

Ethics of Phase I Research

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Geraldine

- 55 yo female
- Developed a right breast mass
- Excision—0.9x0.5 cm mass, 0/15 lymph nodes with ER=0 and PR=538.
- Work-up negative.
- Received XRT and no chemotherapy.
- 3 years later developed a recurrence in liver and lungs.

Geraldine

- Treated with AC then Taxol.
- When cancer progressed in her liver we discussed hospice and Phase I trials.
- She wanted to “fight my cancer”.
- First Phase I agent failed after 2 cycles.
- She wanted another Phase I agent rather than hospice.
- After the second agent failed, she had substantial pedal edema, could barely walk, but came to clinic wanting yet another Phase I agent.

8 Principles for Ethical Research

- 1) Collaborative partnership
- 2) Social value
- 3) Scientific validity
- 4) Fair subject selection
- 5) Favorable risk-benefit ratio
- 6) Independent review
- 7) Informed consent
- 8) Respect for human subjects

Criticisms of Phase I Research

- Risk-benefit ratio is unfavorable.
- Terminally ill patients cannot provide valid informed consent.

Unfavorable Risk-Benefit Ratio

- Phase I research is not intended to benefit the individual participants.
- Phase I research has some risks to the individual participants.
- With no benefits but with risks, the risk/benefit assessment is inherently unfavorable.

Unfavorable Risk-Benefit Ratio

- If the risk/benefit assessment is unfavorable for individual participants, then the research is conducted only to gain knowledge for society.
- If the primary beneficiary of research is society, then individual patients are exploited for the benefit of society.

Unfavorable Risk-Benefit Ratio

The fact that there is no treatment for the condition does not make any intervention “therapeutic” or even “probably therapeutic.” Phase I cancer drug research may not be performed on terminally ill subjects under these guidelines because there is no reasonable probability that it will benefit the subjects.

George Annas

Informed Consent and Exploitation

Relying on valid informed consent by the research participants has been the response to the possibility of exploitation of patients in Phase I oncology research.

Unfavorable Risk-Benefit Ratio

When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject--or, in some rare cases, to the manifest voluntariness of the participation).

The Belmont Report

Invalid Informed Consent

Valid informed consent requires:

- Mental competence
- Disclosure of information by researcher.
- Understanding of this information by the patient.
- Voluntary—uncoerced—consent.

Invalid Informed Consent

Problems with disclosure of information

- Physicians do not provide appropriate or accurate information.
- Physicians stress and exaggerate the benefits while minimizing the risks of research participation.

Invalid Informed Consent

“Consent forms are often very deficient and they over promise. They make Phase I studies sound like the cure for your cancer.”

LeRoy Walters

New York Times

Invalid Informed Consent

Problems with patient understanding.

- Because they are terminally ill, patients cannot understand the true objectives, benefits and risks of Phase I research. Their understanding is clouded by their physical state and their hope for a cure.
- What clear thinking patient would opt to take toxic drugs rather than receive palliative care and comfort measures at the end of life?

Invalid Informed Consent

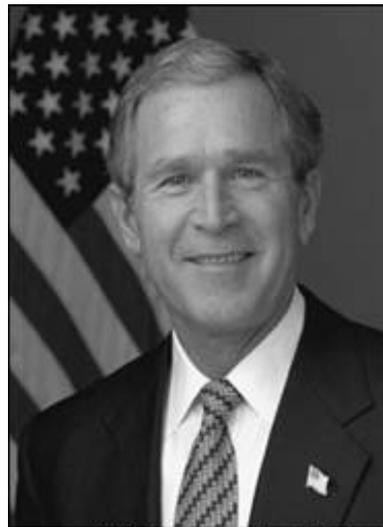
- Because terminally ill patients are not given proper information by their physicians, because they cannot understand the information they are given, and because they are vulnerable, they cannot provide valid informed consent.

Invalid Informed Consent

- Vulnerable populations that cannot provide informed consent are protected through special safeguards.
- These safeguards preclude research that provides no benefits to patients if it also includes greater than minimal risks or a marginal increment over minimal risks.

