Efficacy Endpoints

Clinical, Biomarker, and Surrogate

Peripheral Neuropathy Workshop

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The views expressed are those of the author, and do not necessarily represent an official FDA position

Outline

- Endpoints and Effectiveness
- Characteristics of Endpoints
- Surrogate Endpoint
- Risks from Misleading Surrogates
- Sources of Uncertainty

Endpoint of a Clinical Trial

- Selected to suit objective of study
  - Focus is A&WC studies supporting drug approval, labeling
  - Other studies with other objectives
    - Other endpoints may be valuable for those studies
    - No single endpoint optimal for all studies during course of drug development
- Endpoint
  - Specific patient assessment used as study outcome (OA)
  - Evaluated in study, and analyzed, in a specified way
- To demonstrate Effectiveness
  - Reliably interpreted as a treatment benefit
  - Basis for marketing approval and labeling

Effectiveness

- Treatment benefit
  - A favorable *and meaningful* effect on an aspect of a patient's life
- Feels, Functions, or Survives
  - Meaningful to the patient
- Survival a distinct category of outcome
  - Global
    - All forms of feels
    - All forms of functions

Feels and Functions as Effectiveness

- Feels
  - A patient's physical sensation or perceived mental state related to health <u>within typical 'daily' life</u>
  - Pain
  - Severely low mood (depression)
  - Not the fundamental physical sensory abilities
- Functions
  - A patient's ability to perform an activity that is a <u>meaningful part of typical 'daily' life</u>
  - Not isolated physiologic processes (eg liver metabolic function)
  - Not ability to perform actions not part of usual life
- Generally a complex integrated result of multiple basic systems

Intrinsic Characteristics of an Assessment

- Assessments have certain intrinsic characteristics
- Categories describe a characteristic
  - Not a judgment on acceptability
  - Aids selection or development of an assessment
- Utility as an OA influenced by these characteristics
  - Assessments of different categories have different value in different situations
  - Select assessment for OA based on utility in the specific situation under study

- Direct and Indirect meaningfulness interpretation
- "Clinical" or Biomarker

Direct and Indirect Meaningfulness

- What is the relationship to meaningful patient feeling or functioning?
  - OAs intended to inform regarding some specific conceptualized meaningful aspect of patient's life
  - Direct vs Indirect
  - Indirect means the assessment does not measure the exact directly meaningful concept
    - "indirectness" is a graded characteristic
- Relationship of the OA-measurement to the intended meaningful concept is important to understand
  - Support for the conclusion of treatment benefit
  - Usually not important for non-OA use
- Indirect measures often selected over direct measures

Clinical and Biomarker Assessment Types

- "Clinical" assessment is influenced by patient and/or investigator
  - Consciously or subconsciously
  - Motivation, attention, individual's past experience
  - May be Direct or Indirect measures
- Biomarker is an *objective aspect* of the patient
  - Not influenced by patient or investigator
  - Not a specific *test* (device, test kit, method)
  - Not a direct measure of how a patient feels or functions
    - May be intended to support inference of feels or functions (an indirect measure)
    - May instead be intended for other interpretations

Understanding Outcome Assessments

- Identify the intended meaningful concept
- Identify the intermediate concept being measured for Indirect measures
- Caution regarding name of tool
  - Name of tool does not make it 'something'; its characteristics do
  - Some indirect tools are given a name not reflecting what is measured; can create confusion and miscommunication
- Some OAs are a multicomponent mixture
  - Examine individual components as well as whole
  - A few are a clinical-biomarker borderland

Surrogate Endpoint

- Stands in place of an efficacy endpoint
- Usually intended to *predict a subsequent* clinically meaningful outcome
  - Requires assumptions about future clinical course after biomarker measurement with continued drug treatment
  - *A prognostic does not a surrogate make*

(apologies to T Fleming)

- Clinical endpoint usually intended to describe how a patient feels or functions at the time of measurement

Surrogate Endpoint Aspects to Consider

- Multiple issues to examine prior to adopting biomarker as a surrogate

- Disease related
- Biomarker related
- Time related
- Drug related

- Some answers involve statistical analysis of data, some judgment on current state of scientific knowledge

