

Crossing the Line

When does innovative therapy
become research?



Presentation Overview

- Importance of Distinction
- Primary Research Regulators
 - HHS
 - FDA
- Tricky Situations
 - Innovative surgery
 - Quality improvement
 - Drugs
- Cases for Discussion

Research v. Practice

- Why does the distinction matter?
 - IRB Review
 - Informed Consent standards
 - Regulated differently under Federal and State law
 - Publications



The Regulators: HHS & FDA

- **HHS Office of Human Research Protections** -- regulates federally funded research and research done by entities who have voluntarily agreed to apply federal regulations to all research regardless of funding source.
- **FDA** -- regulates:
 - Drugs -- chemical action; intended for use in the diagnosis, treatment, cure, prevention, mitigation of disease OR affects structure/function of body.
 - Devices – instrument, device, machine, etc.; primary action not chemical; intended for use in the diagnosis, treatment, cure, prevention, mitigation of disease OR affects structure/function of body.

HHS & FDA: Definitions of “Research”

- **Dept. of Health & Human Services**

- Systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. [45 CFR § 46.102(d)].
- Keywords – Systematic, generalizable knowledge

- **FDA**

- “Research” not a defined term per se.
- Drugs: “‘Clinical Investigation’ is any experiment in which a drug is administered or dispensed to , or used involving, one or more human subjects.” [21 CFR § 312.3(b)]
- Devices: “‘Investigation’ means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.” [21 CFR § 812.3(h)]

Practice v. Research Hallmarks

Research	Practice
Test hypothesis – unanswered question	Intervention designed solely to enhance patient well-being
Permit generalizable conclusions to be drawn	Focus is individual patient
New item or procedure	Often well-established item or procedure; but can be innovative
Data collected apart from medical record	Data collected only in medical records
Formal protocol/procedures, randomization, blinding, control group	Patient is expected to benefit
Findings disseminated	

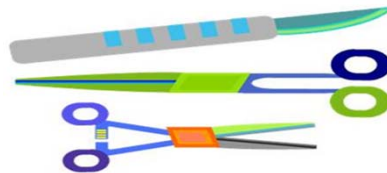
Tricky Situations: Innovative Surgery

- Innovative surgery – Research or Practice?
- Frequently involves new procedure only; no drug or device and therefore no FDA regulation.
- New and untested – not the current standard of care but based on observation, scientific rationale.
- Non-standard method that physician believes will help this patient based on patient's specific physical condition.
- Accumulated changes to procedure made gradually over the course of many surgeries to address challenges presented by disease, anatomy, etc.



Should Innovative Surgery be Done as Research?

- Small change or dramatic change to standard procedure?
- Substantial increase in risk level?
- Want to expand technique to significant population?
- Are research controls (e.g., formal protocol, control group, stringent data collection) needed to determine if innovation should be adopted?



Tricky Situations: Quality Improvement/Quality Assurance

- QI/QA – activities undertaken by health organization to evaluate outcomes, safety and cost-effectiveness of care provided to patients by that organization.
- Two Types:
 - Retrospective Review of Records
 - Prospective Interventional, e.g., comparative effectiveness of two drugs

QI/QA v. Research

- **Retrospective reviews:**
 - Is there a advance commitment within the organization to make a change based on results of review?
 - Does person performing review have authority to make change?
- **Prospective Interventional:**
 - Are both groups of patients receiving a standard of care?
 - Is the intervention that is selected being chosen based on patient's individual needs?
 - Are majority of patients involved expected to benefit ?
 - Are additional risks or burdens being imposed on some patients to make results generalizable?



Cases for Discussion: Checklist Case

- Checklist of 5 CDC recommended steps to take to reduce infection in catheter placement. Implemented checklist and tracked infection rate. Infection rates dropped.
- “Quality improvement (QI) researchers were shocked and dismayed when the Office of Human Research Protections (OHRP) froze a multicenter project investigating the use of checklists to reduce infections in intensive care units (ICU).”
- “Even though this simple intervention had been shown to dramatically cut ICU infection rates, the OHRP opted to halt the study because Johns Hopkins researchers hadn’t run their protocols by the institutional review boards (IRBs) of the 100-plus hospitals participating in the study.”
- [http://www.the-hospitalist.org/details/article/187635/SHM to Challenge OHRPs Checklist Ruling.html](http://www.the-hospitalist.org/details/article/187635/SHM_to_Challenge_OHRPs_Checklist_Ruling.html)

OHRP Guidance

QI Activities that are not usually research:

- Implement practice to improve Pt. Care and
Collect Data re. implementation

- Deliver healthcare and measure and report
provider performance data for clinical, practice of
administrative uses.

