

What Your Research Investigators and IRB May Not Know

**Regulatory and ethical implications for human
subjects research**

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AGENDA

- **Clinical Investigation vs. Practice of Medicine**
- **Dual Role of Physician Researcher**
- **Interventional Research Comparing Standards of Care**
- **Common Issues with INDs, Nutraceuticals, and
Devices-Handout**

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The Difference Between the Practice of Medicine and Clinical Research

**Understanding the dual roles of physician and clinical
Investigator and their ethical implications**

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**Research Compliance
Officer**

**Our physicians are extremely
competent doctors. Why are the same
physicians often non-compliant with
the IRB approved research protocol?**

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**Research Compliance
Consultant**

**So let me guess, more FDA audits with
findings of failure to follow the
investigational plan and consent
issues?**

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Consultant**

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**Research Compliance
Officer**

Yes, and despite additional GCP training, these and other problems continue. Any other ideas on how we can make physicians more aware of their obligations as researchers?

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**Research Compliance
Consultant**

Well, if you listen to these researchers' assessments of whether protocol deviations adversely affect their subjects' rights or safety, they generally tell you they don't because their subjects receive the same good care as their patients.

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**Research Compliance
Officer**

What do they mean by that?

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**Research Compliance
Consultant**

**I think these types of comments are
very revealing about how physicians
perceive their role as researchers.
Let me explain.**

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**Practice of Medicine and Clinical Research are Closely
Related Activities**

- **Acts of patient care are analogous to research experiments: Each patient begins in a baseline state, receives an intervention from a doctor and has an outcome**
- **Observed patient outcomes generate testable hypotheses and provide feasibility for a research study**
- **The results of clinical research inform patient care**

Sacristán (2015)

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**Post-Belmont Report (Respect for Persons,
Beneficence, and Justice), medicine and
research have become distinct activities
and currently remain so under the
regulations**

Office for Human Research Protections (1979)

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FDA: Clinical Research Versus Medical Treatment

	<u>Clinical Research</u>	<u>Medical Treatment</u>
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.

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FDA: Clinical Research Versus Medical Treatment-Continued

	<u>Clinical Research</u>	<u>Medical Treatment</u>
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 gov. agencies, IRBs, 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.

FDA 2018

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Research Compliance Officer

How is the difference between medical treatment and clinical research connected to non-compliance with the research protocol?

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**Research Compliance
Consultant**

When physicians lack meaningful training in the difference between the practice of medicine and the conduct of clinical research, they conduct research almost exclusively from the viewpoint of a practitioner of medicine.

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Research Compliance Consultant

Unless physicians understand the conflicting roles of physician and investigator and learn to conduct research from both perspectives, they won't see the important connection between adhering to the IRB approved protocol and the ethical conduct of research.

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Conflicting Roles of the Physician-Investigator

- **The physician is duty bound to act for the benefit of the individual patient**

- **The investigator's obligation is to carry out the protocol to answer the research question and not for individual subject benefit**

- **The physician-investigator must be made aware of this conflict and how to handle it**

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Patients Trust Their Doctor to Act in Their Best Interest and Subjects Expect the Investigator to Preserve Their Autonomy

- Physicians are obligated to act in the individual patient's best interest and **doctor-patient relationship based on that trust**
- Investigators are obligated to have respect for a person's autonomy through informed consent-**investigator-subject relationship based on that transparency**

Office for Human Research Protections (1979)

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Ethical Dilemma is Created if either the Physician or Investigator Obligations are Overly-Relied On

- If the investigator overly-relies on the physician role and conducts the study on the premise that individual subjects benefit
 - **Subject right to autonomy and volunteerism is compromised**
- If the physician overly-relies on the investigator role and conducts the study based on the premise that answering the research question is more important than individual rights and welfare
 - **Physician fiduciary duty to the individual to do no harm is compromised**

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Most Investigators Overly-Rely on Physician Role in the Conduct of Clinical Research

- **Protocol deviations- undervalue the necessity of protocol mandated activities-default to real-time as needed medical decision making**
 - **Subject safety-lack of adherence to safety monitoring plan or eligibility criteria**
 - **Research data integrity-subject data not useful**
 - Exposes individual subjects to toxicities of test article; time and energy spent in the study without generating useful data

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Most Investigators Overly-Rely on Physician Role in the Conduct of Clinical Research

- **Noncompliance with consent requirements**
 - **Lack of transparency in informed consent**
 - Imply or state benefit even if potential is low
 - Subject believes investigator is acting in the doctor role-terms “study doctor,” study treatment”, “patient or participant”
 - **Diminished autonomy: Undue influence to enroll in the study**

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Case Example: Your patient asks you whether he qualifies for any clinical trials. He technically meets eligibility criteria for one you are actively recruiting for but as his physician you believe he is at increased risk for adverse events. In handling these conflicted roles you would:

1. Withhold information about the clinical trial and make recommendations in best interest of the patient as his physician.
2. Withhold your medical concerns and sell the clinical trial as your patient meets all eligibility criteria and you are under pressure to meet enrollment goals.
3. Inform your patient about the trial, its risks and potential benefits if any, and why you believe the risks may be increased in him and, if appropriate, you would recommend he not enroll.

