Envisioning efficient oncology drug development

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Merriam-Webster SINCE 1828

seamless

DICTIONARY THESAURUS

Definition of SEAMLESS

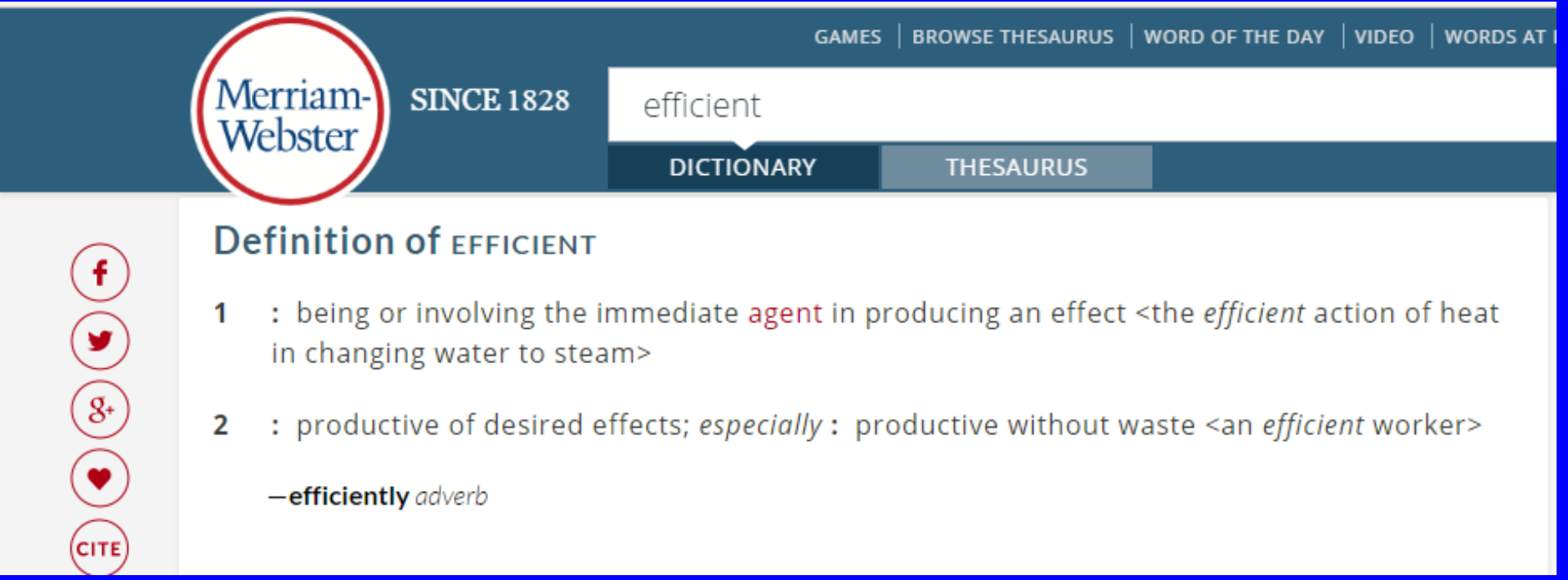
1 : having no seams

2 **a :** having no awkward transitions, interruptions, or indications of disparity <a *seamless* fusion of beauty and intelligence — Jack Kroll *et al.*>

b : PERFECT, FLAWLESS <a *seamless* performance>

—**seamlessly** \-lē\ *adverb*

—**seamlessness** \-nəs\ *noun*



- **Productive of <u>desired effects</u>**
  - **Especially, productive <u>without waste</u>**

"Desired effects" of oncology drug development

- Demonstration of anticancer activity
- Identification of target population(s)
  - Clinical
  - Molecular
- Identification of population dosage and schedule that optimize benefit to risk ratio
- Identification of individual patient factors that require dose modification
  - Clinical
  - Molecular

"Undesired effects" of oncology drug development

- Failing in phase 3
- Identifying the wrong target population
- Identifying the wrong population dosage
  - Too low = ↓efficacy
  - Too high = ↓revenue
- Not identifying individual patient factors that have great impact on efficacy or toxicity

