

Informed Consent: **What Law and Ethics May Require** ***Beyond Current Practices***

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What The Doctor
Didn't Say



THE HIDDEN TRUTH
ABOUT MEDICAL RESEARCH

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The Ethics and Regulation of Research with Human Subjects

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The Ethics and Regulation of Research with Human Subjects

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Sources of Guidance for Consent

- **The Nurenberg Code**
- **Declaration of Helsinki**
- **ICH Guidelines for GCP**
- **Federal Regulations**

Nuremberg Code

Person should have “sufficient knowledge . . . to make an understanding and enlightened decision” about participation

Nuremberg Code

“Enlightened Decision” should presumably require sufficient information about three major options patient could choose:

- **Standard Care**
- **Non-Standard Care**
- **Being in a Research Study**

Sources of Guidance for Consent

Federal Regs, 45 CFR § 46.116:

- Any reasonably foreseeable *risks* or discomforts
- Any *benefits* which may reasonably be expected
- *Alternative* procedures or courses of treatment that might be advantageous

Sources of Guidance for Consent

- **Federal regs are relatively vague regarding details of disclosure**
- **Relatively little guidance on specifics of what to say about risks, benefits, alternatives**
- **How to decide amount and nature of disclosure in specific cases?**

Sources of Guidance for Consent

- **Litigation can be source of guidance**
- **Relatively few litigated research cases**
- **Even absent litigated cases, legal rules allowing lawsuits provide guidance**

Federal Regulations and Right to Sue

- Federal regulations and international codes do not create any right to sue for wrongdoing
- **Robertson v. McGee, 2002 U.S. Dist. LEXIS 4072 (N.D. Okla.); Washington Univ. v. Catalonia, 2006 U.S. Dist. LEXIS 22969 (E.D. Mo.)**

Federal Regulations and Right to Sue

- State *tort law* does create right to sue—a distinct system
- Tort of *negligence*: deviation from *standard of care*
- Inadequate informed consent as negligence (rarely, battery in some states)

Tort Law Rules for Informed Consent

Informed Consent for *Medical Care*:

- As deviation from standard of care, need to decide what standards are
- In case of professionals, law delegates determination of standards to profession
- Informed consent was initially treated that way:
Professional standard

Tort Law Rules for Informed Consent

Informed Consent for *Medical Care*:

- Some courts questioned prof. standard
- Rationale for that standard—profession has special expertise—does not apply to disclosure issue
- *Reasonable person* standard proposed- *Canterbury v. Spence*, 464 F.2d 772 (D.C. 1969)
- About half states use each standard- *Ketchup v. Howard*, 543 S.E.2d 371, 381 (Ga. Ct. App. 2000)

Tort Law Rules for Informed Consent

Informed Consent for Research:

- Disclosure Duties *higher* in research; deviating from accepted standards
- Should apply *Reasonable Person* standard, even if state uses Professional standard for clinical informed consent

Modern Day Problems with Consent

- *Questions to Explore:*

1. Do Consent Forms *Commonly* and *Systematically* Fail to Give Subject Info Needed to Make Informed Choice?

Examples will reflect practices endorsed by federal government (e.g., NCI “gold standard” for consent forms)

Modern Day Problems with Consent

- *Questions to Explore:*

2. Is there a deeper flaw in the structure of consent forms, giving subjects lists of benefits, risks and alternatives?

1. New Treatment – Efficacy Info

- **Consent form: merely say it's uncertain if new treatment is better than standard care**
- **Protocol often has lengthy discussion—yet not a word in consent form**
- **Info on prior studies? Related treatments? Why new treatment might work or not?**

1. New Treatment – Efficacy Info

- **Q: Should Tentative Knowledge Regarding New Treatment Be Given?**

Ex: Metastatic Breast Ca Study

- **A: Chemo alone**
- **B: Chemo plus radiation**

1. New Treatment – Efficacy Info

Consent Form:

- “Purpose is . . .
whether radiotherapy after chemo
will reduce risk of cancer recurrence.”

