Biomarkers in Drug Development

Clinical Study Design for Rare Diseases Symposium

Washington, DC April 2013

Marc K Walton MD, PhD

Associate Director for Translational Medicine

Office of Translational Sciences

CDER-FDA

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

Outline

Biomarker Concept
Types of Biomarkers in Drug Development
Biomarker Roles in Drug Development
Surrogate Endpoints:
    Concept and Risks
    Conceptual Sources of Uncertainty
Paths to Biomarker Acceptance

Biomarker Definition & Categories

An objective patient characteristic that is measured as an indicator of:

- Normal biologic processes
- Pathogenic processes (abnormal biologic processes)
- Biological responses to a therapeutic intervention
- Different than wording of NIH WorkGroup for clarity

A *measurable* characteristic that is not a clinical assessment of the patient

Nomenclature of clinical biomarker types

- Language used to describe & discuss biomarkers
- FDA terminology chiefly relates to uses in Tx development

Types of Clinical Biomarkers (1)

- Categorized by *what it tells us* related to drug development
  - Other ways to categorize biomarkers as well

- Prognostic biomarker
  - Indicates future clinical course of the patient with respect to some specified clinical outcome
    - Absent a subsequent Tx intervention
  - No connection to any particular new Tx
  - Effective Tx would invalidate the preTx inference

Types of Biomarkers (2)

- Predictive biomarker
  - Measured prior to an intervention
  - Identifies patients who are relatively susceptible to a particular drug effect versus less susceptible patients
    - Benefit or harm
    - Exists only for a Tx with some effect
  - Developed Tx by Tx

Types of Biomarkers (3)

- Pharmacodynamic biomarker
  - Response-indicator biomarker
  - Post Tx measurement
    - Stand alone or pre- vs post-Tx comparison
  - Marker that reveals whether, or how large, a particular biological response has occurred in that particular patient
  - May or may not be Tx-specific
    - Development occurs in a Tx by Tx manner

Types of Biomarkers (4)

- Efficacy-response biomarker
  - ❖Efficacy-surrogate biomarker, Surrogate endpoint
  - ➢Subset of general pharmacodynamic biomarkers
  - ➢Predicts a *specific* clinical outcome of the patient at some later time after Tx
  - ➢Different category than prognostic biomarker
    - ❖Usually some prognostic utility so that placebo group measurements may be interpreted
    - ❖Prognostic ability does not imply surrogate utility
  - ➢Developed Tx by Tx

Roles for Biomarkers (1)

- Patient selection tool for study enrollment
  - Prognostic biomarkers
  - Predictive biomarkers
- Patient stratified randomization tool
  - To ensure balance between randomized groups
  - Prognostic and moderate or unconfirmed major predictive biomarkers

Roles for Biomarkers (2)

- Phase 1 study outcome assessment
  - Pharmacodynamic biomarkers
  - Demonstrate drug is bio-active
    - May indicate actions on early cellular effects rather than near to clinical outcome
    - There may be multiple sequential bioactivity steps to evaluate with multiple biomarkers
  - Aid in initial selection dose / regimen for later studies
  - Justify resources for further development
    - Proof of concept

Roles for Biomarkers (3)

- Phase 2 study outcome assessment
  - Pharmacodynamic biomarkers
  - Evaluate dose-response relationship
    - Variation in dose-response across patients
  - Identify response-predictive patient characteristics
  - Design of A&WC studies
    - Selection of doses
    - Uniform vs. Individualized regimen
    - Selection of patient population
    - Estimation of sample size
  - Can be critical to efficient and successful development program

Roles for Biomarkers (4)

- A&WC Studies (Phase 3)
  - Pharmacodynamic biomarkers
  - Secondary endpoint
    - ❖Supportive of primary EP findings
    - ❖Objective, precise
    - ❖Helps decrease uncertainties regarding interpretation of primary efficacy endpoint result
  - Primary Endpoint
    - ❖Surrogate endpoint for a specific *Context of Use*
    - ❖Well established relationship to clinical outcome
      - Conventional marketing approval
    - ❖"reasonably likely to predict…" relationship
      - Accelerated approval provisions of regulations

Surrogate Endpoint

- Stands in place of an efficacy endpoint
  - Feels
  - Functions
  - Survives
- Usually intended to temporally predict a clinically meaningful outcome
  - Requires assumptions about future clinical course after biomarker measurement with continued drug treatment
- Clinical endpoint usually intended to describe how a patient feels or functions at the time of measurement

