Special topics in human subjects protection: acute and chronic conditions in neurology

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Disclosure

- The presenter hereby discloses the following commercial interests/financial interests/relationships/activities/conflicts of interest:
- Takeda Pharmaceuticals
  - Member of Bioethics Advisory Committee

- This presentation will not include information on unlabeled use of any commercial products or investigational use that is not yet approved for any purpose.

Consider: Study 1

- Phase I trial of PND (Promising New Drug) in advanced stage ALS
- 6 week administration of PND via a central line
- Side effects of the drug include significant immune suppression and marked decrease in platelet production

Consider: Study 2

- Phase II study of PND (Promising New Drug) for acute hemorrhagic stroke
- Infusion of drug within 6 hours of stroke
- Side effects include extension of bleed and severe allergic reaction

Consider: Study 3

- Phase III study of PND (Promising New Drug) for Duchenne's Muscular Dystrophy
- 12 month course of bid oral med
- Side effects include bone marrow suppression and severe allergic reaction

All three studies require IRB review

- So…some basics about the IRB and relevant regulations
- And please note:
  - IRB review is **prospective**. We cannot grant retroactive approval – hence plan ahead.
  - Only the IRB can approve a protocol.

The IRB
(Institutional Review Board)

- Protects:
  - Subjects who participate in research
  - Investigators
  - The institution

The IRB responds to

- Federal laws
- State laws
- Case Law
- Condition of Grant Award
- The Boston Globe

All of these influenced by specific events…especially disasters.

Federal laws

- Common Rule*
- FDA regulations*
- HIPAA – Privacy Rule*

*never-ending interpretation and guidance

The Common Rule

Subpart A	General description; defines research, subject, IRB processes
Subpart B	Fetuses and pregnant women
Subpart C	Prisoners
Subpart D	Children

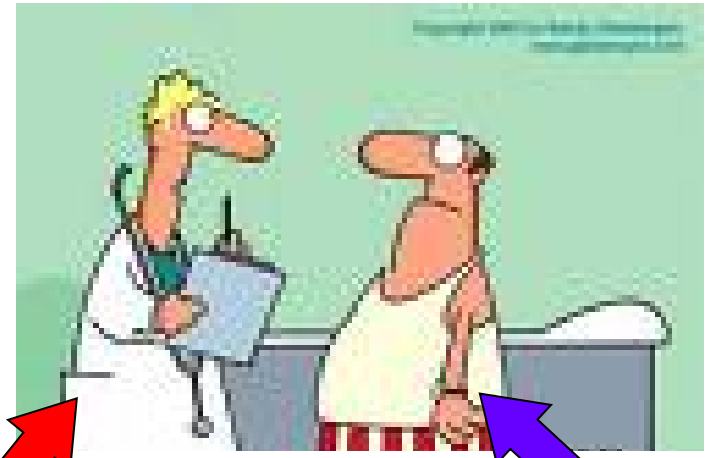
IRB Jurisdiction
Driven by definitions….

- Research
- Human Subject

Research Definition

- Systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Is it Research? Or Care?



Clinician?
Researcher?

Patient?
Subject?

You are a Neurologist

- You have just read an exciting article about an experimental approach for Gillian-Barre syndrome
  - Promises to decrease need for mechanical ventilation in severe cases

You are an Neurologist

- A new patient with progressing GB arrives…
  - You decide to try this new experimental therapy

Treatment or research?

You are an Neurologist

- You decide to alternate between the experimental and routine treatments for the next 6 GB patients.
- A new GB patient arrives.

Treatment or research?

Human Subject Definition

- A living individual about whom an investigator conducting research obtains:
  - Data through intervention or interaction with the individual, or
  - Identifiable information.

IRB Responsibilities

- Initial Review*
  - Full committee or expedited
- Continuing Review
- Approval of Amendments
- Review of Adverse Events, Unanticipated Problems, Deviations
- Reporting to federal agencies as appropriate

* Note reviews are ethical AND scientific

IRB Review

- Scientific and ethical review
- Scientifically invalid research is not ethical
- Research that does not answer the question(s) posed is not ethical
- Research that does not add *something* valuable to medical science is not ethical

What does the IRB look for

- Study design and data and safety monitoring
- Risk-benefit analysis
- Selection of participants
  - Who can be included?
  - Who will be excluded?
  - Is the targeted population vulnerable?
    - If yes – any additional regulatory requirements? Any additional safeguards?
- Recruitment of participants
  - How?
  - Do not over-promise. Avoid coercion.

What does the IRB look for

- Privacy and confidentiality protections
- Informed consent: process and form
  - Process must include specific elements per the regulations
  - Who will interact with the participant to get consent?
  - Who will give consent?
    - Participant?
    - If decisionally impaired:
      - How determined?
      - Who can give surrogate consent
    - If a child
      - Assent?
      - Must consider the pediatric regs
  - When and where will consent be requested?
- Can consent be waived?