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DISCLAIMER

These views merely represent
The Truth.

Responses to Criticisms

Risk-Benefit Ratio

- Is it ethical to conduct Phase I research when there are no expected benefits to enrolled subjects?
- What types of Phase I research is being done?
- What are the actual risks and benefits of Phase I oncology research historically and today?

Risk-Benefit Ratio

- It can be ethical to conduct research without benefits to patients if the knowledge-risk ratio is favorable.
- A favorable knowledge-risk ratio requires that the knowledge gained is socially valuable.

Risk-Benefit Ratio

- Conducting early Phase I oncology research in which the drug doses are too low, may not be socially valuable in terms of knowledge about safety, toxicity, and the MTD.
- Ironically, having a favorable knowledge-risk ratio may require more risk because only then is procuring knowledge possible.

Risk-Benefit Ratio

This thinking argues for use of the more innovative Phase I designs such as:

- Inpatient dose escalation
- Accelerating dose escalation
- Requiring 1 patient rather than 3 at low doses

Risk-Benefit Ratio

- Yesterday's Phase I is not today's Phase I.
- Nature of Phase I oncology studies have changed. They are no longer only trials of “first in man” chemotherapeutic agents.

Risk-Benefit Ratio

Review of 460 CTEP Phase I trials from 1991-2002

- 20% single investigational chemotherapeutic agent.
- 41% single investigational agent of any kind.
- 12% multiple investigational agents.
- 46% include at least one proven agent.

Risk-Benefit Ratio

Estey et al. (1986)

Reviewing 187 trials involving 54 drugs and 6,447 patients between 1974-1982.

- Complete Responses 0.7%
- Partial Responses 3.5%

Risk-Benefit Ratio

Decoster et al. (1990)

Reviewing 211 trials involving 87 drugs and 6,639 patients between 1972-1987.

- Complete Responses 0.3%
- Partial Responses 4.2%
- Toxic deaths 0.5%

Risk-Benefit Ratio

CTEP Database

- 460 trials between 1991 and 2002
- 10,402 patients for response
- 11,935 patients for toxicity

Risk-Benefit Ratio

	RR	CR	SD
Overall (460 agents)	10.6%	3.1%	34.1%
1 Invest Chemo Agent (20%)	4.4%	1.5%	40.8%
Multiple Invest Chemo Agent (2.6%)	11.7%	1.5%	27.5%
Approved and Invest Chemo Agents (19%)	16.4%	5.6%	31.3%
1 Invest Signal Transd. Agent (11%)	3.2%	0.7%	39.3%

Risk-Benefit Ratio

	Death	Grade IV Toxicity
Total (11,935)	0.49%	14.3%
1 Invest Chemo Agent (2,621)	0.57%	15.0%
Approved and Invest Chemo Agent (2,594)	0.77%	14.5%
1 Invest. Signal Transduction (1,565)	0.19%	13.0%

Risk-Benefit Ratio

- **211 Phase I studies published in 2002**
- **6,008 evaluable for toxicity**
- **5,362 evaluable for response**

CR	PR	SD	Deaths
3.8%	15.2%	23.0%	1.1%

Risk-Benefit Ratio

Some remarkable therapeutic benefits in Phase I oncology trials

- Platinum had >50% response rate in testicular cancer and 25% long term survival.
- Gleevac had >90% response rate in CML.

Risk-Benefit Ratio

Must compare these response rates to approved therapies.

- High dose IL-2 for metastatic renal cell
 - CR 5%
 - PR 9%
 - Median duration 20 months
- 1% gain in absolute mortality for adjuvant chemotherapy for Stage I breast cancer.

Risk-Benefit Ratio

- Some data suggest that enrolling in Phase I research is beneficial to the quality-of-life of patients.
- Patients in Phase I had stable QOL and performance status over 1 course of therapy whereas similar patients receiving supportive care had lower levels of QOL.

Informed Consent

Can terminally ill patients provide informed consent?

- Do Phase I researchers misinform patients?
- Do Phase I informed consent documents misinform?
- Do terminally ill patients misunderstand information about Phase I research?
- Are terminally ill patients under a therapeutic misconception?
- Are terminally ill patients vulnerable?
- Are terminally ill patients coerced?

