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Therapeutic misconception and misdirection

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Therapeutic Misconception and Misdirection

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Therapeutic Misconception

- An unfounded belief held by a research participant that he or she will be receiving personalized care. Often accompanied by an unrealistic expectation of benefit.

Research vs Practice

- Practice
  - Goal is to further the best interest of the individual patient.
    - Patient-centered care, tailored to the individual.
- Research
  - Goal is to generate new knowledge that may benefit future patients.
    - Protocol-driven care with little flexibility, designed to produce interpretable data and generalizable knowledge.

Origin of TM

- Fundamentally, a confusion between research and practice.
  - Both doctors (investigators) and patients (participants) are susceptible.

Therapeutic Misconception in participants

- Prevalence
  - 31% expressed inaccurate beliefs regarding degree of individualization of their treatment.
  - 51% expressed an unreasonable belief in the nature or likelihood of benefit.
  - Overall, 62% had one or both of the above.

Applebaum, PS 2004, IRB: Ethics and Human Research 26:1

Why worry about TM?

- Participants that harbor TM are likely to:
  - Overestimate likely benefit
  - Underestimate risks
  - Be confused about randomization
  - Conflate research with ordinary treatment

Therapeutic Misdirection

- Physicians as "double agents"
  - Competing obligations that sometimes conflict
    - Physician: primary obligation is to the patient
    - Investigator: primary obligation is to the research

What is Therapeutic Misdirection?

- Actions taken by an investigator to try and reconcile the competing obligations of clinical medicine with clinical research.
  - Attempt to deliver personalized care in the context of a research protocol
    - Often requires deviating from the protocol
  - Promotes patient-participant TM
  - May compromise scientific validity of the study

WU protocol exception requests

- Examined all protocol exception in eIRB 2008-2011
- Classified into one of 7 categories
- Analyzed
  - Exception type
  - Department of requestor
  - Funding
  - Frequency per protocol
  - Types of protocols
  - Frequency per investigator

