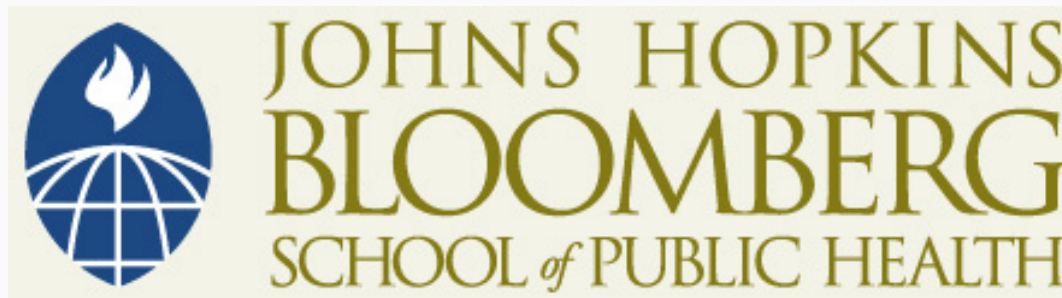


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JOHNS HOPKINS
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Multi-Regional Studies and Bridging Studies

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Rationale

- New/different region
- New age group
- Changes in vaccine manufacture, storage, etc.
- Others?

- Adopted 1998
- Evaluate the impact of ethnic factors on efficacy and safety
- Minimize duplication of clinical data
- Context of extrapolation

- The key terms
 - Bridging
 - Extrapolation
 - Generalization

- Ethnic differences may affect safety, efficacy, dosage, dose regimen
- Characterize medicines as “ethnically sensitive” or “ethnically insensitive”
- In contrast to “intrinsic” factors and “extrinsic” factors

Ethnic Sensitivity

- Pharmacokinetics
- Pharmacodynamics
- Therapeutic range
- Metabolism
- Bioavailability
- Potential for interactions
- Genetic polymorphisms
- Intersubject variability
- Systemic mode of action
- Potential for inappropriate use

Intrinsic and Extrinsic Factors

Classification	Factor	Description
Intrinsic	Genetic	Gender, race
		Polymorphisms
	Physiology and pathology	Age
Liver, kidney, CV		
Extrinsic	Environmental	Climate, pollution
	Cultural	Socioeconomic factors
		Educational status
	Medical practice	Diagnostic and treatment approach