Do Phase I Researchers Misinform Patients?

Do Physicians Misinform?

Tomamichel et al. (1995)

- Recorded informed consent interactions for 32 patients.
- Quantitative analysis indicated that 3 major information points were communicated in almost 80% of cases.
- Use of indirect patient responses was not as good.

Do Physicians Misinform?

Daugherty et al. (1995)

18 Phase I oncologists at U of Chicago

1-2 months added survival	10%
Complete and partial response	15%
Complete response	1%
Life-threatening toxicity	10%
Death	5%

Do Physicians Misinform?

Meropol et al. (2003)

48 physicians and 328 patients considering Phase I

Discussed with Patients	Physicians	Patients
Possible side effects	92%	78%
Possible risks	92%	73%
Possible benefits	90%	79%
Change in length of life	60%	29%

Do Physicians Misinform?

- Benefit from experimental therapy 15%
- Adverse events experimental therapy 10%

Do Physicians Misinform?

- Limited data suggests physicians do not misinform patients and if they do misinform they tend to over-estimate risks more than benefits.

Do Phase I Informed Consent Forms Misinform?

Do Forms Misinform?

Data from a review of 272 Phase I informed consent documents from 1999.

- 40% of Phase I trails had a therapeutic element. For instance, adding a new drug to a known effective drug.

Do Forms Misinform?

- 92% mention safety, dose determination, or toxicity as the purpose of the trial.
- 99% mention that the study is research or an experiment with most of these being prominent or highly prominent in the informed consent form.

Do Forms Misinform?

- 6% explicitly mention that the research is not therapeutic.
- 96% refer to the chemotherapy agent as treatment or therapy, without any modifier such as “experimental”.

Do Forms Misinform?

- Median length of risk and benefit sections

Risk	35 lines
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Benefit	4 lines
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- 67% mention death as a possible risk
- 33% mention death more than once
- 83% mention possibility of serious harms

Do Forms Misinform?

- One of 272 forms mention benefits will definitely accrue to subjects.
- Mentioned as possible benefits

Cure	5%
Life prolongation	20%
Tumor shrinkage	36%
Generalizable knowledge	68%

Do Forms Misinform?

- 96% have separate alternatives section
- Mentioned as alternatives

Palliative care	56%
Standard therapy	88%
No treatment	65%
Other experimental therapy	52%
Hospice	<1%

Do Forms Misinform?

While the documents are not perfect and can be improved, it is hard to say that informed consent documents:

- Over promise benefits and minimize risks
- Disguise the nature of the trial or that it is research
- Promise cure

**Do Terminally Ill Patients
Misunderstand Information
about Phase I Research?**

Do Patients Misunderstand?

Decoster et al. (1990)

- 91% of patients on Phase I trials had prior therapy:
 - 50% chemotherapy alone
 - 25% chemotherapy and radiation therapy
 - 11% radiation therapy alone

Do Patients Misunderstand?

- Daugherty et al. (2000)
- 144 Phase I patients

57% some college or more

Are Patients Vulnerable?

- Meropol et al. (2003)
- 328 patients considering Phase I trials

	ALL	Enroll	Decline
White	86%	85%	90%
Some College	64%	64%	68%

Do Patients Misunderstand?

- Daugherty et al. (2000)

Recall signing consent form	100%
Recall explanation of study as research	98%
Recall explanation of risks and side effects	97%
Recall at least 1 specific side effect	100%
Felt well informed	96%

Quality of the information transfer was associated with higher education.

Do Patients Misunderstand?

Joffe et al. (2001)

Mailed survey of 207 Phase I, II, and III cancer patients.

50 in Phase I studies, but not distinguished in data analysis.

Do Patients Misunderstand?

Joffe et al. (2001)

- 84% read the consent form carefully
- 87% had enough time to learn about the trial
- 93% sufficient time to ask questions
- 48% consent discussion last over 1 hour
- 44% consulted an outside physician

Do Patients Misunderstand?

