Investigating heterogeneity of effect: Interim analysis to assess for representativeness: worth a try or just a tribulation?

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"The Future of Clinical Trials: Towards Diversity and Inclusion"

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Vienna, Austria
Disclosure and Confidentiality

• The ESC covered my travel costs to attend this meeting
• As a professor, I get academic credit by giving presentations like this
Thank you!
Interim analysis to assess for representativeness: worth a try or just a tribulation?

YES, worth a try!
Here is my thought process

1. **How** can we do it? My suggested framework
2. **Why** does it matter?
3. Potential **disadvantages**?
4. **Whose** responsibility is it?
The framework: How should we approach it?
Potential frame-work for using interim analysis for assessing representation

1. Evaluate and report the distribution of the health condition by subgroups in the overall population
2. Determine the ideal proportional representation of each subgroup in the target sample for a trial
3. Adopt the Global Cardiovascular Clinical Trialists Forum strategy for enhancing representation in trials (European Heart Journal 2023;44(11):921-930)
4. Adopt a formal equity frame-work in design, conduct, analysis, and reporting
5. Perform interim evaluation blinded aggregate recruitment data to monitor overall representation
6. Adopt the Kent et al proposal for assessing and reporting heterogeneity in treatment effects in clinical trials (Trials 2010, 11:85)
7. Adopt the ICEMAN criteria for assessing credibility of subgroups effects (CMAJ 2020;192(32):E901-E906)
#1: Evaluate and report the distribution of the health condition by subgroups in the overall population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Target population distribution (%)</th>
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#2: Determine the ideal proportional representation of each subgroup in the target sample for a trial

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<th>Sample distribution</th>
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<td>Total SS: n=XX</td>
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#3: Adopt the Global Cardiovascular Clinical Trialists Forum strategy for enhancing representation in trials (*European Heart Journal* 2023;44(11):921-930)
Improving representativeness in trials: a call to action from the Global Cardiovascular Clinical Trialists Forum


Author Notes


Published: 25 January 2023   Article history ▼
#4: Adopt established frameworks in planning, design, and analysis.
Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use

Shirin Heidar1, Thomas F. Babor2, Paola De Castro3, Sera Tort4 and Mirjam Curno5
Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health

Jennifer O’Neill, Hilary Tabish, Vivian Welch, Mark Petticrew, Kevin Pottie, Mike Clarke, Tim Evans, Jordi Pardo Pardo, Elizabeth Waters, Howard White, Peter Tugwell
#5: Perform interim evaluation blinded aggregate recruitment data to monitor overall representation
<table>
<thead>
<tr>
<th>Variable</th>
<th>Target (%)</th>
<th>Sample distribution: Total SS: n=XX</th>
<th>Interim : n (%)</th>
<th>On track: Y/N</th>
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This means REBs or IRBs should consider requiring representativeness as part of the annual progress report.
#6: Adopt the Kent et al proposal for assessing and reporting heterogeneity in treatment effects in clinical trials (Trials 2010, 11:85)

Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal

David M Kent¹*, Peter M Rothwell², John PA Ioannidis¹,³, Doug G Altman⁴, Rodney A Hayward⁵
Table 4 Checklist for Reporting on Subgroup Analyses & Heterogeneity in Treatment Effects

1. Evaluate and report on the distribution of risk in the overall study population and in the separate treatment arms of the study by using a risk prediction model or index.
   - Report on the distribution of predicted risk (or risk score) in the study population overall and by treatment arm.
   - Risk reporting should allow readers to assess the full distribution of the study population either graphically (e.g., histograms or box & whiskers plots) or by including information on the mean, standard deviation, median and interquartile ranges.

2. Primary subgroup analyses should include reporting how relative and absolute risk reduction varies in a risk-stratified analysis.
   - The risk prediction model should be pre-specified (i.e., fully specified before any analysis of treatment-effect has begun) and preferably externally developed.
   - Both absolute and relative risk reductions must be reported.

3. Any additional primary subgroup analysis should be pre-specified and limited to patient attributes with strong a priori pathophysiological or empirical justification.
   - All primary subgroup comparisons must be pre-specified.
   - Prespecification should include all aspects of the subgroup analysis, including threshold values for continuous or ordinal variables where these are used.
   - All primary subgroup analyses must be justified based upon pathophysiological or empirical evidence that this factor modifies treatment effects.

4. Conduct and report on secondary (exploratory) subgroup analyses separately from primary subgroup comparisons.
   - Secondary subgroup analyses must be reported separately from primary subgroup analyses and clearly labeled as exploratory (potential useful for hypothesis generation and informing future research, but having little or no immediate relevance to patient care).

5. All analyses conducted must be reported and statistical testing of HTE should be done using appropriate methods (such as interaction terms) and avoiding overinterpretation.
   - Reporting must include results for all subgroup analyses conducted and the paper must state that primary subgroup analyses conducted were pre-specified and reported.
   - Statistical comparisons should be limited to reporting for statistical significance of treatment heterogeneity between subgroups using interaction terms. (Testing for the significance of a treatment effect within a subgroup is inappropriate due to poor statistical power).
   - Statistical comparisons should be corrected for the number of primary subgroup analyses performed.
Always adopt an equity lens in reporting

**RESEARCH METHODS AND REPORTING**

CONSORT-Equity 2017 extension and elaboration for better reporting of health equity in randomised trials

Vivian A Welch,1,2 Ole F Norheim,1,3,4 Janet Jull,5 Richard Cookson,6 Halvor Sommerfelt,3,7 Peter Tugwell,2 CONSORT-Equity and Boston Equity Symposium

