials in the US and ask them to name five differences between FDA and ICH Good Clinical Practice.

Clinical trial agreements may not be the best tools for educating the investigator of his/her regulatory responsibilities. In large, sophisticated research centers, the investigator often sees only the signature page of the agreement. In the small, unsophisticated sites that need the education, investigators generally do not read the CTA, and do not understand much of what they do read. On the other hand, these are also the sites least likely to enroll subjects and create compromised data.

The State of the Law

Table 1 contains examples of laws that impact clinical study agreements. Most of the laws are included because they vary from U.S. federal law as applied to commercial enterprises.

Disclaimer: Table 1 is far from complete, does not address legal subtleties, and contains out-of-date, over-simplified, or otherwise erroneous information. Please submit corrections to the author. Consult with your attorney for legal advice.

Table 1: Laws and Other Rules that Impact Clinical Trial Agreements

Adverse events

- **U.S.** VA (Veterans Administration) requires reciprocal reporting of adverse events between investigator and sponsor. Investigator must notify VA.

Attorneys' fees

- **U.S.** Each party generally pays its own attorneys' fees, win or lose.

Alternative dispute resolution

- **U.S.** Some state entities, e.g., in Alabama, may not give up sovereignty by accepting mandatory binding arbitration. Other states allow arbitration if it follows the laws of that state.

Authority

- **U.S.** A VA Research and Development Committee must approve clinical studies performed at VA facilities. However, the VA is not a party to CTAs between sponsors and VA-affiliated entities.
- **Alabama.** State entities must be the contracting entity, rather than the principal investigator, if the principal investigator is conducting the study in the course of his/her employment.

Billing third-parties

- **New Mexico.** Medicare and private insurance coverage is optional for clinical trials other than for cancer, where it is required for routine costs. (13-10-13-10(C)(18)(f), 8-325-6-11, 59A-22-43)
- **New York.** Site may not bill both sponsor and third-party for same study cost.
- **Texas.** Physicians may not attempt to obtain reimbursement for treating adverse events from subject's insurance carrier.

Compensation

- **U.S.** Compensation to clinical investigators must be reasonable and based on their work. (PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results)
- **U.S.** Medicare covers the routine costs of qualifying clinical trials. (National Coverage Decision)
- **U.S.** Bonus and incentive payments to non-profit entities are taxable.
- **U.S.** Federal employees may not receive compensation except from the federal government (e.g., no enrollment incentives) (18 USCS 209)
- **U.S.** If a study is open to VA patients, even if conducted at an academic center that uses its own IRB, the VA receives the greater of \$1,200 or 10% of the per-subject budget for VA patients. (VHA Directive 2003-031)

Eligibility

- **California.** If a legally-authorized representative is involved, informed consent for research must relate to the health of the subject. (H&S 24175)
- **California.** No biomedical research on prisoners. (Penal Code 3502)
- **Texas.** Mentally ill or developmentally disabled persons who have been involuntarily committed to an institution, may not receive placebos or ineffective doses or medications, or be enrolled in a study if prior studies with 100 or fewer patients have found minimal or no proof of safety and effectiveness.
- **EU.** May not enroll incapacitated adults unable to give consent unless study relates to a life-threatening or debilitating clinical condition.

Ethics committees

- **U.S.** VA medical facilities must use their local IRB. Protocol approval through central IRBs is prohibited.

Freedom to contract

- **Arkansas.** State entities cannot accept restrictions on their rights to participate in other studies in a similar field. They can, however, agree not to enter into any contract that would prevent them from carrying out their obligations under the CTA.

Governmental inspections

- **Spain.** Audits are authorized, but do not exist in practice. (223/2004 Royal Decree)

Governing law

- **U.S.** PhRMA members' clinical trials are conducted in accordance with applicable laws and regulations, as well as recognized principles of Good Clinical Practice (GCP), wherever in the world

trials are conducted. (PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results)

- **U.S.** Respective state laws, absent conflict with federal law, govern VA-affiliated non-profit entities.
- **Alabama.** State entities cannot contractually agree to take on the responsibilities to which the Principal Investigator is legally obligated under the Code of Federal Regulations.
- **Alabama.** The exclusive forum for claims against state entities is the State of Alabama Board of Adjustment.
- **Arkansas.** State entities are protected by sovereign immunity, which may not be waived. All claims must be brought through the Arkansas Claims Commission. (Ark. Code Secs. 19-10-201 – 19-10-210, specifically 19-10-204(a))
- **Louisiana.** Louisiana law, based upon the Napoleonic Code, is unique within the United States. The law of other states is based on English common law.
- **Nevada.** Institutions of higher education may not accept governing law or jurisdiction other than Nevada. (Chancellor Memo 02-04)
- **ICH.** ICH E6 Guideline for Good Clinical Practice is legally enforced in various countries other than the U.S.
- **International.** Some countries require that their law must govern for an agreement to be enforceable.