Surrogate Endpoint Potential Hazards

- Failure of surrogate's prediction
  - False presence (or absence) of benefit
  - Misleading amount
- Limited safety experience
  - Dataset often more limited than with clinical endpoint
  - Risks of drug may not be clearly observed (#'s)
  - "Off-target" effects of drug may occur later than biomarker measurement
- Risk of using a drug with unfavorable benefit-risk comparison or abandonment of efficacious drug
- Cause
  - Alternate mechanisms of action
  - Shape of the Biomarker-Clinical relationship

Illustrative Example: Acute MI

- Clinical outcome is mortality
- Intravenous thrombolytic agent is the treatment
- Biomarker is the concept of arterial blood flow
  - How and when is blood flow evaluated?
- Development of reteplase (R-PA)
- RAPID-2 Study
  - Evaluated biomarker
- GUSTO-III Study
  - Evaluated clinical outcome

Acute MI

RAPID 2 - % of patients achieving flow

	TIMI 3 - %		TIMI 2&3 - %	
	60 min	90min	60min	90min
R-PA	**51**	**60**	**82**	**83**
T-PA	37	45	66	73

- R-PA superior to T-PA
  - Irrespective of which amount or when the concept of arterial blood flow is assessed

Acute MI

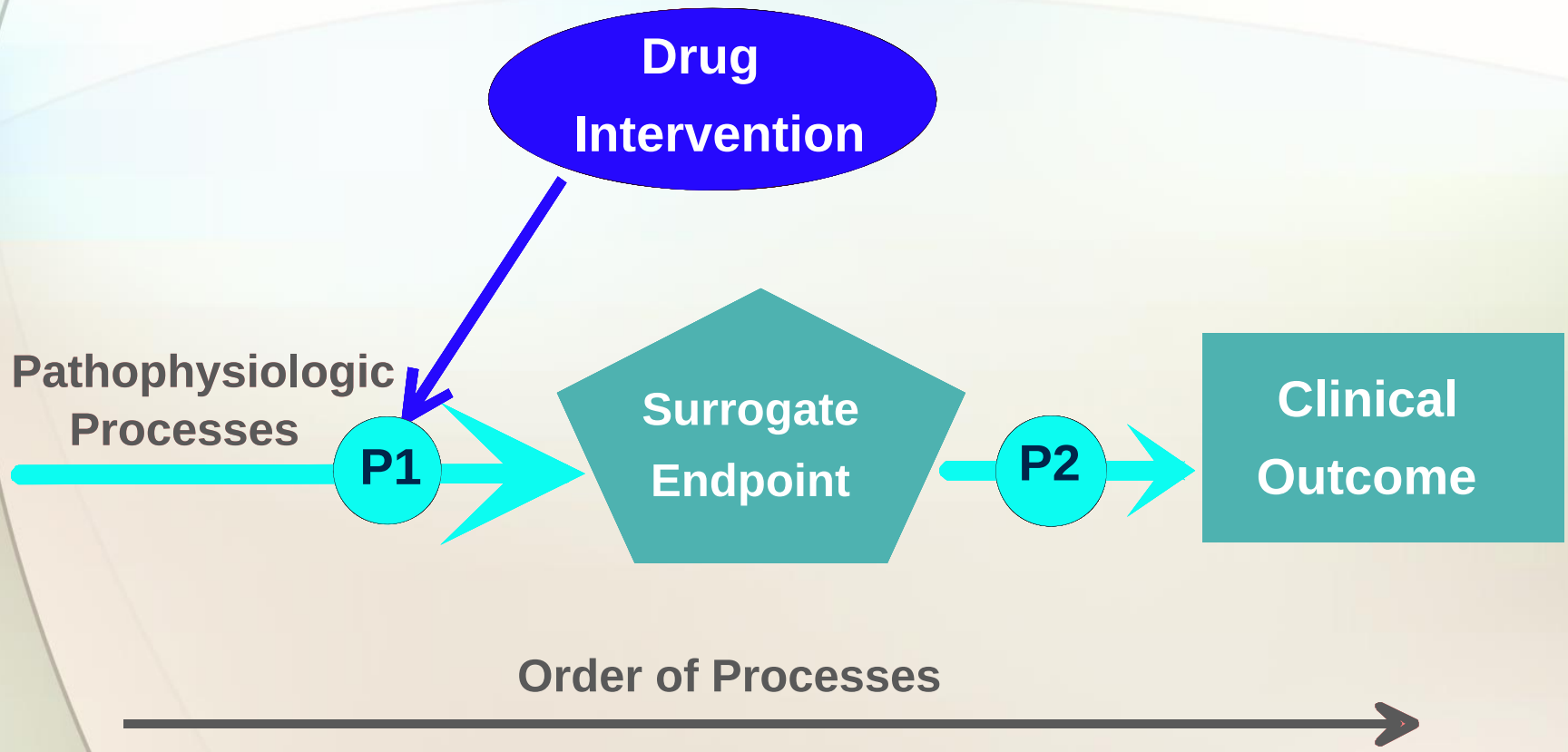
RAPID 2

	TIMI 3 - %		TIMI 2&3 - %		30 min	
	60 min	90min	60min	90min	TIMI3	TIMI2&3
R-PA	**51**	**60**	**82**	**83**	27	**67**
T-PA	37	45	66	73	**39**	**66**

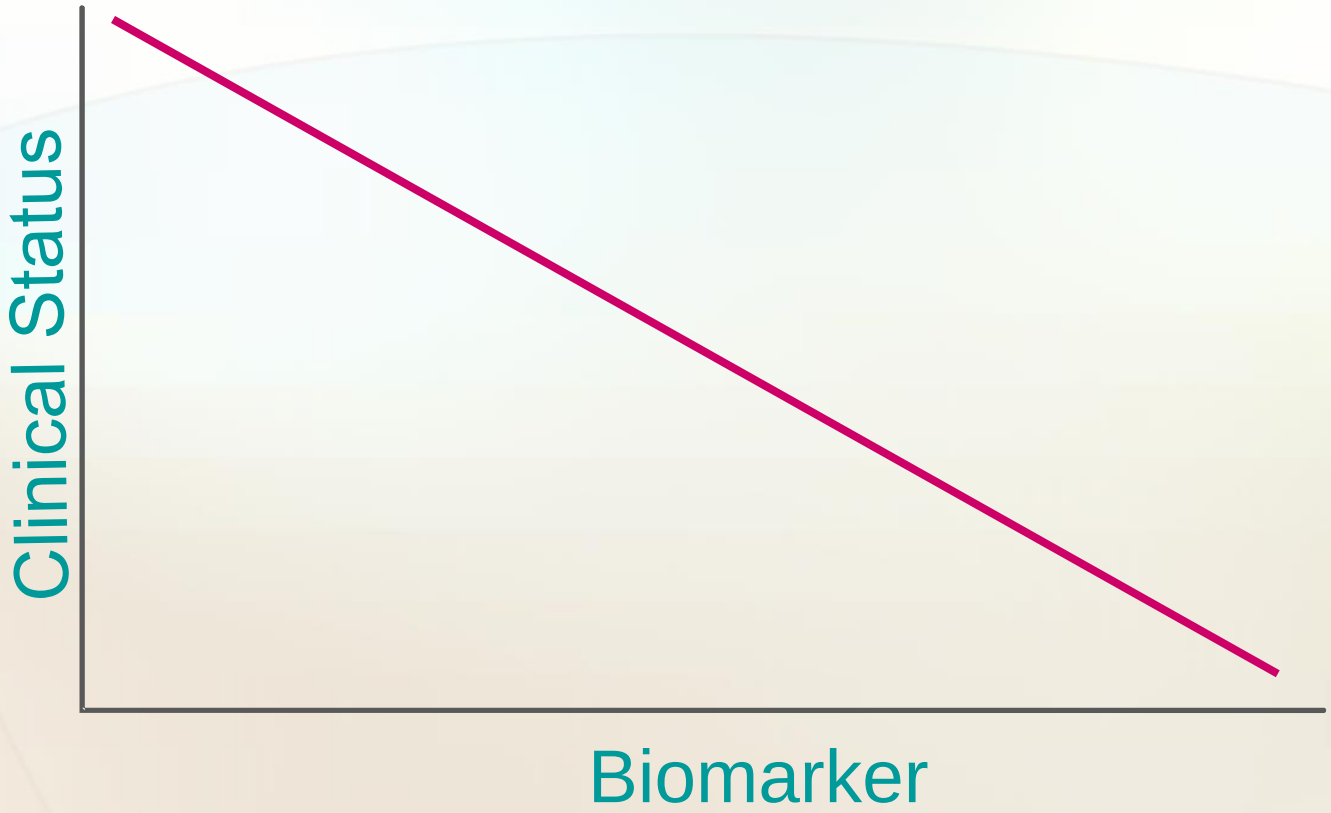
GUSTO-III		
R-PA	7.5	Mortality %
T-PA	**7.2**	

- Concept indicating efficacy is blood flow
  - How and When should it be measured?
  - What is the shape of the relationship?

