

Harmonizing Research and Treatment Goals: *Patient perspectives* on clinical trials design

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The views expressed are the results of independent work and do not necessarily represent the views of organizations to which the author is associated, or all patients with cancer.

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What our group wants to do is explore ways to increase participation in clinical trials so that progress can be made against the disease.

One way to do this, we think, is to find ways to harmonize research and treatment goals.

We recognize, however, that clinical studies must be designed in ways that produce clear and reliable information, so that we can have confidence in the treatments we receive.

Bibliography:

1. "When Science offers Salvation" - Rebecca Dresser
2. CancerConsultants.com™ - Internet Interest in trials.
3. Understanding Cancer Patients' Needs, Concerns is Key to Improving Clinical Trial Participation. - UC Davis Cancer Center study
4. Informed consent in cancer clinical trials. – ASCO 2002, Debora A Paterniti, Primo N Lara Jr., Ben A Rich, Ted Wun,
5. University of California, Davis Cancer Center, Sacramento, CA.
6. Public Attitudes Toward Participation in Cancer Clinical Trials
Robert L. Comis, Jon D. Miller, Carolyn R. Aldigé, Linda Krebs, Ellen Stoval - jco.org Journal of Clinical Oncology, Vol 21, Issue 5 (March), 2003
7. Cancer therapy and the randomized clinical trial: good medicine? - Kaufman D.
8. Each Subsequent Therapy Results in Diminishing Response Rate and Duration of Response in Low Grade or Transformed Low Grade Non-Hodgkin's Lymphoma. - ASCO 2001 Abstract 1165
9. Horning S, Rosenberg S: The natural history of initially untreated low-grade non-Hodgkins lymphomas. N Engl J Med. 1984;311:1475-1484

Our Goals

- What our group wants to do:
 - Increase participation in clinical trials to make progress against the disease.
 - Harmonize research and treatment goals.

We recognize the need for good study design, however. – That the FDA role is vital:

- We must have confidence in the treatments we will receive.

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THIS SLIDE WAS NOT USED. DISCUSSED WHILE VIEWING PREVIOUS SLIDE.

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Harmonizing Research & Treatment Goals – *Patient Perspectives*

- Patient Input on Trial Design
- Background on Trial Participation
- What Makes a Study Desirable?
- Recommendations from the Front Lines

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Here's what will cover:

We'll make the case for routinely involving patient consultants in the design phase of clinical trials.

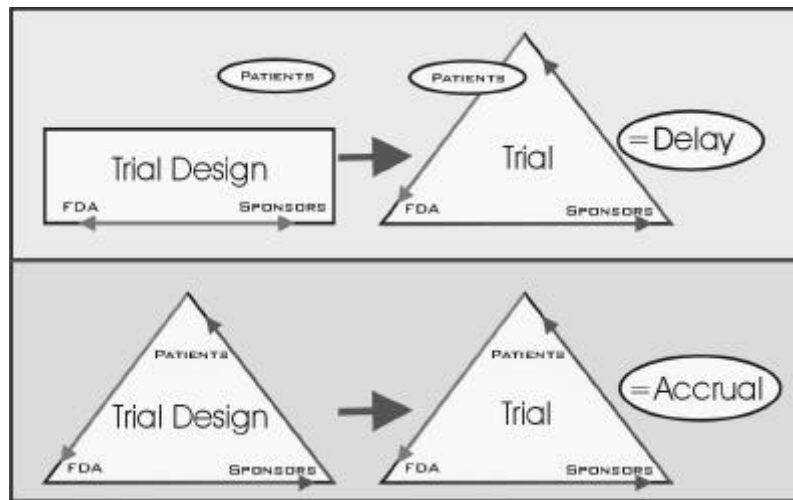
We'll provide some data about trial participation – who participates and why.

We'll examine what patients are looking for in clinical trials, and what they'll tend to avoid.

And we'll provide some general recommendations from the patient community.

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Patient Input on Trial Design ...



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Here's an illustration that shows the logic of getting patients involved earlier.

We think it is bound to result in fewer surprises and faster accrual.

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Patient Input on Trial Design

How to Locate Qualified Patient Consultants?

- Non-profits
- Locate individuals who:
 - Understand the disease
 - Have the disease
 - Understand purpose & requirements of studies
- Confidentiality agreements

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Probably the best way to locate qualified patient consultants is to contact one of the many non-profit organizations.

