

# QUESTIONS THAT CAN BE ANSWERED ONLY BY CLINICAL TRIALS

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## **A. Is this study drug effective when standard treatments are not?**

Because cancer cells can develop resistance (become refractory) to standard treatment, there's an urgent need to answer this question by testing new agents that target cancer cells in new ways.

Patients with refractory cancer urgently need such studies to be completed, and may also benefit early by participating in dose-finding (phase I and II) safety studies.

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## **B. Which therapy is best as first therapy?**

For patients there might be no more important clinical question to answer, because our first therapy is generally considered the best opportunity to cure or improve our survival.

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## **C. Which therapy is best to get a durable remission at relapse?**

Unfortunately, because relapse following initial therapy is still common, there's an urgent need to develop and test therapies that can lead to long-lasting remissions in this circumstance.

*As with Question C, patient participation in trials is required to answer this critical question.*

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## **D. Can this new treatment cure a cancer that is not yet cured with standard treatments?**

Patients will of course identify with this research objective, but we must also inquire about the potential increased risks that may emerge from any new approach, and how we will be monitored for safety.

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## **E. Can this new treatment manage my condition better than observation?**

With the emergence of targeted therapies there's an increased potential to manage indolent cancers by treating as needed, perhaps regularly with less toxic protocols.

However, if the net effects of the intervention are modest, studies may require a control group and random selection to objectively measure and compare benefits and risks. Here's an exception in oncology where a placebo control *might* be required.

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## **F. Does adding a study drug to an effective treatment improve the results acceptable added risk?**

*This question applies to study questions B, C, D, and E.*

Note: Clinical trials closely monitor participants for side effects. Doses can be held or modified as needed

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## **G. Can we remove a drug from a curative therapy to decrease toxicity without decreasing its efficacy?**

Treatment for cancers can have significant side effects. Patients of course do not want to receive more therapy than we need to achieve the treatment goal. However, reducing the toxicity of a protocol could decrease the cure rate. A possible solution to this dilemma is to remove some parts of the therapy based on response indications (so called response-adapted therapy), such as with PET imaging.

We see this important question asked for the treatment of Hodgkin's lymphoma, which has a very high cure rate: Can we eliminate radiation therapy to improve the safety without reducing the cure rate?

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## **H. Can use of a lower toxic therapy delay the need for more toxic therapy?**

This question applies mainly to the indolent (slow growing) cancers, which can be observed until therapy is needed. *See also Question E.*

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## **I. Who will benefit from a treatment, and who will suffer only the side effects?**

Arguably, for some types of cancers, we do not need another active drug nearly as much as tests that predict who will benefit from which drug.

This important so-called correlative research will require patients to enroll in studies and also to

contribute blood and tissue samples that can be analyzed in order to find factors in the samples that may be strongly associated with response and safety.

### INFORMED CONSENT:

**The study protocol must also be a good fit as a treatment decision – having the potential to be as good or better than the standard of care for your clinical circumstance.**

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## Evidence 101

**Clinical benefit** is defined as a measurable improvement in quality of life or survival resulting from therapy for a life-threatening medical condition. In clinical studies, benefit is measured by comparing survival (or an endpoint thought to reasonably predict it) compared to the natural course of the disease or the disease treated differently.

**IMPORTANT NOTE:** Reproducing a study result is the key to providing *confidence* that the study finding reliably predict real-world outcomes.

### What is measured in clinical trials?

- A. Response rate and duration, versus,
- B. Toxicities and risks secondary to toxicity, and
- C. Living longer (Overall survival)

Survival is the most reliable measure (endpoint) of "clinical benefit," because it accounts for known and unknown treatment effects – positive and negative. However, for indolent

cancers where survival is long, opportunities to try other treatments will confuse assessment.

In such cases, progression free survival (**PFS**) is a commonly used measure of benefit; however, its significance depends on how long the remission lasts (years or months?) and possible offsetting toxicities.

Note: Clinical benefit is a net effect, considering also side effects. An **active drug** leading to responses is not necessarily an **effective drug**.

**The Gold standard for study design** is the randomized, controlled clinical trial of adequate size, which has pre-specified aims and methods.

Such design minimizes bias that can lead to unreliable comparisons about risks and benefits, such as patient selection bias: excluding patients with higher-risk disease.

**To run randomized studies there is genuine uncertainty** about which treatment arm is better.

**A randomized controlled study is not required** in earlier phase studies, and also in pivotal trials when the refractory status of the patients is well documented.

### Why not use historical controls?

Comparing study outcomes with past results can be unreliable, because each study can have different ways of selecting patients (such as lower-risk disease, or age), different protocol administrations, and ways of measuring outcomes. However, such comparisons may be adequate if the participants' risk factors are well accounted for, the study is large

enough, and the magnitude of the benefit (net effects) are compelling relative to historical results in similar trials.

### Why is observation in usual care unreliable?

Individual outcomes can be misleading and can't predict outcomes for others.

*"For centuries doctors used leeches and lancets to relieve patients of their blood. ... Everyone knew of a friend or relative who had been at death's door until bloodletting "cured" him. Doctors could recount thousands of successful cases."*

Why We Need Science: "I saw it with my own eyes" Is Not Enough <http://bit.ly/aDMeWi>

### Common misconception about trials:

Placebo controls (a sugar pill) are uncommonly used in oncology trials – they may be added to the standard therapy or when observation (there is no need to treat) is acceptable for the type of cancer studied.

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## Clinical Trials Serve the Interests of Patients

- **LEADS TO THE APPROVAL OF NEW EFFECTIVE DRUGS.**
- **IDENTIFIES BETTER USES OF APPROVED DRUGS**, guiding treatment decisions and advancing the standard of care.

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