Centre for Biomedical Ethics
Yong Loo Lin School of Medicine

The Failure to Disclose Unexpected Benefits in Consent for Clinical Trials

Jerry Menikoff, MD, JD, MPP

2 December 2024

Informed Consent

- Obtaining appropriate informed consent is a key requirement for clinical trials
- Are we doing a good job in implementing that requirement?
- In particular, are we telling participants what they need to know about possible benefits (and the lack thereof)?

Benefits – Phase 1 Oncology

- For years, there have been arguments that practices in disclosing benefits in phase 1 oncology and other trials have been inadequate
- Participants in such trials regularly believe that their chance of directly benefiting will be much higher than it actually is
- Questions arose whether language in consent forms was playing a role in causing this misunderstanding

The New England Journal of Medicine

Special Article

DESCRIPTIONS OF BENEFITS AND RISKS IN CONSENT FORMS FOR PHASE 1 ONCOLOGY TRIALS

SAM HORNG, B.A., EZEKIEL J. EMANUEL, M.D., PH.D., BENJAMIN WILFOND, M.D., JONATHAN RACKOFF, B.A., KAREN MARTZ, M.S., AND CHRISTINE GRADY, PH.D.

ABSTRACT

Background Ethicists have suggested that written consent forms encourage participants in phase 1 cancer trials to expect benefit from the experimental agent and to overlook serious risks.

Methods To evaluate the written description of direct benefit as well as risk, all consent forms for 1999 phase 1 cancer trials were compiled from 80 percent of the National Cancer Institute–designated cancer centers and from six of eight large pharmaceutical developers of anticancer drugs. In each case, we evaluat-

rate of death from toxic effects at approximately 0.5 percent.[8-11]

The few empirical studies that have been conducted of subjects in these trials suggest that many subjects do not understand critical aspects of the research.[12-16] Only one third of the subjects could identify the purpose of a phase 1 cancer trial as safety testing, and most of them anticipated clinical benefits such as tumor shrinkage and decreased symptoms.[12-16]

Many commentators have expressed ethical con-

Benefits – Phase 1 Oncology

- 2002 “Special Article,” from a dream team of top bioethicists, asked whether the language in Phase 1 oncology trial consent forms was playing a role in participants having inflated expectations of benefit
- Researchers looked at 272 consent forms, determined that only 1 form promised benefits
- Most consent forms had language such as “you may or may not benefit,” to avoid suggestion that participants would definitely benefit
- Researchers concluded that benefits section of consent forms were not a problem, and were not cause of inflated expectations

Benefits – Phase 1 Oncology

- Was that conclusion correct?
- What do people think when told ”you may or may not benefit”?
- What if you asked them to give likelihood of benefit?
- Assume the clinical trial took place in prestigious medical center, probably requiring millions of dollars

Benefits – Phase 1 Oncology

- Randomized research (by myself and others) looked at this
- Result: consent forms were indeed very problematic
- Saying “you may or may not benefit” sends an optimistic message
- Whereas actually telling people there is a very low likelihood of benefit makes a big difference

Benefits – Phase 2 & 3 Oncology

- Does a similar issue occur in other types of clinical trails?
- What about the benefits sections of phase 2 and phase 3 oncology trials?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron

ABSTRACT

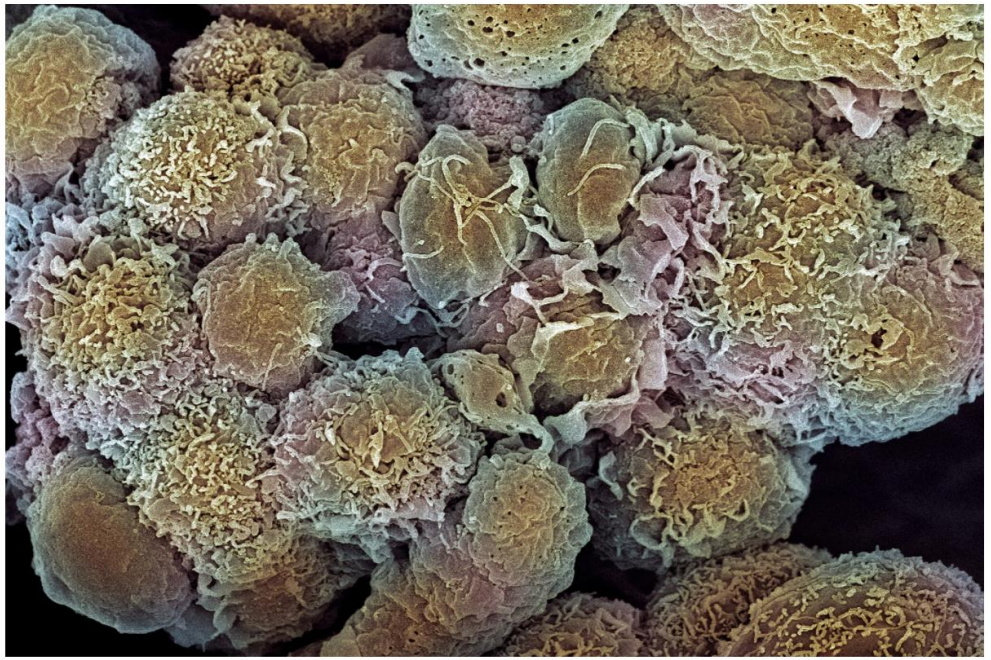
BACKGROUND

Among breast cancers without human epidermal growth factor receptor 2 (HER2) amplification, overexpression, or both, a large proportion express low levels of HER2 that may be targetable. Currently available HER2-directed therapies have been ineffective in patients with these "HER2-low" cancers.