Back to Study 1

- Phase I trial of PND (Promising New Drug) in advanced stage ALS
- 6 week administration of PND via a central line
- Side effects of the drug include significant immune suppression and marked decrease in platelet production

The First Potential Subject

- 67 y.o. white male – college education
- Mobility limited to wheelchair – beginning to have some respiratory compromise
- Lives with daughter and her family
- Has been taken care of by same neurologist for 2 years

You may be interested…

His doctor is frustrated and after numerous phone calls has finally gotten this patient an appointment with the “best.” His doctor told his patient:

“If anyone can help you – it is this doctor”

You may be interested…

His doctor is frustrated and after numerous phone calls has finally gotten this patient an appointment with the “best.” His doctor told his patient:

“If anyone can help you – it is this doctor”

AND – YOU are that doctor!

Why are Patients Desperate?

- They may have a disease with:
  - no therapy
  - only minimally effective therapy
  - with therapy that is painful or has numerous side effects
- They may have financial desperation
- They may be desperate to please their doctor or others

And Remember….

- Desperate patients often have desperate families
- Desperate patients often have desperate doctors

Informed Consent in Research

"The need for patients to fully understand is greater in clinical research because participation is voluntary, alternatives may exist, and the participant may not benefit and could be harmed by participation."

BMJ 327:731:2003

Informed Consent Must Include

- Discussion of potential benefits
- Discussion of risks
- Voluntariness

Pitfalls of Presenting Potential Benefits

- Everyone wants to say (and to hear) that there is a benefit
- Painful to state that there may not be any personal benefit
- Tempting to fall back on “one never knows…”
- Subject may already “know” what the benefit is

Therapeutic Misconception

- Patient initiated
  - Belief and/or desire that this is therapy
- Physician/researcher initiated
  - Belief that the procedure is therapy
  - Researcher vs provider schizophrenia
  - Recruitment strategy
- Payer initiated
  - Reimbursement for research procedures

And Remember….

- In desperate situations there often is no standard of care – every clinical decision is experimental

Mixed Messages

- Research vs “cutting edge” medical care
- The concepts of therapeutic and non-therapeutic research
  - Are Phase II cancer studies therapeutic?
  - Are Phase I cancer studies therapeutic?
- Reimbursement of research drugs/devices/procedures

Mixed Messages

- Consent is often obtained by a healthcare provider
  - Looks like a doctor…must be a doctor
- Consent is often obtained in the care setting
  - Concept of the institution as a provider of care

Presenting Risk

- Receptiveness to risk affected by:
  - The source of the information
  - The nature of the risk
- Sensitivity to risk is increased if risk is:
  - Of high consequence
  - Involuntary or inescapable
  - Poorly understood
  - Subject to contradiction

Presenting Risk

- The investigator is only one source of information
- Other health professionals
- “Unofficial experts”
- The media
- Blind trust in technology

Presenting Risk

- Trust is the key to communicating risk
  - Lying destroys trust
  - Deluging with numbers and minutia does not build it
- Is it possible to distinguish between trust in a doctor and trust in an investigator?
- It is easy to see the research as an extension of usual clinical practice

Informed Consent Issues in Desperate Patients

- Patient is already convinced of the benefit
- Patient may not want to or be unable to hear about risks
- Patient sees no other options

Desperate Patients

- The “Battle” metaphor
- Grateful for any forum in which they can continue the fight
- Fear of being perceived as a quitter

Hastings Center Report: 30(4):19:2000

Options

- Provide additional protections
  - Risk-benefit analysis may need to be modified
  - Informed consent form and process need additional attention
  - Investigator needs additional training
  - Clinician needs additional training
  - Clinician-investigator needs a boatload of additional training

Options

- Avoid all desperate patients
- Refer them elsewhere

Consider: Study 2

- Phase II study of PND (Promising New Drug) for acute hemorrhagic stroke
- Infusion of drug within 6 hours of stroke
- Side effects include extension of bleed and severe allergic reaction

Consider: Study 2

- Patient with acute hemorrhagic shock meets study criteria. Patient is comatose.
- What do you do?

Surrogate consent

- Plan ahead – this is not a last minute issue
- Know your institutional policies
  - Which will reflect state and local laws
- Who can give surrogate consent
- What to do when/if participant gains competence

Consider: Study 3

- Phase III study of PND (Promising New Drug) for Duchenne's Muscular Dystrophy
- 12 month course of bid oral med
- Side effects include bone marrow suppression and severe allergic reaction

