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

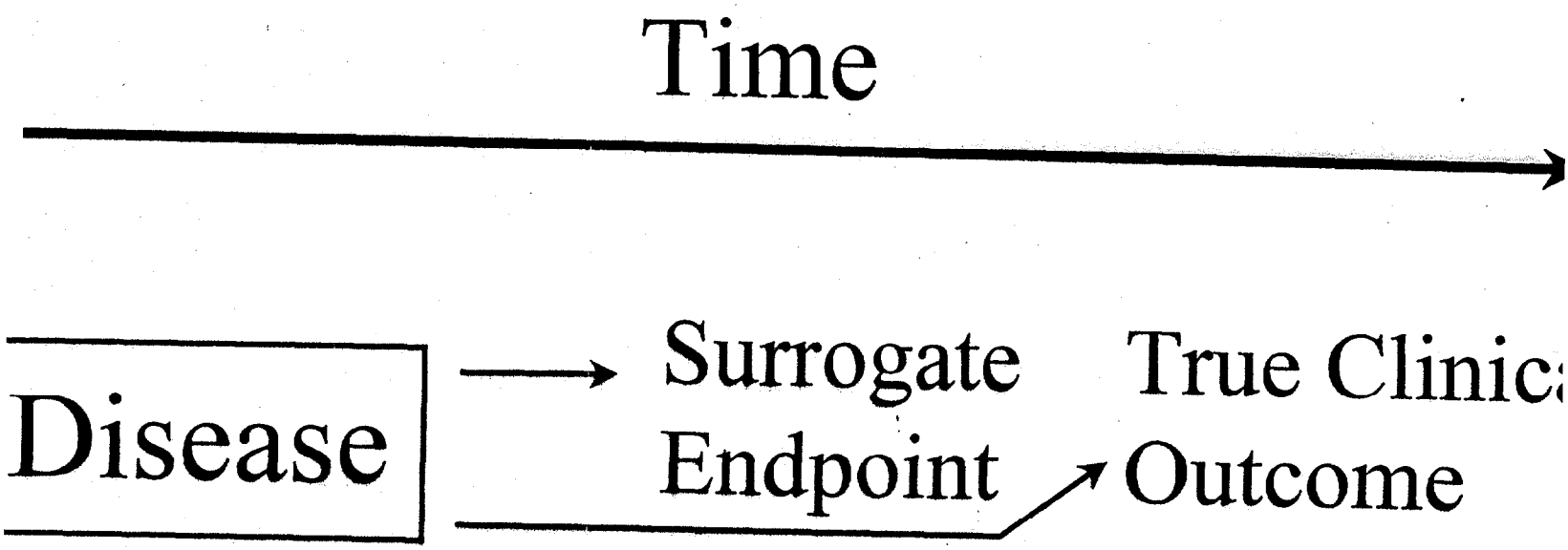
-Definitive Evaluation:
Clinical Efficacy