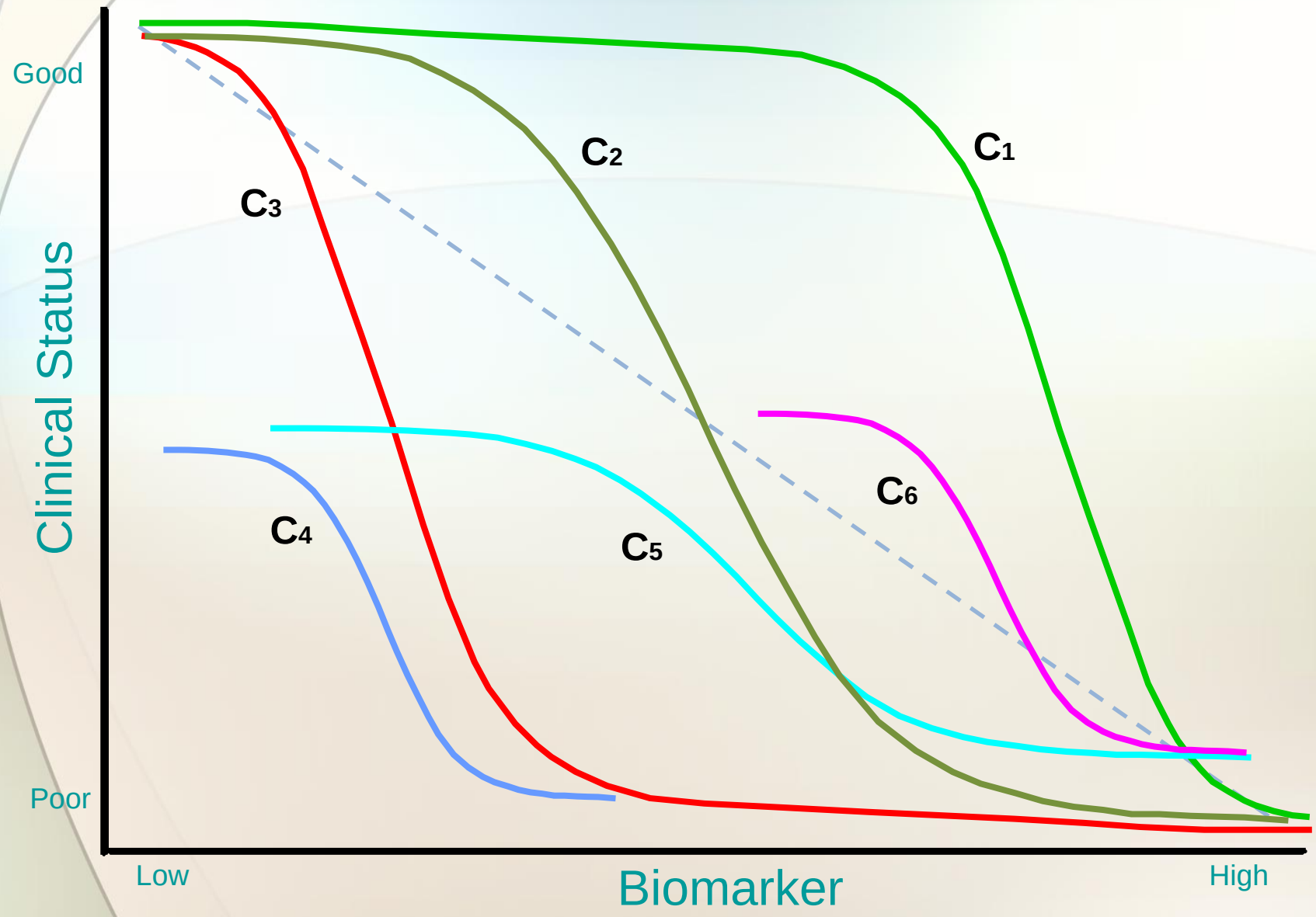
Understanding the Surrogate Measure: Idealized



