Pre-Registration, Pre-analysis, and Transparent Reporting: *Perspectives from biomedical research*

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Summer Institute
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Outline

• History
• Registry: www.ClinicalTrials.gov
  – Is it working? What could be improved?
• Reporting Guidelines: CONSORT
  – Is it working? What could be improved?
• Extensions to observational research
• Innovations in design and analysis: combining pre-specification and flexibility

June 2015
BITSS Summer Institute
A brief history of clinical trial registration

Early 2000s:

• Patient advocacy for access to trial information (enrollment possibilities and results)
  – Ethical Principles as outlined in Belmont Report
    1. **Respect for persons**: protecting the autonomy of all people; Researchers must be truthful and conduct no deception;
    2. **Beneficence**: "Do no harm" while maximizing benefits for the research project and minimizing risks to the subjects
    3. **Justice**: the fair distribution of costs and benefits

• High profile cases bring publication bias (results suppression) to the public eye
  – Selective Serotonin Reuptake Inhibitors (SSRIs) and suicide
  – Cox-2 Inhibitors (Vioxx) and Heart Attacks/Death

Gill CJ. *BMJ Open* 2012;2:e001186
High profile cases bring publication bias to the public eye

• Vioxx and heart attacks
  – Wall St Journal 2004 cites unpublished FDA study estimating >27,000 avoidable heart attacks and sudden cardiac deaths attributable to use of Vioxx.
  – Subsequent lawsuit and 4.85 Billion $ settlement by Merck

• SSRIs and suicide among children/adolescents
  – FDA report 2004: Increased suicide risk in children
  – “What is disturbing about the recent report is that the purported link between Paxil and suicidal thinking comes from an unpublished study sponsored by Paxil's manufacturer, GlaxoSmithKline. In fact, GlaxoSmithKline has published only one of its nine studies of Paxil in children and adolescents to date.” (NY Times Op Ed: Friedman 2004)
Ex. Publication Bias in Antidepressant Trials

74 Studies with data submitted to FDA (1987-2004)

- 36 “negative”
  - 3 published as negative
  - 11 published to imply positive
  - 22 not published

- 38 “positive”
  - 37 Published

Push to improve objectivity in the conduct, reporting and dissemination of clinical research

- Stricter conflict of interest standards/reporting
- Stricter requirements on financial disclosures
- Changing marketing practices by Pharma
- Open access to publications and data
- Registration of trials and results summaries
- Transparent reporting
2004: Major medical journals require trial registration as precondition for publication

“In return for the altruism and trust that make clinical research possible, the research enterprise has an obligation to conduct research ethically and to report it honestly. Honest reporting begins with revealing the existence of all clinical studies, even those that reflect unfavorably on a research sponsor's product.”
US Federal Law mandates registration of all clinical trials

- 1997: Registration required for selective trials
- 1999: Registry created (ClinicalTrials.gov)
- 2007: Registration/reporting requirements expanded; functionality for results upload added

• National Institutes of Health/National Library of Medicine
  – Currently: 192,170 studies; 190 Countries
• Registration of clinical trials required
  – Protocol summary prior to enrolling patients
  – Results summary within 1 year of completion (for many trials)
• Registration of other health studies optional
  – Observational
    • Definition: Investigators did not assign the intervention
  – Including patient registries
• Other registries also available
  – Ex: World Health Organization: www.who.int/ictrp
“Trial Life Cycle”: D. Zarin, NLM

1. Initial registration
2. Updates, as necessary
   - Enrollment
   - Key dates
   - Recruitment status
   - Other protocol changes
3. Initial results reporting
4. Updates, as necessary
   - All changes tracked
Let’s look at the site…