Indemnification and liability

- **U.S.** Any federal employee named as a party to a lawsuit is represented by the U.S. Department of Justice in any settlement decision. (28 U.S.C. 516)
- **U.S.** VA's liability for the negligence of its employees in performing their duties is governed exclusively by the provisions of the Federal Tort Claims Act. (28 U.S.C. 1346(b) & 2671 – 2680).
- **U.S.** State and federal entities cannot indemnify, cannot offer warranties, cannot waive immunity, have limited liability, are responsible only for their own negligence and that of their employees, may not agree to injunctions or equitable relief, or waive other rights such as consequential damages, injunctions or equitable relief.
- **U.S.** Most states have a statute of limitations for contract disputes of seven or eight years.
- **Alabama.** The University of Alabama is self-insured for the negligence and omissions of its employees within the scope of their employment. It has no insurance coverage applicable to third-party acts, omissions or claims, and can undertake no obligation that might create a debt of the state.
- **Alabama.** Because public entities cannot create a debt of the State, they must have full indemnification for their conduct of the trial including indemnification against property damage and third party claims. (This interpretation of state law by the University of Alabama may be changing.
- **California.** Non-economic damages in medical malpractice cases are capped at \$ 250,000. (Cal. Civil Code § 3333. 2)
- **Nevada.** Indemnification and tort liability is limited to \$50,000 per occurrence (NRS 41.035).
- **Utah.** Public Entities have a one-year statute of limitations for contract disputes.
- **Australia.** A local company must provide sponsor's indemnification.
- **Singapore.** A local company must provide sponsor's indemnification.

Informed consent

- **U.S.** State laws vary as to the wording and placement of the Minor Assent Statement for pediatric studies. Some states require that it be in a separate document.
- **U.S.** State laws vary as to ages of consent and assent.
- **U.S.** Some states have additional requirements for consent of people with HIV/AIDS.
- **U.S.** VA requires a witness signature to the subject's signature

- **California.** Subjects must sign Patients' Bill of Rights along with the informed consent form. (CA Health & Safety Code 24172)
- **California.** Age of majority is 18. Minors need parental permission. Age of consent for medical care is 15 except for mental health care where it is 12.
- **California.** Informed consent form must include numerous items, including witness signature, statement of placebo use, if any, and recovery time.
- **California.** Priority order for legally-authorized representative is (1) agent via a health care directive, (2) conservator or guardian, (3) spouse, (4) adult child, (5) custodial parent, (6) adult sibling, (7) adult grandchild, and (8) closest available adult kin. If there are two or more of same priority, unanimity is required for consent. (H&S 24178)
- **California.** If subject has previously appointed a health care power of attorney (POA), he/she can appoint a "surrogate" who controls over POA by personally informing the supervising health care provider. (H&S 24175)
- **Texas.** Age of majority is 18. Minors need parental permission, but others, such as grandparents may give permission if a parent is unavailable. Age of consent for medical care and mental health care is 18, except for some types of care where age of consent is 16 if subject is independent.
- **Texas.** Priority order for legally-authorized representative is (1) spouse, (2) adult child of patient with waiver and consent of all other adult children, (3) majority of reasonably available adult children, (4) parents, (5) person last identified by patient prior to incapacity, (6) nearest living relative, and (7) member of clergy. If there are two or more of same priority, majority rules. (H&S § 313.004)
- **Massachusetts.** Subjects must sign Patients' Bill of Rights along with informed consent form.
- **Argentina.** M.D. must obtain consent. Witness must be present and sign informed consent form.
- **Brazil.** Fingerprint is acceptable if subject or legal representative cannot sign name.
- **Chile.** Witness is required if subject or legal representative is illiterate.
- **Mexico.** Fingerprint is acceptable if subject or legal representative cannot sign name. Two witnesses must sign and state their relationship to subject.
- **Spain.** If subject is illiterate, a witness is required.