They will be able to refer you to willing individuals who have the disease, and also have a background in science.

To safeguard intellectual property, you can require that consultants sign confidentiality agreements.

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We need each other

- **Importance of timely participation** – delays are costly to sponsors and to patients.



If patients fail to sign on in adequate numbers ...
... the **assessment of the therapy** will not be made
no matter how well the study is designed from the
point of view of regulators and scientists.

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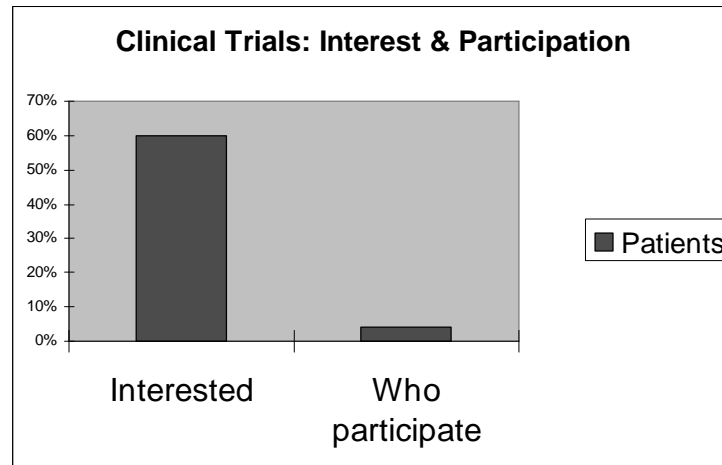
I think it's evident that we need each other, and that we need to communicate better.

Delays in trial enrollment are costly to sponsors, and costly to patients.

Indeed, the urgency of our situation requires that the evaluation system becomes as efficient as it can be.

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Patients Motivated, but Hesitant



* **CancerConsultants.com™ - Internet Interest in trials.**

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On this slide we have the results of a survey conducted by
CancerConsultants.com

It found that 60% of patients are actively seeking access to clinical trials, ...

...but that less than 5% participate.

This shows that the primary problem with accrual is not the attitudes of
patients.

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Patients Hopeful About Cancer Vaccines

The good news:

- Informed patients have favorable expectations about the potential of cancer vaccines.
 - Active immunity considered the Holy Grail.
- But the selection of pretreatments (if any) are also important to patients.

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We believe that informed patients have favorable expectations about the potential of cancer vaccines.

And this expectation should translate to faster enrollment for studies of this type.

However, the pretreatments (if any) are key to how desirable a protocol will be.

More on this later.

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How to Increase Patient Interest

Ensure that the boarder patient community learns about:

- the **true risks** of the disease,
- **limitations** of standard treatments. ¹
- The **potential advantages** of emerging therapies.



1. Each Subsequent Therapy Results in Diminishing Response Rate and Duration of Response in Low Grade or Transformed Low Grade Non-Hodgkin's Lymphoma. - [ASCO 2001 Abstract 1165](#)

Denial is a natural tenancy that's common among cancer patients, and it works against trial participation.

To further increase patient interest in clinical trials the the boarder community must also becomes better informed about:

the true risks of the disease,
the limitations of standard treatments.
and, the potential advantages of emerging therapies, such as cancer vaccines.

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Steps: Information Exchanges

- Encourage “trial talk:”



– Patients to routinely, consult physicians & outside experts

– Physicians to routinely discuss trials with patients

- Provide physicians with:

- Literature on investigational agents
- Clinical trials for various settings.

- Use ClinicalTrials.gov

- See www.lymphomation.org for lymphoma-specific queries of this database.



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We need to make the discussion of clinical trials (trial talk) routine when patients talk to their doctors, or to outside experts.

And we need to provide treating physicians with up-to-date information about investigational agents and trials that are recruiting patients.

Today, patients and physicians can use Clinicaltrials.gov to find clinical trials.

And from our website, patients and doctors can easily locate lymphoma-specific studies in this database by clicking on pre-built queries.

DISCUSSION POINTS:

Here we received suggestions from the audience at the end of our talk:

- Encourage sponsors to distribute summary information about trials organized by disease type and setting (frontline, refractory) to treating physicians.

- Contact CRO – Clinical Research Organizations – that often design studies for sponsors.

