Beth Israel Deaconess Medical Center

A teaching affiliate of HARVARD MEDICAL SCHOOL

Last Resort Cancer Clinic Legal Issues

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Agenda

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- Information Privacy
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Introduction/Context

- Is it clinical research or medical treatment?

Clinical Research Versus Medical Treatment		
	Clinical Research	**Medical Treatment**
Intent	Answers specific questions through research involving numerous research volunteers.	Addresses the needs of individual patients.
Intended Benefit	Generally designed and intended to benefit future patients.	Intended to benefit the individual patient.
Funding	Paid for by drug developers and Government agencies.	Funded by individual patients and their health plans.
Timeframe	Depends on research protocols.	Requires real-time decisions.
Consent	Requires written informed consent.	May or may not require informed consent.
Assessment	Involves periodic and systematic assessment of patient data.	Based on as-needed patient assessment.
Protections	Protected by government agencies, institutional review boards, professional standards, informed consent, and legal standards.	Guided by state boards of medical practice, professional standards, peer review, informed consent, and legal standards.
Certainty	Tests products and procedures of unproven benefit to the patient.	Uses products and procedures accepted by the medical community as safe and effective.
Access to Information	Considered confidential intellectual property.	Available to the general public through product labeling.
Release of Findings	Published in medical journals, after clinical research ends.	Individual medical records are not released to the general public.

http://www.fda.gov/ForPatients/ClinicalTrials/ClinicalvsMedical/default.htm

Off-label Treatment with FDA-approved Drugs/Devices

A. Does the FDA Regulate Off-label Activities?

- FDA Regulatory Basics:
  - Federal Food, Drug, and Cosmetics Act ("FDCA")
  - FDA Regulations
  - FDA Guidance
- The FDA approves all new drugs and devices (and their labels) before they can be sold to the public.
  - Each drug or device is approved for a specific use or purpose. However, often, these drugs and devices can be used to treat other conditions as well.
- "Off-label use" is the use of a drug or device in a manner not specified by the FDA's approved packaging label, or insert.

Off-label Treatment with FDA-approved Drugs/Devices

- The FDA does not regulate the practice of medicine.
  - "Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship." 21 U.S.C. §396.

- However, the FDA does restrict the ability of manufacturers to promote off-label uses for their products.
  - The FDCA does not explicitly prohibit manufacturers from promoting FDA-approved drugs for off-label purposes, but two related statutory provisions — on labeling and misbranding, respectively — have operated to that effect.

Off-label Treatment with FDA-approved Drugs/Devices

B. Does the Federal Policy for the Protection of Human Subjects (the "Common Rule") Regulate Off-label Activities?

- The Common Rule Regulatory Basics:
  - The Common Rule is codified in separate regulations by several Federal departments and agencies, including the Department of Health and Human Services ("HHS").
  - The HHS Common Rule regulations, found at 45 C.F.R. part 46, include four subparts A, B, C, and D.

- The Common Rule does not apply to standard clinical care (absent research-driven data collection or other research intervention).

Off-label Treatment with FDA-approved Drugs/Devices

c. Clinical Informed Consent

- Generally, requirements for informed consent in the treatment context are less prescriptive than the requirements for informed consent in the research context.

- Often common law prescribed rather than by regulation, except in certain contexts (i.e. sensitive information such as genetics, etc.).

- Information material to an informed decision must be provided.

Off-label Treatment with FDA-approved Drugs/Devices

D. Malpractice Liability

- Malpractice laws vary from state to state.
  - Courts have held that physicians do not have to disclose to patients that a proposed use is off-label.
- Likely Causes of Actions:
  - Physician's Failure to Obtain Informed Consent
    - A physician must present the patient with material information about proposed treatments and their alternatives, and about the risks and potential benefits of the alternatives, then allow the patient to decide which course of action to pursue.
    - Prevailing standard in most states is "reasonable physician" standard.
    - In Massachusetts it is the "reasonable patient" standard.
  - Physician's Negligence
    - Plaintiff has to prove all four elements of a negligent malpractice claim: (1) The physician owed the plaintiff a duty to act reasonably; (2) The physician breached that duty; (3) The plaintiff suffered actual harm; and (4) The harm was proximately caused by the breach of duty.