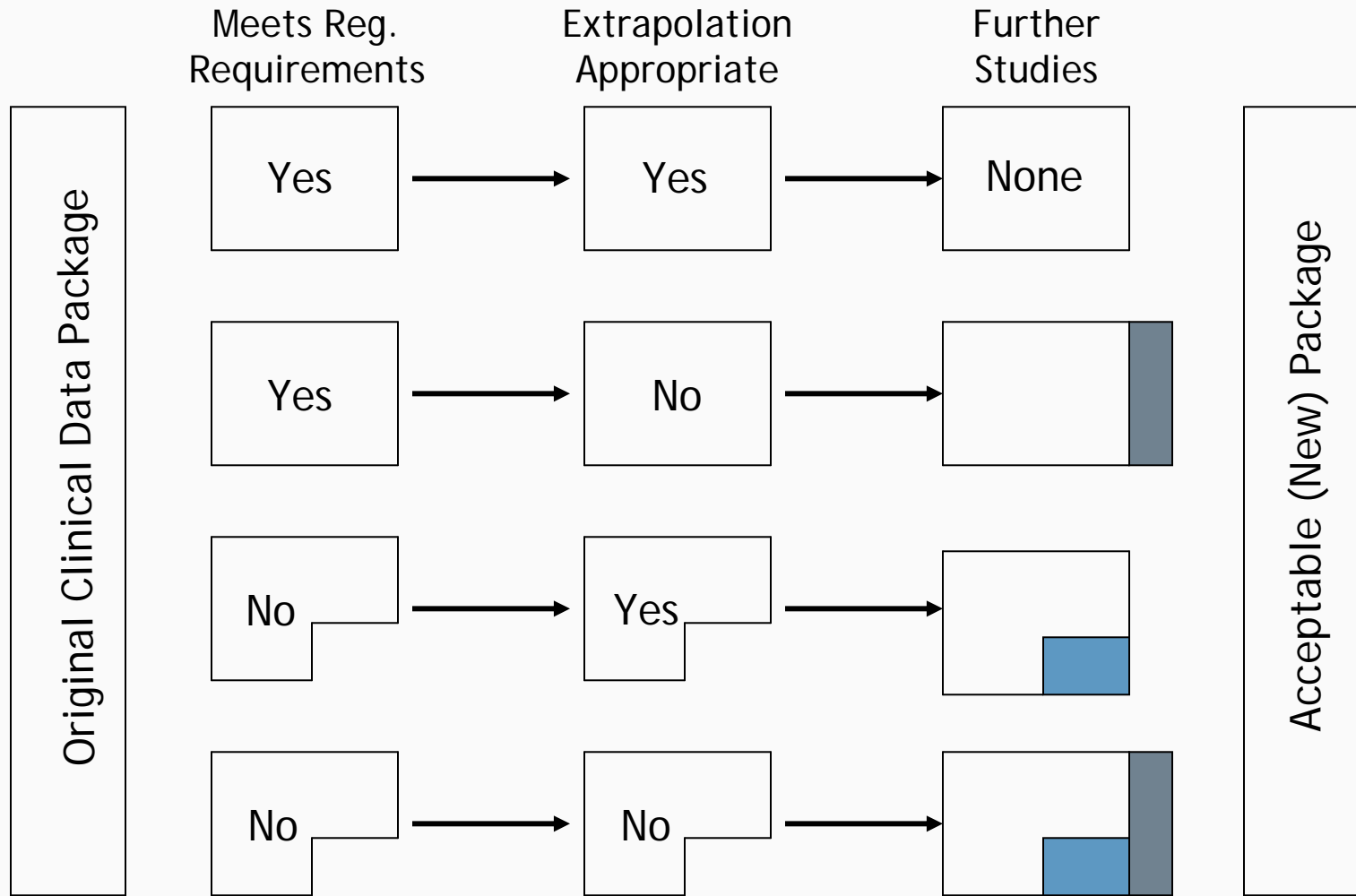
“Bridging Studies”

- To avoid replication of large, expensive trials
- To avoid replication of whole development programmes
- To fill in the gaps
- To show relevance (i.e., link or build a bridge) between completed studies and local (regional) factors

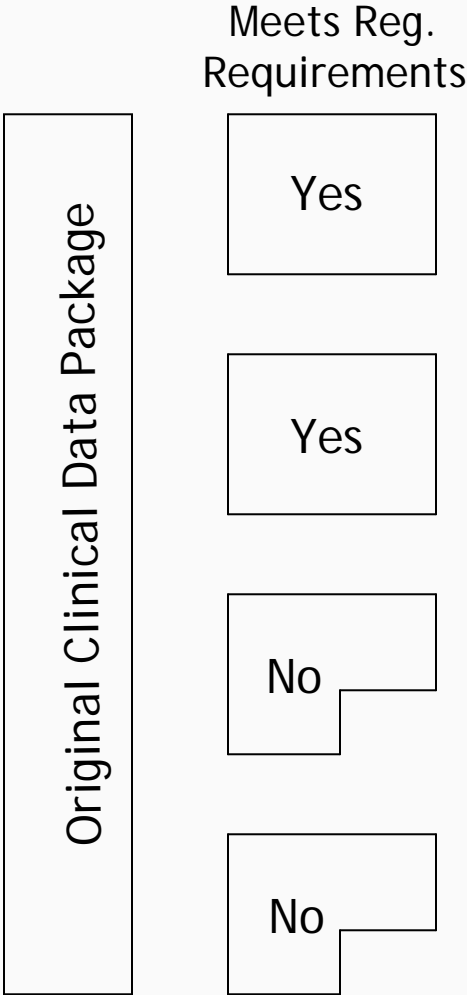
When Are Bridging Studies Needed?: An Overview