Productive without waste

- Waste of time
  - Delays due to government regulations
  - Delays due to corporate bureaucracy
    - Sponsor/CRO
    - Sites
  - Delays due to inefficient clinical trial design
- Waste of money
  - Administrative excess
    - Studies
    - Sites
    - Patients
    - Data
  - Inefficient trial design
  - Studies that are not designed to provide reliable results
    - Reliance on historical controls

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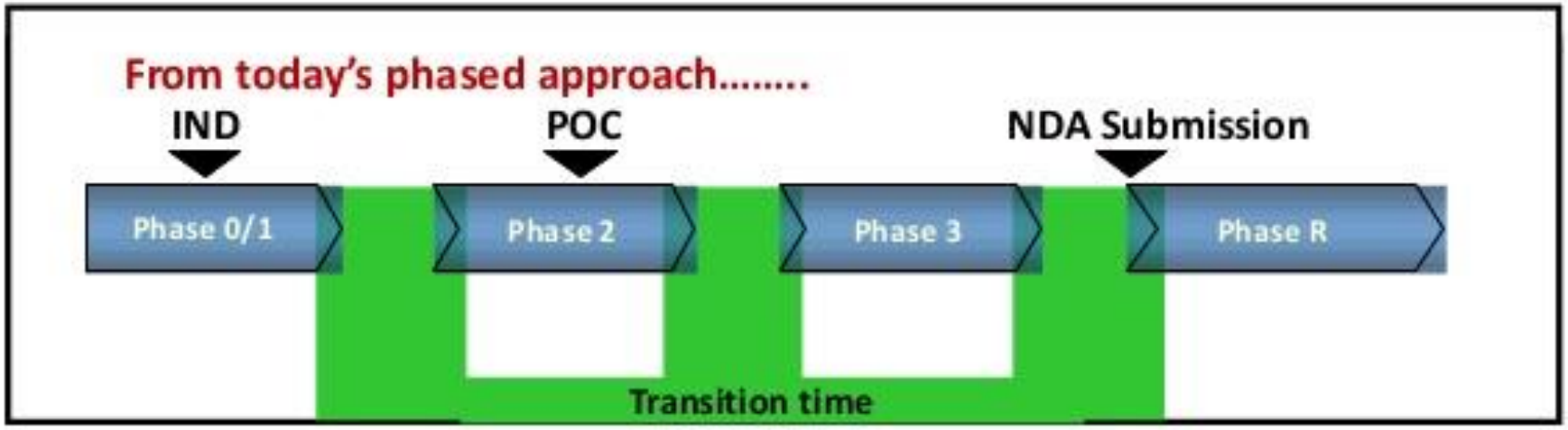
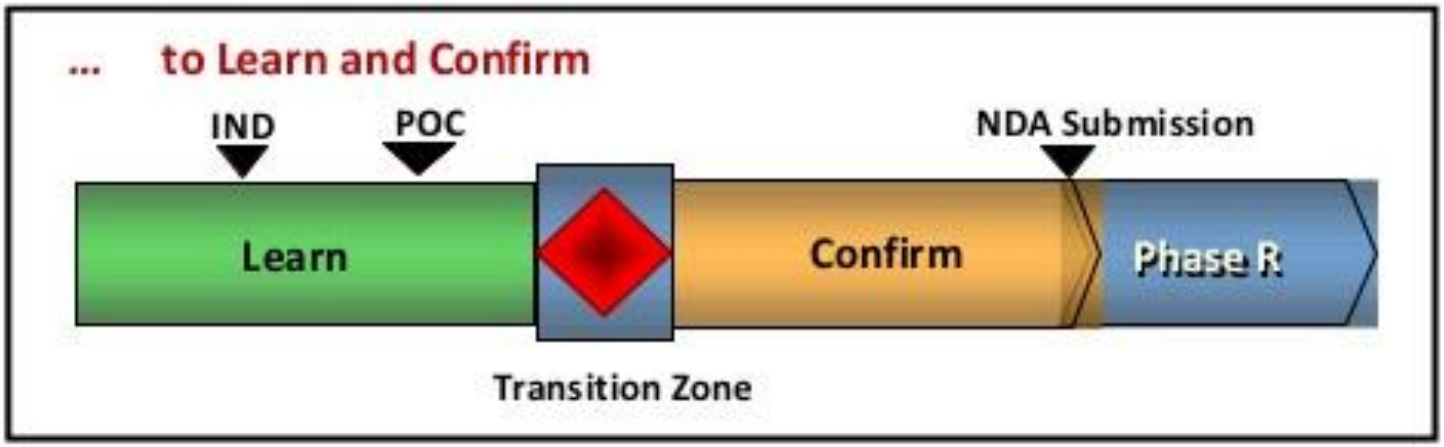
COMMENTARY