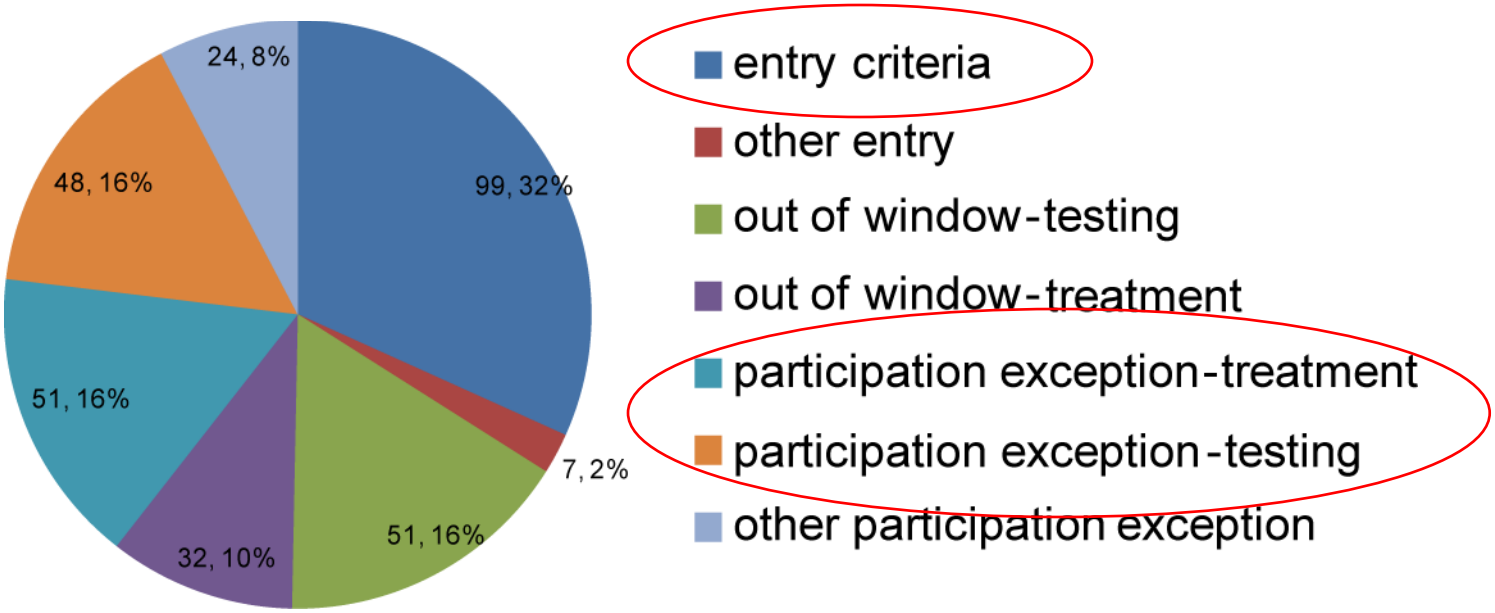
Exception classifications

Exception type	Description
Entry criteria	Enrolling subjects that are ineligible according to inclusion/exclusion criteria
Other entry	enrolling subjects that would not otherwise be permitted to enroll, but not due to ineligibility according to I/E criteria Example: • Enrolling a non-english speaking person in a study not approved for non-english speaking persons • Utilizing an LAR for a study not approved to enroll cognitively impaired subjects.
Out of window-testing	Performing a test, either for enrollment purposes or during the trial, outside the protocol specified time window
Out of window-treatment	performing a treatment or intervention (other than diagnostic testing) outside of the protocol specified time window
Treatment participation exception	altering a treatment intervention outside of what is in the approved protocol Examples: • Changing drug dosing or delivery • holding a drug, • Allowing a subject to continue treatment despite lab value that specifies holding treatment.
Testing participation exception	altering a research test intervention outside of what is in the approved protocol Examples: • not performing a scan or diagnostic test that is prescribed in the protocol.
Other participation exception:	Other changes to conduct of the study, that occur to the subject once already enrolled in the study, but not captured in above categories