- 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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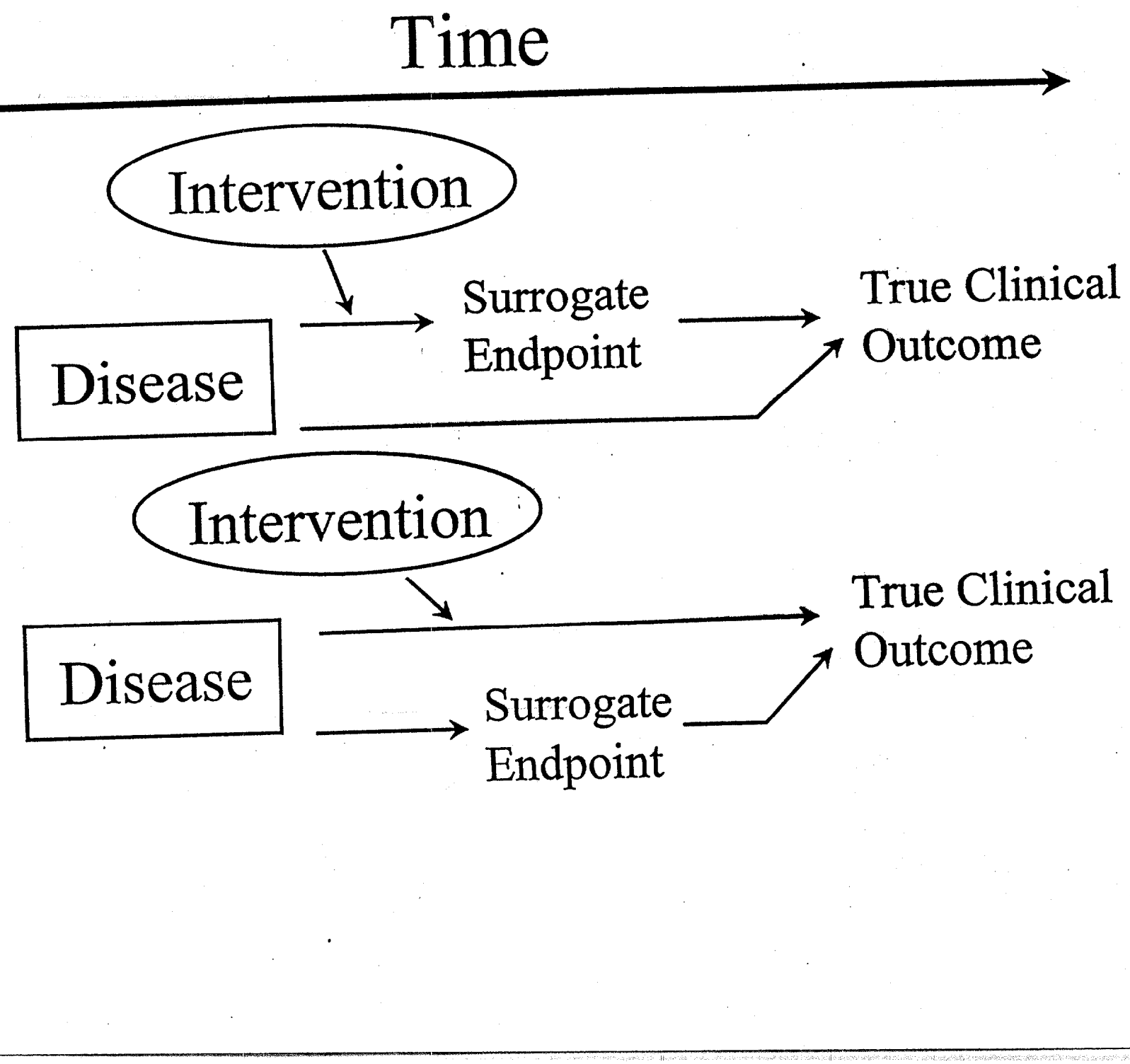
