Multi-Regional Studies and Bridging Studies

Simon Day, PhD
Johns Hopkins University
Rationale

- New/different region
- New age group
- Changes in vaccine manufacture, storage, etc.
- Others?
ICH E5

- Adopted 1998
- Evaluate the impact of ethnic factors on efficacy and safety
- Minimize duplication of clinical data
- Context of extrapolation
ICH E5

- The key terms
  - Bridging
  - Extrapolation
  - Generalization
ICH E5

- 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
<table>
<thead>
<tr>
<th>Classification</th>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrinsic</td>
<td>Genetic</td>
<td>Gender, race</td>
</tr>
<tr>
<td></td>
<td>Polymorphisms</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>Physiology and pathology</td>
<td>Liver, kidney, CV</td>
</tr>
<tr>
<td>Extrinsic</td>
<td>Environmental</td>
<td>Climate, pollution</td>
</tr>
<tr>
<td></td>
<td>Cultural</td>
<td>Socioeconomic factors</td>
</tr>
<tr>
<td></td>
<td>Medical practice</td>
<td>Educational status</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diagnostic and treatment approach</td>
</tr>
</tbody>
</table>
“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
<table>
<thead>
<tr>
<th></th>
<th>No bridging</th>
<th>Bridging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study medication</strong></td>
<td>Insensitive to ethnic factors</td>
<td>Sensitive to ethnic factors</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td>Similar</td>
<td>Dissimilar</td>
</tr>
<tr>
<td><strong>Medical practice</strong></td>
<td>Similar</td>
<td>Different: need controlled trials</td>
</tr>
<tr>
<td><strong>Drug class</strong></td>
<td>Familiar: need only pharmacodynamics</td>
<td>Unfamiliar: need controlled trials</td>
</tr>
<tr>
<td><strong>Clinical experience</strong></td>
<td>Sufficient</td>
<td>Insufficient: need controlled trials</td>
</tr>
</tbody>
</table>
When Do You Need What?

Original Clinical Data Package

Meets Reg. Requirements

- Yes → Yes → None
- Yes → No → None
- No → Yes → None
- No → No → None

Extrapolation Appropriate

Further Studies

Acceptable (New) Package
When Do You Need What?

Meets Reg. Requirements

Yes

Yes

No

No

Original Clinical Data Package
When Do You Need What?

Original Clinical Data Package

- **Meets Reg. Requirements**
  - Yes → **Extrapolation Appropriate** Yes
  - Yes → No
  - No → No

Reg. Requirements: Yes → Extrapolation Appropriate: Yes

Extrapolation Appropriate: Yes

No
When Do You Need What?

Original Clinical Data Package

- Meets Reg. Requirements
  - Yes
  - Yes
  - No
  - No

Extrapolation Appropriate
- Yes
- No

Further Studies
- None

Acceptable (New) Package

Bridging Studies
When Do You Need What?

Original Clinical Data Package

Meets Reg. Requirements

Yes

Yes

No

No
When Do You Need What?

Original Clinical Data Package

Meets Reg. Requirements

Yes

Yes

No

Extrapolation Appropriate

Yes

No
When Do You Need What?

Original Clinical Data Package

Meets Reg. Requirements

Yes

Yes

No

Extrapolation Appropriate

Yes

Further Studies

Clinical Studies

Acceptable (New) Package

No

No

No
When Do You Need What?

Original Clinical Data Package

- Meets Reg. Requirements
  - Yes
  - Yes
  - No
  - No

Extrapolation Appropriate

Further Studies

Acceptable (New) Package

Bridging Studies

Clinical Studies
When Do You Need What?

Original Clinical Data Package

Meets Reg. Requirements
- Yes
- Yes
- No
- No

Extrapolation Appropriate
- Yes
- No
- Yes
- No

Further Studies
- None
- None
- None
- None

Acceptable (New) Package

Bridging

Clinical
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”