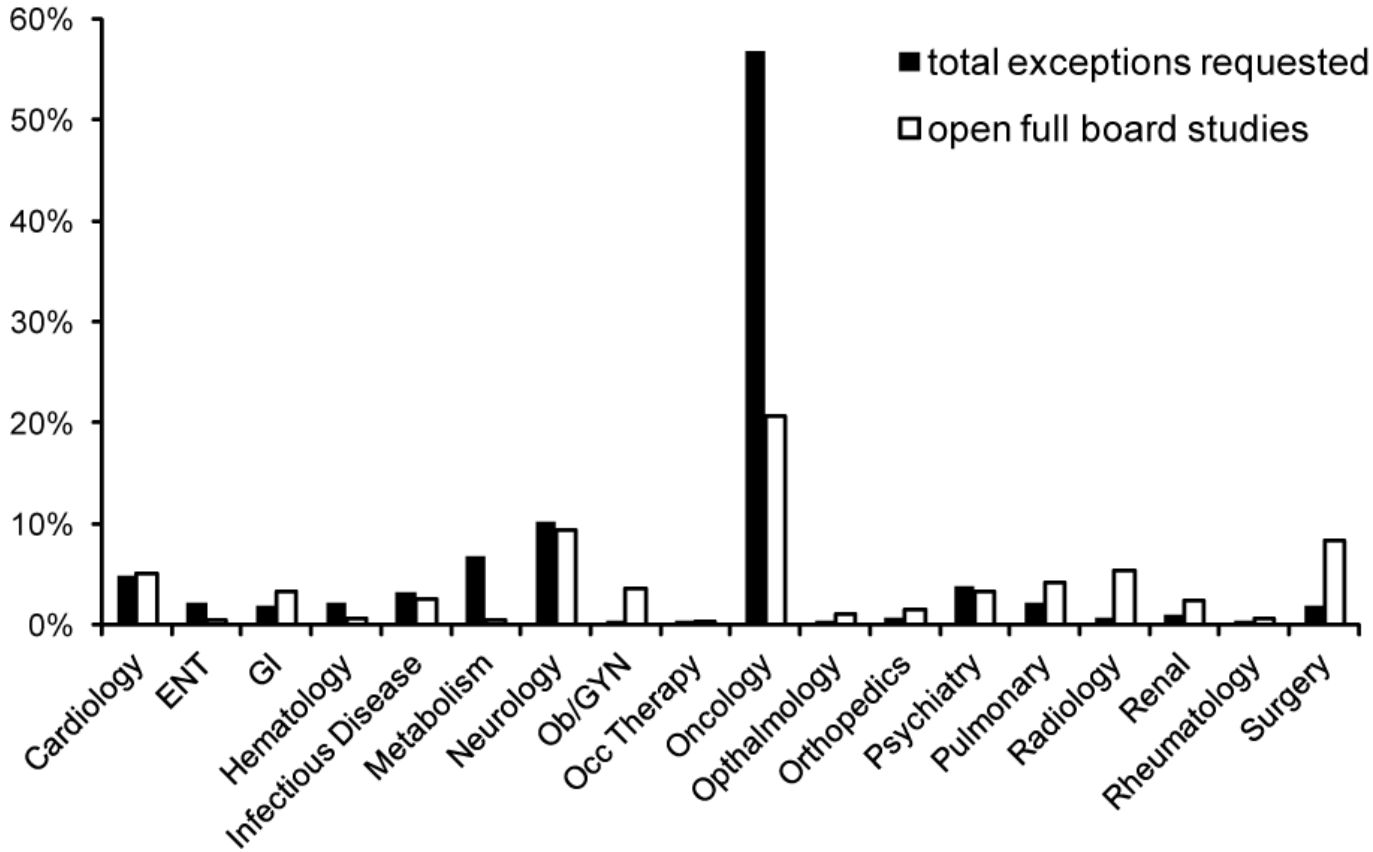
Results

- 1509 open protocols being conducted by 439 Principal Investigators during time period examined.
- 106 PI's requested 312 exceptions in 177 separate protocols
  - 11% of open protocols had an exception request
  - 24% of Investigators requested at least 1 exception