Learning versus confirming in clinical drug development

Lewis B. Sheiner, MD *San Francisco, Calif.*

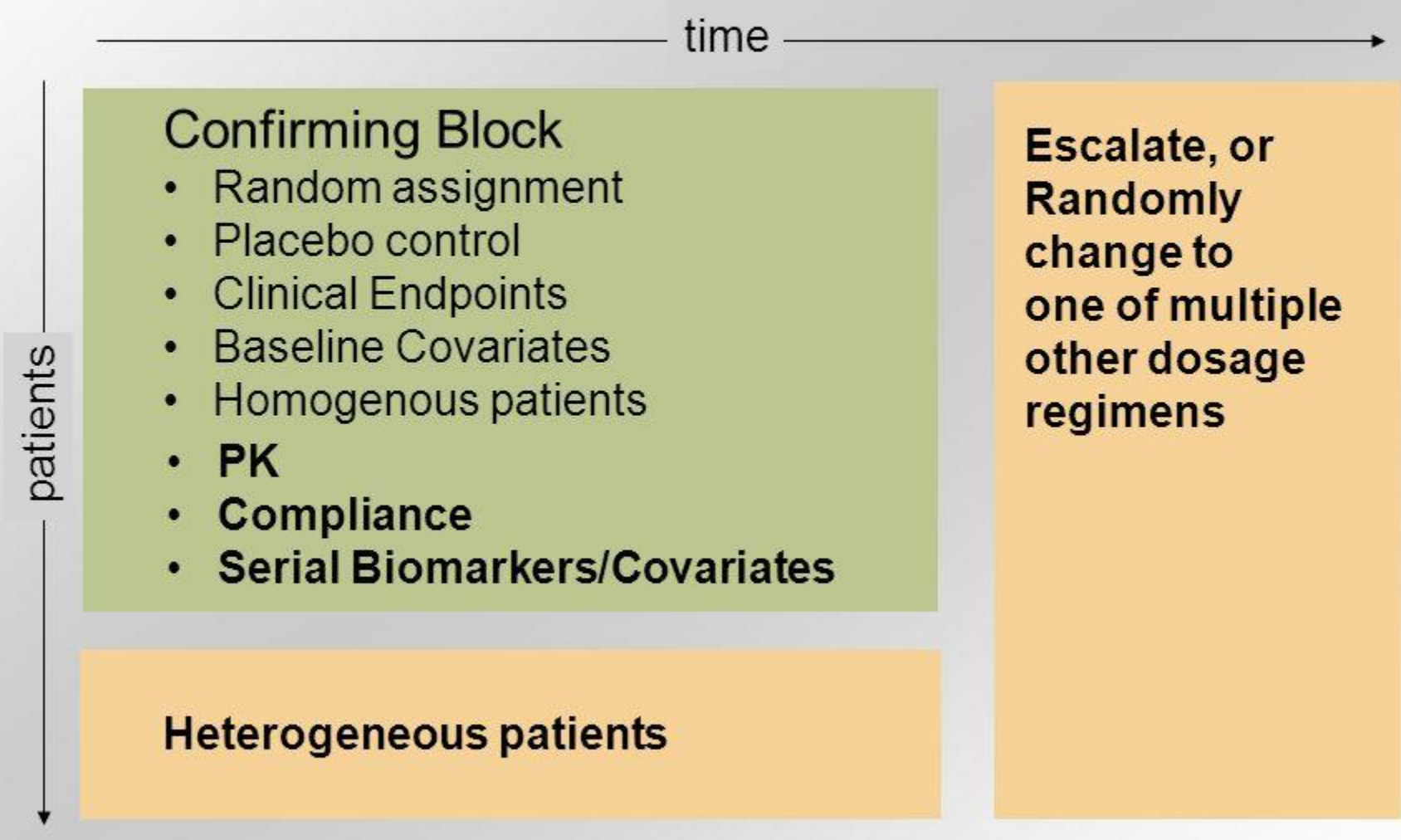
Study Design
From "phased" to "seamless"