• **Ex. Ongoing study: HPTN 052**

• **Look at**
  – Required Elements (by ICMJE, WHO also)
  – Views- Tabular
  – Linked to PubMed and publications automatically
  – Clinical trial #- searchable: show in Pubmed…
  – Outcomes and intervention, but not full analysis plan
    • Show can link to the protocol from the publication… Nov 2006
  – Look at changes- see complete history
    • Note under description- cross over of control to intervention arm due to DSMB May 2011
Use of the Registry

www.clinicaltrials.gov/ct2/resources/trends
Registry provides a searchable record of unpublished studies

- <25% of registered studies published

- 22.4% of registered RCTs completed pre 2005 and 2005 -2010
  - Published by 2012

Shamliyan & Kane 2014 *Journal of Epidemiology and Global Health* 4: 1-12
Imperfect Compliance

- 323 trials Indexed 2008 in high impact journals
- 45.5% adequately registered
  - Before the end of the trial
  - Primary outcome clearly specified
- Of these, 31% had discrepancies between the outcomes registered vs. published.

Mathieu et al.; JAMA. 2009;302(9):977-984
Results reporting on the registry

Number of Registered Studies With Posted Results Over Time
(as of June 09, 2015)

Source: http://ClinicalTrials.gov

www.clinicaltrials.gov/ct2/resources/trends
Minority of Studies Report Results

- 13,327 registered trials classified as “likely that results reporting required”
- 38% reported results
  - 13% reported results within 12 months of completion
  - After adjustment for FPs, legal compliance ~80% for industry, ~50% in NIH
  - 10% of registered trials not highly likely required to report results did so

Let’s look at the site...

• Ex 1. High profile trial without results: HPTN 052
  – “Breakthrough Study to end the HIV Epidemic”
  – Technically ongoing, but primary endpoint has been analyzed
  – Linked to open access publication, online supplementary materials.

• Ex. 2: Completed study with results: Healthy Love
  – Advanced Search: “HIV behavioral”, interventional, completed, with results
  – Look at changes
    • Changes to primary outcomes post- date study completion
  – Look at results
  – What is and is not reported
  – Link to publication
Is results reporting useful?

• Provides an additional data source
  – Random sample 600 registered drug trials with results posted
    • Posted median 19 mo after completion (IQR 14,30)
    • 50% unpublished
    • Of those published, participant flow, efficacy and adverse events reporting more likely complete in the registry
  – Meta-analyses/systematic reviews increasingly searching registry
  – Only 34% of reviewers consult the registry
• “The usefulness of ClinicalTrials.gov ultimately depends on whether responsible investigators and sponsors make diligent efforts to submit complete, timely, accurate, and informative data about their studies” (Zarin 2011 NEJM)

ClinicalTrials.gov: Lessons Learned

• Journals can have a transformative impact
• Minority of trials report results
  – Legal compliance higher, especially among industry sponsored late phase trials (~80-90%)
• Registration does not prevent
  – Publication bias
  – Lack of transparency in analysis, reporting trial results
  – Selective outcome reporting
• Registry does provide a valuable, searchable record
• Translating this into greater accountability?
  – Growing literature based on analyzing the registry
  – Changing norms, reviewer practices
  – Legal Enforcement
Transparent Reporting Initiatives

- **CONSORT: Consolidated Standards of Reporting Trials**
  - [www.consort-statement.org](http://www.consort-statement.org)
- **Objective:** “Create Unified Standards to improve the quality and transparency in reporting of clinical trials”
  - Development led by medical journal editors, clinical trialists, epidemiologists, and methodologists
  - 1996; updated 2010
- **25 Item Checklist**
  - Reporting how the trial was designed, analyzed, and interpreted
- **Flow Diagram**
  - Progress of all participants through the trial
- **Required or endorsed by many journals**
CONSORT Checklist (1)