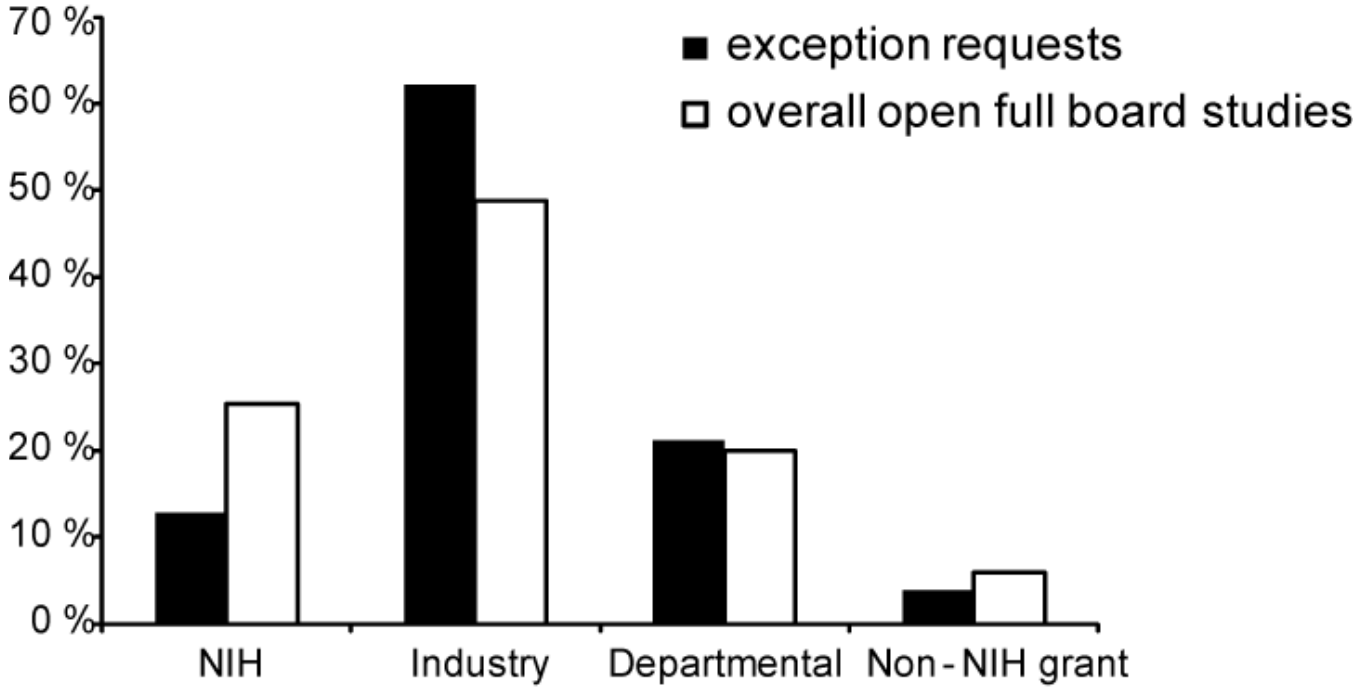
Distribution of exception types



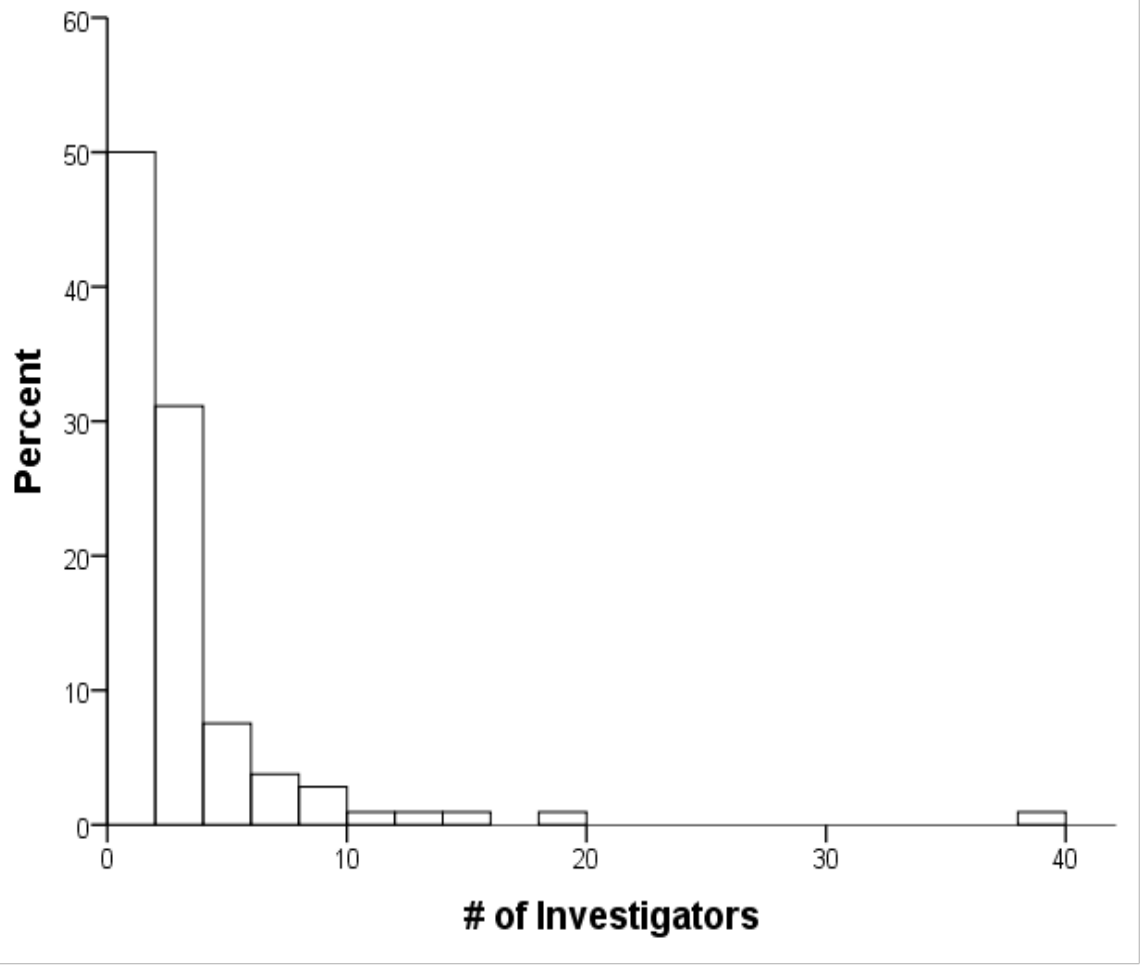
Frequency of exceptions and open protocols by Department



Does funding matter?