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Resolution of the Physician-Investigator Dual Role Conflict

3. Inform your patient about the trial, its risks and potential benefits if any, and why you believe the risks may be increased in him and, if appropriate, you would recommend he not enroll.

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Research Compliance Officer

How can the research compliance team promote and support a dual role training model?

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Physician-Investigator Dual Role Training Model

- Early training on ethical based compliance with research regulations
- Principal Investigator conducts continual compliance training with the research team as part of regular research meetings; regulatory training or updates by research compliance during these meetings
- Principal investigator creates SOPs and trains key research staff to train new personnel
- Principal investigator avoids referring to compliance as a thing that is a burden but rather encourages a good relationship with IRB, HRPP and research compliance as people who are there to help
- Principal investigator creates a culture of no fear in admitting mistakes

Antes (2018)

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Physician-Investigator Dual Role Training Model

- Engage investigator mentors to train investigators to be leaders and role models for ethical and compliant behavior
- Train investigators and research staff on a research code of conduct separate from that of healthcare: Institutional and/or research site level
- Train investigators and research staff on informed consent process and provide feedback
- Emphasize that interacting with our human subjects is a privilege and they deserve our deep appreciation.

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Carl Schneider
The Censor's Hand (2015)

“When his studies let the scholar meet, talk with, and get to know the people the law regulates, he is blessed indeed...Americans are almost madly generous with their time and their intimacy. If the researcher cares about them, they will invite him into their lives, show him their world, and teach him their thoughts. The fortunate researcher finds in his work preceptors to heed, people to admire and friends to cherish.”

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The Difference Between an Interventional and Observational Study

Misconceptions concerning research interventions
considered “standard of care”

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Observational Studies: Intervention is NOT “protocolized”

- Research about interventions *delivered in the course of medical care by a healthcare provider*
- Research activities limited to use of patient data/biospecimens
- Study associated risks limited to loss of privacy or confidentiality
- Risks associated with intervention are not risks of the research

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Interventional Studies: Intervention is “protocolized”

- Subjects are assigned to the intervention (usually randomized) by the protocol to answer a research question
 - Clinical investigations of unapproved or approved test articles used “off-label”
 - Comparative effectiveness research (CER) or pragmatic clinical trials (PCT)
 - Comparison of approved drugs and devices used as per labeled indication
 - Comparison of standards of care/usual care
- Risks associated with protocolized interventions are risks of the research

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What is the Controversy?

In CER, when comparing two or more treatments (SOC) widely practiced by the medical community, the main controversy is whether risks of the SOC are risks of the research.

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The Controversy: Point

- In CER, randomized clinical trials comparing two or more SOC, risks associated with the SOC interventions are not risks of the research as subjects *would* have received one of the treatments in the course of clinical care

The Controversy: *Counterpoint*

- *The risks of SOC are risks of the research because the research subject :*
 - *has an altered clinical course -care is not physician directed*
 - *may receive care that is not SOC or usual care for that particular healthcare entity*
 - *is unable to choose which treatment and therefore which risks and benefits to accept*

Shepherd (2017)

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The Controversy: Point

- CER should qualify as minimal risk research with a waiver or alteration of consent because
 - No evidence that SOC assigned by a protocol, instead of a physician, increases risk
 - Risks associated with medical care are understated
 - Risks associated with CER are overstated
 - Overstating risks will lead to under-enrollment and enrollment bias
 - Not practicable to consent thousands of patients at hundreds of sites

Mckinney (2015); Lantos (2018)

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The Controversy: *Counterpoint*

- *Subject autonomy and volunteerism are compromised*
- *Patients trust their physician to act in their best interest*
- *Patients seeking medical care could be viewed as subjects of convenience*

Shepherd (2017)

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Shepherd (2017)

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SUPPORT TRIAL

- Over 1300 preterm infants
- Randomized to lower oxygen or higher oxygen delivery range
- Study outcomes were severe retinopathy or death
- Parents were not informed about specific risks associated with higher and lower oxygen levels
- Unexpected difference in infant mortality with increased mortality in lower oxygen arm

