Surrogate Markers as Measures of Efficacy: Limitations & Complexities
Criteria for Study Endpoints

- **Sensitive to Treatment Effects**
  
  Eg: Analgesic in terminally ill
  - Pain Relief, not Survival

- **Clinically Relevant**

  - **Screening Evaluation:** Biological Activity
    - Viral load
    - Immunophenotypic
    - Immunofunctional markers

  - **Definitive Evaluation:** Clinical Efficacy
    - Survival duration
    - Symptomatic events
    - Functional status
Obtaining Definitive Evidence of Clinical Efficacy

Treatment effects on Surrogate Endpoints

- Establish biological activity
- Do not establish clinical efficacy
Disease → Surrogate Endpoint → True Clinical Outcome
Illustration:
Chronic Granulomatous Disease

- CDG → Recurrent Serious Infections
- Gamma-INF ...Increase Bacterial Killing and Superoxide Production?

International CDG Study Group Trial
Gamma-INF:
- 70% Reduction in Recurrent Serious Infections
- Essentially No Effect on Biological Markers
Disease $\rightarrow$ Surrogate Endpoint $\rightarrow$ True Clinical Outcome

Intervention
### Pooled Analysis of Immediate vs. Deferred AZT

<table>
<thead>
<tr>
<th>Year of Follow-up</th>
<th>No. AIDS/Death Events</th>
<th>Hazard Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-</td>
<td>209</td>
<td>0.52 (0.39 - 0.68)</td>
</tr>
<tr>
<td>1-</td>
<td>357</td>
<td>0.94 (0.76 - 1.16)</td>
</tr>
<tr>
<td>2-</td>
<td>440</td>
<td>1.05 (0.87 - 1.27)</td>
</tr>
<tr>
<td>3-</td>
<td>369</td>
<td>1.12 (0.91 - 1.38)</td>
</tr>
<tr>
<td>4-</td>
<td>307</td>
<td>0.98 (0.78 - 1.23)</td>
</tr>
<tr>
<td>5+</td>
<td>226</td>
<td>1.10 (0.84 - 1.43)</td>
</tr>
</tbody>
</table>

*Immediate vs. deferred AZT
Large Randomized Trials with Long-Term Follow-up are Needed

- Short-term trials cannot address long-term risks and benefits

- Small studies cannot reliably assess treatment differences in clinical outcomes
### Clinical Endpoint Trial

<table>
<thead>
<tr>
<th>HIV+ Patients</th>
<th>CD4+ &lt; 300</th>
<th>CD4+ ≥ 300</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART + Immune BasedRx</td>
<td>(750)</td>
<td>(2000)</td>
</tr>
<tr>
<td>ART</td>
<td>(750)</td>
<td>(2000)</td>
</tr>
</tbody>
</table>

5 years follow-up

Outcome: Progression to AIDS/Death
Survival
How does one validate a surrogate endpoint?
Prentice’s Sufficient Condition

1. The surrogate endpoint must be correlated with the clinical outcome

2. The surrogate endpoint must fully capture the net effect of the treatment on the clinical outcome
\( Z = 1 : \text{Control} \quad ; \quad Z = 0 : \text{Treatment} \)

\( S(t) : \text{Surrogate Endpoint at } t \)

\[
\lambda(t \mid Z) = \lambda_0(t) e^{\alpha Z} \tag{1}
\]

\[
\lambda(t \mid Z, S(t)) = \lambda_0(t) e^{\beta Z + \gamma S(t)} \tag{2}
\]

Proportion of treatment effect explained by the surrogate endpoint:

\[
p = 1 - \frac{\beta}{\alpha}
\]
Meta-analyses are required to explore the validity of surrogate endpoints.
Validation of Surrogate Endpoint

Statistical
- Meta-analyses of clinical trials data

Clinical
- Comprehensive understanding of the
  ~ Causal pathways of the disease process
  ~ Intervention’s intended and unintended mechanisms of action
Surrogate Markers -
Another Significant Limitation

Even if, for treatment $Z$, 
$S$ is a valid Surrogate Marker for $T$, 
it may not be for treatment $Z^*$
if $Z$ and $Z^*$ have differing mechanisms of action.

Example

$S$ - CD-4 Levels
$T$ - AIDS / Death
$Z$ - Nucleoside Analog
$Z^*$ - Vaccines for Early R
Use of Surrogate Markers

In Screening Trials...
Primary Endpoints

In Definitive Trials...
Supportive Data on Mechanism of Acti