1. New Treatment – Efficacy Info

Protocol:

- “It appears that postmastectomy radiation [reduces] breast cancer deaths.”
- Benefit magnitude unclear: ≤ 3 nodes
- Q: Would reasonable woman care about difference between world where (a) no info on rad. effects, v. (b) radiation effective in 4+ nodes?

2. Standard Care – Efficacy Info

- **Should *efficacy of standard care*,
and *risks of new treatment not working*,
be disclosed?**

Ex: Heart Surgery, high bleeding risk

- **A: Standard fibrin sealant**
- **B: Experimental fibrin sealant**

2. Standard Care – Efficacy Info

Not in Consent Form:

- **Any info re Standard Care Efficacy**
- **Info re consequences if new fibrin sealant is less effective**

2. Standard Care – Efficacy Info

Would subjects view participation differently:

- Where standard care great, v.**
- Where standard care sucks?**
- Should specific risk of new treatment being less effective than standard care be mentioned and consequences discussed in Risks section?
(Spine fracture/brace example)**

3. Benefits Info

A very common practice:

- Merely saying benefits are “uncertain”

Ex: High cholesterol, on statin

- A: New Drug X – 8 weeks
- B: Placebo

3. Benefits Info

Consent Form:

- **Benefits: “May have a good response . . . or no direct benefit.”**
- **Q: What is chance that 8-week lowering of cholesterol has much health effect?**

3. Benefits Info

NCI “Gold Standard”:

- If you agree to take part in this study, there may or may not be direct medical benefit to you.
- Benefit Likelihood – *missing*
- Benefit Type – *missing*

3. Benefits Info

Phase I Study

- To find highest safe dose
- Chance of benefit extremely low
- Subjects routinely overestimate benefits: the question is *why?*

3. Benefits Info

“Special Article” in NEJM, 12/2002

- NIH Bioethics Center reviewed consent forms
- Conclusion: consent forms “unlikely to be primary source of misunderstanding”
- *Reason: the forms almost never promise direct benefit*

3. Benefits Info

- **Study revealed 94% of the forms “communicated uncertainty” about benefits**
- **Is it OK to merely say “benefits uncertain,” and not specifically say, e.g., “Likelihood of your benefiting is near zero”?**
- **Authors say yes: trial may involve approved drugs also, may be psychological benefits**

4. Alternatives Info

**Should getting “experimental treatment”
arm off-study be disclosed?**

A Story

- 1979
- Women with metastatic breast cancer
- Limited treatment options
- Standard chemotherapy gave 10-15% remission rate

A Story

- **An Idea: use stronger chemo**
- **Problem: chemo destroys bone marrow**
- **Solution: autologous bone marrow transplant**
- **High Dose Chemotherapy – Autologous Bone Marrow Transplant (HDC-ABMT)**

A Story

- High dose chemo very harmful
- Early patients young & “healthy”
- Nonetheless 15-20% died from chemo
- Controversial at outset – researchers were “rebels” (Kolata - NYT)

A Story

- **Late 1980s: anecdotal results**
- **HDC-ABMT remissions: 50-60%**
- **Low dose chemo: 10-15%**
- **Former rebels now heroes**

A Story

“It seemed so logical. It started getting accepted without clinical trials.”

- Dr. Larry Norton,

Memorial Sloan-Kettering

A Story

Number of HDC-ABMT Patients:

- 1989: 271
- 1991: 749
- 1990s: 30,000

A Story

- **For-profit companies**
- **Response Technology,
\$128 million in 1998**

A Story

- Academic medical centers followed
- Early 1990s: at virtually every major med center
- Bone marrow transplants became “cash cow for cancer service”
- Money, power & prestige to Drs

A Story

Who was paying?