Off-label Treatment with FDA-approved Drugs/Devices

- Factors the FDA suggests physicians should consider when using a product for an indication not in the approved labeling:
  - Physicians should be well informed about the product
  - Physicians should base their off-label use of the product on firm scientific rationale and on sound medical evidence
  - Physicians should maintain records of the product's use and effects
  - Although not required, physicians may choose to request IRB review (or other institutional oversight) of the proposed use

Off-label Treatment with FDA-approved Drugs/Devices

E. Possible Protective Measures

- Review Committee/ Ethics Board (i.e. innovative care committee, Clinical Ethics Committee, etc.)
- Approved clinical protocols
- Obtain meaningful informed consent (see above)
- Insurance coverage (is the clinic already covered under AMC's insurance, or would the institution need to purchase supplemental insurance for the clinic?)

Clinical Trials: Investigating Off-Label Use of FDA-approved Drugs/Devices

A. FDA Regulations: 21 C.F.R. Parts 50, 56, 312, 812

- When do they apply?
  - Clinical Investigations (determining the “safety” and “efficacy”) of FDA regulated products (gain approval or change label)
  - Focus on human subject protection and data integrity
- IND/IDE?
  - If a company wants to conduct a clinical trial on a drug/device, in general, it first needs to obtain regulatory approval by submitting an investigational new drug (IND) or an Investigational device exception (IDE) application to the FDA.
  - Many studies of off-label approved drugs will be exempt from the IND requirements if the investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk associated with the use of the drug product.

Clinical Trials: Research Involving Off-Label Use of FDA-approved Drugs/Devices

- Institutional Review Board ("IRB") Oversight?
  - IRB review and approval is required before a clinical investigation regulated by the FDA can be initiated.
- Informed Consent?
  - No clinical investigation covered by FDA regulations may commence unless the legally effective informed consent of the subject or the subject's legally authorized representative has been obtained.
  - Basic elements of informed consent: (1) Study involves research; (2) Study description; (3) Reasonably foreseeable risks and discomforts; (3) Benefits; (4) Disclosure of alternative procedures/treatments; (5) Confidentiality of records; (6) Compensation and treatment for injury; (7) Contact Information; (8) Voluntary participation
  - Content more prescribed than clinical context.

Clinical Trials: Research Involving Off-Label Use of FDA-approved Drugs/Devices

B. The Common Rule

- When does it apply?
  - Research funded by HHS
    - The institution must execute a "federalwide assurance" ("FWA") with the Office for Human Research Protections ("OHRP").
    - An FWA is a contract with the government through which the institution agrees to comply with applicable regulations and terms of the assurance.
  - Institutional Policy - Sometimes institutions agree to apply the Common Rule to all research regardless of funding.
- IRB Oversight?
  - Similar requirements to the FDA regulations.
- Informed Consent?
  - Similar requirements to the FDA regulations, with the exception that the Common Rule permits broad waiver of informed consent for certain minimal risk research.

Clinical Trials: Research Involving Off-Label Use of FDA-approved Drugs/Devices

C. Funding Agency Requirements
   - Depending on which agency is funding the clinical trial, different requirements may attach to the funding.

D. State Laws
   - Some state statutes impose requirements on various aspects of human research that are either in addition to existing federal requirements or fill the gap where no federal law applies.

E. Intellectual Property (“IP”)
   - Typically, the rights to intellectual property originating in the context of a clinical trial are apportioned through the terms of the clinical trial agreement between the sponsor (if any) and institution.

Clinical Trials: Research Involving Off-Label Use of FDA-approved Drugs/Devices

F. Subject Injury

- How are subjects going to be made whole if injured?
  - Institutional policy (not FDA regulations or the Common Rule) determines whether compensation and medical treatment(s) will be offered to injured subjects.
  - The Common Rule and FDA regulations are silent on whether the treatment of subjects' injuries ought to be the responsibility of the sponsor, the researcher, or the test subjects.
  - Declaration of Helsinki and some countries require compensation/treatment for harmed subjects.
  - However, the Common Rule and FDA regulations both require:
    - For research involving more than "minimal risk", the subject must be told whether any compensation and any medical treatment(s) are available if injury occurs and, if so, what they are, or where further information may be obtained.
    - Any statement that compensation is not offered must avoid waiving or appearing to waive any of the subject's rights or releasing or appearing to release the investigator, sponsor, or institution from liability for negligence.

Clinical Trials: Research Involving Off-Label Use of FDA-approved Drugs/Devices

G. Professional Liability
- Claims of negligence in research context
  - Plaintiff has to prove all four elements of a negligence claim: (1) The researcher owed the plaintiff a duty to act reasonably; (2) The researcher breached that duty; (3) The plaintiff suffered actual harm; and (4) The harm was proximately caused by the breach of duty.
  - In 2001, a court first addressed the issue of whether researchers owe a duty of care to research participants in *Grimes v. Kennedy Krieger Institute*. The court decided that informed consent agreements in research give rise to a duty the researcher has to the subject.
  - The court also held that informed consent agreements in non-therapeutic research can constitute contracts as well as special relationships from which special duties arise, and if breached, may independently give rise to negligence claims.