See http://www.acrpnnet.org/index_fl.html

Competition for Patients

Factors:

- Increasing number of clinical trials testing new therapies.
- Need to recruit mainly untreated patients?
- The need to enroll large numbers of patients to prove benefit in some settings.

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As competition for patients increases – and there are many factors contributing to this – the need to make trials attractive to patients also increases.

For cancer vaccines there could be a need to recruit patients who are not in need of immediate treatment. This group will be more cautious and selective.

For indolent cancers, there could be a need to enroll larger numbers of patients in order to get significant outcome data.

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Emerging Tests That May Increase Patient Confidence/Incentives

- Increasing confidence:
 - DNA typing and biomarkers that may predict:
 - Response to the investigational agent or the pretreatment.
- Increasing incentives:
 - Tests that may help predict:
 - The clinical course of the patient's disease, or
 - Likely response to standard treatments.

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Emerging tests, such as DNA typing, and the identification of biomarkers, can help to increase patient confidence in trials.

And increase incentives as shown here. [PAUSE TO READ]

We believe that sponsors that use these tests could have a significant advantage when recruiting patients.

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Features of Desirable Studies

- When the investigational protocol offers the possibility of:
 - Cure, especially when standard therapies do not
 - Increase duration of response, especially without adding toxicity
 - Keeping the cancer at bay, with minimal toxicity
 - Improving quality of life
- And protocols that:
 - Administer the least toxic agents first.
 - Are not likely to burn treatment bridges . . .



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These are the characteristics that patients are looking for in trials.

The potential to cure is number one, of course, especially when standard therapies do not.

As you can see, patients are keen to try new therapies that appear safer than standard therapies.

And, they don't want to limit future treatment options, and will avoid studies that appear to do so.

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Other Barriers to Patient Accrual

Not understanding patient needs, concerns:

- Lack of resources
- Health insurance restrictions
- Confusion about research and medical care, and study procedures
- Excessive or undesirable tests:
 - Bone marrow biopsies
 - Exposure to excessive amount of radiation
- Disqualifications

(1) Understanding Cancer Patients' Needs, Concerns is Key to Improving Clinical Trial Participation. - UC Davis Cancer Center study

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Here we list some well-known barriers to patient enrollment in clinical trials.

Limited patient resources – that can make travel to a study site impossible. Health insurance restrictions, or the belief that these restrictions are present.

Confusion about research and medical care, and study procedures

Patient confusion about the goals of research.

Excessive or undesirable tests, such as multiple bone marrow biopsies.

And patient anticipating they are likely to be disqualified by one entry criteria or another.

DISCUSSION POINTS:

- Timing
- Multiple CT scans

Watch & Wait: A Lost Opportunity

- Patients in “watch & wait” provide an opportunity for testing new agents.
 - Better immune competence
 - Less tumor burden
 - No prior exposure to toxic treatments
 - Potential to improve quality of life
 - Potential to learn without precluding standard treatment options
- Patients are keen to try frontline immune-based therapies, and avoid chemotherapy

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Here we list some of the advantages for frontline low toxic therapeutics, like cancer vaccines that do not require chemotherapy.

[PAUSE TO ALLOW READING]

From our perspective the ideal time to get creative is early when a response to treatment is not required and when we are more likely to benefit from the approach.

Importantly, patients will be highly motivated to participate in this type of study.

As an example, a pilot frontline vaccine study at Stanford completed enrollment in 2 weeks.

DISCUSSION POINTS:

- A speaker referred to this point, favorably, in his talk the following day.

Flexible Protocol Design?

Patient Questions

- Can protocols adapt to patient differences?
 - Immune competence and characteristics
 - Clinically unique disease & response to treatment
- Can alternative methods be tried when the first way does not achieve an immune response?
 - Different number or timing of injections?
 - Intratumoral administration?
 - Alternative adjuvants?
- Booster vaccines?

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Perhaps this is a dream we have, but here goes.

These are questions for investigators:

- Can study protocols be made more flexible?
- Can they adapt to patient differences?
- Can alternative methods be tried when the first way fails to induce an immune response?

DISCUSSION POINTS:

- We have concerns that these proposals might contribute to the difficulty of regulatory assessments.
- Larger studies may offset confounding variables.

Protocol Design: the Placebo

**“It’s a great experiment, but ...”
– patient comments**

Concerns:

- Biopsy to “blind” a placebo?
- Does placebo cause carrier suppression?
- Crossover allowed on relapse?