From www.slideshare.net/josepmariabadenas/globalization-of-clinical-trials-2010-josep-m-badenas

Learning While Confirming



α

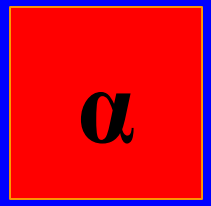
Proof of Concept, Range of Active and Tolerable Doses

β

Modeling Dose (Exposure) versus Efficacy and Toxicity

γ

Confirmation of Acceptable Safety and Efficacy at Selected Dose(s)



Proof of Concept, Range of Active and Tolerable Doses

- **Rapid escalation (100%) in small cohorts (1-2 patients) until**
  - **Evidence of activity**
  - **Expected (mechanism-related) toxicity**
  - **Unexpected (off-target) toxicity**
- **Adaptive randomized dose-escalation design assigning patients to pharmacologically active and plausibly safe doses**

β

Modeling Dose (Exposure) versus Efficacy and Toxicity

- **Randomized dose-ranging design assigning patients to doses considered for labeling**
  - **Based on results of** α
  - **Eligibility narrowed to reduce patient heterogeneity**

γ

Confirmation of Acceptable Safety and Efficacy at Selected Dose(s)

- Adaptive randomized trial to confirm results of β

α

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Guidance for Industry and Review Staff

Target Product Profile — A Strategic Development Process Tool

DRAFT GUIDANCE

March 2007

B. Attributes of a TPP

Ideally, the TPP provides a statement of the *overall intent* of the drug development program, and gives information about the drug *at a particular time* in development. Usually, the TPP is organized according to the key sections in the drug labeling and links drug development activities to specific concepts intended for inclusion in the drug labeling. The sponsor can draft and update pertinent sections of the template that are intended to support the specific statements in labeling. The sponsor can also use these updated versions of the TPP in preparation for discussions with FDA review staff to identify the most important development goals for the drug. The TPP is a *dynamic* summary that changes as knowledge of the drug increases. For optimal use, we recommend that the TPP be updated regularly to reflect new information about the drug and changes in the clinical development program.

- **Overall intent**
- **Dynamic**
- **Organized by key sections in labeling**
  - **Indication(s)**
  - **Adverse reactions**
  - **Clinical pharmacology**

α

Proof of Concept, Range of Active and Tolerable Doses

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Confirmation of Acceptable Safety and Efficacy at Selected Dose(s)

PROTOCOL AMENDMENT BEFORE IMPLEMENTATION

α

Proof of Concept, Range of Active and Tolerable Doses

β

Modeling Dose (Exposure) versus Efficacy and Toxicity

REQUIRES AMENDMENT BEFORE IMPLEMENTATION

γ

Confirmation of Acceptable Safety and Efficacy at Selected Dose(s)

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Proof of Concept, Range of Active and Tolerable Doses

β

Modeling Dose (Exposure) versus Efficacy and Toxicity

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Confirmation of Acceptable Safety and Efficacy at Selected Dose(s)

Oncology drug development can be efficient without sacrificing scientific rigor

- Use of a target product profile (i.e., label-based drug development)
  - Absolutely critical for combination development
- Dynamic and flexible statistical designs, particularly in regard to dose assignment
  - Aim to develop models of drug response
- Expectations for significant protocol amendments, as information accrues