- Almost all patients participating in Phase I studies feel well informed and are satisfied by the informed consent process:

Study	# of Patients	% Satisfied
Daugherty	144	96%
Tomamichel	31	96%
Joffe	207	90%

**Do Terminally Ill Patients have
a Therapeutic Misconception
about Phase I Trials?**

Therapeutic Misconception?

<u>Study</u>	<u># Subjects</u>	<u>Results</u>
Yoder	37	70% to get best care 85% shrink tumor
Tomamichel	31	59% medical benefit
Cheng	30	60% medical benefit

Therapeutic Misconception?

- Daugherty et al. (2000)

Patients views of purpose of Phase I

- Anticancer Response 61%
- Toxicity Determination 27%
- Combination 8%

Therapeutic Misconception?

Meropol et al. (2003)

Maximum Benefit of Experimental Therapy
37% of studies only investigational agents

- Totally cure 39%
- Reduce cancer 26%
- Control cancer 30%
- Improve symptoms 3%
- Nothing 2%

Therapeutic Misconception?

Joffe et al. (2001)

- 75% reported that the main reason for trials was to improve treatment of future patients
- 71% there may not be “direct medical benefit to me.”
- 48% report treatments and procedures in the trial are standard for their cancer

Elizabeth

“I know you want me to say that this trial is about safety. But the doctors wouldn’t start the trial without hoping they could prove the drug would be effective in stopping cancer in future trials.”

Are Terminally Ill Patients Vulnerable?

Are Patients Vulnerable?

Vulnerable population is a technical term meaning those patients who for reasons of

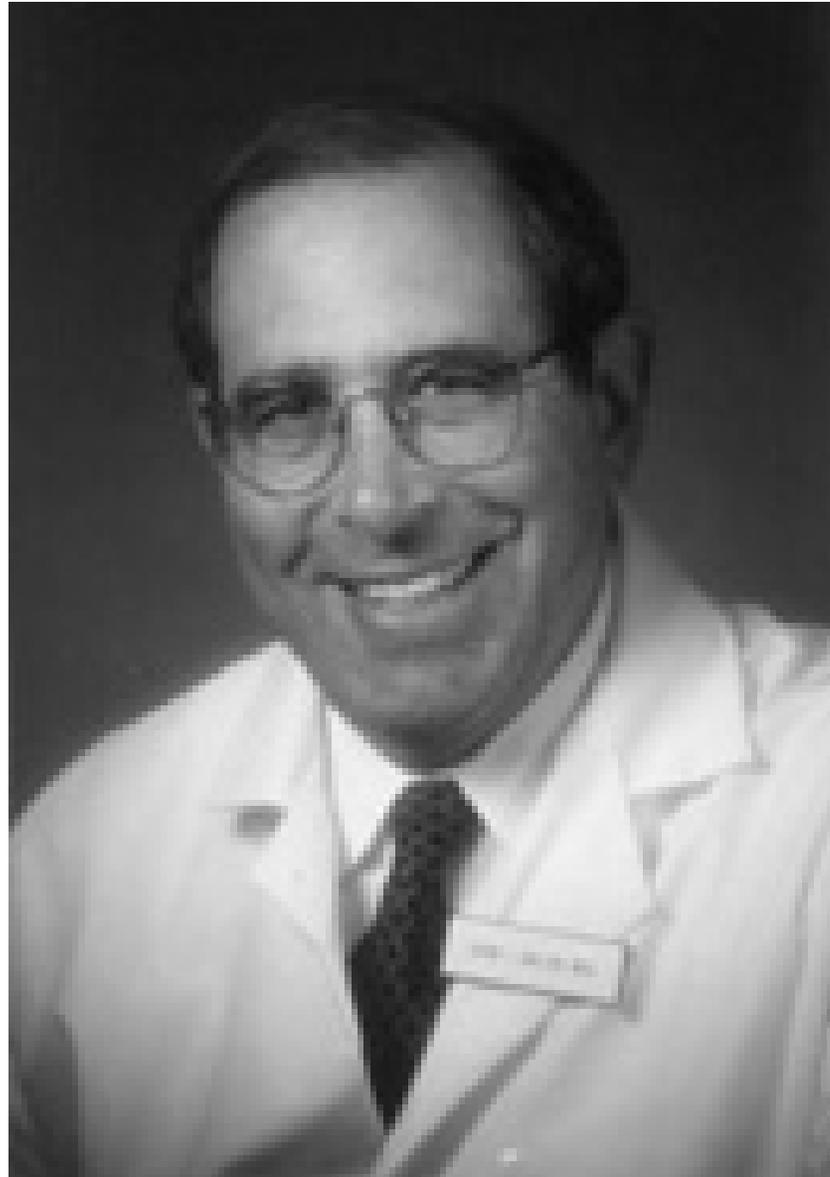
- mental incapacity
- physical environment, such as prison
- history of discrimination and powerlessness, such as African-Americans

