

Therapeutic misconception and clinical equipoise

Naynesh Kamani, MD

April 2012

К ПОЕЗДАМ ДО СТАНЦИЙ:



СМОЛЕНСКАЯ • КИЕВСКАЯ
ПАРК ПОБЕДЫ • СЛАВЯНСКИЙ БУЛЬВАР
КУНЦЕВСКАЯ • МОЛОДЁЖНАЯ
КРЫЛАТСКОЕ • СТРОГИНО
МЯКИНИНО • ВОЛОКОЛАМСКАЯ
МИТИНО



ПЛОЩАДЬ РЕВОЛЮЦИИ
КУРСКАЯ • БАУМАНСКАЯ
ЭЛЕКТРОЗАВОДСКАЯ •
СЕМЁНОВСКАЯ • ПАРТИЗАНСКАЯ
ИЗМАЙЛОВСКАЯ • ПЕРВОМАЙСКАЯ
ЩЁЛКОВСКАЯ

9

ПЕРЕХОД НА СТ. "БОРОВИЦКАЯ" / В ЦЕНТРЕ ЗАЛА /

9

1

НА СТ. "БИБЛИОТЕКА ИМ. ЛЕНИНА"
/ В КОНЦЕ ЗАЛА /

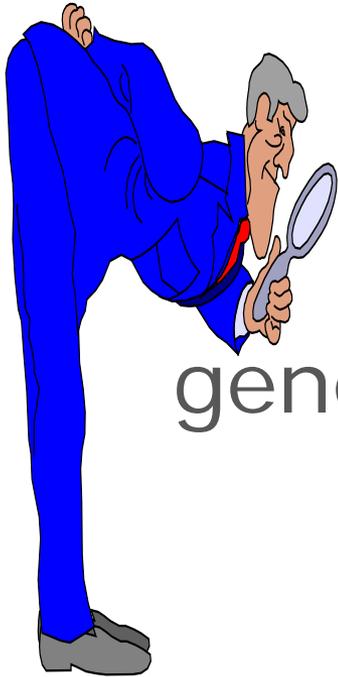
НА СТ. "АЛЕКСАНДРОВСКИЙ САД"
/ В КОНЦЕ ЗАЛА /

4

Regulatory Requirements for IRB Approval (4)

- Informed consent will be sought & appropriately documented (45 CFR 46 section 116)
 - **Statement that the study involves research**
 - Explanation of purpose(s) of research
 - Expected duration of subject's participation
 - **Description of procedures**
 - **Identification of experimental procedures**
 - Description of any reasonably foreseeable risks
 - Description of any benefits to the subjects/others
 - Disclosure of appropriate alternative procedures/Rx

Research



A systematic investigation
designed to develop or
contribute to
generalizable knowledge

(45 CFR 46.102(d))

Therapy/Research continuum

- Pure Therapy
 - Physician
 - Patient
 - Cure
- Pure Research
 - Researcher
 - Subject
 - Generalizable knowledge

PIs play a dual role

Conflict of Commitment

Therapeutic Misconception

Therapeutic misconception

- TM occurs “when a research subject fails to appreciate the distinction between the imperatives of clinical research and of ordinary treatment, and therefore inaccurately attributes therapeutic intent to research procedures”
- TM is “the belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge” (National Bioethics Advisory Commission 2001)

Therapeutic misconception

- Informed Consent in clinical trials should clarify the difference between the standard clinical care (therapy) and research procedures
- Therapeutic misconception arises when human subjects misunderstand the primary purpose of a clinical trial as being therapeutic.
 - Scientific purpose
 - Study procedures
 - Uncertainty
 - Adherence to protocol
 - Clinician as investigator

Five Draft Dimensions of Research that Should Be Understood by Trial Participants

1. Scientific Purpose

Clinical research is designed to produce generalizable knowledge and to answer questions about the safety and efficacy of intervention(s) under study in order to determine whether or not they may be useful for the care of future patients.