	No bridging	Bridging
Study medication	Insensitive to ethnic factors	Sensitive to ethnic factors
Region	Similar	Dissimilar
Medical practice	Similar	Different: need controlled trials
Drug class	Familiar: need only pharmacodynamics	Unfamiliar: need controlled trials
Clinical experience	Sufficient	Insufficient: need controlled trials

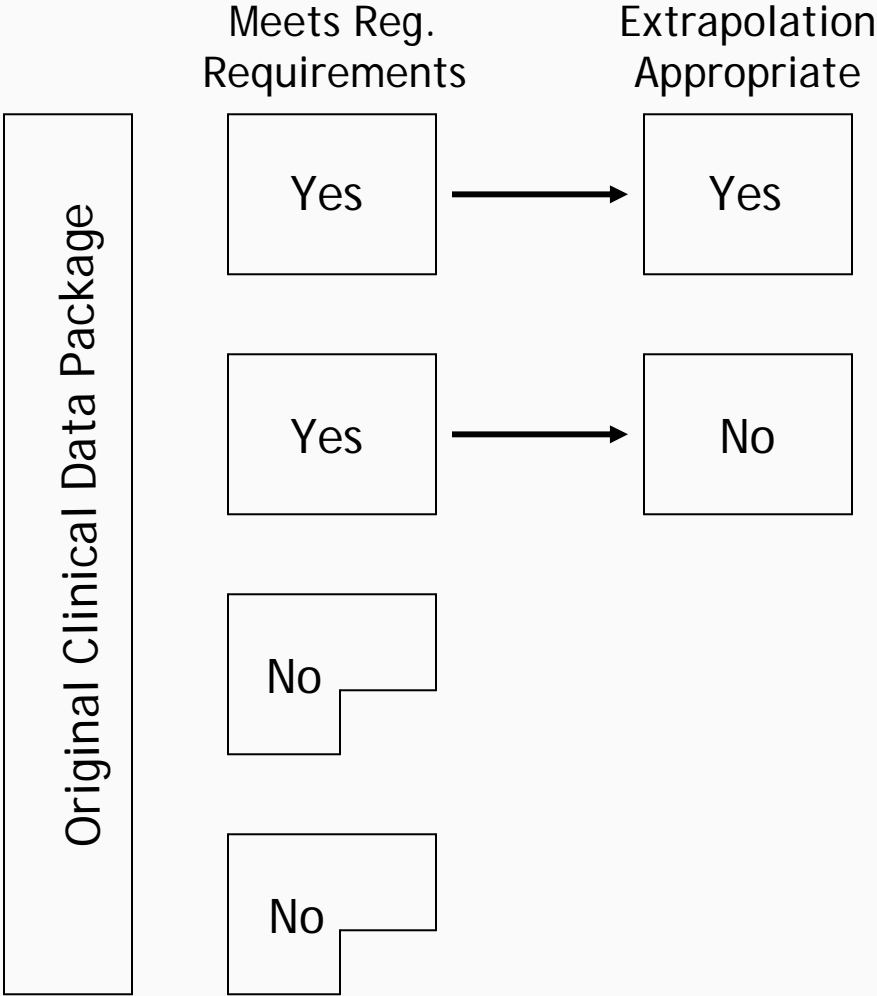
When Do You Need What?



