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St. Joseph's Healthcare Hamilton

The Research Institute of St. Joe's Hamilton

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

Lehana Thabane

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

July 5-6, 2023

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!

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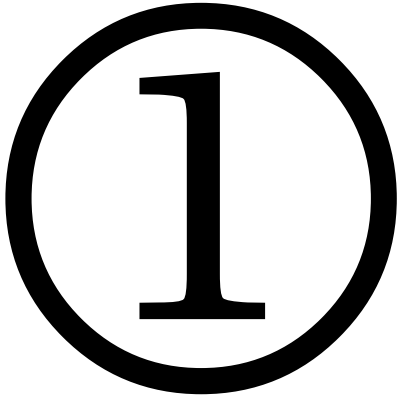
Interim analysis to assess for representativeness: worth a try or just a tribulation?

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

Variable	Target population distribution (%)
SEX: M F	
Ethnicity: A B C	
Social Demographic Index: Low Middle High	

#2: Determine the ideal proportional representation of each subgroup in the target sample for a trial

Variable	Target (%)	Sample distribution Total SS: n=XX
SEX: M F		
Ethnicity: A B C		
Social Demographic Index: Low Middle High		

#3: Adopt the Global Cardiovascular Clinical Trialists Forum strategy for enhancing representation in trials (*European Heart Journal* 2023;44(11):921–930)

JOURNAL ARTICLE

Improving representativeness in trials: a call to action from the Global Cardiovascular Clinical Trialists Forum

Lynaea Filbey, Jie Wei Zhu, Francesca D'Angelo, Lehana Thabane, Muhammad Shahzeb Khan, Eldrin Lewis, Manesh R Patel, Tiffany Powell-Wiley, J Jaime Miranda, Liesl Zuhlke, Javed Butler, Faiez Zannad, Harriette G C Van Spall ✉

Author Notes

European Heart Journal, Volume 44, Issue 11, 14 March 2023, Pages 921–930,
https://doi.org/10.1093/eurheartj/ehac810

Published: 25 January 2023 **Article history** ▾


Suboptimal recruitment and consent processes
Recruitment in inaccessible ambulatory settings
Lack of cultural competence in recruitment and consenting processes
Inability to address participant concerns
Language and cultural barriers
Restrictive eligibility criteria
Unjustified exclusion of women (including those pregnant or lactating), older adults or children
Ineligibility due to comorbidities or language barriers
Burdensome follow-up processes
High time and cost of attending in-person visits
Inadequate compensation for trial participation
Patient financial or caregiving responsibilities
Homogeneous trial leadership
Trial leadership teams composed of men-only researchers
Trial leaders geographically based in Europe and/or North America
Inadequate regional research capacity
Insufficient research funding
Lack of research infrastructure - health information technology, biobank, laboratory capacity
Inadequate research expertise, networks, collaborations
Inadequate accountability
Suboptimal adherence to guidance from regulatory and funding agencies for representative enrollment
Targeted, culturally competent recruitment
Create accessible and multilingual recruitment material
Use clinic-based, community-based and virtual recruitment
Consider adaptive recruitment strategies
Provide cultural competency training for frontline personnel
Select recruitment sites strategically
Inclusive eligibility and consent
Eliminate unjustified exclusion criteria
Avoid using language, education level, cognitive ability and socio-economic status as eligibility criteria
Use person-centered consent process including digital consent
Consider inclusion of next of kin or informal caregivers in discussion
Patient-centered processes
Engage with community advisory boards and patient advocacy groups
Minimize and reimburse costs of participation
Offer virtual follow-up and flexible clinic hours
Consider integration of trial with registry or administrative data to determine clinical outcomes
Diverse trial leadership
Ensure equal access to training, mentorship, funding and advancement opportunities for under-represented researchers
Build diverse collaborative networks with attention to gender, geography, ethnicity
Stronger research infrastructure
Promote research readiness
Collaborate with local citizens to identify barriers to participation
Invest in electronic medical research records, research facilities, databases and other resources that strengthen research capacity
Transparent reporting
Report consent rates by demographic characteristics
Use subgroup analysis to assess for effect modification in under-represented groups

#4: Adopt established frameworks in planning, design, and analysis

Heidari *et al. Research Integrity and Peer Review* (2016) 1:2
DOI 10.1186/s41073-016-0007-6

Research Integrity and Peer Review

REVIEW Open Access

Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use

Shirin Heidari[1], Thomas F. Babor[2*], Paola De Castro[3], Sera Tort[4] and Mirjam Curno[5]

Table 1 Sex and Gender Equity in Research (SAGER) guidelines

General principles

- Authors should use the terms *sex* and *gender* carefully in order to avoid confusing both terms.
- Where the subjects of research comprise organisms capable of differentiation by sex, the research should be designed and conducted in a way that can reveal sex-related differences in the results, even if these were not initially expected.
- Where subjects can also be differentiated by gender (shaped by social and cultural circumstances), the research should be conducted similarly at this additional level of distinction.