Insurance

- **Arkansas.** Because of sovereign immunity, state entities do not carry general liability insurance; many employees are covered under the sovereign immunity protections. (Ark. Code Sec. 19-10-305)
- **Florida.** Minimum malpractice insurance requirement is \$100,000/\$300,000.
- **International.** Insurance requirements and availability vary substantially by country and are generally inadequate by U.S. standards.
- **EU.** Investigator and Sponsor must have insurance or indemnification for subject injury liability.
- **Latin America.** Suitable liability insurance is not available in many countries in Latin America and elsewhere.
- **Chile.** Sponsor must provide insurance for medical treatment for adverse events that are a consequence of investigational drug administration or subject's participation in the study.
- **South Africa.** Malpractice insurance does not cover staff.

Intellectual property

- **U.S.** Any information, invention, discovery, innovation, suggestion, idea, communication or report conceived, reduced to practice, made or developed by a VA-employed principal investigator or using resources provided by the Department of Veterans Affairs, must be disclosed to both the VA and the sponsor. (35 U.S.C. 102 & 200-212, 37 C.F.R. Part 501, and 38 C.F.R. §§ 1.650 - 1.663)
- **U.S.** Federal government obtains a right in any invention made by a government employee during working hours, with contribution of government facilities, equipment, material, funds or information,

or which has a direct relation to the duties of the inventor. However, release of government rights is permitted in some circumstances. (Executive Order 10096, 37 C.F.R. 501.6 (a)(1), 37 C.F.R. 501.6 & 501.7, 37 C.F.R. 501.6 (a)(2) – (4) & 501.7)

- **U.S.** Copyright protection is not available for any work prepared by an officer or employee of the federal government as part of that person's official duties. (17 U.S.C. sec. 101 & 105).
- **Alabama.** State entities must retain ownership of raw data and information contained within patient medical records.
- **Alabama.** State entities cannot waive rights to intellectual property they would own, but must receive fair market value.

Investigator disclosure of financial interests and conflicts-of-interest

- **Louisiana.** Tulane University requires Principal Investigators to sign a disclosure of financial interests and conflicts-of-interest statement annually and update as necessary during the year.
- **EU.** Special consent required to send investigator's (and spouse's) personal information out of the EU to countries (including the U.S.) not recognized as having equivalent privacy laws. (Data Protection Directive)
- **Argentina.** No disclosure required.

Languages

- **Spanish-speaking Countries.** "Violation" sounds like "violación," which means "rape" in Spanish.
- **Brazil.** Request that Investigator's Brochure be translated into Portuguese.
- **Quebec, Canada.** Informed consent forms must be in both English and French.

Privacy

- **U.S.** VA requires confidentiality for records related to drug abuse, alcoholism or alcohol abuse, HIV/AIDS and sickle cell anemia. (38 U.S.C. 7332)
- **Virginia.** When protected health information is disclosed to a third-party, that third-party is obligated to keep it confidential.

Publication

- **U.S.** In most cases, educational and non-profit entities must retain publication rights to avoid Unrelated Business Income Tax on sponsored research.
- **U.S.** Non-profit educational institutions that accept Federal funding must have access to study data and results, and the right to publish without editorial control by the sponsor.
- **U.S.** There will be timely communication of meaningful study results, regardless of the outcome of the study. The results must be reported in an objective, accurate, balanced and complete manner, with a discussion of the limitations of the study. Study sponsors will not suppress or veto publications. (PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results)
- **U.S.** Any investigator who participated in the conduct of a multi-site clinical trial will be able to review relevant statistical tables, figures, and reports for the entire study at the sponsor's facilities, or other mutually agreeable location. (PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results)
- **U.S.** Only those who make substantial contributions to a publication should receive acknowledgement as an author or contributor to the publication. (PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results)
- **International.** Authorship credit should be based on (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published. Authors should meet all three criteria. (International Committee of Medical Journal Editors Uniform

Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, adopted by over 500 publications)

- **Brazil.** Provide copy of publication to ethics committee. If study is not completed or data is not published, provide explanation.
- **Spain.** Sponsor must publish study results.