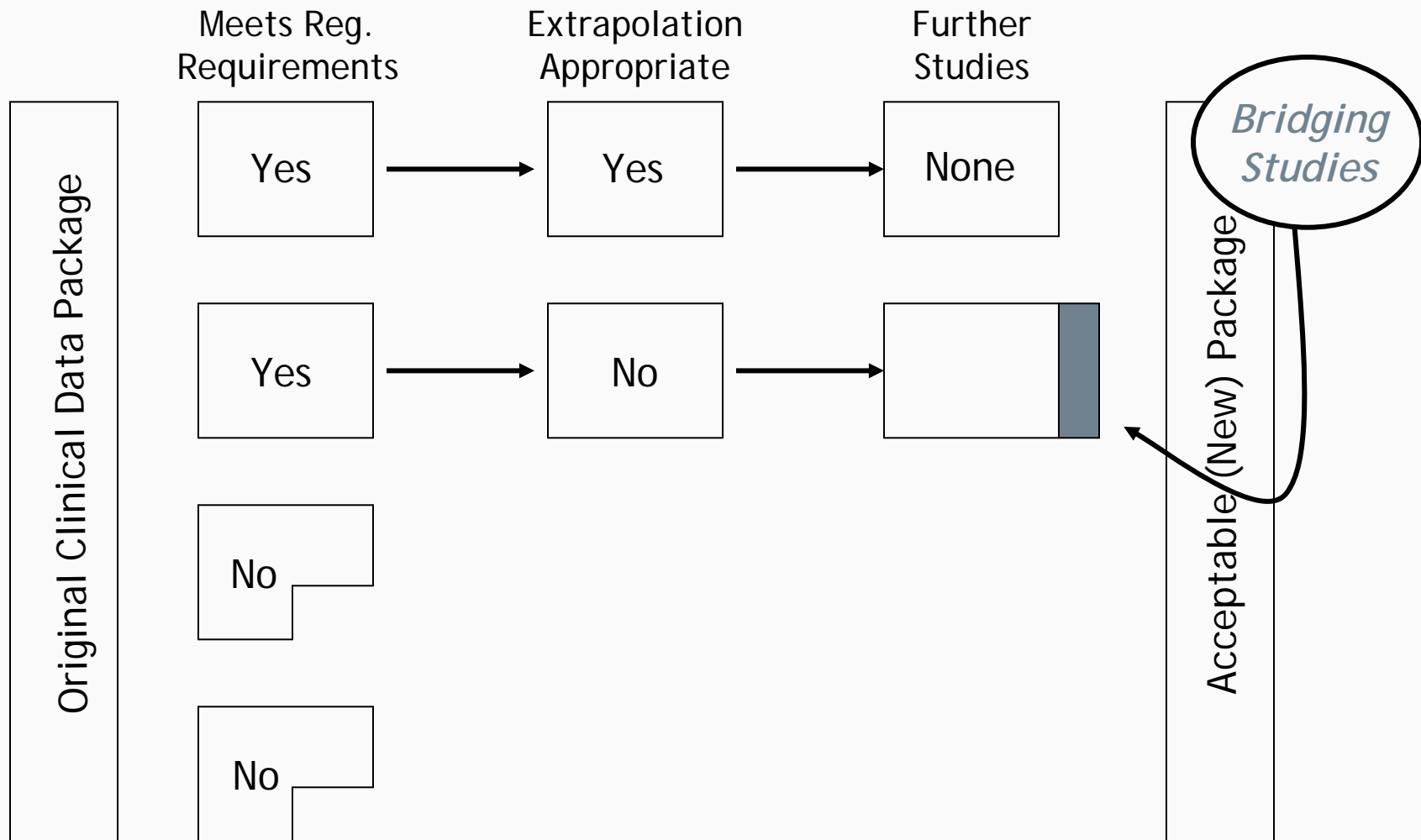
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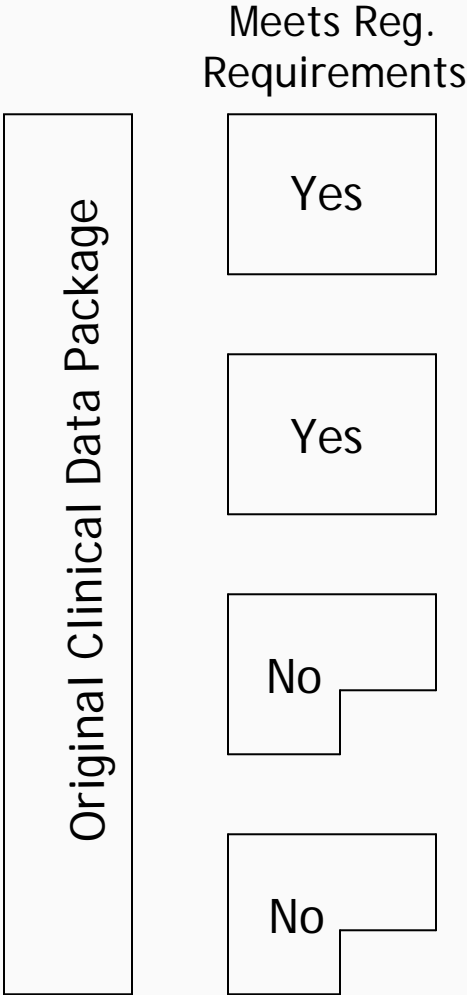
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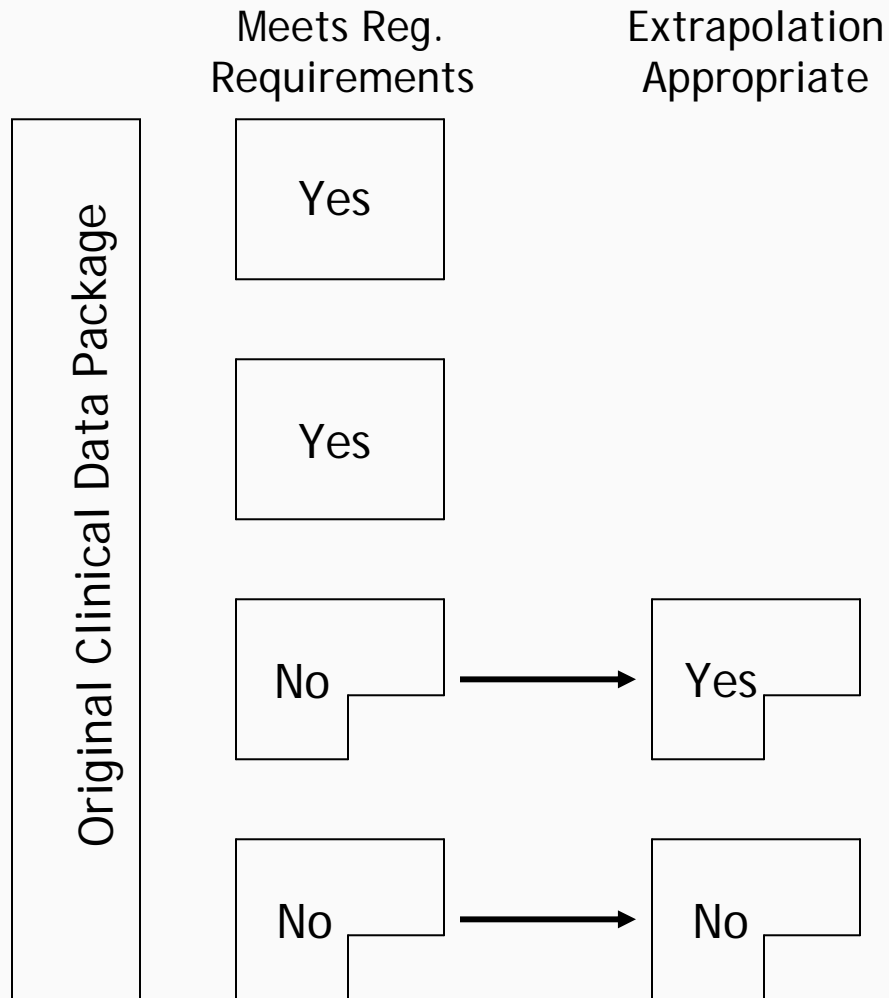
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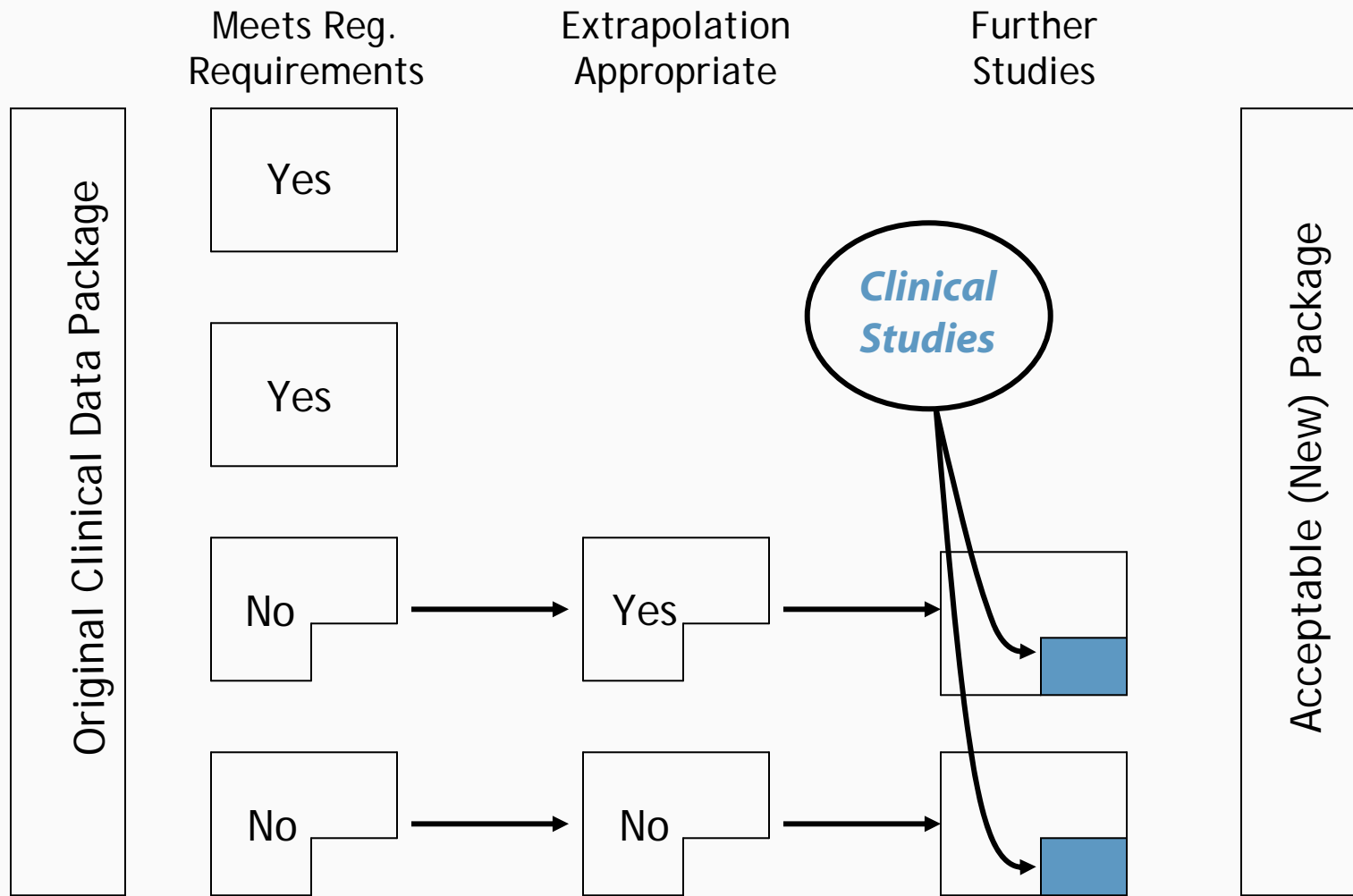