Recommendations per section of the article

Title and abstract	If only one sex is included in the study, or if the results of the study are to be applied to only one sex or gender, the title and the abstract should specify the sex of animals or any cells, tissues and other material derived from these and the sex and gender of human participants.
Introduction	Authors should report, where relevant, whether sex and/or gender differences may be expected.
Methods	Authors should report how sex and gender were taken into account in the design of the study, whether they ensured adequate representation of males and females, and justify the reasons for any exclusion of males or females.
Results	Where appropriate, data should be routinely presented disaggregated by sex and gender. Sex- and gender-based analyses should be reported regardless of positive or negative outcome. In clinical trials, data on withdrawals and dropouts should also be reported disaggregated by sex.
Discussion	The potential implications of sex and gender on the study results and analyses should be discussed. If a sex and gender analysis was not conducted, the rationale should be given. Authors should further discuss the implications of the lack of such analysis on the interpretation of the results.

J Clin Epidemiol. 2014 Jan;67(1):56-64. doi: 10.1016/j.jclinepi.2013.08.005. Epub 2013 Nov 1.

Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health

Jennifer O'Neill [1], Hilary Tabish, Vivian Welch, Mark Petticrew, Kevin Pottie, Mike Clarke, Tim Evans, Jordi Pardo Pardo, Elizabeth Waters, Howard White, Peter Tugwell

PROGRESS+

- **P**lace of residence
- **R**ace/ethnicity/culture/language
- **O**ccupation
- **G**ender/sex
- **R**eligion
- **E**ducation
- **S**ocioeconomic status
- **S**ocial capital
- + Other contextual factors

#5: Perform interim evaluation blinded aggregate recruitment data to monitor overall representation

Variable	Target (%)	Sample distribution: Total SS: n=XX	Interim : n (%)	On track: Y/N
SEX: M F				
Ethnicity: A B C				
Social Demographic Index: Low Middle High				

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)

Kent *et al. Trials* 2010, **11**:85
http://www.trialsjournal.com/content/11/1/85

METHODOLOGY Open Access

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

David M Kent[1*], Peter M Rothwell[2], John PA Ioannidis[1,3], Doug G Altman[4], Rodney A Hayward[5]

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 interquantile 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.

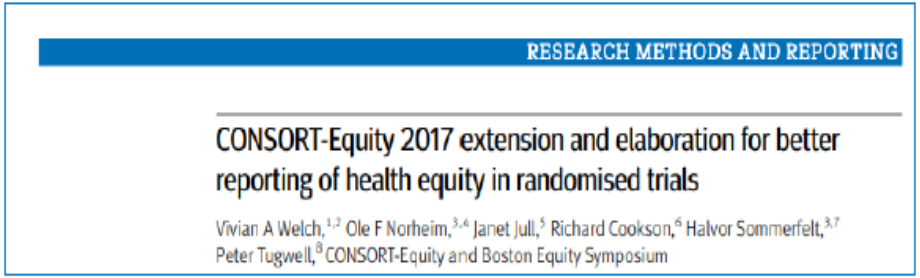
4. Conduct and report on secondary (exploratory) subgroup analyses separately from primary subgroup comparisons.

- 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,[3,4] Janet Jull,[5] Richard Cookson,[6] Halvor Sommerfelt,[3,7] Peter Tugwell,[8] CONSORT-Equity and Boston Equity Symposium