Clinical Trials: Research Involving Off-Label Use of FDA-approved Drugs/Devices

H. Possible Protective Measures

- Review by IRB
- Obtain meaningful informed consent (see above)
- Insurance coverage
  - Coverage of research specifically
- Transparent communication with research authorities (ex. Basket Studies and pre-approval of alternative research trial design)

Expanded Access

- Expanded access provides a pathway for patients to gain access to investigational drugs and devices for serious diseases or conditions.
  - Such investigational drugs/devices have not yet been approved by the FDA and they have not been proven to be safe and effective.
- FDA has three categories under which expanded access (for investigational drugs) can be approved:
  - Expanded access for individual patients
  - Expanded access for intermediate-size patient populations
  - Expanded access for widespread treatment use
- Two types of regulatory submissions:
  - a new IND or
  - a protocol amendment to an exiting IND
- Individual patients are not able to apply for expanded access, only a licensed physician may do so.

Expanded Access

- What does the FDA consider when reviewing a request for expanded access to investigational drugs?
  - Serious disease/condition
  - Immediately life threatening
  - There is no comparable or satisfactory alternative therapy
  - Patient cannot obtain the drug under another IND or protocol, and
  - Providing the investigational drug will not interfere with the clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.
- While the FDA often works with companies to facilitate wider access to a drug/device, it is ultimately the manufacturer's decision whether to grant expanded access to a drug or not.

Expanded Access

- Case law related to patient demand for access to investigational products off-protocol:
  - Cacchillo v. Insmed Inc. 2013 WL 622220 (2013)

- "Right to Try" Legislation: Several states have introduced legislation intended to address various aspects of the compassionate use process.
  - In Massachusetts, Bill H. 3270 "An Act Providing a Right to Try" was introduced to the Senate on January 20, 2015 and was referred to the House Committee on Public Health.
  - In pertinent part, the law would allow eligible patients to have access to an investigational drug or device.

Lifestyle Changes/Herbal Supplements/Other Therapies (Single Patient Treatment or Clinical Trials)

- State Laws (consumer protection laws)
- FDA
  - Dietary Supplement Health and Education Act of 1994
    - Amended the FDCA
    - Regulates labeling and holds supplement manufacturers to what are known as "good manufacturing practices" (i.e., industry standards for maintaining product quality).
  - Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006
    - Requires "adverse event reporting" to the FDA of any incidents related to a product once it is on the market.
- Federal Trade Commission ("FTC")
  - Maintains authority over dietary supplement advertising.
  - Section 5(a) of the FTC Act is a broad consumer protection statute which declares as unlawful unfair methods of competition and unfair or deceptive acts or practices in or affecting commerce.

Information Privacy

- HIPAA
  - Health Insurance Portability and Accountability Act of 1996
  - Prohibits the use and disclosure of certain health information (Protected Health Information or “PHI”) absent authorization from the individual or another applicable exception
  - Single Patient Treatment vs. Clinical Trials
    - Rules for use and disclosure of PHI differ in the treatment vs. research context
    - Can generally use/disclose PHI to treat a patient or seek reimbursement for treatment
    - For research uses, authorization or a research-specific exception is required
- State Privacy Laws

Banking and Downstream Uses

- Different requirements attach to clinical vs. research databases
- Maintaining health information and specimens for treatment or quality improvement purposes is acceptable
- Storing identifiable information or specimens for research use is considered “research”
  - IRB oversight and informed consent attach
  - HIPAA rules applicable to research uses attach

Analogous Efforts in the U.S. and Internationally

- University of Washington's "Center for Cancer Innovation"
  - A site where patients, researchers, clinical trial coordinators, and oncologists can connect.
  - "All for one. One for all."
- UK Medical Innovation Bill ("Saatchi Bill")
  - Designed to allow doctors to test cutting edge new treatments on patients to help find cures for cancer and other serious illnesses.
  - Aims to provide greater clarity (negligent and dangerous practice vs. careful and reasonable innovation) and remove the threat of litigation for doctors who administer innovative treatments to patients.
  - In February 2014, the Liberal Democrats vetoed the bill, which killed off the proposed legislation in the current UK's parliament.
- "Right to Try" Legislation (U.S.)