Objectives

- Describe the concept of ethics.
- Analyze ethical principles in medicine today.
- Explore the role of ethics in clinical research.
- Discuss possible solutions and ways to address ethical issues in MS patient management.
Faculty Disclosures

• Nada Gligorov has disclosed no significant financial relationships.
• Amy Perrin Ross, Fred Lublin, and Aliza Ben-Zacharia, have disclosed all relevant relationships which are listed in the disclosures section of the CMSC program guide.

Who is here today?

a. Physician
b. Advanced Practice Nurse or Physician’s Assistant
c. Registered Nurse
d. Therapist (PT, OT, other)
e. Researcher
f. Other
Ethics

Provides a systematic process for identifying and analyzing human behavior in terms of what **OUGHT** to be done

So the question becomes: What **OUGHT** we to do?

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**Bioethics in the 21st Century: Rethinking Core Principles**

Nada Gligorov, Ph.D.
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• What is Ethics?
• Why Ethics in Medicine?
• Principles and Concepts:
  • Beneficence
  • Autonomy
  • Truth Telling/ Informed Consent
  • Justified Paternalism
  • Surrogate Decision Making

What is Ethics?

Normative Ethics: discipline concerned with what individuals ought to do. (Is a particular act right or wrong?)
• Holds a monopoly over its work and enjoys relative autonomy
• Medicine serves a social need and healthcare professionals’ behavior should be the outcome of the social contract with the community that they serve.
• The practice of medicine entails commitment to ethical principles.

- Ethics Committees
- Ethics Consultation
- Patient Representatives
Beneficence and Do no Harm

“I will apply dietetic measures for the benefit of the sick according to my ability and judgment. I will keep them from harm and injustice.”

Hippocratic Oath

Autonomy

Autonomy: The ability to be a good ruler over oneself.
• Four elements of Decisional Capacity:
  • Communicate a Choice
  • Understanding Relevant Information
  • Appreciate the Situation and Its Consequences
  • Reason about Treatment Options (Manipulating Information Rationally)

• Understanding
  • Optimism bias
  • Impact bias
  • Gain frame bias

• Intentionality
  • Status quo bias
  • Availability heuristic
  • Ambiguity aversion bias
Veracity is supported by:

1. Respect for autonomy
2. Obligations of fidelity, promise-keeping, and contract
   - Entering into a contract that obligates the healthcare professionals to tell the truth
3. Trust in the relationship with a healthcare professional

- 90% of patients wanted to be told if they had cancer (Mack and Smith 2012).
- 71% of patients want shared decision making with physician (Chewning et al. 2010)
Patient attitudes:
- Patients think that physicians should make decisions

Healthcare Professional attitudes:
- Think of informed consent primarily as a legal formality
- Physicians see only superior and inferior treatments
- There is little to be gained by letting the patient decide (Litz et al. 2012)

Nocebo effects:
- GI symptoms
- Sexual dysfunction
- Pain (Wells and Kaptchuk 2012)

Paternalism is the intentional overriding of one person’s preference of actions by another, where the person who overrides justifies this action by appeal to the goal of benefiting or preventing or mitigating harm to the person whose preferences or actions are overridden (Beauchamp and Childress, 2009).

In most cases either because of legal or ethical guidelines the necessary condition for justifying paternalism is lack of capacity.
Confidentiality is the obligation to protect information disclosed within a confidential relationship.

Healthcare professionals have both the legal and ethical obligation to protect the confidentiality of medical information.

Justified breaches of confidentiality in medicine are in part defined by the duty to warn.

Confidentiality

“What I may see or hear in the course of the treatment or even outside of the treatment in regard to the life of men, which on no account one must spread abroad, I will keep to myself, holding such things shameful to be spoken about.” Hippocratic Oath
The EMR creates a medical record that is accessible to other providers in a way that paper charts are not.