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)</td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
<td></td>
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<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
<td></td>
</tr>
<tr>
<td>Methods</td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>7a</td>
<td>How sample size was determined</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
<td></td>
</tr>
<tr>
<td>Randomisation:</td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
<td></td>
</tr>
<tr>
<td>Implementation</td>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
<td></td>
</tr>
<tr>
<td>Blinding</td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those analysing outcomes)</td>
<td></td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>-----</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12b</td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participant flow</td>
<td>13a</td>
<td>For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
<td></td>
</tr>
<tr>
<td>Recruitment</td>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>14b</td>
<td>Why the trial ended or was stopped</td>
<td></td>
</tr>
<tr>
<td>Baseline data</td>
<td>15</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
<td></td>
</tr>
<tr>
<td>Numbers analysed</td>
<td>16</td>
<td>For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
<td></td>
</tr>
<tr>
<td>Outcomes and</td>
<td>17a</td>
<td>For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td>estimation</td>
<td>17b</td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
<td></td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
<td></td>
</tr>
<tr>
<td>Harms</td>
<td>19</td>
<td>All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
<td></td>
</tr>
<tr>
<td>Discussion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limitations</td>
<td>20</td>
<td>Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
<td></td>
</tr>
<tr>
<td>Generalisability</td>
<td>21</td>
<td>Generalisability (external validity, applicability) of the trial findings</td>
<td></td>
</tr>
<tr>
<td>Interpretation</td>
<td>22</td>
<td>Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence</td>
<td></td>
</tr>
<tr>
<td>Other information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>23</td>
<td>Registration number and name of trial registry</td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>24</td>
<td>Where the full trial protocol can be accessed, if available</td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>25</td>
<td>Sources of funding and other support (such as supply of drugs), role of funders</td>
<td></td>
</tr>
</tbody>
</table>

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).*
CONSORT Flow Diagram

1. Enrollment
   - Assessed for eligibility (n= )
     - Excluded (n= )
       - Not meeting inclusion criteria (n= )
       - Declined to participate (n= )
       - Other reasons (n= )
   - Randomized (n= )

2. Allocation
   - Allocated to intervention (n= )
     - Received allocated intervention (n= )
     - Did not receive allocated intervention (give reasons) (n= )
   - Allocated to intervention (n= )
     - Received allocated intervention (n= )
     - Did not receive allocated intervention (give reasons) (n= )

3. Follow-Up
   - Lost to follow-up (give reasons) (n= )
   - Discontinued intervention (give reasons) (n= )
   - Lost to follow-up (give reasons) (n= )
   - Discontinued intervention (give reasons) (n= )

4. Analysis
   - Analysed (n= )
     - Excluded from analysis (give reasons) (n= )
   - Analysed (n= )
     - Excluded from analysis (give reasons) (n= )
Example 1: HPTN 052

- 10,838 (5,419 couples) screened for study
  - 7,312 (3,656 couples) excluded before randomisation
  - 1,763 HIV-1 infected participants with an HIV-serodiscordant partner were randomly assigned
  - 886 assigned to early treatment
  - 877 assigned to delayed treatment
    - 2 enrolled in the USA excluded
    - 213 started antiretroviral treatment at a median of 3.8 years
    - 33 discontinued follow-up before May 11, 2011
      - 11 (33%) died
      - 15 (46%) refused further participation
      - 3 (9%) unable to adhere to schedule
      - 1 (3%) relocated
      - 1 (3%) investigator decision
      - 2 (6%) unable to contact participant
    - 853 in follow-up on May 11, 2011
      (median follow-up 2.1 years)
    - 848 in follow-up on May 11, 2011
      (median follow-up 2.1 years)

Example 2: “Healthy Love”

Fig. 1 Flow diagram of participant recruitment, allocation and retention in an evaluation of the Healthy Love Workshop, Atlanta, Georgia, 2006–2007 (Note: k refers to number of groups; n refers to number of women)

Groups screened for eligibility (k = 58)

Groups excluded (k = 28):
- No follow-up by group contact person (k = 10)
- Participants did not arrive for workshop (k = 7)
- Insufficient number of participants (k = 6)
- Insufficient interest in workshop (k = 5)