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OHRP 2014 Draft Guidance in Response to SUPPORT Trial

“OHRP’s general position is that in research studies designed to evaluate the risks of standards of care:

- (1) the risks of standards of care that at least some subjects would be exposed to by participating in a research study that are different from the risks of therapies the subjects would be exposed to outside the study are risks of the research that the IRB must consider when evaluating the research (45 CFR 46.111(a)(2)); and,
- (2) the identified risks the research proposes to evaluate as one of the purposes of the study are reasonably foreseeable risks that generally must be disclosed to prospective subjects when seeking their informed consent (45 CFR 46.116(a)(2)).”

Final guidance not yet issued

Office for Human Research Protections (2014)

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OHRP 2014 Draft Guidance in Response to SUPPORT trial

In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research.... (45 CFR 46.111(a)(2)).

The risks of the research do not include the subject’s underlying medical condition **or medical care/procedures received outside of the research.**

Not intended to be construed that research procedures that are SOC are not part of the research

Office for Human Research Protections (2014); Shepherd (2017)

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FDA Position

“... When usual or standard care is dictated or constrained by the protocol, for example when a study involves randomization of usual or standard care, then the informed consent document must include a description of that treatment, exams, tests, and procedures as well as their risks.

We recognize that the need to include the risk information for tests, interventions and procedures required by the protocol may add some length to the risk section of the consent form, however, we encourage you to develop mechanisms to convey the risks that are common and those that are serious to subjects in a clear and concise manner. Moreover, it is helpful to subjects to distinguish how their care would be similar and how it would differ from routine clinical care depending on whether they participate in research. *A driving factor as to whether the risks of standard of care are described in the informed consent document is not whether the care would usually be given outside of the research setting, but instead whether standard of care is “protocolized”.*

Personal email communication from an FDA policy analyst 3-21-17

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IRB Regulatory Analysis

- Determine whether SOC is protocolized
 - Randomization
 - Phase 4 post-marketing study mandated by FDA
 - Patient choice rather than physician prescribed but choices limited by protocol
 - Intervention not actually prescribed by the subject's physician
- If SOC is protocolized, then the study is an interventional study
 - Is the study minimal risk?
 - Yes, expedited review
 - No or uncertain, full IRB review

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IRB Regulatory Analysis

- *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45 CFR 46.102(j))
- Should the standard be healthy individuals or subjects in the research study who routinely undergo more invasive medical procedures?
- OHRP current thinking is healthy individuals but regulations are not clear.

Department of Health and
Human Services (2018)

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IRB Regulatory analysis

- Advantages of full IRB review
 - Avoid audit findings of use of expedited review to circumvent full IRB
 - Document discussion and resolution of controverted issues with rationale in meeting minutes
 - Opportunity to discuss whether a broader interpretation of minimal risk is appropriate*
 - More protective of subjects
- Develop policies and procedures for these studies to guide IRB decision-making
 - Provide examples
 - Train expedited reviewers

*McKinney (2015); Lantos 2015

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Other Unintended Consequences of IRB Determination that an Interventional Study is Observational

- IND and IDE status of drugs and devices not addressed
- Review and reporting of unanticipated problems
- Injury risk language
- Clinicaltrials.gov

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Organizational Considerations

- Failure to provide informed consent = erosion of public trust
 - Patient advocacy groups access public information
 - FDA warning letters
 - OHRP determination letters
 - Patient complaints or AE/UP
 - Whistleblowers

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Ethical Consideration: Protecting subjects' right to informed consent is one of the primary oversight functions of the IRB

- Does the consent include reasonably foreseeable risks of the SOC?
 - Does not need to include all risks
 - Most common and rare but serious
- What is the purpose of the research?
- How is it different from clinical care?
 - Randomization
- What questions are the researchers proposing to answer by comparing these SOC?
 - Describe safety and effectiveness outcomes the research is proposing to measure

Shepherd (2017); OHRP (2014)

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The FDA Regulatory Landscape of Sponsor-Investigator INDs, Nutraceuticals, and Devices

What the Investigator and IRB may not realize

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Definitions

- IND – Investigational New Drug
- Sponsor-investigator: An individual who both sponsors and conducts a clinical investigation
- Nutraceuticals – a food containing health-giving additives and having a medicinal benefit (Oxford Dictionary). A subcategory of dietary supplements
- Device – an article , instrument apparatus or machine that is used in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some health purpose (World Health Organization)