QI Activities that are research;

- Introduce untested clinical intervention to improve
care AND to collect information about patient
outcomes to establish scientific evidence to
determine how well intervention achieves intended
results.

Tricky Situation: Use of Non-FDA Approved Substance

- **Non-FDA Approved Materials or Substances**
- **Drugs** -- chemical action; diagnosis, treatment, cure, prevention, mitigation of disease OR affects structure/function of body.
- **Dietary Supplements** – product intended to supplement the diet that bears or contains one or more of the following dietary ingredients: vitamin, mineral, herb, botanical, amino acid, substance that supplements dietary intake.
- **Food** – articles used for food or drink for man/animals; chewing gum; and components of such articles.
- An item can have more than one classification at the same time.



Tricky Situation: Use of Non-FDA Approved Substance

- Practice of Medicine Exception
- FDA does not regulate the practice of medicine
- Practice of medicine is regulated by state
- FDA does regulate introduction of new, unapproved drugs into interstate commerce



Practice of Medicine?

- US. Attorney's Office, San Diego, CA, Jan. 23, 2013
- “In a hearing before U.S. Magistrate Judge Bernard Skomal on January 15, Dr. Joel I. Bernstein entered a guilty plea to a single count of introducing an unapproved drug into interstate commerce—in this case, a cancer drug called “Mabthera” intended for market in Turkey—and administering it to patients.”

<http://www.fbi.gov/sandiego/press-releases/2013/la-jolla-oncologist-and-medical-practice-plead-guilty-to-dispensing-unapproved-drugs>

Tricky Situation: Off-Label Use of Drugs

- “If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner *when the intent is the "practice of medicine"* does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.”

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm>

Off-Label Use of Drugs

- Why the different approach between regulation of unapproved drugs and off-label use of approved drugs?
- Safety and Efficacy
 - Is establishing safety enough?
- When do you need an IND?
- Informed consent issues
 - State law does not always require patient to be informed that drug is being used off-label



Cases for Discussion

- ***Ancheff v. Hartford Hospital***, 799 A.2d 1067, 260 Conn. 785 (Conn., 2002) – Hospital instituted program per which Gentamicin was administered at higher dose 1x/day as result of QA program showing better results, as opposed to then current standard of lower dose 3x per day. Pt. went deaf (know side effect of drug) and sued, claiming he had been enrolled in medical research without proper informed consent.

Ancheff Facts

- Plaintiff:
- Doctor originally prescribed 3 mg/kg 3x per day by injection; hospital pharmacy instituted change.
- Hospital dose of Gentamicin had not been tested on humans. 7 mg/kg v. 3 mg/kg
- At time of incident, hospital was only one in US to use this dose on entire classes of patients.
- Not FDA approved dose or method of administration (1x day injection v. 3x day)
- Hospital administered drug per protocol and described dose and administration as “radical.”
- In publications, hospital stated program was radical.
- Data collected apart from medical record.
- Publications & lectures.

Ancheff Facts

- Defendant:
- Hospital instituted program after review by ID, pharmacy, antibiotic and medical exec. committees.
- Program based on voluminous pharmacokinetics data. Shown to maximize killing of bacteria and discourage drug accumulation.
- Studied for many years before implementation.
- No controls, randomization, blinding.
- No funding; no reporting to FDA or any sponsor.
- At least as safe and effective as approved dosing.
- At time of case, 80% of hospitals were following the program.

Jury Instructions



- You the jury will have to determine:
- Whether at time of incident, the dose of Gentamicin given was “experimental or research or substantiated by medical literature and not something that was research.”
- Whether the standard of care was that the hospital, having data it had at time of incident, would be required to get IRB approval of this change in dosing regime and get written informed consent.

Cases for Discussion

- ***Perez v. Nidek Co. Ltd.***, 657 F.Supp.2d 1156 (S.D. Cal., 2009) – Use of laser “off-label” to correct farsightedness was not research requiring more detailed informed consent under state law because use of the laser was reasonably related to improving health of individual subject.

QUESTIONS?

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