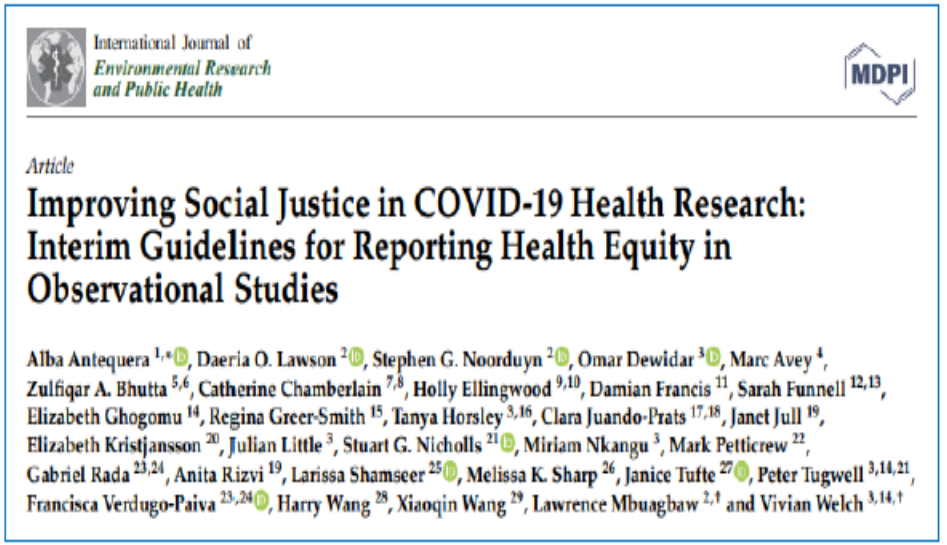
Mbuagbaw et al. International Journal for Equity in Health (2017) 16:93
DOI 10.1186/s12939-017-0591-1

International Journal for Equity in Health

COMMENTARY Open Access

Considerations and guidance in designing equity-relevant clinical trials

Lawrence Mbuagbaw[1,2*], Theresa Aves[1], Beverley Shea[3], Janet Jull[4], Vivian Welch[5,6,7], Monica Taljaard[8,9], Manosila Yoganathan[10], Regina Greer-Smith[11], George Wells[6,12,13] and Peter Tugwell[6,7,13,14]



International Journal of Environmental Research and Public Health

MDPI

Article

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

Alba Antequera [1,*], Daeria O. Lawson [2], Stephen G. Noorduyn [2], Omar Dewidar [3], Marc Avey [4], Zulfiqar A. Bhutta [5,6], Catherine Chamberlain [7,8], Holly Ellingwood [9,10], Damian Francis [11], Sarah Funnell [12,13], Elizabeth Ghogomu [14], Regina Greer-Smith [15], Tanya Horsley [3,16], Clara Juando-Prats [17,18], Janet Jull [19], Elizabeth Kristjansson [20], Julian Little [3], Stuart G. Nicholls [21], Miriam Nkangu [3], Mark Petticrew [22], Gabriel Rada [23,24], Anita Rizvi [19], Larissa Shamseer [25], Melissa K. Sharp [26], Janice Tufte [27], Peter Tugwell [3,14,21], Francisca Verdugo-Paiva [23,24], Harry Wang [28], Xiaoqin Wang [29], Lawrence Mbuagbaw [2,†] and Vivian Welch [3,14,†]

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#7: Adopt the ICEMAN criteria for assessing credibility of subgroups effects (*CMAJ* 2020;192(32):E901-E906)

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CANADIAN MEDICAL ASSOCIATION JOURNAL

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Research

Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses

Stefan Schandelmaier, Matthias Briel, Ravi Varadhan, Christopher H. Schmid, Nivedítha Devasenapathy, Rodney A. Hayward, Joel Gagnier, Michael Borenstein, Geert J.M.G. van der Heijden, Issa J. Dahabreh, Xin Sun, Willi Sauerbrei, Michael Walsh, John P.A. Ioannidis, Lehana Thabane and Gordon H. Guyatt

CMAJ August 10, 2020 192 (32) E901-E906; DOI: https://doi.org/10.1503/cmaj.200077

Table 1: Comparison of the core questions of the 2 versions of the Instrument for assessing the Credibility of Effect Modification Analyses

Core question	Version; question no.*	
	Randomized controlled trials	Meta-analyses
Is the analysis of effect modification based on comparison within rather than between trials?	–	1
For within-trial comparisons, is the effect modification similar from trial to trial?	–	2
For between-trial comparisons, is the number of trials large?	–	3
Was the direction of effect modification correctly hypothesized a priori?	1	4
Was the effect modification supported by prior evidence?	2	–
Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?	3	5
Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?	4	6
Did the authors use a random-effects model?	–	7
If the effect modifier is a continuous variable, were arbitrary cut points avoided?	5	8

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

TRI-COUNCIL POLICY STATEMENT

Ethical Conduct for Research Involving Humans

2014

Article 1.1:The guidelines in this Policy are based on the following three core principles:

- ❑**Respect for Persons**
- ❑**Concern for Welfare**
- ❑**Justice**

THE BELMONT REPORT

Office of the Secretary

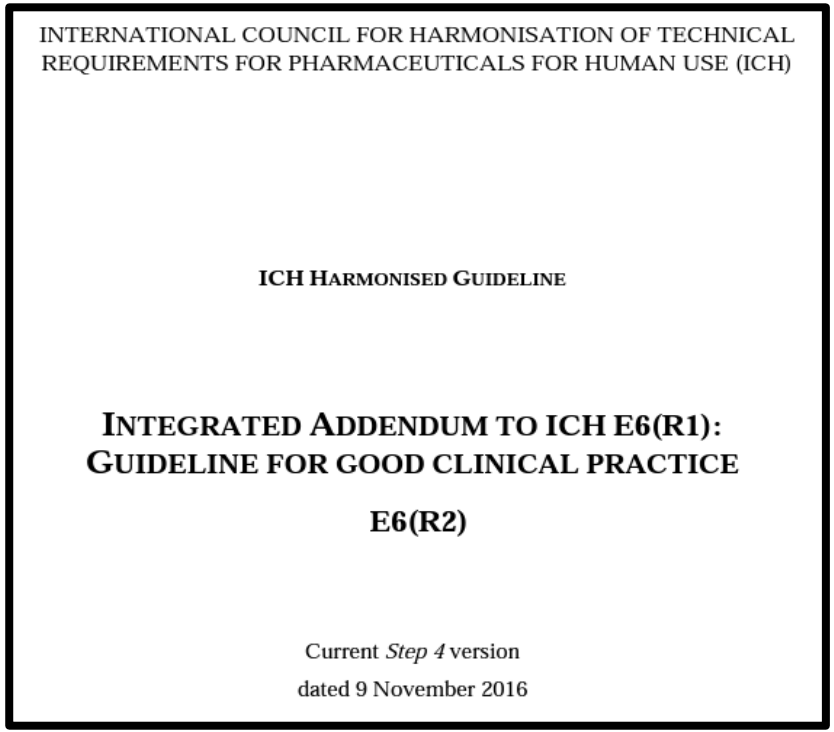
Ethical Principles and Guidelines for the Protection of Human Subjects of Research

The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research

April 18, 1979

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



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

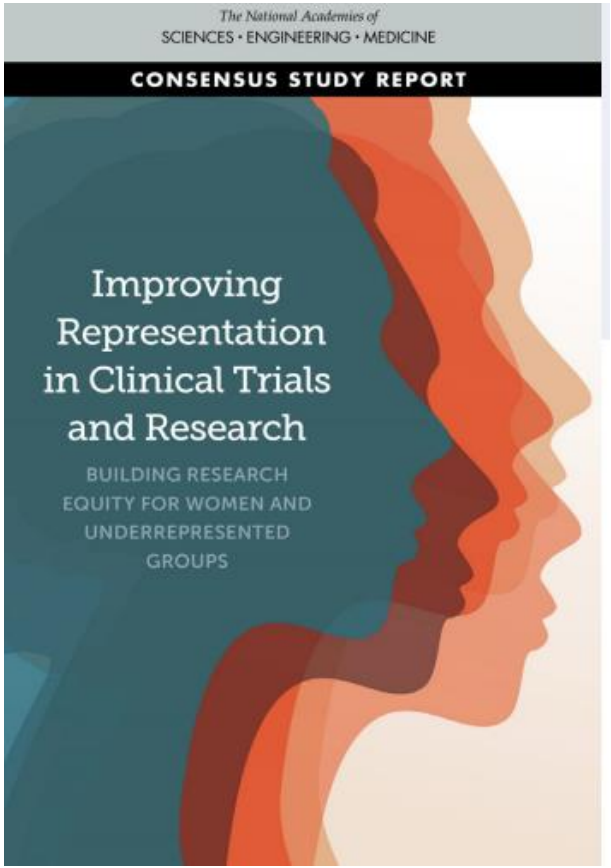
INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R2)

Current *Step 4* version

dated 9 November 2016

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

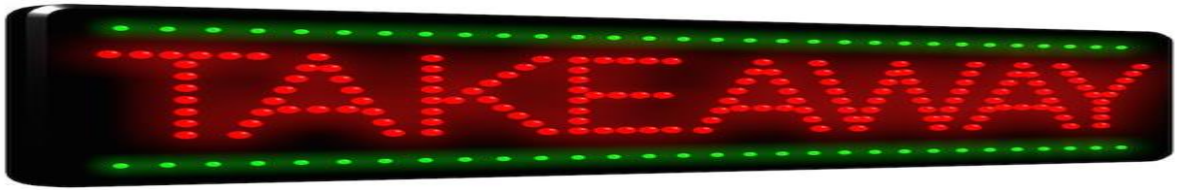
No apparent disadvantages

- ✓It doesnot 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 doesnot 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
danke
謝謝
ngiyabonga
شكراً جزيلاً
рахмат
teşekkür ederim
Баярлалаа
mersi
kia ora
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