Potential of Pharmacodynamic Biomarkers

- Many potential advantages in trial duration, size, accuracy of result

BUT:

- May mislead if discordant with clinical outcome
  - Falsely indicate presence or absence of benefit
  - False optimization of dose / regimen / population
  - Inaccurate estimate of size or frequency of benefit
- May result in a failed next trial for an effective drug
- Cause
  - Alternate pathophysiology- and drug action-mechanisms
  - Shape of the Biomarker-Clinical relationship

Biomarker Example: Acute MI

- Clinical outcome: Mortality
- Treatment: Intravenous thrombolytic agent
- Biomarker concept: Blood flow (patency)
  - 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 of, or when, the concept of blood flow is assessed

Acute MI

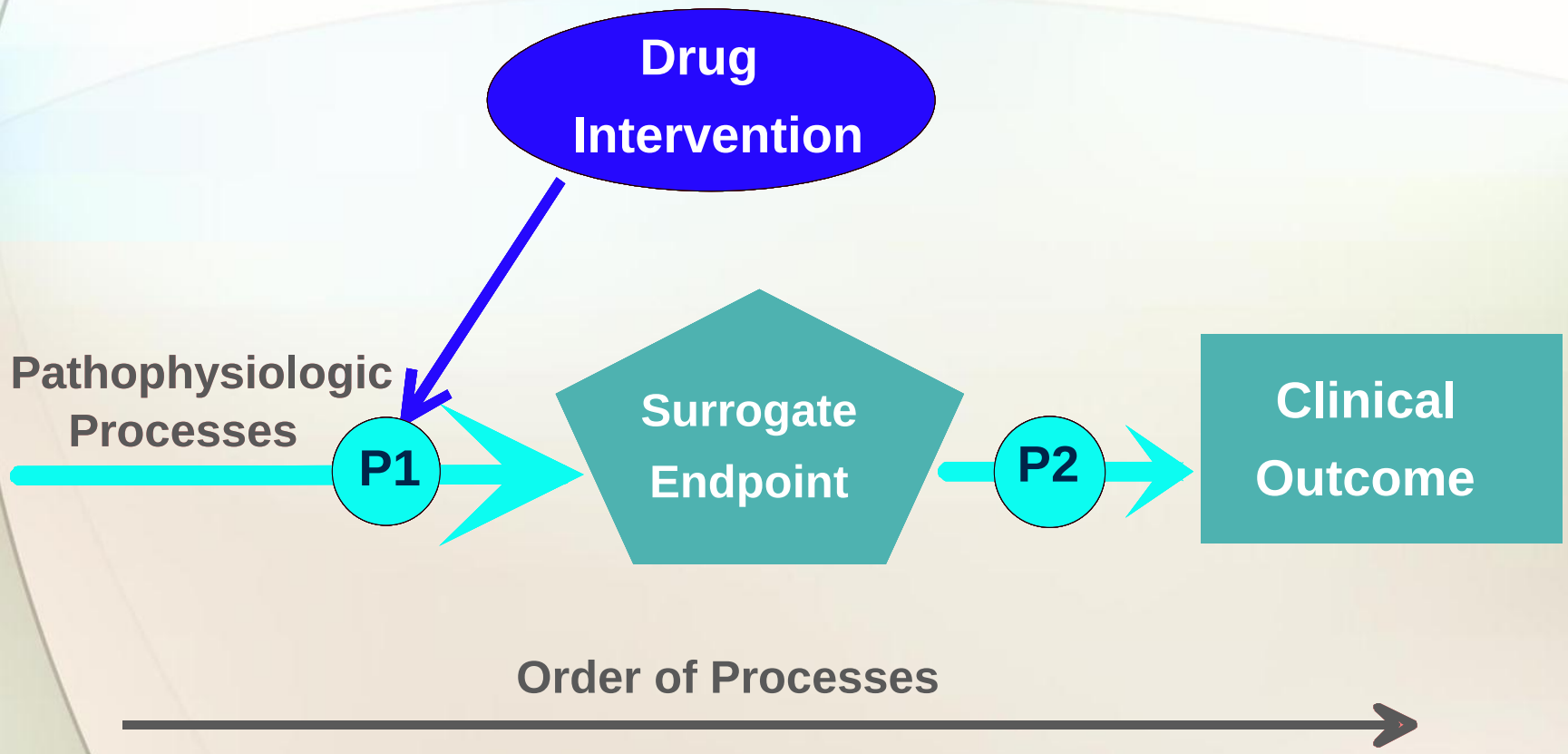
RAPID 2

	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**

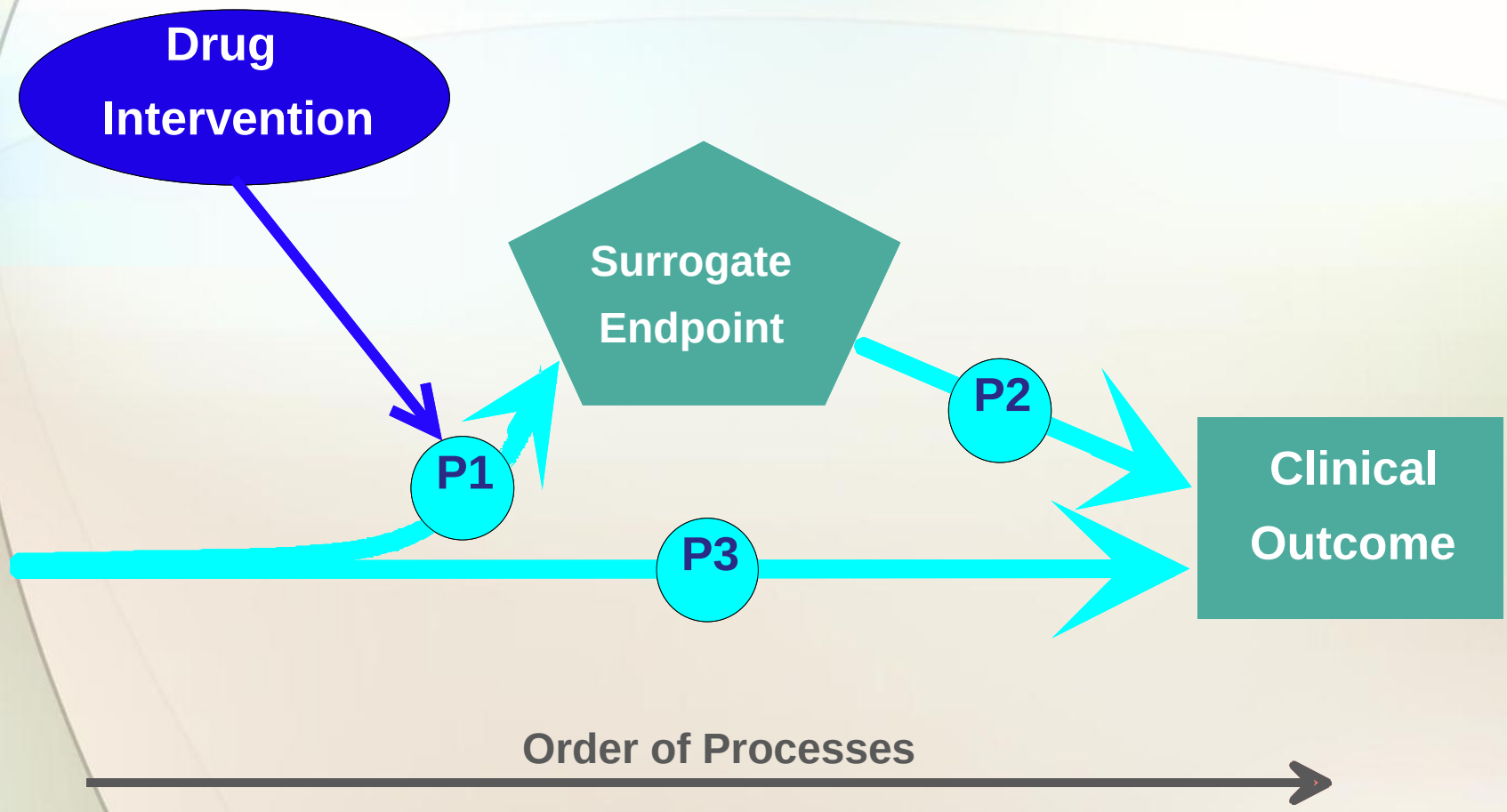
GUSTO-III		
R-PA	7.5	Mortality %
T-PA	**7.2**	