cannot defend their own interests through informed consent and need added protections.

Are Patients Vulnerable?

The characteristics of patients on Phase I research trials are:

- Sex: 57% male
- Age: Mid 50s.
- Race: 88% white
- Education: 2/3 have some college education
- Hair: All are bald



Are Patients Vulnerable?

This is not the socio-demographic picture of a vulnerable population.

Are Patients Coerced?

Agrawal Study

- 163 patients interviewed at 5 cancer centers:
- In person interview immediately after consenting to Phase I and before first treatment.
- Had cancer for an average of 4.8 years.
- Average of 3.0 prior chemotherapy regimens.

Are Patients Coerced?

	No Pressure	Little Pressure	Moderate/ A Lot Pressure
Family	80%	11%	9%
Clinical Researcher	87%	6%	7%
Growing Cancer	17%	8%	75%

What is Going On?

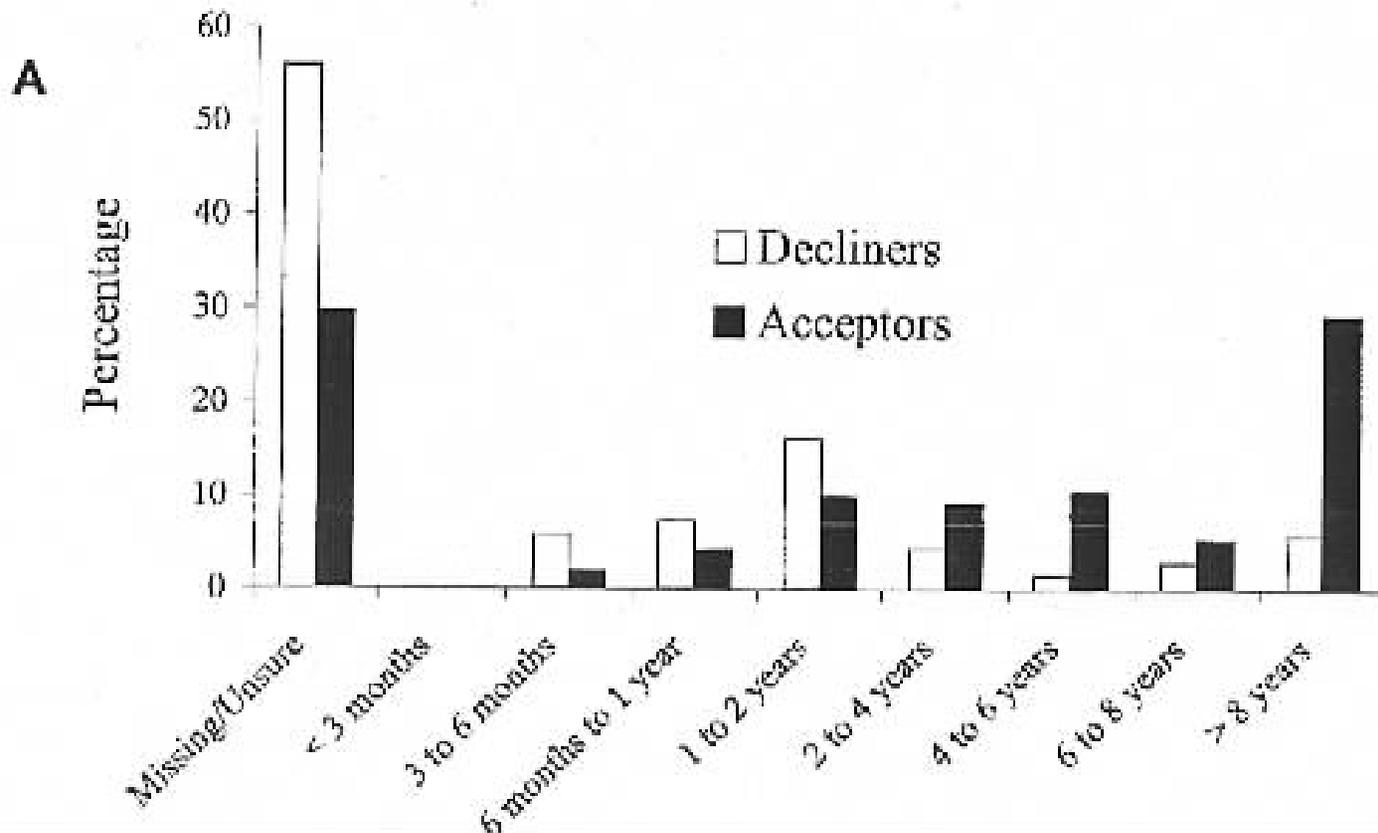
**Why are Terminally Ill Patients
Enroll in Phase I Studies?**