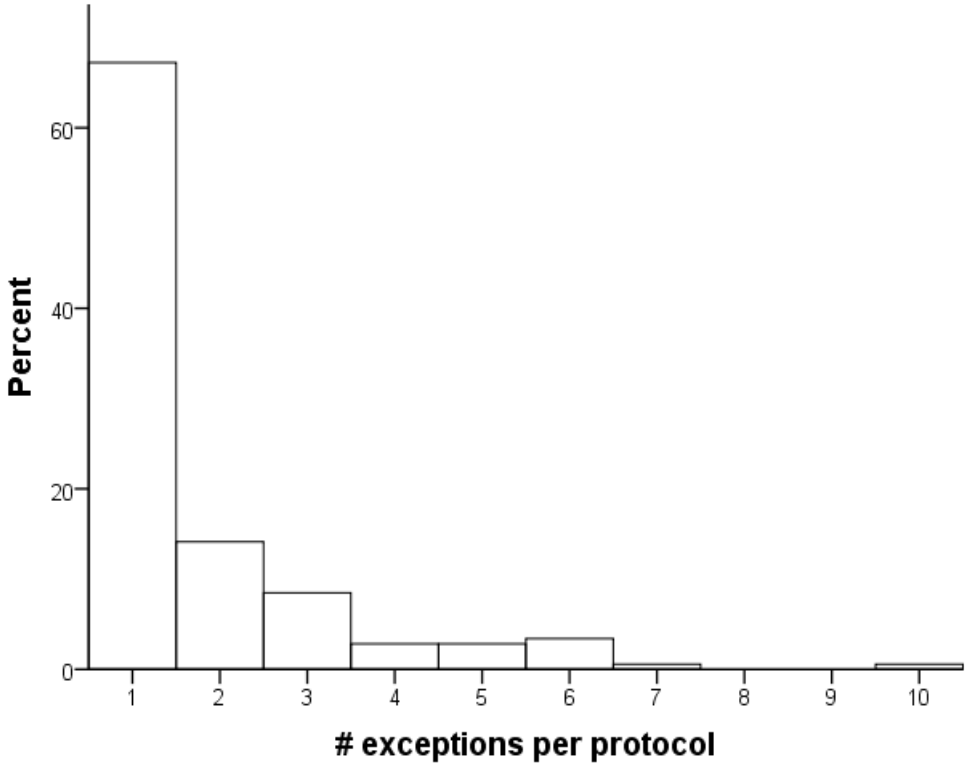


Frequency of exceptions per PI



Number of Investigators	Number of exception requests
53	1
18	2
15	3
5	4
3	5
3	6
1	7
2	8
1	9
1	10
1	12
1	15
1	18
1	38

Exception frequency per protocol



Number of Studies	Number of exception requests
119	1
25	2
15	3
5	4
5	5
6	6
1	7
1	10

- 10 exceptions for 1 protocol
  - Phase 1 hematologic malignancy trial
    - Eligibility criteria – 8
      - Different disease
      - Labs out of range
      - Had prior excluded therapies
    - Out of window test-1
    - Other participation exception – 1
  - Reasons given by PI
    - "enable patient to receive treatment"
    - "combination treatment will offer patient a better outcome"

Phase 1 trials

- Overall Efficacy
  - CR+PR= 10.6%
  - CR=3.1%, PR=7.5%, SD + <PR=34.1%
- Overall toxicity
  - Deaths 0.49%
  - Grade 4 toxicity 14.3%

Horstmann et al, 2005 NEJM 352:9

- Phase 1 trials
  - 50 protocols (29%)
  - 72 exception requests (23% of total)
- Phase 2 trials
  - 49 protocols (28%)
  - 88 exception requests (28% of total)
- Phase 3 trials
  - 17 protocols (10%)
  - 21 exception requests (7% of total)

Prospect of benefit?

- Exception requests in Phase 1 trials
  - 38 -Eligibility criteria
  - 7 – Out of window-testing
  - 12 - Out of window-treatment
  - 10 - Treatment participation exception
  - 3 - Testing participation exception
  - 2 - Other participation exception
- 23/38 indicated it would allow patient to have “treatment”.
- 7/38 state the patient will benefit by receiving the investigational drug.

Why?

- Competing obligations and inherent conflicts
  - Are we doctors trying desperately to treat a dying patient or investigators trying to determine if the drug is safe and effective? Can we do both at the same time?
  - Pressure to enroll and complete trials

What's the downside?

- Effect on the science
  - At best it muddies the water, at worst, invalidates the data.
- Effect on the patient-participant
  - Further promotes their own therapeutic misconception.
- Effect on the investigator
  - Further blurs the distinction between roles and obligations
- Potential to effect overall risk/benefit analysis of the study.

Conclusions

- Requests to deviate from the approved protocol are relatively frequent among protocols and investigators
  - Protocol deviations are a reasonable way to measure therapeutic misdirection
- Exceptions are not limited to trials in which the drug has evidence of safety and efficacy.
- Physician expectation of benefit is common in requesting an exception
- Physicians attempt to use established trials as a mechanism for “expanded access”

Thanks to.....

- Christine Bear
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