Group pairs matched and randomized (k = 30)

Healthy Love Workshop
(k = 15; n = 161)

HIV 101 Comparison Workshop
(k = 15; n = 152)

3-Month follow-up
72.0% retained (n = 116)

6-Month follow-up
75.2% retained (n = 121)

3-Month follow-up
76.3% retained (n = 116)

6-Month follow-up
77.0% retained (n = 117)

CONSORT Lessons Learned

• Highly cited; high profile
• Change practice? Probably some
  – Meta-analysis of studies looking at compliance with CONSORT
  – Post- CONSORT and endorsing journals have more complete reporting by some measures
    • Adverse events, participants analyzed, baseline data
• Compliance is imperfect even among endorsing journals
  – Variability in how endorsing journals apply/enforce guidelines
• Guidelines for reporting analyses are vague
  – Ex: # 18: “Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory”

Turner et al, Systematic Reviews 2012 1:60
A limitation of both...

- Much of the clinical trial transparency framework works best for unadjusted comparisons of outcomes between randomization groups....
  - Easy to pre-specify and harder to manipulate
  - But limiting, and does not reflect practice
    - 50% of a random sample of trials reported adjusted results for primary outcome (Saquib et al, BMJ 2013)

- More complex methods needed (and often used) to
  - Improve power
  - Reduce bias due to loss to follow up/missing data
  - Answer more complex questions
    - As treated effects, effects among compliers, mediation effects, spill over...

- Neither the registry nor reporting guidelines capture the many analytic decisions that go into these analyses
Analysis Plans in Practice: Ex HPTN 052

- Registry: Primary and secondary outcome specification
- Data Protocol
  - Hyperlinked from primary publication
    - *This is not the norm
  - Dated
  - See TOC
  - More detail, but still a lot left unspecified
    - P. 99
- Fully specified Analysis Plan
  - Likely on file
  - Not (to my knowledge) registered
Full analysis plans are rarely pre-specified

- 200 trials published 2009 in highest impact journals

<table>
<thead>
<tr>
<th>Trial registration (n=199)</th>
<th>Design paper (n=199)</th>
<th>Author response (n=199)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (n=37)</td>
<td>No (n=169)</td>
<td>No (n=133)</td>
</tr>
<tr>
<td>Yes (n=162)</td>
<td>Yes (n=30)</td>
<td>Yes (n=66)</td>
</tr>
<tr>
<td>Registration information accessible online</td>
<td>Full text available online</td>
<td>Full protocol provided</td>
</tr>
<tr>
<td>No (n=4)</td>
<td>No (n=3)</td>
<td>No (n=12)</td>
</tr>
<tr>
<td>Yes (n=158)</td>
<td>Yes (n=27)</td>
<td>Yes (n=54)</td>
</tr>
<tr>
<td>Adjustment information available</td>
<td>Adjustment information available</td>
<td>Adjustment information available</td>
</tr>
<tr>
<td>No (n=149)</td>
<td>No (n=6)</td>
<td>No (n=14)</td>
</tr>
<tr>
<td>Yes (n=9)</td>
<td>Yes (n=21)</td>
<td>Yes (n=40)</td>
</tr>
</tbody>
</table>

**Total No of trials with available adjustment information from registry, design paper, or protocol (n=61)**

- Of those that did, analysis plan and publication differed in 47%

Saquib et al, *BMJ* 2013;347:f4313
A tough problem...