Publicity

- **U.S.** Government employees, in their official capacity, may not endorse products except for official purposes. (5 C.F.R. 2635.702).
- **U.S.** Federal funding sources require that applications for funding disclose current and pending sources of support, including sponsor's name and brief description of project objectives.
- **International.** Publication must acknowledge sponsor's name. (International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, adopted by over 500 publications)

Record retention

- **U.S.** Investigator must retain records and reports for two years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been notified. (21 CFR 312.57 & 312.62)
- **U.S.** Federal entities retain study records for five years after completion of a research project and/or publication of a final report. (Privacy Act, 34 VA 12)
- **Illinois.** Medical records should be retained for ten years after the most recent patient care usage. (Hospital Licensing Act)
- **ICH.** The sponsor must inform the investigator when retention is no longer required.
- **ICH.** Retention period is the same as under FDA rules, except the rules may apply while the drug is under investigation for *any* indication, not just the one investigated in the study.
- **ICH.** Sponsor or regulatory authorities may subsequently require an additional period of retention beyond that specified in the CTA.
- **Canada.** Retention period is 25 years.
- **Mercosur.** CRF must be retained for 5 years after study final report.
- **Argentina.** Retention period is 15 years.
- **Germany.** Medical records must be retained for 15 years. Study records must be retained per ICH rule (4.9.5). A provision of the proposed Amendment 12 of the German Drug Law would require retention of study records for five years after study completion.

Referral fees

- **U.S.** Physicians may not refer Medicare and Medicaid patients for "designated health services" to entities with which they (or an immediate family member) have a financial relationship. (Stark law)
- **U.S.** Kickbacks related to transactions with Federal health care programs are prohibited. (41 U.S.C. 51.58)
- **U.S.** Payment by or to a physician solely for the referral of a patient is fee splitting and is unethical. (American Medical Association Code of Medical Ethics E-6.02)
- **U.S.** In a clinical sponsored by a U.S. company, it may be illegal for an investigator in a foreign country to pay a subject referral fee to someone who is a government employee if the payment would be illegal in the United States. (Foreign Corrupt Practices Act)
- **Hawaii.** Referral fees are prohibited by legal codification of AMA Code of Medical Ethics. (453-8(a)(9))

- **Kentucky.** Referral fees are prohibited by legal codification of AMA Code of Medical Ethics. (63-6-214(b)(1))
- **Ohio.** Referral fees are prohibited by legal codification of AMA Code of Medical Ethics. (311.597(4))
- **Tennessee.** Referral fees are prohibited by legal codification of AMA Code of Medical Ethics. (4731.22(B)(18))

Shipping hazardous materials

- **U.S.** VA requires pharmaceuticals related to a clinical study to be processed through its Investigational Drug Service.
- **Brazil.** Biological samples not used for study must be disposed of.

Sponsor confidential information

- **U.S.** Federal Entities grant public access to most information. (Freedom of Information Act) Most states have similar laws.
- **U.S.** Confidentiality cannot apply to information that is required to be disclosed by law because that would conflict with legal requirements.
- **Alabama.** Because Alabama is an “open records state,” state entities must be allowed to disclose confidential information that it is required by law to disclose, including the terms and conditions of clinical trial agreements.
- **Oregon.** Records relating to the conduct of the public’s business are publicly accessible. However, trade secrets and other information submitted in confidence where such information should reasonably be considered confidential may be kept confidential.
- **Tennessee.** Confidentiality excludes “information required by law to be disclosed.”

Sponsor responsibilities

- **Argentina.** Sponsor or its legal representative has responsibility for study approval at all regulatory levels, informing the investigator, and monitoring the study.

Statement of Investigator

- **Mercosur.** Investigator must comply with GCP. (Res. #129) Principal investigator must abide by Nuremberg, Helsinki and Tokyo declarations.
- **Argentina.** Investigator signs statement that he/she will comply with 5330-1997 GCP Requirements, but nothing else found in FDA 1572.

Study personnel qualifications

- **Chile.** Study coordinators must have a five-year university degree in the biological sciences (including post-graduate studies) valid in Chile (i.e., granted by a Chilean University), have completed a GCP course, and maintain an annually-updated CV. (Norma Técnica N 57 June 2001- Ministerio de Salud (Ministry of Health) de Chile)
- **Mexico.** Principal Investigator may be any qualified health professional.
- **Spain.** If study has multiple sites in Spain, must specify an Investigator-Coordinator.

