Clinical Research v. Innovative Medical Treatment:

Understanding the Differences and Avoiding Unnecessary Risk

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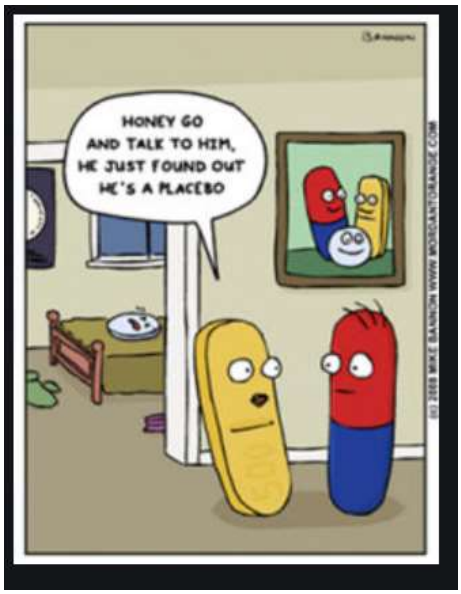
TRIAL versus TREATMENT



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What Patients Want

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What Doctors Understand

AMA

Research “is intended to contribute to the advancement of knowledge and the welfare of society and future patients, rather than to the specific benefit of the individuals who participate as research subjects.”

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Clinical Research Versus Medical Treatment		
	Clinical Research	**Medical Treatment**
Intent	Answers specific questions through research involving numerous research volunteers.	Address 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 the research protocol.	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.

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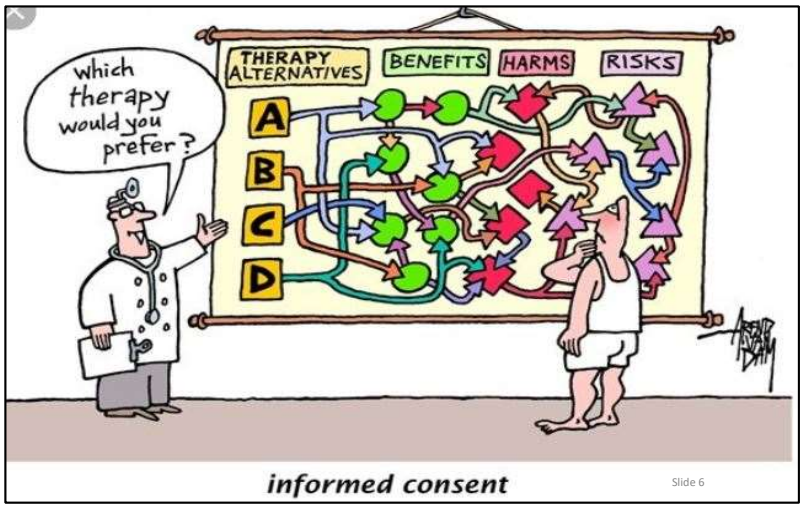
Anxiety + Confusion = Risk



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Aligning Internal Procedures to Minimize Risk

- Clinical Research
- Humanitarian Use Devices
- Compassionate Use
- Emergency Use Authorization
- Right to Try
- IRB approval
- FDA involvement

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Clinical Research

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Clinical Research (continued)

- It is critical that providers and their patients understand that:
  - (1) clinical research is not treatment tailored to the individual patient; and
  - (2) a clinical trial is a scientific study intended to answer generalizable questions that are not specific to the individual patient according to a protocol that is not designed to benefit the individual patient.

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Clinical Research (continued)

- To obtain informed consent for clinical research:
  - The prospective subject must understand that he or she is being asked to participate in research;
  - The prospective subject must be given adequate information to allow him/her to make an informed decision whether to participate in the clinical trial;
  - The information must be provided in a way that facilitates the prospective subject's understanding of the information;
  - The prospective subject must have an appropriate amount of time to ask questions and to discuss with family and friends the research protocol and whether he/she should participate;
  - The prospective subject's informed consent requires his/her voluntary agreement to participate in the clinical trial;
  - The process is ***ongoing***. The research term must continue to provide information as the clinical trial progresses or the subject/situation requires.

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Clinical Research (continued)

- **21 C.F.R. § 50.20:** requirements for informed consent for clinical research subject to FDA regulation
- **46 C.F.R. § 46.116:** requirements and elements for informed consent for clinical research subject to the Common Rule/HHS regulation

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Clinical Research (continued)

- Differences between potential liability for treatment v. clinical research
  - For treatment, the most common claim is medical malpractice, which asks whether the provider when treating the patient deviated from the standard of care in the relevant medical community and that deviation resulted in the injury.
  - For clinical research, the more common claims center around the adequacy of the informed consent and potentially resulting battery, fraud, wrongful death, and violations of the federal regulations concerning the protection of human subjects in research.

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Humanitarian Use Devices

- Benefit patients in the treatment or diagnosis of a disease or condition affecting not more than 8,000 individuals in the United States per year
- May be used in Medical Treatment or Clinical Research.
- BUT all uses of HUDs must be reviewed and approved by the IRB as defined by Federal regulations.

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Humanitarian Use Devices (continued)

Use only after FDA approves HDE and IRB approves use

What about informed consent?