The record is also portable, easily distributed, and vulnerable to hacking in ways that paper records are not.
Potential Surrogates: Advance Directives:
- Legal Guardian
- Healthcare Proxy
- Family member
- Friends
- Physicians

Living will
Proxy designation
DNR/ DNI
Expressed preferences

Problems related to competency and informed consent
- Can't be sure the patient was competent or informed

2. AD’s are sometimes ambiguous or vague
- It is hard to specify preferences for all possible contingencies.

3. Problems with choosing the right proxy
- Might choose the wrong person
- The proxy might become less willing to make decisions
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Questions, discussion
Break time

Ethical Issues in Clinical Research

Fred D. Lublin, M.D.
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Placebo Controlled Trials
Questions

- Are placebo controlled trials ethical for forms of MS where treatments are available?

- Is informed consent truly “informed”? Can it ever be?

- Are there alternatives to placebo controlled studies?
  - Single-blind, open label?
  - Study sub-groups, e.g.
  - Add-on studies?
  - Rx failures?
  - Natural history controls?
  - Active treatment controls?
  - Others?

- What are the statistical and practical implications of alternative designs?

Partial treatments are available for RR & SP MS
Better treatments need to be found
RCTs remain the “gold standard” for MS trials
Placebo-controlled trials are most efficient
Mechanisms of Worsening of MS

- Incomplete recovery from exacerbations in relapsing forms (step-wise worsening)
- Gradual, progressive worsening independent of relapses - progressive forms

Do exacerbations count?

- Residual deficits after exacerbations
- Change in mean and ‘confirmed’ EDSS
- Long term data - placebo doesn’t catch up
- Changes in MRI T2
- Atrophy
- Conversion of Gad+ lesions to black holes (Comi)
- IFN beta1b long term survival study
Relapse Residual in AFFIRM

(Lublin, MSARD, 2014)

- Placebo
- Natalizumab

\[ P = 0.0170 \quad P = 0.0953 \]
Conclusions

- Exacerbations produce measurable residual deficits of 0.24 - 0.57 EDSS units which are durable through at least two subsequent evaluations 2-5 months post exacerbation
- Conservative estimates
- Confirms the presence of step-wise worsening
- IMPACT ON POTENTIAL ESCAPE RULES

QUESTIONS:

- Are placebo-controlled MS trials still ethical?
- Are placebo-controlled MS trials practical?
SPECIAL REPORT

Placebo-Controlled Clinical Trials in Multiple Sclerosis: Ethical Considerations

Fred D. Lublin, MD,1 Stephen C. Reingold, MD,2 and the National Multiple Sclerosis Society (USA) Task Force on Placebo-Controlled Clinical Trials in MS

The availability of partially effective therapies for some forms of multiple sclerosis (MS) raises practical and ethical issues for future placebo-controlled clinical trials. An international Task Force of physicians, statisticians, ethicists, and patients was convened to discuss these issues and develop consensus. The Task Force concluded that placebo-controlled clinical trials in forms of MS for which partially effective therapies exist are ethical, as long as study subjects were fully apprised of the uncertainty of such therapies and were encouraged to pursue them outside of a clinical trial. Patients who decline to utilize available treatments, after proper explanation and counseling, or those that fail all therapies can be considered to have been treatment refractory and thus may participate in a placebo-controlled trial.

Ann Neurol. 2003;53:477-481

Randomized controlled clinical trials have been acknowledged as the gold standard used in full assessment of safety and efficacy of new therapeutic agents for multiple sclerosis (MS). The four clinical trials of new agents with regulatory approval in the United States and in other countries to reduce frequency of relapses and to slow progression of physical disability in relapsing MS have all used data from placebo-controlled randomized clinical trials to obtain regulatory registration. To these ends, particular attention was paid to the use of adequately powered, well-defined subject randomized assignments among treatment arms, robust statistical analysis of the clinical trial.1 When use of a placebo control arm or a “no treatment” control arm exposes the patient population to an increased risk of death or disability, clinical equipoise is not present. It is widely acknowledged that placebo-controlled clinical trials are usually the most efficient, cost-effective, and decisive avenues of testing the safety and efficacy of a new drug. However, for disease or forms of disease for which safe and effective agents are available, the conduct of further placebo-controlled trials for new agents or new forms of existing agents must be considered by some to be unethical. For instance, relapses in MS are