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

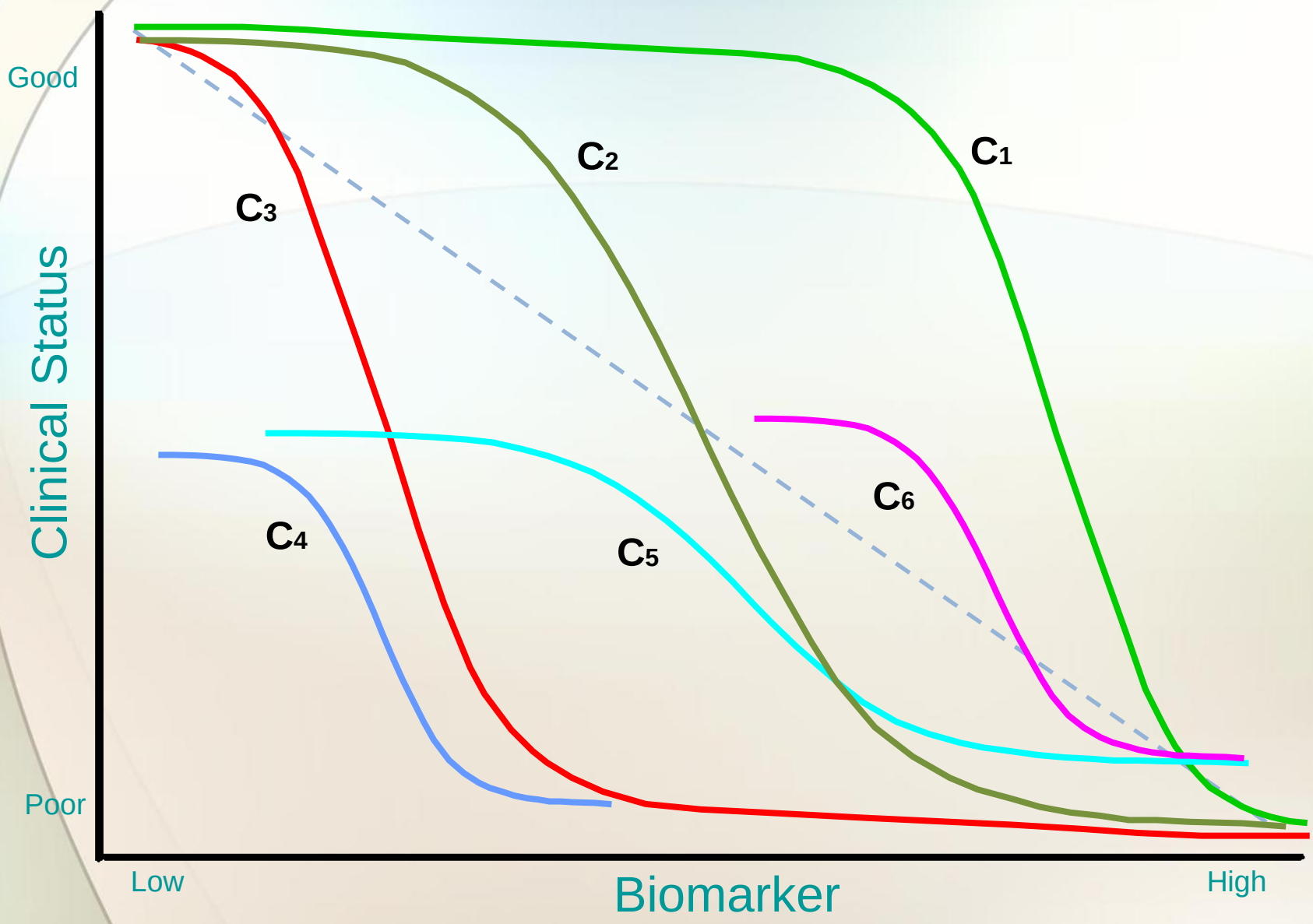
Understanding the Surrogate Measure: Idealized