Subject injury

- **U.S.** Medicare covers the cost of diagnosing and treating subject’s injuries. (National Coverage Decision)
- **U.S.** VA medical facilities provide necessary medical treatment to subjects injured as a result of participation in a research study approved by a VA Research and Development Committee and conducted under the supervision of a VA employee. (38 C.F.R. 17.85)
- **U.S.** The definition of “injury” and the statute of limitations vary by state.

- **Illinois.** The statute of limitations starts running when a reasonable person would know or should know that something out of the ordinary or unnatural caused an injury, defined as an invasion of a legally-protected interest.
- **Argentina.** Study sponsor is responsible when the injury is related to the study drug or participation in the study, possibly including when there is negligence by investigator.
- **Australia.** Members of the Australian Pharmaceutical Manufacturers Association must provide compensation to injured subjects.

Subject privacy

- **U.S.** Many states (e.g., Illinois) have laws covering the confidentiality of people with HIV/AIDS, for example, prohibiting divulgence of the result of an HIV/AIDS test.
- **California.** Disclosure of lab results via electronic means is prohibited.
- **California.** Pharmaceutical companies (but not medical device firms) may not disclose medical information about a subject without his/her consent.
- **California.** Investigator must sign confidentiality pledge to enroll developmentally disabled subjects. (17 CCR 50421)
- **Georgia.** HIPAA requires certain law enforcement-related disclosures and disclosures to the Secretary of DHHS for the purpose of investigating compliance with HIPAA that are otherwise prohibited by state law.
- **Oregon.** Any person authorized by law or by an individual or an individual’s representative to obtain, retain or use an individual’s genetic information or any DNA sample must maintain the confidentiality of the information or sample and protect the information or sample from unauthorized disclosure or misuse. (ORS 192.531 to 192.549, 659A.303 and 746.135)
- **Brazil.** Patient database and medical history data to be used for research must be reviewed by the Comissão de Pesquisa e Ética em Saúde. Commitment to protect data confidentiality is required. (Resolução Normativa 01/97)

Subject stipends and reimbursements

- **EU.** No incentives or financial inducements are permitted for minors or incapacitated adults unable to give consent.
- **Spain.** No stipends are permitted except for expense reimbursement and compensation for not working for (a) minors, (b) vulnerable subjects, and (c) any subject who directly benefits from study.

Subject medical care

- **U.S.** Some states require that counseling be available for subjects who test positive for HIV/AIDS.

Terminology

- **U.S.** Public and non-profit institutions avoid language that appears to characterize an agreement as commercial or profit-oriented. Clinical drug testing for FDA purposes is not a tax-exempt activity without a research and information dissemination purpose. Preferred and non-preferred terms are listed in Table 2.

Table 2: Non-commercial Terminology

Use	Don’t Use
Clinical Research Agreement	Clinical Trial Agreement
Study	Trial
Research	Service
Institution University Non-Profit Organization	Contractor Vendor Provider Business Associate
Funding Support Grant	Payment

Validation

- **ICH.** Computer system validation is required and legally enforced in some countries other than the US. (ICH E6 .5.3(a))

Warranties

- **U.S.** A warranty by a public or non-profit entity may cause a contractual relationship to be characterized as commercial, give the other party an argument that the agreement is covered by the Uniform Commercial Code, and expose the entity to Unrelated Business Income Tax on sponsored research. It may also void the immunity of governmental entities and expose them to liability.

The author has not identified legal variations that impact the following CTA sections (although many certainly exist):

- Investigator and site responsibilities
- Advertising and recruiting for subjects
- Assignment
- Conflict between Agreement and Protocol
- Counterparts
- Debarment and disqualification
- Delegation of responsibilities
- Electronic signatures and data (e.g., eCRFs)
- Force majeure
- Protocol violations and deviations
- Relationship of the parties

Resources for Clinical Research Laws and Regulations

The following resources are or were available, although tragically not to the author during the writing of this paper.

- Barnett Educational Services recently published “State Clinical Trial Requirements Pocket Guide,” a guide to U.S. state laws and regulations. (www.barnettinternational.com/edu-pubs1.jsp)
- Medical Research Law has announced a new book and Internet service covering laws and regulations for the UK. The initial scope of their coverage is limited but will expand over time. (<http://www.medreslaw.com/>)
- Thompson Publishing Group until recently published extensive information about U.S. state laws and regulations. Unfortunately, the web service went off line in June 2004. The authors are seeking a new publisher, so it may reappear. (<http://www.thompson.com/libraries/fooddrug/claw>)

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