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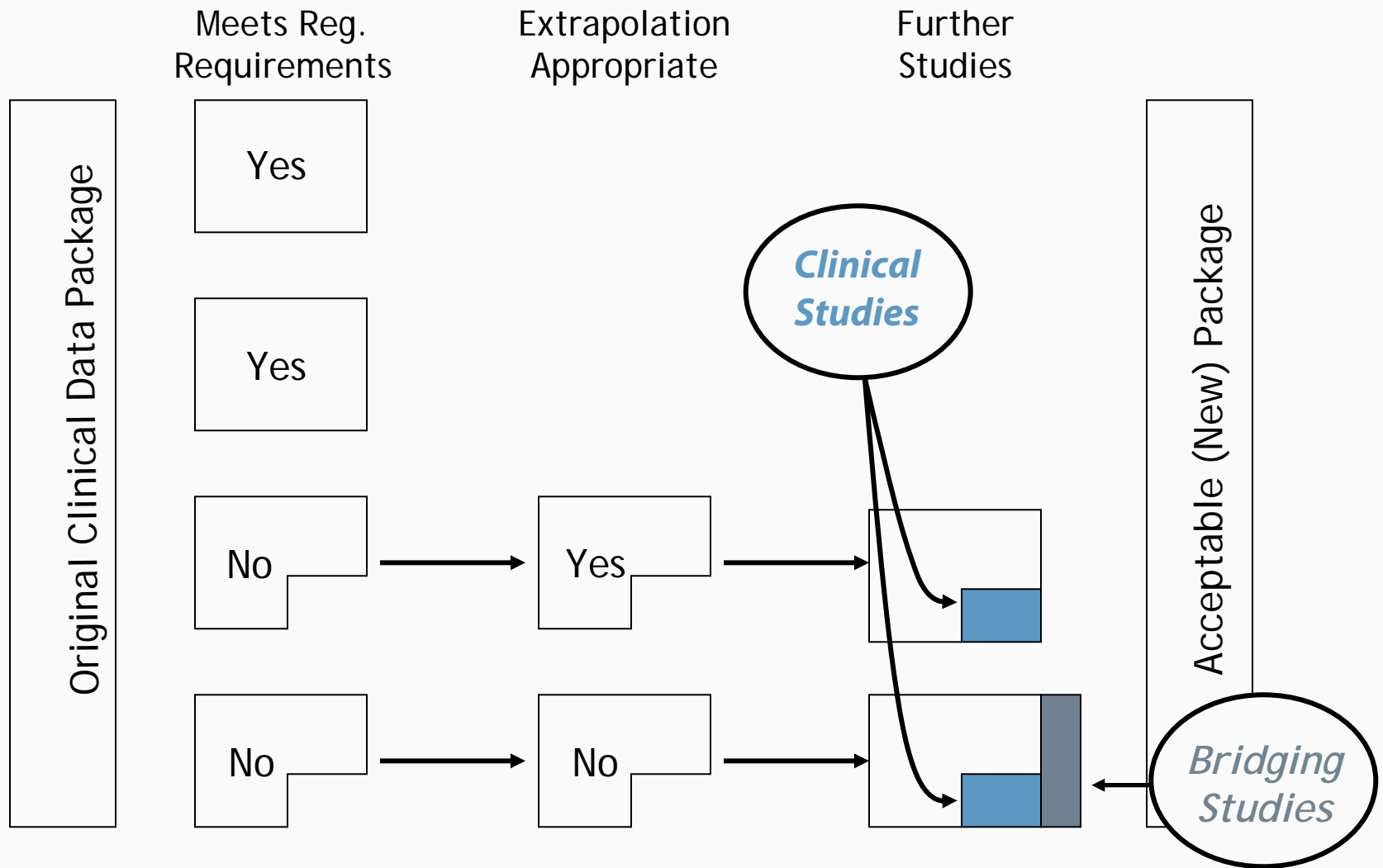
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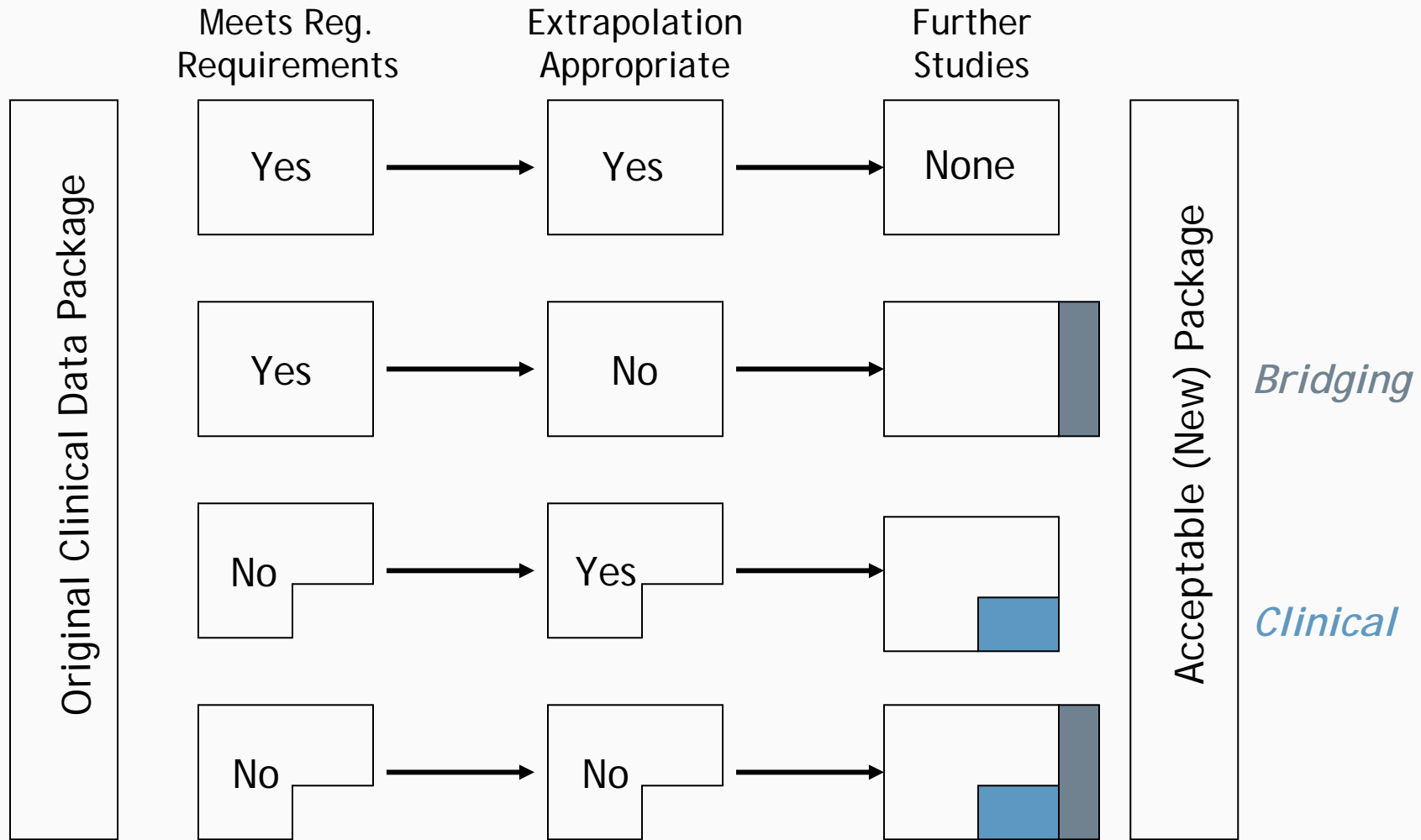
When Do You Need What?



When Do You Need What?



When Do You Need What?



International Nature of Endpoints

- Thresholds for seeking medical attention
- Thresholds for treating (or not) the disease
- Varying health care systems
 - Payment
 - Primary/referral

Cultural Nature of Endpoints

- Example
 - “Have you ever thought about committing suicide?”
- Example
 - Resource utilisation
 - Cost effectiveness studies

Post-Hoc Arguments: For and Against

- Justifications are always easy but usually futile
- We do multi-centre (-country; -region) trials because . . .
 - It increases recruitment rate
 - It (Informally) gives “wider applicability”
- “Wider applicability” is lost if opportunity is not taken

What Population (Indication)

- “. . . to what population will the results apply?”
 - Consider before the trial to what population (not sample) you want the results to apply
 - Consider after the trial to what population the results might be expected to apply

In the Next Lecture We'll Look at . . .

- Interim monitoring
 - Some history
 - Data monitoring committees
 - Individual responsibilities
 - Other trial “committees”