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Patients have technical and ethical concerns about placebo vaccines.

Is the resection of a lymph node an ethical way to blind a study?

Can exposing patients to the adjuvants (conjugates) in a placebo vaccine preclude them from benefiting from the cancer vaccine in the future.

Can the pretreatments do the same?

Can crossover provisions be used to relieve these concerns?

From our perspective, placebo vaccines are bound to slow accrual and delay assessments.

Proving Survival Benefit for Indolent Cancers?

- Difficult to prove for indolent cancers.
- FDA on drugs with favorable toxicity profiles:
 - “47% of regular oncology drug approvals had response rate or time to tumor progression as the primary or co-primary end point in trials supporting approval.” ...
 - ... given the favorable toxicity profiles associated with hormonal drugs compared to conventional cytotoxic agents, RR and TTP are considered adequate surrogates for a better life.”

See Endpoints and US FDA Approval of Oncology Drugs, April 2003

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For patients with indolent cancers, survival is not an ideal endpoint for proving benefit.

Assessments will be confounded by patient access to numerous treatments, including investigational treatments on relapse.

The good news is that the FDA seems to agree that drugs having a favorable toxicity profile may win approval by other means.

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FDA Accelerated Approval

FDA Risk/Benefit Assessments

- Cancer vaccines & Accelerated Approval?
- Answer need for effective therapies that do not:
 - Preclude use of standard treatments
 - Impair immunity or general health
 - Undermine QOL

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We believe that cancer vaccines are good candidates for accelerated approval path based on what they potentially do not do:

- Preclude the use of subsequent standard treatments.
- Impair immunity, or general health
- Undermine quality of life.

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Challenges for Competitors Pool Resources and Data to:

Can competitors share data and resources to advance the science?

- Better identify and validate surrogate endpoints?
- Conduct DNA typing?
- Correlate DNA types or immune parameters that may predict response to treatments?

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Patients worry that each individual study will be too small to validate important biomarkers – and that only by pooling the data can we hope to advance the science. So we ask, can this be done?

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DISCUSSION POINTS:

- Not easy to merge data from different sources
- Differences in protocols may not lead to information that's not credible to the FDA.

Summary

- Include patient consultants early in trial design
- Harmonize research and treatment goals to increase patient participation.
 - Keep patient goals/needs in mind
 - Avoid burning treatment bridges

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Now a brief review:

We think it's important to routinely consult patients when designing protocols
You can contact non-profits to identify qualified consultants.

Consider designing study protocols that are in harmony with patient goals:
Is the protocol:

a reasonable treatment choice?
as flexible as it can be?

Does it avoid burning treatment bridges?

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Summary

- **Investigators:** Consider testing novel frontline immune-based therapies for patients in watch & wait status.
- **Sponsors:** Create innovative trial designs and offer them to the FDA. Try to pool data to advance the science –
- **FDA:** Allow for flexible protocols; factor in the favorable properties of immune-based therapies in assessments.

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We urge investigators to fully consider ways to overcome the Catch 22 for indolent cancers, and design protocols that test treating early without chemotherapy when appropriate to the disease.

We urge sponsors to create innovative trial designs and offer them to the FDA.

We urge sponsors to pool data and share technologies when possible to advance the science – to compete with lead products, but cooperate where and when you can.

We will continue to urge the FDA to allow for flexible protocols, and factor in the favorable properties of immune-based therapies in assessments of benefits and risks.

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Summary

- Competition for patients
- Need for develop desirable protocols:
 - Rethink proving **survival benefit** for indolent cancers
 - Fully consider the **caveats of placebo** vaccines
- Identify and overcome common barriers to accrual.

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There are many pragmatic considerations in trial design.

Patients must enroll for the answers to be found, and competition for patients is increasing.

Therefore, there's a need to make clinical trial protocols as attractive to patients as you can.

Consult patients to help.

* Rethink proving survival benefit for some cancers.

* Avoid, when possible, protocols that burn treatment bridges.

Fully consider the caveats of placebos to the patient and the study.

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And identify and try to overcome the common barriers to enrollment:

Such as

Lack of patient resources,

Health insurance restrictions,

Misunderstandings of the illness and its severity,

Excessive or undesirable tests

Think like a patient.



Consult patients!

The end.

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Thank you for listening. It's appreciated.

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