- Insurers initially balked
- Policies excluded “experimental” treatments
- Lawsuits brought

A Story

- **Insurers lost many cases**
- **Judges reluctant to let pt die**

A Story

“Although moved by the tragic circumstances and the seemingly needless loss of life . . . the law gives us no choice.”

Cannon v. Grp Health, 10th Cir. 1996

A Story

- **Bad press even if insurer won**
- **Most insurers gave in**
- **1994 – coverage for fed employees**
- **About 12 states required coverage**

A Story

- **Some doctors still doing trials**
- **Randomized:**
 - **50% to low dose chemo**
 - **50% to HDC - ABMT**

A Story

- **Very hard to enroll subjects**
- **Cleveland Clinic enrolled 0 subjects despite “monumental efforts”**
- **“If someone says they can cure you,”
pts go there**
- **Ovarian cancer trials collapsed**

A Story

- **1999: Results of clinical trials**
- **3 out of 4: no difference**
- **South African study: falsified data**

A Story

“None of the usual methods of analysis identified any group of patients . . . who benefited.”

NEJM Editorial, 2000

A Story

Conclusion:

Difficult to enroll subjects in randomized trial if standard care is poor and “new treatment” is available off-study

The Flip Side: An Ethical Issue

We are commonly seeing non-disclosure of off-study availability.

More subjects enroll, but is it ethical?

Is Off-Study Availability Common?

- **Q: How common is this scenario?**
- **A: Very common!**

Is Off-Study Availability Common?

Legal Barriers to off-study use:

- Malpractice laws
- Regulatory prohibitions (FDA)

Is Off-Study Availability Common?

Malpractice laws:

- Standard care is not always required
- “Reasonable” deviations are OK
- Not every pt wants or needs standard care
- Consent plays a major role

Is Off-Study Availability Common?

FDA regulations do not prevent:

- **New procedures (surgical, etc.)**
- ***New use of* FDA-approved devices**
- ***New use of* FDA-approved drugs**

Is Off-Study Availability Common?

- **FDA acknowledges lack of authority over how Drs practice medicine**
- **Once drug approved for one use, Drs can use it for other conditions**
- **FDA does control marketing of drug**

Is Off-Study Availability Common?

Off-label use of medications:

- 25%-60% of all prescriptions written
- 65% of all anti-cancer drug use
- Significant % of pediatric drug use

The Ethical Dilemma

- **Assume a study randomizes: standard care v. “new” treatment**
- **Should subjects be told “new” treatment might be obtained off-study?**

The Ethical Dilemma

Assumptions:

- Not requiring the investigator provide the “new” treatment off-study
- Disclosure would include appropriate warnings about risks, etc.

Non-Disclosure is Common

- IRBs commonly see such non-disclosure
- Federal policies encourage this
- Prominent examples
- Prominent defenders of non-disclosure

Non-Disclosure is Common

A Legal Case:

- Daniel Klais, age 45 in 1990
- Head & neck cancer discovered
- Told of Cleveland Clinic study

Non-Disclosure is Common

- Uncertain if adding chemo helpful
- Randomization to either:

A: radiation & surgery

*B: radiation, surgery & chemo
(cisplatin and 5-FU)*

Non-Disclosure is Common

- Klais was assigned no-chemo arm
- Tumor appeared destroyed
- 1995 – recurrent tumor discovered
- Klais died in 1997
- Chemo now known very effective

Non-Disclosure is Common

Klais sued CCF claiming:

- **He told Drs he wanted chemo**
- **Never told of phase II results**
- **Never told of off-study availability**

Non-Disclosure is Common

Stewart v. CCF, 736 N.E.2d 491 (Ohio Ct. App. 1999):

Appellate Court reversed summary judgment

Subsequent settlement

Non-Disclosure As Federal Policy

Old Standard for consent forms: NCI

**Created *Comprehensive Working Group on
Informed Consent in Cancer Clinical Trials***

**Involved 2 years of study, focus groups with
subjects, etc.; great improvement!**

Non-Disclosure As Federal Policy

Instructions about Alternatives:

- Mention “option of no anticancer treatment . . . or treatment *with standard therapy*”
- No reference to disclosing experimental (non-standard) therapies

Non-Disclosure As Federal Policy

template for consent forms is explicit:

“You may get _____ even if you do not take part in the study”

“Non-investigational treatments”

should be used to fill in the blank.