Why?

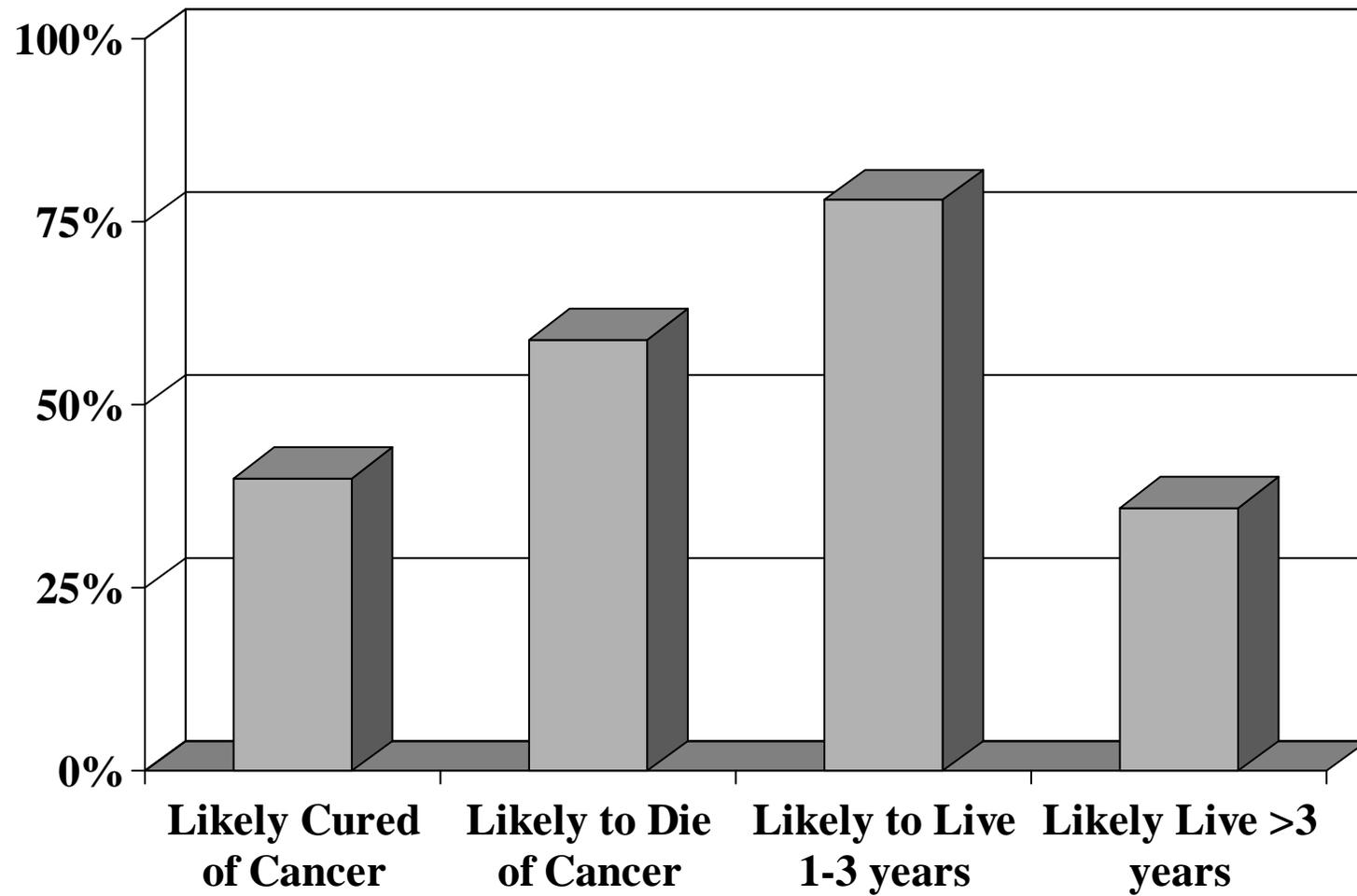
- They deny or refuse to acknowledge death
- They want to go out fighting
- They know their options
- Nothing—or almost nothing—would preclude them from enrolling