CONFERENCE REPORT

Ethics of placebo-controlled clinical trials in multiple sclerosis

A reassessment

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ABSTRACT

The increasing number of established effective therapies for relapsing multiple sclerosis (MS) and emerging consensus for early treatment raise practical concerns and ethical dilemmas for placebo-controlled clinical trials in this disease. An international group of clinicians, ethicists, statisticians, and representatives from the pharmaceutical industry convened to reconsider prior recommendations regarding the ethics of placebo-controlled trials in MS. The group concluded that placebo-controlled trials can still be done ethically, with restrictions. For patients with relapsing MS, for whom established effective therapies exist, placebo-controlled trials should only be offered with rigorous informed consent if the subjects refuse to use these treatments, or if these treatments are not available to them for other reasons (e.g., economic). Suggestions are provided to protect subject autonomy and improve informed consent procedures. Recommendations are similar to previously published guidelines for placebo-controlled trials but are not as stringent.

GLOSSARY

ECT: established effective therapy, MS: multiple sclerosis; PRMS: primary progressive MS; SPMS: secondary progressive MS

With the availability of multiple agents for the treatment of relapsing and some forms of secondary progressive multiple sclerosis (SPMS), many patients worldwide have access to evidence-based therapy that can reduce the likelihood of relapses and in some cases slow progression of disability.4 However, these agents are only partially effective, some halt relapses or progression, and all have problematic side effect profiles that are
CONSIDERATIONS (1)

- Effectiveness of current agents
  - RR MS; SP MS; other forms of MS
- Justification for any clinical trial
  - "clinical equipoise"
- International Codes/Agreements
  - Declaration of Helsinki
  - International Conference on Harmonization...
  - guidelines of Council for International Organizations of Medical Sciences (CIOMS)

CONSIDERATIONS (2)

- US Food and Drug Administration (FDA)
- European Agency for Evaluation of Medicinal Products (EMEA)
- Country-by-country variance in practice
- Perceived patient needs
- Known or perceived regulatory needs
- Known or perceived corporate sponsor needs
ETHICS (1)
Are pbo-controlled MS trials ethical?

- Yes, in certain circumstances
  - If no agent is “available”
  - If an agent is available
    - With additional emphasis on informed consent
    - Need to explain available treatment options and URGE use
    - Need to obtain affirmative declination from patient of available treatments
    - Need to update informed consent on ongoing basis

- No
  - If effective treatment is available for a patient offering a pbo-controlled trial is NOT ethical
  - Investigator must offer available therapy first and urge its use
  - If the patient declines, then participation in a pbo-controlled trial can be addressed
ETHICS (3) for “treatment failures?”

- Yes
  - But, if multiple therapies are available, a patient who has not derived benefit from one should be offered available alternatives prior to being offered a pbo-controlled trial.

ETHICS (4) outside of regulatory/regional guidelines?

- Yes
  - With full informed consent, but no special ethical considerations.
  - Such patients are strictly “without treatment options”.
  - Regional variation in “availability” noted.
ETHICS (5)
shorter trials, smaller N?

- No
  - Shortening trials or reducing sample size does not overcome ethical concerns
  - Term and N must be sufficient to adequately test hypothesis
  - A scientifically unsound protocol is inherently unethical

ETHICS (6)
in “resource poor” environments?

- Maybe
  - Must be responsive to the “health needs of the host country”
    - Demographic/ethnic issues in MS
  - Must have high probability that agent will be made available widely if proven safe and effective
    - Financial/political/practice barriers
ETHICS (7)
alternative trial designs to pbo?

- Cross-over studies with pbo
  - Same ethical dilemmas if Rx is available
- Active control arm studies
  - Yes, but MUST be able to demonstrate “therapeutic superiority,” not just therapeutic equivalence or non-inferiority
- Add-on trials
  - Yes, if all subjects have access to available Rx
- Historic controls
  - Unlikely: currently not possible to “model” expected behavior to serve as control

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Practical Issues of Future PBO Trials

- Will not be as generalizable to larger population
- Enrolled patients may have inherent clinical/other bias
  - Non-responders to available Rx
  - Less clinically active
  - Phobics
  - Enriched populations
- Recruitment will be more complicated
- Drop out may be higher
  - N, power implications
- May require increased numbers of centers
CONCLUSIONS