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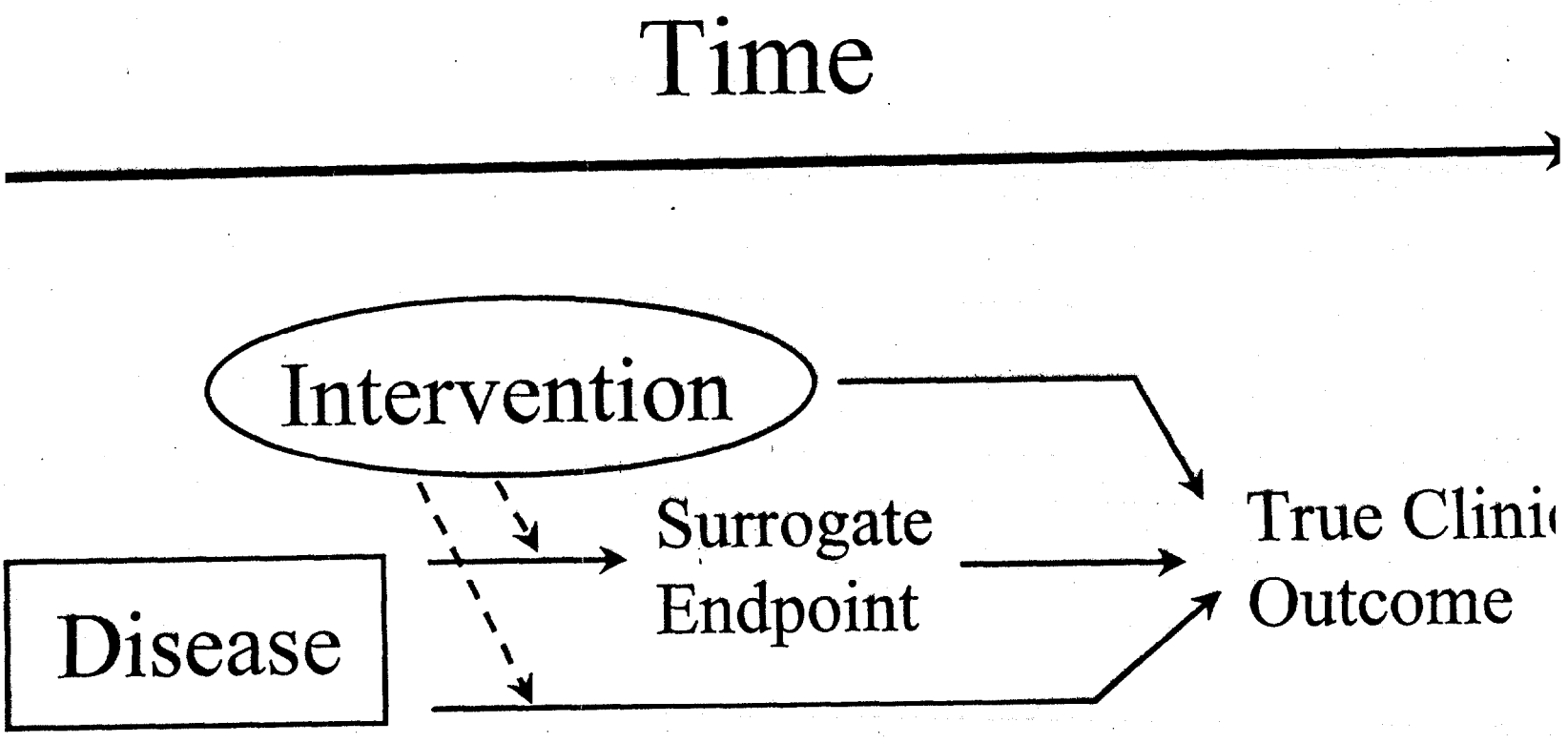
Surrogate Endpoint