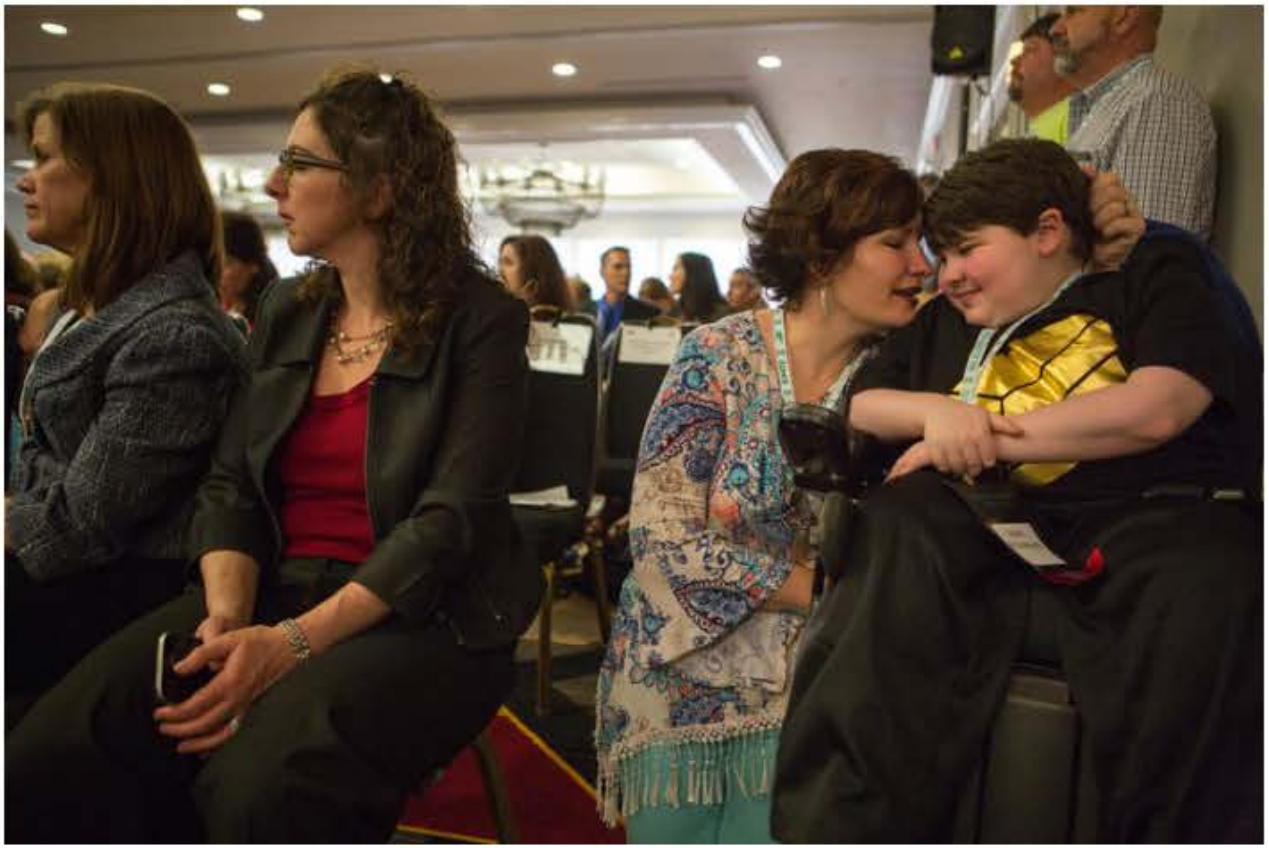
Consider: Study 3

- First potential participant is a 12 yo boy
- Parents know about the following information

BUSINESS DAY

F.D.A. Approves Muscular Dystrophy Drug That Patients Lobbied For

By SABRINA TAVERNISE SEPT. 19, 2016



Stacie Al-Chokhachi, second from right, and her son, Dalton, who has Duchenne, at an F.D.A. meeting in April. Eric Kruszewski for The New York Times

WASHINGTON — The Food and Drug Administration approved the first drug to treat patients with the most common childhood form of muscular

Controversy at FDA: Dr. Ellis Unger

- “By allowing the marketing of an ineffective drug, essentially a scientifically elegant placebo, thousands of patients and their families would be given false hope in exchange for hardship and risk,” he wrote in a July 18 dispute report. “I argue that this would be unethical and counterproductive. There could also be significant and unjustified financial costs — if not to patients, to society.”
- He added that approval “would send the signal that political pressure and even intimidation — not science — guide FDA decisions… A standard this low would undercut FDA’s ability to ensure that drugs that are approved are effective; it would call into question much of what we do. Lowering the bar to this level would be tantamount to rolling back the 1962 Kefauver-Harris Drug Amendments to the Federal Food, Drug and Cosmetic (FD&C) Act, which have served Americans well for some 54 years.”

https://www.statnews.com/pharmalot/2016/09/19/sarepta-fda-duchenne-behind-the-decision/

Consider: Study 3

- Parents demand the drug as therapy
- Parents state that they can crowd source using their advocacy website and conduct any experiment without you.
- What do you do?

In conclusion

- Patients with serious, debilitating, difficult (or impossible) to treat diseases are desperate
- Neurologists see many of these patients
- Research with these patients is critical
- These patients are vulnerable and require additional safeguards.
- Investigators must be aware of the need for additional safeguards