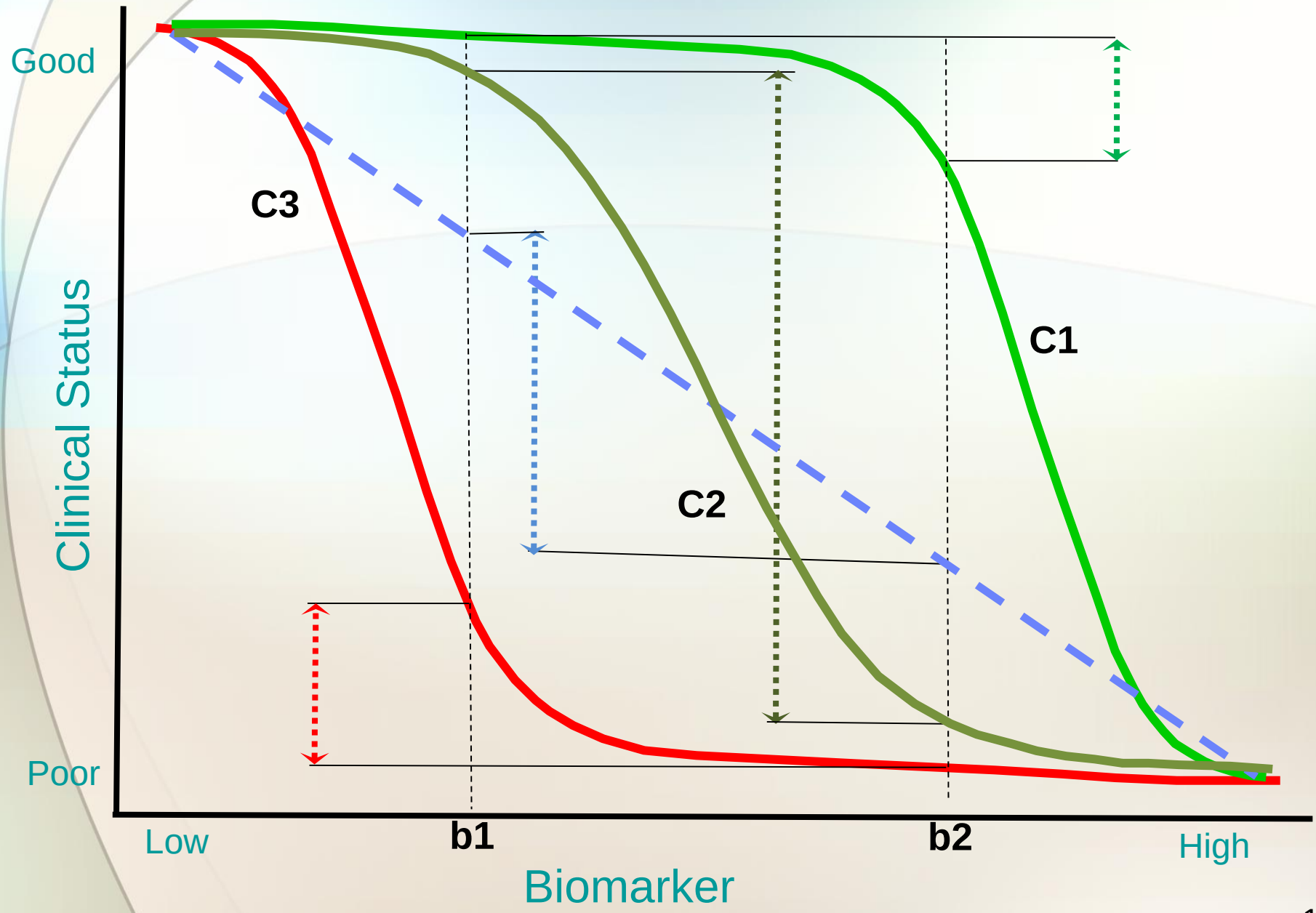
Shape of the Surrogate - Clinical Relationship



