



NEW HORIZONS GIST

Celebrating 20 years of GIST Treatments

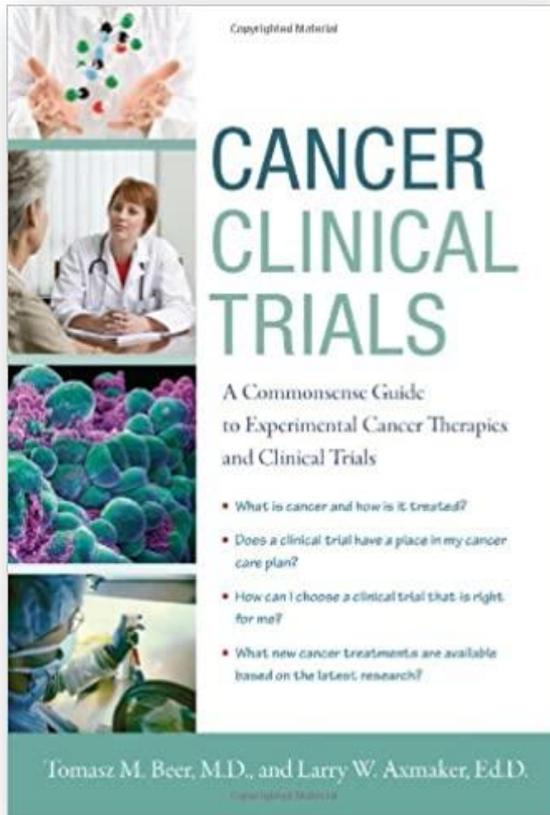
Clinical Trials

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In memory of Elsie Hernandez.

Disclaimer: I am not a physician. I am a scientist (biochemistry/ toxicology) with some experience in cancer research. Nothing in this presentation should be regarded as medical advice or as a substitute for consulting with your doctors.

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Cancer Clinical Trials: A Commonsense Guide to Experimental Cancer Therapies and Clinical Trials

2012

Tomasz M. Beer and Larry W. Axmaker

“Clinical trials are *experiments* – highly organized and complex experiments that test new therapies in volunteers”

“New therapies” may be:

- **New drugs (or drug combinations)**
- **Surgical or radiological techniques**
- **Diagnostic techniques, *e.g.*, genetic testing**
- **Preventive methods, *e.g.* anti-estrogens / breast cancer**

**“Nearly *one in three* clinical trials fail to enroll a single patient”.
About *half* “fail to attract enough participants to finish the job, even when they are conducted at dozens of centers”.**

(Beer and Axmaker)

Greater participation in clinical trials would speed the development of new cancer treatments.

Clinical Trial Phases (for new drugs)

Phase I: Safety Testing

Designed mainly to test the safety of a new drug at various doses

Why would someone *volunteer* for a Phase I study?

- Access to the newest drugs
- Potential for a treatment breakthrough

Why would someone *avoid* a Phase I study?

- Risk of unknown/ unanticipated side effects
- Low chance of success

Clinical Trial Phases

Phase II: Efficacy Testing – does the drug work?

Phase II trials are the “workhorses” of cancer-treatment research.

Ethically appropriate when no effective alternative treatment exists

Small groups (up to hundreds max.) of patients

Often *randomized, e.g.*, between two different drugs or doses
– the “arms” of the study

“*Crossover*” may be incorporated, *e.g.*, switch patient to the higher-dose arm if the lower-dose treatment is ineffective.

Principle of *equipoise*:

A trial begins with the *null hypothesis*: there is no evidence that the new drug will be superior to the existing treatments, *i.e.*, there is “genuine uncertainty” over whether the new treatment will be beneficial.

As the trial progresses, the findings *may* provide evidence of efficacy.

Once a certain threshold of evidence is passed, there may *no longer* be genuine uncertainty about the most beneficial treatment; at this point, there is an ethical imperative for the investigator to *provide the superior intervention to all participants*.

- Wikipedia: “Clinical equipoise”

It seems “obvious” that if the new drug proves to be effective, the trial should be stopped early, and the new drug should be made available to all of the participants.

But

There is a danger of a “quit while you are ahead” (“lucky winning streak”) effect, especially in trials with small numbers of patients (often the case, for GIST-specific trials).

Clinical Trial Phases

Phase III: Comparison with standard care

Larger numbers of patients

**Direct comparison of the new treatment to the
“standard of care”**

Up to thousands of patients

***Many treatments that appeared successful at Phases I
and II subsequently failed at Phase III.***

Questions to ask, before entering a trial

- **What are the possible benefits?**
- **What are the possible risks?**
- **What will happen to me during the trial?**
- **How long will the trial last?**
- **Who will pay for the costs - drugs, exams, travel ...?**

Randomized clinical trials (RCTs) vs Real-world evidence (RWE)

Real-world evidence: based on analysis of data collected from claims, billing data, product and disease registries, and *patient-generated data*.

“21st-Century Cures Act” 2016: required FDA to develop guidance on the use of RWE in studies of outcomes for post-approval studies.

The COVID-19 vaccine trials illustrate the impact of the difference between RCT and RWE: for example, the virus was mutating and evolving between the RCT and the RWE, so it is not surprising that the efficacy numbers were different.

Randomized clinical trials (RCTs) vs Real-world evidence (RWE)

	RCT	RWE
<i>Number of patients</i>	Smaller	Larger
<i>Eligibility criteria</i>	Rigid	Relaxed
<i>Treatment setting</i>	Academic centres	Community clinics
<i>Compliance</i>	Monitored	?
<i>Follow-up</i>	Extensive	Limited

Compared with RCTs, RWE “better reflects the *actual clinical environments* in which medical interventions are used, including *patient demographics, co-morbidities, adherence, and concurrent treatments.*”

Bartlett *et al.*, Feasibility of using real-world data to replicate clinical trial evidence, *JAMA Network Open* 2019

Risks of RWE: biases and errors in monitoring and reporting outcomes