- Placebo-controlled MS trials are ethical under certain circumstances
- Special emphasis needs to be made on nature of informed consent
- Future PBO trials will create new problems for generalizability to a larger population
- As more effective therapies become available, this perspective will change

QUESTIONS:

- Are placebo-controlled NMO trials ethical?
- Are placebo-controlled NMO trials practical?
- A more emotional discussion than for MS

Appreciation to Dr. Bruce Cree
The case for equipoise in NMO treatment

- Case series provide suggestive evidence of efficacy
- Proof requires randomized controlled trials with validated endpoints
- What about using an active comparator?
- There are no proved treatments, therefore any comparisons made against a treatment that is actually harmful could result in assigning benefit to a treatment that had no effect and only appeared to be beneficial because the alternate treatment caused harm
  - Example: flecainide or encainide in the cardiac arrhythmia suppression trial (CAST)


The case for placebo

- Placebo control can provide unequivocal evidence of proof of efficacy
- The number of subjects participating in a placebo controlled study will be smaller than for an active comparator trial
- The number of events needed to prove efficacy will also be smaller for a placebo controlled trial
  - All trials require medically relevant events in order to determine differences between treatment groups
  - Not all placebo controlled trials are unpalatable
Design considerations in using placebo

- The details of study design are all important for assessing individual participant risk
  - Unequal allocation
  - Time to first event
  - Rescue therapy
  - Limited duration of placebo exposure
  - Availability of open-label active treatment extension study until approval may make participation attractive for some patients
- Use of placebo reduces potential treatment related harm due to unexpected off-target effects
- Historical controls unreliable, as the definition of NMO has morphed

But is there equipoise?

- Equipoise requires
  - 1) Genuine uncertainty regarding the relative scientific and clinical merits of each treatment arm
  - 2) Requires that each treatment arm be consistent with best medical practice
- This second requirement is at the crux of the debate regarding use of placebo in NMO trials
- How can no treatment be considered competent medical treatment?
Risks and Benefits

- Every empirically used NMO treatment is associated with potential serious adverse events
- Azathioprine: of 99 NMO patients treated with AZA, 3 developed lymphoma
  - Lymphoma was diagnosed in 3 patients at a median of 18 months after azathioprine initiation (range 9–36 months) and included non-Hodgkin lymphoma, 2 and Hodgkin lymphoma, 1
- Is this an acceptable risk for an unproved therapy?

Costanzi et al. 2011 Neurology 77:659-666

What is Needed

- Pressing need for international collaborative efforts to create cohorts of NMO patients to understand therapeutic response
- Randomized controlled trials are one of the best ways to assemble such cohorts
- RCTs have a clear primary goal: to determine whether a given treatment is effective
- RCTs provide the basis for regulatory approval
- Regulatory approval provides the basis for payer support
- Payer support is the mechanism that enables providers to prescribe medications to their patients
What To Gain

- Approved readily available therapies whose side effect profiles are well documented in NMO will enable providers to accurately counsel our patients regarding their therapeutic options.

- Clinical trials can form the basis for lasting collaborations including long term follow up studies and comparative efficacy studies.

- Clinical trials provide an unparalleled resource for acquisition of biological samples that could lead to the next breakthroughs in understanding disease pathogenesis.
  - T cell immunology, B cell immunology, microbiome

- Example: the impact of vitamin D levels on MS disease activity from the BENEFIT study (Interferon beta-1b in CIS).


Final Thoughts

- We have the opportunity to have a profound impact in the lives of our NMO patients.

- Assuming that these trials are successful, the contributions of the study subjects and the investigators will directly benefit the lives of thousands of others affected by NMO.