2. Study Procedures

Participation in a trial may involve procedures or tests, in addition to the intervention(s) under study, that are intended only or primarily to generate scientific knowledge and that are otherwise not necessary for patient care.

e.g. PK studies, additional imaging or biopsy procedures

Five Draft Dimensions of Research that Should Be Understood by Trial Participants

3. Uncertainty

For intervention(s) under study in clinical research, there often is less knowledge and more uncertainty about the risks and benefits to a population of trial participants than there is when a doctor offers a patient standard interventions.

e.g. Phase I trials

4. Adherence to Protocol

Administration of the intervention(s) under study is typically based on a strict protocol with defined dose, scheduling, and use or avoidance of concurrent medications, compared to administration of standard interventions.

5. Clinician as Investigator

Clinicians who are in health care settings provide treatment; in a clinical trial setting, they are also investigating safety and efficacy of an intervention.

Therapeutic misconception

Clinical trials:

- Primary goal: knowledge generation
- Other consequences:
 - Direct benefit
 - Inclusion or collateral benefit

Therapeutic misconception

- Presumption acquired in clinical treatment and brought over to the research setting
- Subjects' hopes for benefitting from research participation ('therapeutic optimism')
- Shortcomings of the informed consent process

Therapeutic misconception matters

Overestimation of clinical benefit

- e.g. Phase I trials; placebo controlled trials

Underestimation of potential risk or harm

Confusion about randomized assignment

Generally conflate research with ordinary
treatment

Therapeutic misconception matters

Generally conflate research with ordinary treatment

Phase I trials: intent of these trials often
misinterpreted (altruism is rarely the reason)

Clinical trial 'branding': trial names such as
ALIVE, MAGIC, MIRACL, PROVED

Advertising of clinical trials

clinicaltrials.gov "the latest in cancer care"

'participants are among the first to receive new
treatments before they are widely available'

'Clinical trials offer high quality cancer care'

'Clinical trials are a treatment option for many people
with cancer'