Prominent Example



Study of Tamoxifen and Raloxifene

Can Raloxifene prevent breast cancer

(in high risk w) as well as Tamoxifen?

5 years, randomized, double-blind

10,000 women get one drug or other

Prominent Example

Tamoxifen: FDA approved to prevent breast cancer

Raloxifene: FDA approved for osteoporosis, but *not* to prevent breast cancer

Both are SERMs

Prominent Example

MORE Study:

Raloxifene v. Placebo, 2:1

Primary Goal: Osteoporosis efficacy

**Secondary Goal: Breast Cancer
prevention**

Prominent Example

MORE Results, JAMA 1999

• Raloxifene Arm: 13/5129 Breast Ca

• Placebo Arm: 27/2576 Breast Ca

• Relative Risk 0.24, $P < .001$

Prominent Example

TORE Results, JAMA 1999

Among postmenopausal women with
osteoporosis, risk of invasive breast
Ca decreased by 76%

Prominent Example

JAMA Editorial about MORE Results

“Large, well-designed trial” shows
“that raloxifene significantly reduced
the risk for estrogen receptor-
positive breast Ca among
postmenopausal women with
osteoporosis”

Prominent Example

But MORE study fails to resolve:

Issue of raloxifene use in women w/o

osteoporosis, pre-menopausal

FDA's desire for more data before

approving raloxifene for preventing

breast CA

Prominent Example



STAR Consent Form (approved by FDA & NCI):

**Instead of being in this study, you can . . .
ask your doctor to prescribe tamoxifen for
you”**

Request surgery to remove both breasts.”

No mention of asking doctor for raloxifene

Prominent Example

***Beneca v. Lilly* lawsuit, 1999, surveyed Drs
re raloxifene use:**

***35% of physicians will sometimes
prescribe it primarily to prevent breast
cancer***

***11% of prescriptions are primarily to
prevent breast cancer***

Non-Disclosure Ethical?

Nuremberg Code: Give info needed to make “an understanding & enlightened decision”

Federal regulations: Disclose “appropriate alternative procedures . . . *that might be advantageous to the subject*”

Arguments for Non-Disclosure

It's too risky to offer "clinically"

STAR leader Dr. D. Lawrence Wickerham:

"It's too early to use raloxifene to prevent

cancer outside of a clinical trial . . . We

don't yet know [its] long-term benefits or

risks."

Arguments for Non-Disclosure

BUT: are there reasons to think that it is sometimes (often?) acceptable for a patient to be offered the “experimental” arm therapy outside the study?

Evaluating the Arguments

Look at the *risks* and *benefits* to a person who is considering enrolling in a randomized study comparing standard care to an experimental therapy

Evaluating the Arguments

- ***Risks:*** Getting the experimental therapy outside the study will in many (most?) cases involve no greater risks than getting it in the study

Evaluating the Arguments

Benefits: Experimental arm should already be in *clinical equipoise* with standard care, else study is unethical

Meaning: There is “honest disagreement about comparative merits of treatments within the expert community.”

Evaluating the Arguments

Thus, presumption that it is not that unreasonable to use experimental therapy for given purpose

Evaluating the Arguments

Special benefits from off-study access:

New York Times: “Few people sign on . . . out of pure altruism. They *want the experimental drugs a study provides,* often regarding them as ‘treatment’, even when their safety and effectiveness have not yet been proven.”

