Clinical interpretation and validity of trials: when do they become practice – changing

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Clinical trials: the 5 phases and their actors

- Design
- Conduct
- Analysis
- Reporting
- Interpretation

The clinical investigators and the statisticians

The patients and an army of people
INTERPRETATION

SO WHAT?
INTERPRETATION

SO WHAT?

Can be very challenging:

- CALGB vs FIRE III
- IDEA
IDEA trial: Primary Efficacy Analysis

Presented by: Qian Shi, PhD on behalf of IDEA collaborators
The hard road to data interpretation: IDEA

- ASCO, June 1, 2017: risk based
- ASCO, June 1, 2017: only 6 months
- Japan, July 10, 2017: regimen based
- ESMO, Sept 7, 2017: pt based

!!!!!
Clinical interpretation of new data

• Are these data true?
• Are they relevant?
• Are they practice-changing?
Clinical interpretation of new data

1. Are these data true?

<table>
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<tr>
<th>CONCEPT</th>
<th>BASIS</th>
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<td>methodology</td>
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<td>• Identification primary aim</td>
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<td>• Endpoint</td>
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<td>• ITT analysis</td>
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<td>Biological and clinical plausibility</td>
<td>logic</td>
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Clinical interpretation of new data

1. Are these data true?
   - Internal validity
   - Internal consistency
   - External consistency
   - Biological and clinical plausibility

2. Are they relevant?
   - Size of the benefit
   - External validity/generalizability
   - (Degree of innovation)

3. Are they practice-changing?
2. How relevant? Size of benefit

1. Which endpoints? Cure, OS, RFS, QOL, PFS, RR
2. How were these expressed? Median, HR, % at….
3. Under which condition?
4. Which toxicity?
5. How much inconvenience?
The four ways to assess OS benefit

OS BENEFIT

HR and gain in MST
- Small benefit for many
  - Hard to understand
  - Hard to communicate to pts

Absolute and proportional gain in long term OS (2–3 years)
- Large benefit for few
  - Highly desirable, easily communicated, but rarely available

Sobrero et al Clin Ca Res 2015
2. How relevant? Size of benefit

1. Which endpoints? Cure, OS, RFS, QOL, PFS, RR
2. How were these expressed? Median, HR, % at....
3. Under which condition?
4. Which toxicity?
5. How much inconvenience?
2. How relevant : How generalizable ?

EXTERNAL VALIDITY

- Pt characteristics
- Comparator arm
- Therapeutic regimen
- Compliance
Clinical interpretation of new data: known ‘problems’ with FIRE III and CALGB 80405

1. Are these data true?
   • Internal validity          FIRE III  CALGB
   • Internal consistency
   • External consistency
   • Plausibility

2. Are they relevant?
   • Size of the delta benefit
   • External validity/generalizability
   • Degree of innovation

3. Are they practice-changing?
   • True and relevant enough
   • feasible
   • affordable
Clinical interpretation of new data

1. Are these data true?
   - Internal validity
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The Technology Adoption Curve
As captured by Everett Rogers in his book Diffusion of Innovations, people tend to adopt new technologies at varying rates. Their relative speed of adoption can be plotted as a normal distribution, with the primary differentiator being individuals’ psychological disposition to new ideas.

Innovators (2.5%) are risk takers who have the resources and desire to try new things, even if they fail.

Early Adopters (13.5%) are selective about which technologies they start using. They are considered the “one to check in with” for new information and reduce others’ uncertainty about a new technology by adopting it.

Early Majority (34%) take their time before adopting a new idea. They are willing to embrace a new technology as long as they understand how it fits with their lives.

Late Majority (34%) adopt in reaction to peer pressure, emerging norms, or economic necessity. Most of the uncertainty around an idea must be resolved before they adopt.

Laggards (16%) are traditional and make decisions based on past experience. They are often economically unable to take risks on new ideas.
Relationships between extent of benefit and degree of certainty

- **Ideal**: Limited benefit, but high certainty
- **Huge benefit, but low certainty**: Limited benefit, and low certainty
- **Limited benefit, but high certainty**
How about after the new data have become practice-changing?
What is Evidence-Based Medicine (EBM)?

- Clinical judgement
- Relevant scientific evidence
- Patients’ values and preferences

EBM, evidence-based medicine.