- On the one hand... without pre-specification -> bias and misleading inference
  - “protocols need to be entirely transparent and their analysis plans explicit in detail upfront. There should be no room for flexibility in the collected data and performed analyses.” Ioannidis, Philos Ethics Humanit Med 2008

- On the other hand... Optimal analysis often requires flexibility

- Examples of both from Social Sciences coming up next... (Kate Casey)
Observational data are even more challenging

- Even with a pre-specified hypothesis, observational analyses often entail many more analytic decisions
  - Identification strategy
    - Difference in difference, adjustment for measured confounders, IV, etc.
  - Estimator
    - Outcome regression methods, propensity score matching/adjustment/reweighting, etc.
  - Model specification
    - Which adjustment variables to include in outcome regression, functional form, etc..
- And what about exploratory analyses, hypothesis generation, unexpected findings...?
- Both registration and pre-specification challenging- and arguably more important than ever...
Where are we with observational studies?

Registration

• Available (Ex. www.clinicalTrials.gov)
• Not required by major journals
• Rarely done
  – 90+% of studies published each year are observational
  – 18% of studies registered at ClinicalTrials.gov are observational
    • N=31,449
  – Those registered are largely secondary analyses of registered trials, or have purely descriptive aims
• Registered pre-analysis plans rare
  – Some information often available in “concept sheets” that must be approved prior to some database release

www.clinicaltrials.gov/ct2/resources/trends
Where are we with observational studies?

Transparent Reporting

• Standardized Reporting Guidelines
  – Ex. Strengthening Reporting of Observational Studies in Epidemiology (STROBE)
  – www.strobe-statement.org

• Journal endorsement still not the norm (but growing)

• Distinct checklists for various study designs
  – Example: Cohort checklist
### STROBE Statement—Checklist of items that should be included in reports of cohort studies

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Title and abstract** | 1. Indicate the study’s design with a commonly used term in the title or the abstract  
2. Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | Explain the scientific background and rationale for the investigation being reported |
| **Objectives** | State specific objectives, including any prespecified hypotheses |
| **Methods** | 4. Present key elements of study design early in the paper |
| **Setting** | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| **Participants** | 6. (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up  
(b) For matched studies, give matching criteria and number of exposed and unexposed |
| **Variables** | 7. Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| **Data sources/measurement** | 8. For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| **Bias** | 9. Describe any efforts to address potential sources of bias |
| **Study size** | 10. Explain how the study size was arrived at |
| **Quantitative variables** | 11. Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| **Statistical methods** | 12. (a) Describe all statistical methods, including those used to control for confounding  
(b) Describe any methods used to examine subgroups and interactions  
(c) Explain how missing data were addressed  
(d) If applicable, explain how loss to follow-up was addressed  
(e) Describe any sensitivity analyses |
# Strobe Checklist (2)

## Results

| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed  
| | | (b) Give reasons for non-participation at each stage  
| | | (c) Consider use of a flow diagram  
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  
| | | (b) Indicate number of participants with missing data for each variable of interest  
| | | (c) Summarise follow-up time (eg, average and total amount)  
| Outcome data | 15* | Report numbers of outcome events or summary measures over time  
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included  
| | | (b) Report category boundaries when continuous variables were categorized  
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period  
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses  

## Discussion

| Key results | 18 | Summarise key results with reference to study objectives  
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias  
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence  
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results  

## Other information
Where are we with observational studies? Transparent Reporting

- **Transparency declaration: BMJ 2013**
  - “The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.”

- Given the complexity of many observational analyses, what does this mean in practice?

Altman DG, Moher D. BMJ 2013: 347
Should we register observational studies?

The Registration of Observational Studies—When Metaphors Go Bad

Making Prospective Registration of Observational Research a Reality
The Debate: Be careful!

- Growing discomfort with how often we get things wrong
- Need to maintain our foundation for valid statistical inference

Why Most Published Research Findings Are False

John P. A. Ioannidis
Should we register/pre-specify observational studies? Yes

• Same rationale as randomized trials
  – Ethics
  – Knowledge dissemination/avoidance of unnecessary duplication
  – Guard against publication bias
  – Ideally detailed analysis plans would also be registered

• Little burden
  – Observational studies need IRB approval
  – Register the protocol

• Can incorporate flexibility
  – Register changes to protocol
  – Delineate between pre-specified and post-hoc hypotheses

The Debate: Use data fully!