Evaluating the Arguments

From a *benefits* viewpoint, for a non-altruistic subject who is *interested in access to the experimental therapy*, a 50% chance at it in the study is far less beneficial than a 100% chance outside of the study

Evaluating the Arguments

summarize:

Risks to subject may be the same, in-study or out-of-study

Benefits may be much greater off-study

Thus, it seems very reasonable for subject to opt for out-of-study access, and thus disclosure is *ethically mandated*

Evaluating the Arguments

Granted, in many cases there may be special higher risks when a therapy is given outside of a study

But the burden should be to demonstrate this possibility in a particular study, instead of routinely assuming the appropriateness of nondisclosure

Dilemma

• Recall *Clinical Equipoise*: There is “honest disagreement about comparative merits of treatments within the expert community.”

Dilemma

Clinical Equipoise assures that a subject is not inappropriately harmed by being denied standard care

Can CE exist, yet it would be “wrong” to provide new therapy off-study?

Dilemma

es!

**Strong CE: Nature of uncertainty
about risks, benefits such that it is
OK to give off-study**

Weak CE: too risky to give off-study

Dilemma

Off-study use may be too risky due to special protections (to lower risks)

only available in study

For example, researchers may have

access to risk monitoring equipment

not available elsewhere

Dilemma

Off-study use may be too risky due to nature of uncertainty about new treatment—e.g., uncertain if it cures cancer as well as standard care (and no reason to think higher cure rate)

Nonetheless may be substantial benefits to future patients from answering res. q.

Example

Dilemma

Assume getting a new therapy off-study is
so bad that no doctor should provide it;

then 50% chance of being exposed to this

“bad” option is presumably also bad

Thus, *being in study is bad for subject*

Dilemma

consent form should clarify to non-altruistic pt
that this *is a non-beneficial study*:

The experimental arm is so risky that we would
never let a doctor give it to you outside of this
study. The only reason we are allowing you to
be exposed to it is to help determine the right
treatment for future patients.”

Dilemma

Consent form should say (but won't):

If you want to do what is best to treat your medical condition, you should not be enrolling in this study.”

Dilemma

Thus, either:

Study is non-beneficial, and subject should be warned of that; *or*

Getting new therapy off-study is perfectly acceptable, and that option should be disclosed

Dilemma

**Whether or not doctors are providing
the new therapy outside of a study
irrelevant to disclosure issue**

**Pt can always ask researcher: will
you give it to me off-study?**

Specific Example

Judy, invited into STAR study

She has osteoporosis, thus known benefit to being on raloxifene

She has concerns about endometrial cancer (which tamoxifen may cause, and raloxifene may not)

Specific Example

AR study testing can be duplicated by
Judy's doctor: breast exams, blood tests

Strong evidence re raloxifene breast Ca
prevention in Judy's case

Why shouldn't she choose raloxifene, instead
of enrolling in the study with only a 50%
chance of getting raloxifene?

Patient Interests v. Research Interests

“Protecting the patient” is not a legitimate reason for non-disclosure

Protecting the viability of research is of course a valid goal, but this cannot be done in an unethical manner

Patient Interests v. Research Interests

If we want to assure that sufficient subjects enroll in clinical trials, perhaps change the law:

- *Don't permit doctors to prescribe experimental therapies if there are on-going research trials*

Patient Interests v. Research Interests

- **Note that this is exactly how we resolve this dilemma in a “never-approved” drug: patients can only get the drug in a study, therefore 50% chance is better than 0%**

Patient Interests v. Research Interests

- **Absent a change in the law, subjects deserve to know their reasonable options**
- **Failing to tell them in the consent form is unjust; the least informed are likely to bear the majority of research risks**

Patient Interests v. Research Interests

- **Savvy patients—like women who sued to get HDC-ABMT—already know that experimental therapies are often available from their doctors**

Patient Interests v. Research Interests

- **STAR recruiter noted difficulty recruiting: “The sense in the community was, ‘Well, I can just take raloxifene. Why do I have to be in a trial?’”**