- Medical Treatment
  - FD&C Act and FDA—no informed consent requirement
  - Local law may require informed consent
  - IRB may require informed consent
- Clinical Trial
  - Informed consent required

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Humanitarian Use Devices (continued)

- IRB has not approved use of the HUD
- Emergency situation
- IRB approval cannot be obtained in time to prevent serious harm or death to patient
- May be administered

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Compassionate Use

- Serious disease or condition, or immediate life-threatening condition
- No comparable or satisfactory alternative therapy
- Enrollment in clinical trial is not possible
- Benefit justifies potential risks
- Will not interfere with clinical trials that could support development or approval for the treatment indication

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Compassionate Use (continued)

- IRB reviews protocol and consent and determines if patient is informed about nature of treatment
- FDA reviews request and determines if treatment may proceed

What about informed consent?

- Medical treatment not research, but still requires informed consent

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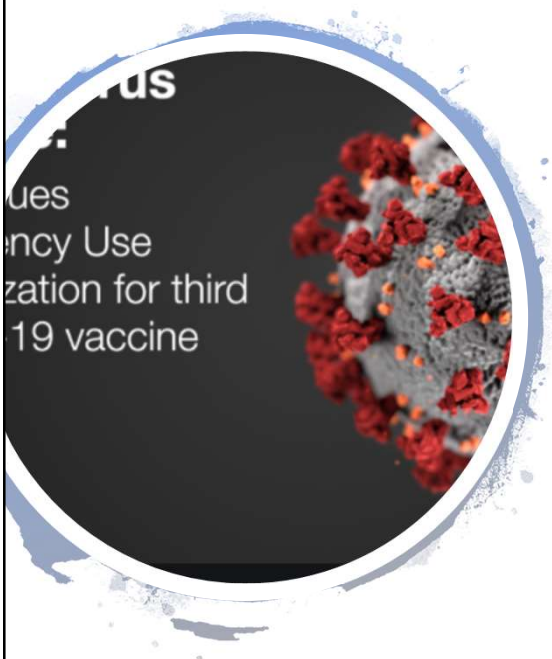

Emergency Use Authorization

For an unapproved product and for an unapproved use of an approved product, FDA must establish conditions to ensure that health care professionals who administer the EUA product are informed:

- That FDA has authorized the emergency use of the product;
- The significant known and potential benefits and risks of the emergency use of the product, and the extent to which such benefits and risks are unknown; and
- The available alternatives and their benefits and risks.

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Emergency Use Authorization (continued)

- A request for an EUA should include a “Fact Sheet" for health care professionals or authorized dispensers that includes essential information about the product, including:
  - A description of the disease/condition;
  - Any contraindications or warnings;
  - Dosing information (if applicable), including any specific instructions for special populations; and
  - Contact information for reporting adverse events and additional information about the product.

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EUAs—*What about informed consent?*

Medical treatment not research.

- FDA has authorized emergency use of the product;
- Significant known and potential benefits and risks associated with the product, and extent to which such benefits and risks are unknown;
- Patient has the option to accept or refuse the EUA product and of any consequences of refusing administration of the product;
- Any available alternatives to the product and of the risks and benefits of available alternatives.

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EUAs and Liability—The PREP Act

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Right To Try

- Patient must be diagnosed with life-threatening disease or condition
- Patient must have exhausted approved treatment options
- Patient must be unable to participate in a clinical trial involving the investigational product as certified by a doctor

What about informed consent?

- Medical treatment not research, but still requires informed consent
- Patient must give written informed consent regarding the risks associated with taking the investigational treatment

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Right To Try (continued)

- Qualifying Treatments
  - Completed FDA-approved Phase 1 clinical trial
  - In an active clinical trial that the manufacturer intends to use as the basis for effectiveness in an application for FDA approval and is the subject of an active investigational new drug application already has been filed with FDA
  - Ongoing active development or production
    - Not discontinued by manufacturer
    - Not placed on clinical hold

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Innovative Treatments and IRB Approval

- During the course of their medical practice, providers may employ innovative treatments when more commonly used treatments are ineffective or otherwise do not meet the individual patient's needs.
- These innovative treatments are not, as a matter of course, research if used occasionally and solely for clinical purposes. In this case, they do not generally require IRB review.

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Innovative Treatments and IRB Approval

- Definition of Research under the Common Rule:

  Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. …

  45 C.F.R. § 46.102(l)

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Innovative Treatments and IRB Approval

- However, the line between innovative treatment and clinical research is not entirely clear.

- HHS, Institutional Review Board Guidebook (1993):

  27. Question: Can treatment of a single patient constitute "research?"

  Answer: Yes, if there is a clear intent before treating the patient to use systematically collected data that would not ordinarily be collected in the course of clinical practice in reporting and publishing a case study. Treating with a research intent should be distinguished from the use of innovative treatment practices.

  IRB Guidebook: Chapter II Regulations and Policies (archive-it.org)

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Innovative Treatments and IRB Approval

- If the treatment was part of a systematic investigation designed to develop or contribute to generalized knowledge (*even if just in part*), then the innovative treatment is research and subject to to IRB review (if the other requirements for IRB review are met).

- There may also be state-specific requirements. It is important to check with the laws, regulations, and policies of the relevant state, including any position statements of the state medical board.

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Innovative Treatments and FDA Involvement

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Innovative Treatments and FDA Involvement (continued)

- Offering unapproved new drugs for sale in interstate commerce
- Selling adulterated and misbranded medical devices in interstate commerce
- Using approved drugs or devices off-label when well informed about the product, bases use on firm scientific rationale and sound medical evidence, and maintains records of use and effects.
- Gathering new information on multiple patients for publication purposes, or to obtain approval for a new device or new use of an approved device.

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Questions and Open Discussion

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