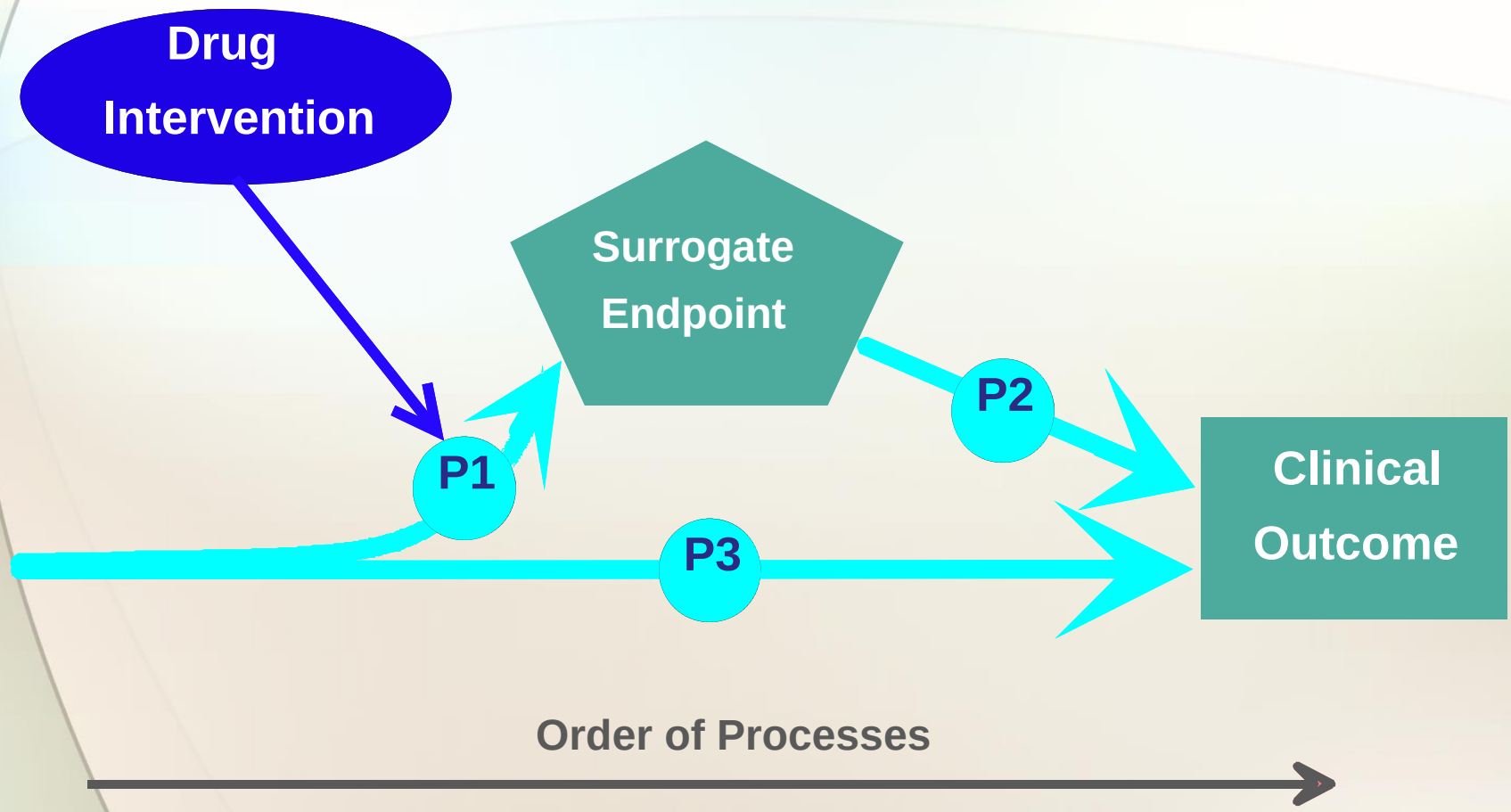
Clinical – Biomarker Relationship



Clinical Effects of Biomarker Change



Understanding the Surrogate: Complexity



Selection of Outcome Assessment

- Relationship to meaningful aspect of feels or functions can be established
  - Assessments useful for diagnosis or prognosis may have little to no relationship of changes in assessment to effectiveness
- Suited to disorder
  - Is, or related to, an important aspect of disorder
- Suited to time-frame of study
  - Amount of change in assessment expected during study