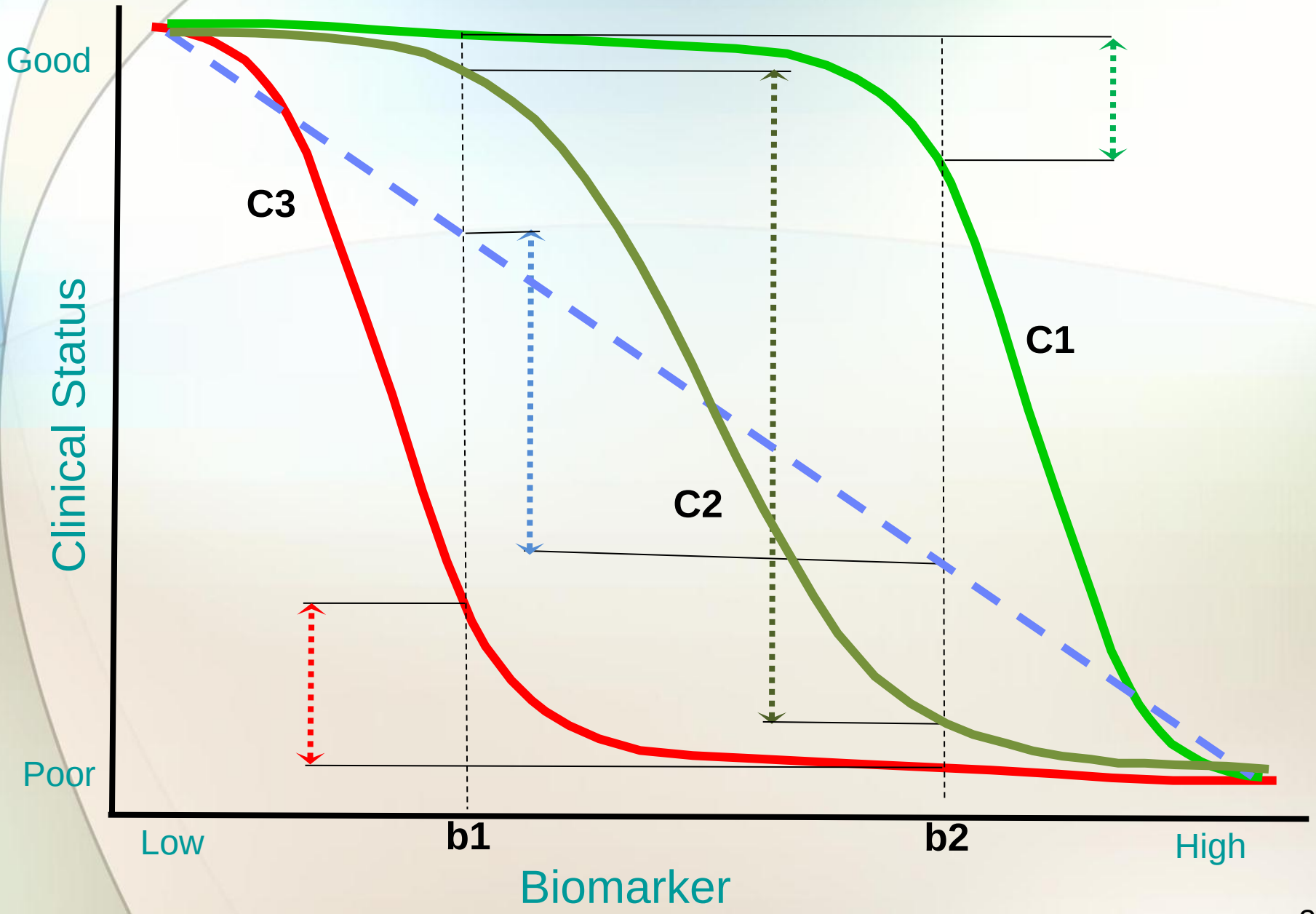
Understanding the Surrogate: Complexity



Clinical – Biomarker Relationship



Clinical Effects of Biomarker Change



How can Biomarkers Become Accepted?

- Case by case consideration within IND/NDA/BLA
- General use accepted over extended period

- Co-development of drug and test
  - Companion diagnostics

- Biomarker Qualification Process
  - Outgrowth of Critical Path Initiative

Biomarker Qualification

- A conclusion that within a carefully and specifically stated "context of use" the biomarker has been demonstrated to reliably support a specified manner of interpretation and application in drug development
  - Utility in drug development, particularly regulatory decisions, is central to purpose of qualification
  - Particularly for biomarkers expected to have application in multiple different drug development programs
- Validation ??
  - Context of Use !
- Not how IOM decided to use term

Evidence to Support Qualification

- Biomarker Qualification is formal FDA Guidance
  - Support should provide confidence that use of biomarker will benefit, and not cause damage to, the drug development program
  - Clear recommendation of how to use biomarker
    - How to apply
    - Utility of use
    - Precision as warranted by use
- Extent and breadth of data needed will vary with the consequences of mistaken recommendation
  - Prognostic biomarker
  - Clinical monitoring safety biomarker
  - Surrogate endpoint biomarker