Generalizability of results from randomized trials; A systematic overview of possible approaches

Piet N Post, CBO, The Netherlands
Gordon H Guyatt, McMaster University, Hamilton ONT, Canada
Background

- RCTs are conducted in restricted populations
- many patients seen in practice excluded
Objective

• When are RCT results generalizable to patients *not* represented in RCTs?

• How can we decide this?
Methods (I)

- Systematic review of the literature
- Systematic search of:
  - Textbooks in clinical epidemiology from 1980
  - Medline and Embase from 1990
Results

- 3 approaches identified
  - 1. Resemblance with eligibility criteria
  - 2. Use observational studies
  - 3. Assume generalizability unless compelling reasons not to do so
1. Resemblance with eligibility criteria

- Check whether your patiënt was represented
  - If yes: generalize
  - If no: do not generalize
2 Use observational studies

- Evidence from observational studies
  - broader patiënt group
3. Assume generalizability unless

- Check whether biological, social and economic and epidemiological issues could limit generalizability
Example: spironolactone

- Spironolactone appeared to reduce both morbidity and death among patients with severe heart failure.
- Does this apply to patients > 70 years?

1. Check eligibility criteria

- Patients > 70 not represented
  - Do not generalize
2. Observational studies

- In 1999: no guidance
- In 2004: increased morbidity and mortality due to hyperkalaemia (Juurlink, 2004)
  - Do not generalize

3. Assume generalizability unless

- Generalize?
- Check issues that could limit generalizability
  - In 1999 RCT no hyperkalemia
  - but exclusion patients with K>5 mmol/l
  - phase 2 trial in 1996:
Results of phase 2 trial (1996)

- Am J Cardiol 1996;78:902-90
- Spironolactone increases risk of hyperkalaemia
- “We recommend careful monitoring of serum potassium levels.”
Overview of the three approaches

• Avantages and disadvantages
1. Resemblance with eligibility criteria

- Very strict approach
- No guidance if not represented
- Eligibility criteria incompletely reported
2. Observational studies

- If conflicting with RCT evidence
  - RCT result would be more trustworthy
  - Observational study evidence would not provide guidance
3. Assume generalizability

- Time consuming
- Subjective judgement?
Recommendations

• Assume generalizability unless compelling reasons
  - Check whether biological, social and economic and epidemiological issues could limit generalizability
  - Use evidence from observational studies (adverse effects) to help decide on these issues
Discussion point

- Who should do the assessment of generalizability?
- Guideline developers (?)