CLINICAL QUESTIONS THAT CAN BE ANSWERED ONLY BY CLINICAL TRIALS

A. Is this new drug effective when other agents are not?

Here a randomized study is not needed if the refractory status of the disease is well documented (the participant is not responding to available therapies). Studies in this population is the fastest path to marketing approval of new drugs – the so called **accelerated approval** path.

B. Is protocol A better than B as first therapy?

This question is vital to advancing the standard of care and making evidence-based treatment decisions.

However, randomized comparative studies can take a long time to accrue participants and for the data to mature.

Notably, first treatment could be the best opportunity to cure lymphomas or induce the most durable remissions, which can suggest a survival benefit (clinical benefit).

C. Is protocol A better than B at relapse?

A reliable answer to this question also requires large comparative randomized studies.

D. Is this protocol curative, and if so does the curative potential outweigh the risks?

The data to answer this question can take a long time to mature – perhaps 8 years or more for indolent lymphomas.

Limits of historical controls: It can be unreliable to compare the results of one trial to another because each can have very different methods of selecting patients (with higher or lower risk), different protocol administrations, and ways of measuring outcomes. Such comparisons may be sufficient, however, if the participants' risk factors are well accounted for, the study is large, and the magnitudes of the measured improvements are compelling.

KEY CONCEPT: **reproducibility** is the cornerstone of confidence that outcomes from any study can reliably predict outcomes in others.

E. Does this protocol manage the condition better than observation? Does it improve survival or quality of life?

With the emergence of targeted therapies we have an increased potential to manage indolent lymphoma by treating as needed, perhaps regularly with less toxic protocols.

However, if the net effects are modest and need to be given more often, definitive studies will require a control group and random selection to objectively measure and compare benefits and risks.

F. Does adding a new agent (concurrently or sequentially) to an effective protocol improve outcomes without substantially increasing risks?

This question could apply to study questions B, C, D, and E.

Historic example: Does adding Rituxan to CVP improve outcomes in follicular lymphoma, compared to CVP alone?

G. Can we remove an agent from a curative protocol to decrease toxicity without compromising its efficacy?

We see this important question being asked in Hodgkin lymphoma for radiation, which has a very high cure rate.

H. Can use of a lower toxic protocol delay the need for cytotoxic therapy without burning bridges?

(Similar to Question E) We see this question being studied for Rituxan as first therapy for indolent lymphoma.

I. Who will benefit from a treatment, and who will suffer unproductive side effects - should we do something else?

Arguably, for lymphomas, we do not need another active drug nearly as much as tests (biomarkers) that predict who will benefit from a drug. This important type research will require standardized capture, storage and analysis of biospecimens.

Evidence 101

What is measured to determine if an intervention provides meaningful clinical benefit?

A. Response rate?
B. Duration of response?
C. Toxicities and risks secondary to toxicity, such as infection?
D. Impact on subsequent therapies?
E. Survival benefit?

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

Clinical benefit is defined as an improvement in quality of life or survival – or a surrogate endpoint thought to reasonably predict improved survival relative to the natural course of the disease or the disease treated differently.

Note: Survival is not always a practical endpoint for studies of indolent lymphomas because of the long survival and opportunities we have to try other treatments, which confound assessment of any one intervention. In such cases, progression free survival (PFS) is a commonly used surrogate endpoint; however, it significance depends on the magnitude (years or months?) and potentially offsetting toxicities.

In our view, Quality of Life should be compared in any study using PFS as a primary study endpoint.

GOLD STANDARD for Reliable Study Design:

Prospective design – a study having pre-specified aims, methods, and numbers of participants (a denominator) that assigns participants to the study group by chance (with random selection) to reduce bias, notably selection bias: such as "cherry picking" younger patients with lower-risk disease.

Clinical Trials Serve the Interests of Patients in Two Important Ways

(1) THE APPROVAL OF NEW EFFECTIVE DRUGS.

By law, the sponsor must submit clear and convincing evidence that a new drug provides clinical benefit (survival or a surrogate for survival).

The evidence requires independent data monitoring and commonly a controlled and blinded study administered in multiple centers.

(2) IDENTIFIES BETTER USES OF APPROVED DRUGS, which guide treatment decisions and advances in the standard of care.

Individual outcomes from treatment administered in regular clinical practice cannot advance clinical science in any meaningful way, because these outcomes cannot predict how others (even with the same diagnosis) will do if treated similarly.

Clinical Questions That Can Be Answered Only By Trials

Observation and "Clinical Experience" are not reliable:

"For many centuries doctors used leeches and lancets to relieve patients of their blood. They KNEW bloodletting worked. EVERYBODY said it did. When you had a fever and the doctor bled you, you got better. 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."

COMMON MISCONCEPTIONS

(1) It's not true that a placebo control (a sugar pill) is used in oncology trials.

(2) It's generally not true that participants in randomized studies may receive sub-standard care.