**Article**

Improving Social Justice in COVID-19 Health Research: Interim Guidelines for Reporting Health Equity in Observational Studies

Alba Antequera 1,4, Daeria O. Lawson 2,3, Stephen G. Nendaynu 2,3, Omar Dewidar 4,5, Marc Avery 4, Zarifa A. Bhutta 1,6, Catherine Chamberlain 7,8, Holly Ellingwood 5,10, Damian Francis 5, Sarah Funnell 10,11, Elizabeth Ghogomu 1, Regina Greer-Smith 2, Tanya Hersley 3,11, Clara Juande-Prats 7,11, Janet Jull 1,2, Elizabeth Kristjansson 1, Julian Little 1, Stuart G. Nicholls 1,10, Miriam Nkangu 3, Mark Petticrew 11, Gabriel Rada 21,29, Anita Razi 27, Larissa Shamser 22,10, Melissa K. Sharp 26, Janice Tufte 27,10, Peter Tugwell 1,2,21, Francisco Verdugo-Paiva 23,24, Harry Wang 29, Xiaojia Wang 29, Lawrence Mbuagbaw 1,2 and Vivian Welch 1,4

**COMMENTARY**

Considerations and guidance in designing equity-relevant clinical trials

Lawrence Mbuagbaw 22, Theresa Aves 1, Beverley Sheu 9, Janet Jull 1, Vivian Welch 1,6,7, Monica Taljaard 6,9, Manosila Yoganathan 10, Regina Greer-Smith 2,11, George Wells 4,12,13, and Peter Tugwell 1,7,11,14
#7: Adopt the ICEMAN criteria for assessing credibility of subgroups effects (CMAJ 2020;192(32):E901-E906)
<table>
<thead>
<tr>
<th>Core question</th>
<th>Version; question no.*</th>
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<tbody>
<tr>
<td>Is the analysis of effect modification based on comparison within rather than between trials?</td>
<td>1</td>
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<td>For within-trial comparisons, is the effect modification similar from trial to trial?</td>
<td>2</td>
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<tr>
<td>For between-trial comparisons, is the number of trials large?</td>
<td>3</td>
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<td><strong>Was the direction of effect modification correctly hypothesized a priori?</strong></td>
<td>4</td>
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<tr>
<td>Was the effect modification supported by prior evidence?</td>
<td>2</td>
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<tr>
<td>Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?</td>
<td>5</td>
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<tr>
<td>Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?</td>
<td>6</td>
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<tr>
<td>Did the authors use a random-effects model?</td>
<td>7</td>
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<tr>
<td>If the effect modifier is a continuous variable, were arbitrary cut points avoided?</td>
<td>8</td>
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Why does this matter?
Representativeness is integral to the fundamental principle of “justice” ingrained in most research ethics guidelines.
Justice = The obligation to treat people fairly and equitably
Article 1.1: The guidelines in this Policy are based on the following three core principles:
- Respect for Persons
- Concern for Welfare
- Justice

Three basic principles, ..., are particularly relevant to the ethics of research involving human subjects: the principles of respect of persons, beneficence and justice.
These basic ethical principles—respect for persons, beneficence, and justice—are permeate all other GCP principles.
The consequences of lack of diversity or under-representation are serious!
DIVERSE REPRESENTATION IN CLINICAL RESEARCH MATTERS

By failing to achieve a more diverse clinical trial and clinical research enterprise, the nation suffers serious costs and consequences, including the following:

- Lack of representation compromises generalizability of clinical research findings to the U.S. population.
- Lack of representation costs hundreds of billions of dollars.\(^2\)
- Lack of representation may hinder innovation.
- Lack of representation may compound low accrual that causes many trials to fail.
- Lack of representation may lead to lack of access to effective medical interventions.
- Lack of representation may undermine trust.
- Lack of representation compounds health disparities in the populations currently underrepresented in clinical trials and clinical research.

\(^2\) The committee used the Future Elderly Model to value how chronic conditions differentially affect the lives of older Americans.
Lack of diversity costs lives and money

It is costly due to
• Premature deaths
• Poor health

It saves money
If just 1% of health disparities were alleviated by improved diversity in clinical trials, the Schaeffer model estimates that would result in more than $40 billion in gains for diabetes and $60 billion for heart disease.
Any potential disadvantages?
Interim analyses

• What is it?
  – Planned analysis of accumulating RCT data before the trial is complete

• Why: Provides several options and opportunities for the trial to
  – modify the trial design (re-estimate the sample size, drop/add some arms, etc)
  – stop the trial for efficacy, safety, or futility
  – continue the trial as originally planned
No apparent disadvantages

✓ It does not involve use of alpha-spending
✓ It is based on aggregate data—preserves blinding
✓ This is about monitoring fairness and equity in research inclusion, especially of vulnerable subgroups
✓ It provides opportunity to course correct
Who is responsible?
Monitoring overall representation is a collective responsibility

✓ Investigators
✓ Trial Steering Committees
✓ Research Ethics Boards/Institutional Review Boards
✓ Data Safety Monitoring Boards or Committees
✓ Research Ethics Guideline Developers
✓ Funders
✓ Sponsors
✓ Journal Editors
Using interim analysis to explore representativeness is worth exploring.

It is a collective responsibility aligned with the principle of "justice" in research.

It has no apparent cons, but lots of benefits:
- It does not involve use of alpha-spending or unblinding.
- It provides opportunity to course correct.
- Having a frame-work to guide process would need to include use of other frame-works for design, conduct, analysis and reporting.
thank you