• Increasing access to huge rich data sets, increasingly available in real time = opportunity
  – Lots of subjects, lots of variables, lots of “complexity”

• Optimizing impact means finding ways to accelerate, not slow, the cycle of learning from data

Data Scientist: The Sexiest Job of the 21st Century

Meet the people who can coax treasure out of messy, unstructured data.
by Thomas H. Davenport and D.J. Patil

70 Harvard Business Review October 2012
Should we register/pre-specify observational studies? No

• We will test many **fewer hypotheses**
  – Reduce new and unexpected findings

• **We may test them less rigorously**
  – Prespecified analyses may give us less valid hypothesis tests
  – “Protocol adaptations can improve recruitment, allow more accurate measurement of study variables, implement alternative analyses to control confounding, and incorporate new knowledge published by others.” (Lash, Epidemiology 2010)

• We will learn **more slowly**
  – The drug approval process is notoriously slow
  – “cancerous growth of bureaucracies to protect human subjects in observational studies”(Editors, Epidemiology 2010)

• Simply allowing for post-hoc analyses designated as such is not sufficient
  – If analyses not pre-registered and fully pre-specified are penalized in the review and publication process
Towards an adaptive learning paradigm...

- Accelerating the cycle of learning from and responding to data
  - Optimize flexibility in a pre-specified way -> maintain statistical rigor

1. **Pre-specified adaptation in design**
- **Sequentially Randomized Trials** to evaluate adaptive interventions
  - Interventions that assign or alter an individual’s treatment over time based on the evolving characteristics (such as response) of that individual
- **Adaptive Trial Designs:**
  - Change your trial design (eg. primary hypothesis) based on looking at the data
  - Modify what types of subjects you enroll, what arms you randomize them to...

1. **Pre-specified adaptation in analysis**
- **Targeted Learning**
  - Combine machine-learning and statistical inference
  - Look at the data to decide which variables to adjust for, model specification
- **Data-adaptive parameters**
  - Choose your estimand based on looking at the data
Ex.1: Sequentially Randomized Trials

• Also called Sequential Multiple Assignment Randomized Trials (SMART)

• Evaluation of “Adaptive strategies”: Strategies for assigning intervention over time based on evolving individual characteristics

• Design

1. Subjects randomized to a 1st line intervention

2. At pre-specified decision points, randomized to a 2nd line intervention,

• Set of arms randomized to at each stage can depend on the past
“An Adaptive Strategy for Preventing and Treating Lapses of Retention in HIV Care (AdaPT-R).”

- PIs: Elvin Geng (UCSF), Petersen
- 2500 Adult HIV patients in Kenya
- Best (most effective and cost effective) strategy to keep them engaged in care?
SMART: Evaluate and compare wide range of adaptive strategies

- “Embedded strategies”
  - Ex: 1st line: SMS for all patients; 2nd line: SMS + Voucher for those that fail 1st line

- Strategies with a greater degree of personalization (“tailoring”)
  - 1st line: Voucher for patients who live “far” from clinic, SMS for the rest
  - 2nd line: Peer Navigators for those that fail 1st line and report “low” satisfaction with care, SMS + Voucher for those who fail 1st line and report “high” satisfaction
  - Can estimate how best to define “far” and “low” without sacrificing inference
Conclusion

• Biomedical research grappling with this issue for a while
  – Some good progress
    • Awareness/Culture change
    • Registration systems in place and being used (even if imperfectly)
    • Move towards more transparent reporting
  – And a long way to go
    • Registered fully pre-specified analysis plans remain rare
    • Continued debate on whether and how to extend to observational studies

• Convergence between the biomedical and social sciences
  – Subject matter: Health behaviors, health and development, ...
  – Methodology: Big Data, Transparency, Replication...

• Biomedicine can learn a lot from the transparency movement in the social sciences...