Deny Death

PATIENT AND PHYSICIAN PERCEPTIONS OF PHASE I TRIALS



Deny Death



Go Out Fighting

We who are struggling to escape cancer do not, obviously, want to die of it. We do prefer death in the struggle to life under cancer's untender rule. The enemy is not pain or even death, which will come for us in any eventuality. The enemy is cancer, and we want it defeated and destroyed...

Go Out Fighting

This is how I wanted to die—not a suicide and not passively, but eagerly in the struggle.

George Zimmer

Phase I patient University of Chicago

Know Options

	Know of Option	Consider Option for Self
No cancer treatment	NA	7%
Palliative care	84%	10%
Hospice care	81%	6%
Other clinical trial	69%	35%

Nothing Will Dissuade Them

Would this side effect prevent you from enrolling in the Phase I research trial?

Losing hair	4%
Gaining 20 pounds	5%
10% chance of dying from side effect	9%
Drugs that don't kill cancer cells	1%
Drugs that temporarily undermine ability to think	24%

The Problem

There is one major problem with Phase I trials:

Communication about life expectancy.

The Problem

- Only 24% of patients “discussed life expectancy with their oncologist” a moderate amount or a lot.
- Only 14% were told a specific time frame.

The Problem

This was problematic for some patients.

- “He wouldn’t answer the question I asked [about survival].”
- “I tried to discuss it [life expectancy] but he will not tell me ‘you have a year or less.’”

The Problem

- Obviously, discussing life expectancy for someone who has less than 1 year to live is not easy or pleasant. We all avoid it.
- But it is necessary for some patients.
- Ironically, it might increase enrollment in Phase I trials since people are enrolling even when they think they have long life expectancies.

Conclusions

- Risk-benefit ratio for Phase I trials has changed because the type of Phase I trials have changed.
- Patients who enroll
 - Have sufficient information disclosed to them.
 - Are satisfied by the amount of disclosure.
 - Understand most of the information disclosed.

Conclusions

- Like Gerialidine, patients who enroll in Phase I trials want to fight their cancer and almost nothing will dissuade them.
- Oncologists need training to provide better information about life expectancy. But this may only increase enrollment in Phase I trials.

Better Informed Consent Forms

- Shorter forms
- More readable forms
- More organized forms

Better Informed Consent Forms

- Eliminate duplications of statements.
- Put text in places where text goes. No risks or benefits in the purpose section.
- Simplify language and make shorter sentences.
- Use tables and bullets for clarity.
- Don't give side effects for each drug only for all chemotherapy together.

Comparison

	Traditional Form	Shorter Form	Difference
Total Words	2870	1536	1334 54%
Words per sentence	22	14	8 63%
Reading level	11.4 grade	7.7 grade	