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IND Exemption Categories

- Clinical investigations using lawfully marketed drugs if meet IND exemption criteria for drugs.
- Bioequivalence/bioavailability studies
- Studies using radiolabeled or cold isotopes
• Studies using dietary supplements or foods
- Studies using endogenous compounds
- Pathogenesis studies using modified organisms
- Studies using wild-type organisms in challenge models
- Studies that do not have a commercial purpose

Devices Exempt from IDE Regulations Under 21 CFR 812.2(c)

- Applies to devices not lawfully marketed in US or
- Lawfully marketed devices not used in the study in accordance to its approved indication.
- Most common exemption category is:
 - A diagnostic device that
 - is noninvasive
 - does not require an invasive sampling procedure
 - does not introduce energy into the subject
 - not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic procedure.
- Other categories include: devices undergoing consumer preference testing, a custom device and others-refer to 21 CFR 812.2(c)
- If the device does not meet the criteria under 21 CFR 812.2(c), then it is subject to IDE regulations as a significant risk or non-significant risk device

FDA (2020b)

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Criteria: Significant Risk (SR) Device 21 CFR 812.3 (m) Subject to IDE Regulations

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
 - Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
 - Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
 - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- ❖ A non-significant risk device is one that does not meet the above criteria and is also subject to IDE regulations but these are abbreviated and do not required an IDE application

FDA (2006)

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What Do Sponsor-Investigator INDs, Nutraceuticals, and Devices Have in Common?

- Investigators and IRBs may lack familiarity with complex or special regulations
- May result in regulatory compliance gaps identified in an FDA audit

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Sponsor-Investigator INDs

- Commonly held by investigators at academic centers
- Investigator-initiated research studies
- IRB oversight generally limited to verification of IND
 - IND number
 - 30 days has elapsed
 - No clinical hold
- But is the sponsor-investigator fulfilling IND maintenance obligations after study is approved?
- No one may know until the investigator submits the results of an FDA audit to the IRB

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Sponsor-Investigator Obligated to Meet Numerous IND Requirements of Both Sponsor (1571) and Investigator (1572)

- IND amendments- amendments to existing protocols, addition of new protocols or new investigators
- IND safety reports to FDA-and distribute to sites
- IND annual Reports to FDA
- Study sponsor monitoring activities- includes all sites
- Investigational drug disposition and records
- ClinicalTrials.gov registration, results information, certifications AND
- All investigator responsibilities under 1572

FDA (2015); FDA (2017); FDA (2020c)

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Sponsor-Investigator INDs

- **Most common FDA warning letter violations:**
 - Lack of adequate clinical trial monitoring
 - Failure to submit annual reports
 - Continuing clinical trial enrollment after IND terminated by FDA
 - Failure to obtain investigator agreements-1572
 - Failure to obtain IND

O'Reilly (2013); FDA (2019); FDA (2020a); FDA (2021)

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O'Reilly (2013); FDA (2019); FDA (2020a); FDA (2021)

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When Does a Nutraceutical/Dietary Supplement Require an IND?

- If a nutraceutical's intended use is to diagnose, cure, mitigate, treat, or prevent disease, it is a drug and requires an IND under FDA regulations part 312
 - **Example: A research study proposes to evaluate the effectiveness of a fiber supplement in treating diarrhea or constipation**
- Nutraceutical will also require an IND if it is already the subject of a research study conducted under an IND unless
 - Previously marketed as a nutraceutical and
 - Intent is not to conduct research as a drug study

FDA (2013); FDA (2021)

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When Does a Nutraceutical/Dietary Supplement Require an IND?

- A dietary supplement or nutraceutical is not a drug and not subject to an IND if its intended use is to evaluate its affect on the structure or any function of the body
- If protocol is written with intent of evaluating the affect of the supplement on the structure or function of the body then no IND is required
 - Example: A research study proposes to evaluate the effectiveness of dietary fiber on maintaining normal bowel function

FDA (2013)

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Compliance Gaps in IRB Review of

- IND is needed because protocol aims consistent with a drug study or intent is not clear
 - Not recognized by IRB and approved without an IND

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IRB Device Determinations

- Identify all medical devices under investigation in a study and if not marketed or not used per their marketed indication
 - Consider IDE exemptions first under 21 CFR 812.2(c)
 - If not exempt from an IDE
 - Then determine whether device is SR and requires an IDE application
 - Reserve NSR determinations for final consideration
- NO device determination should be made without FDA approval letter (for lawfully marketed devices), device manual and sponsor request for an NSR determination (including rationale for why it is not an SR device)

FDA (2020b); FDA (2006)

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FDA (2020b); FDA (2006)

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