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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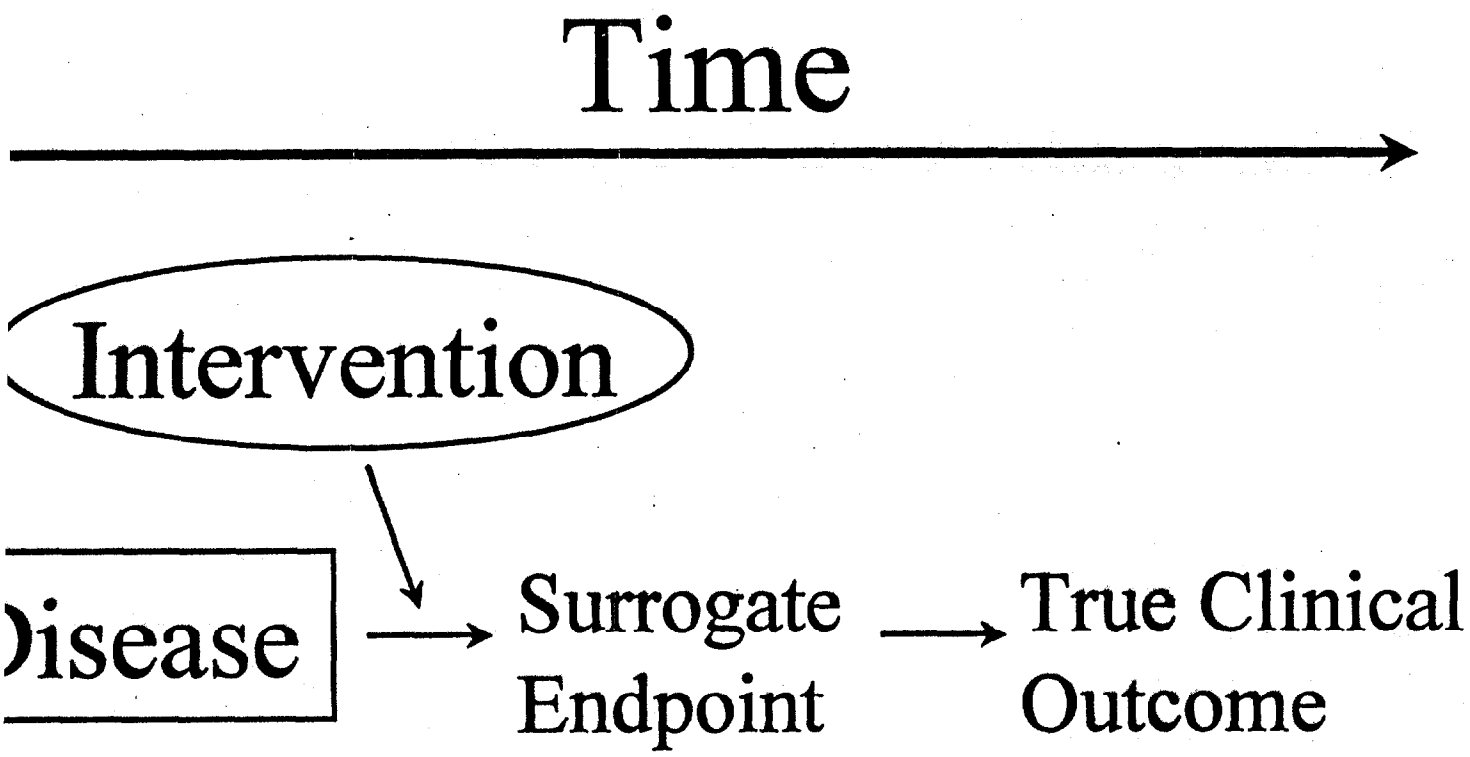
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Pooled Analysis of Immediate vs. Deferred AZT

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

*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

HIV+ Patients	CD4+ < 300	CD4+ ≥ 300
(R) < ART + Immune Based R_x	(750)	(2000)
(R) < ART	(750)	(2000)

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 treatm on the clinical outcon

$Z = 1$: Control ; $Z = 0$: Treatment

$S(t)$: Surrogate Endpoint at t

$$\lambda(t \mid Z) = \lambda_0(t)\, e^{\alpha Z} \qquad (1)$$

$$\lambda(t \mid Z, S(t)) = \lambda_0(t)\, e^{\beta Z + \gamma S(t)} \qquad (2)$$

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 Endpoir

Statistical

- Meta-analyses of clinical trials data

Clinical

- Comprehensive understanding of the
  - ~ Causal pathways of the disease proc
  - ~ Intervention's intended and uninten
    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 actio

Example

S - CD-4 Levels
T - AIDS / Death

Z - Neucleoside Analogu
Z* - Vaccines for Early R

Use of Surrogate Marke

In Screening Trials…

Primary Endpoints

In Definitive Trials…

Supportive Data

on Mechanism of Acti