- Choosing to participate is siding with the path of medical progress regardless of whether the trials are ultimately successful with respect to therapeutic efficacy.
Role of a DSMB

- **Ongoing review of the data by an independent committee (DSMB)**
  - Assures trial can continue without jeopardizing patient safety
  - Ensures trial conducted according to the highest scientific and ethical standards
  - Ensures high quality, validity and scientific integrity of the study results
  - Assists in determining if any of the treatment procedures practiced should be altered or stopped

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects - 2013

- **Use of Placebo**
  - 33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
    - Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    - Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
    - Extreme care must be taken to avoid abuse of this option.
The 7 Ethical Requirements

- Social or scientific value
- Scientific validity
- Fair subject selection
- Favorable risk-potential benefit ratio
- Independent review
- Informed consent
- Respect for potential and enrolled subjects

from Emanuel EJ, Wendler D, Grady C. JAMA 2000; 283:2701-2711

Fried’s Equipoise

“A physician may offer trial enrollment to her patient only when the physician is genuinely uncertain as to the preferred treatment.”

Clinical Equipoise

“A state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment.”


Case Study
Ethics Conference
CMSC 2016

Aliza Ben-Zacharia, DNP, ANP
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**Case Study - JG**

- Hispanic male, 45 years old
- Spinal cord C6 ASIA A
- MS dx in his 30s
- Family support:
  - Mother died - lung disease
  - Father died – Liver disease
  - Brother has MS
  - Married with 2 children

**Case study – JG**

- MS
- Brain stem disease
- Multiple brain stem relapses
- Serial brain MRI - intermittent enhancing lesions
- Dysarthria & Dysphagia

Purchased from Gettyimages.com; ABZ
DMT Discussion

- GA
- IFN
- CombiRx
- Dimethyl Fumarate
- Discussions
- Natalizumab
- JC Positive
- Fingolimod
- Teriflunomide

JG - Hospitalization

- What next?
- Mental status
- Sepsis
- Brother
- Tracheostomy

Purchased from istockphoto.com; ABZ
Brother & ABZ Meeting

* Friday Afternoon
* JG needs to be trached
* Under sedation since intubated
* “Let me go”
* “Just kill me”
* “Don’t want this”

Discussion – 1 hour with brother
* What to do?
* Yes or No?
* The hardest decision!

JG – What’s Next?

What next?
Proxy
Dysphagia
DMT
Feeding Tube

Purchased from istockphoto.com; ABZ
JG - Feeding Tube

* Percutaneous endoscopic gastrostomy (PEG)
* JG decision
* SP aspiration pneumonia
* Discussion with local MD
* 2nd aspiration pneumonia

Emotional & Social Issues

* http://dx.doi.org/10.4172/2376-0389.1000140
* Lives alone in parents house
* Brother wanted to move in but his wife refused
* Aunt & Uncle
* Mild depression
* 24 hours HAs
* Financial issues
Approaching the Near Future!

* Decision Making?
* Discussing advance directives?
* NP
* RN
* SW
* MD

Case Study - KD

* 34 yr old female
* Progressive cerebellar disease
* Pain
* Mother & sister
* Discussion about advanced directives
* SW & NP
Decision making

- Gradual progression
- Discussion regarding gastric tube
- A few years later
- Discussion about tracheostomy
- Emotional response of mother
- Remote & Local team
- Coordination of care
- Pain management
- Support service
- Hospice home care

Mother-Daughter

- Protective & Close relationship
- Care & Cure
- Mother – administrator in a physician office
- Sister – an Occupational therapist
Approaching the Near Future!

* Decision Making?
* Discussing advance directives?
  * NP
  * RN
  * SW
  * MD

When & How?

* At Diagnosis?
* Facing disease progression?
* Family meeting?
* Follow up visit of patient?
* Have social worker in the room?
* Supportive environment!
Conclusion

* Need a brochure for patients with MS
  * Proxy
  * Living will
  * Early decision
  * Early intervention
  * MS Team

Purchased from offset.com; ABZ

Panel Discussion
Can Ethics Help?

- Formulate the ethics question:
  - What values are at stake?
- Gather information relevant to resolving the case
- Synthesize case information and analyze the ethical concerns
- Explain synthesis to those involved in the case
- Support the overall process of ethics consultation
  - Are there underlying systems/process issues?

Conclusions

- Describe the concept of ethics.
- Analyze ethical principles in medicine today.
- Explore the role of ethics in clinical research.
- Discuss possible solutions and ways to address ethical issues in MS patient management.
Thank You!

QUESTIONS?