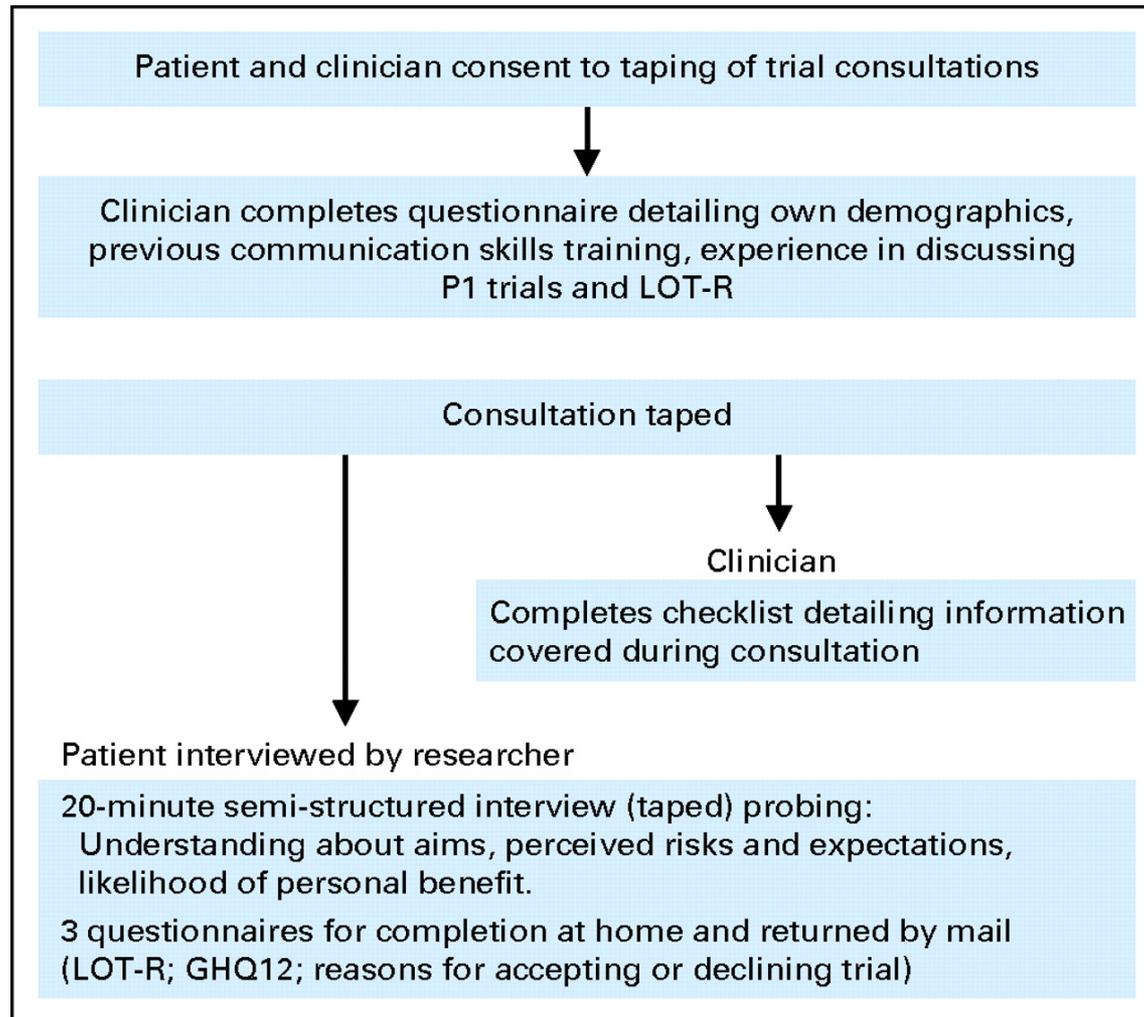
Definition of Therapeutic Misconception

- Therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial.

Phase I Oncology trials

- Fundamental goal
 - Assess toxicity
 - PK studies often a part of phase I trials (MTD)
- Is there prospect for direct benefit in phase I trials?
- What are the alternatives? What are the risks?
- Therapeutic optimism

Timing and administration of questionnaires.



Jenkins V et al. JCO 2011;29:61-68

JOURNAL OF CLINICAL ONCOLOGY



THE GEORGE
WASHINGTON
UNIVERSITY
MEDICAL CENTER
WASHINGTON DC

Phase I oncology trials

- **What Oncologists Believe They Said and What Patients Believe They Heard: An Analysis of Phase I Trial Discussions, Jenkins V et al. JCO 2011;29:61-68**

Findings:

- 1) *Fundamental components of communication and information sharing are missing from IC sessions of phase I trials*
- 2) *Discussions about prognosis and options for supportive care (nihilism about palliative care)*

Clinical equipoise

- *Clinical equipoise* defines the ethical standard for including a patient in a randomized clinical trial (RCT).
i.e. for a randomized clinical trial to proceed ethically, a state of clinical equipoise must exist at the trial's inception
- The standard of 'clinical equipoise' is met "if there is genuine uncertainty within the expert medical community – not necessarily on the part of the individual investigator – about the preferred treatment."
 - Freedman, B. (1987) 'Equipoise and the ethics of clinical research'. The New England Journal of Medicine, 317, (3):141-145.

Clinical equipoise

- Clinical equipoise involves an assessment of whether, given all the available evidence, there is sufficient reason to believe that the risk-benefit profile of an intervention is at least as favorable as the risk-benefit profile of the available alternatives. If the risk-benefit profile is at least as favorable, the intervention “satisfies” clinical equipoise. If the risk-benefit profile of the intervention is less favorable by any margin than the risk-benefit profile of available alternatives, it “fails” to satisfy clinical equipoise.

Clinical equipoise

- Placebo controlled RCT
 - There is no standard treatment
 - Standard therapy has been shown to be no better than placebo;
 - Evidence has arisen creating substantial doubt regarding the net therapeutic advantage of standard therapy;
 - Effective treatment is not available to patients due to cost constraints or short supply

Clinical equipoise

- Placebo controlled RCT
 - In a population of patients who are refractory to standard treatment and for whom no standard second-line treatment exists;
 - Testing add-on treatment to standard therapy when all subjects in the trial receive all treatments that would normally be prescribed; or
 - Patients have provided an informed refusal of standard therapy for a minor condition for which patients commonly refuse treatment and when withholding such therapy will not lead to undue suffering or the possibility of irreversible harm of any magnitude.