The au
grees,
pendix
modis
Sloan I
Ave., N

Breast Cancer Drug Trial Results in 'Unheard-Of' Survival

For some patients with metastatic tumors not significantly affected by other forms of chemotherapy, the treatment halted their cancer's growth.



A colored scanning electron micrograph of breast cancer cells. Patients treated with the new drug trastuzumab deruxtecan survived for 23.9 months. Steve Gschmeissner/Science Source

By Gina Kolata

June 7, 2022

Benefits – Phase 2 & 3 Oncology

- June 2022: at oncology meeting, results of drug trial announced
- Participants had metastatic breast cancer that was “HER2 low” (low in membrane protein affecting cell growth)
- For women with HER2+ cancers – lots of this protein - good drug treatments created by blocking these HER2 receptors
- But HER2+ cancers only represent 15-20% of breast cancers
- Much harder to treat women with HER2 low cancers

Benefits – Phase 2 & 3 Oncology

- The results of the clinical trial announced at the June 2022 meeting: tested treatment extended the survival of women with HER2 low metastatic breast cancer
- As *New York Times* headline stated, results showed “unheard-of” survival rates
- Results were “so impressive that researchers received a standing ovation”
- Last such standing ovation had been 20 years earlier

Benefits – Phase 2 & 3 Oncology

- By how much did this “stunningly successful” treatment extend the lives of these patients?
- **Audience Participation:** In your mind, decide right now what time period you would guess.

Benefits – Phase 2 & 3 Oncology

- By 6 months

Benefits – Phase 2 & 3 Oncology

- If you told the average person about the standing ovation, and then asked them, by how much did the treatment extend the lives of the patients, what would they say?
- What would they say if you asked them the same question about the “average” breast cancer clinical trial?

Benefits – Phase 2 & 3 Oncology

- From *New York Times*: “It is unheard-of for chemotherapy trials in metastatic breast cancer to improve survival in patients by six months,” said Dr. Moore, who enrolled some patients in the study. Usually, she says, success in a clinical trial is an extra few weeks of life or no survival benefit at all but an improved quality of life.
- Note: that quote is referring to the results in a successful trial. As this audience knows, most trials are ***not*** successful.

Benefits – Phase 2 & 3 Oncology

- The ethical and regulatory issue: What are participants with metastatic breast cancer being told about possible benefits when asked to enroll in clinical trials?

Benefits – Phase 2 & 3 Oncology

- The consent form for that 2022 breakthrough trial does not appear to have been made public
- However, U.S. law now requires consent forms for most federally-funded clinical trials to be posted online. Most are posted at *clinicaltrials.gov*
- A search on that website for registered studies involving treatments for breast cancer that is HER2 negative, and that have a posted consent form, produces approximately 30 results

Benefits – Phase 2 & 3 Oncology

- Looking at the benefits sections of those consent forms, almost all of them are variations on the type of language that appear in phase 1 consent forms
- They use language that tells participants that they may or may not benefit
- They sometimes have lawyerly language (to protect the researchers and their institutions) stating that no benefit is guaranteed
- Only one of the consent forms includes specific language describing how unlikely a benefit will be (NCT02957968): “It is unlikely that the combination of decitabine and pembrolizumab will help you live longer.”

Conclusion

- The 2022 breakthrough trial demonstrates that, at least in breast cancer, the likelihood of a trial extending a woman's life by a very substantial period of time is very low.
- The average woman would likely be guessing at a higher likelihood and a much longer possible extension of her life.

Conclusion

- Adhering to the core ethical requirements of informed consent would mean that consent forms should be informing these women of the correct information about what participation in these trials will mean in terms of extending their lives.
- It would be very easy to provide such correct information. A person reading the New York Times story would know much more than someone reading an IRB-approved consent form.

Conclusion

- Consider writing this benefits section: “It is unheard-of for chemotherapy trials in metastatic breast cancer to improve survival in patients by six months. Usually, success in a clinical trial is an extra few weeks of life or no survival benefit at all but an improved quality of life. And only a small percentage of clinical trials are successful.”
- Of course, that sort of language in consent forms is almost – ***unheard of!***

Conclusion

- Failing to provide such straightforward information in oncology consent forms is a serious ethical failing.
- It is likely that similar failings exist in the consent forms for many other types of clinical trials.
- Why aren’t ethics review boards, IRBs, and bioethicists more concerned about this?

THANK YOU!

jerry.me@nus.edu.sg

ChatGPT, using prompt "Write an intro for Jerry Menikoff as a short standup sketch"

Comedian: "Hey folks, how's everyone doing tonight? So, let me tell you about this guy. You ever heard of Jerry Menikoff? Yeah, he's not your average Joe. No, no, he's like the superhero of bioethics. Picture this: a doctor and a lawyer walk into a research lab, and bam! Out comes Jerry Menikoff! He's the guy you want when you're knee-deep in ethical quicksand, trying to navigate through those murky waters of healthcare policy." [The audience chuckles.]

Comedian: "Seriously though, he's like the Sherlock Holmes of healthcare ethics. Solving mysteries, protecting rights, and making sure everyone plays by the rules. And let me tell you, when Jerry speaks, you listen. The man knows his stuff. He's like the Gandalf of healthcare, waving his ethical staff and saying, 'Thou shall not pass...without informed consent!'"