Interpreting and Publishing Trial Results

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Disclosures

- NONE

Outline

- Interpreting Trials
  - Selection, Randomization, Blinding
  - Interventions, Outcomes, Effect Size
- Publishing Trials
  - Trial Registration
    - ICMJE
  - Trial Reporting
    - CONsort
  - Manuscript preparation tips

Interpreting Trial Results

‘All meanings, we know, depend on the key of interpretation’

- *George Eliot*

(English novelist, journalist, and translator: 1819-1880)

Key Issues for Interpreting Randomized Trials

1. Subject selection
2. Randomization
3. Blinding
4. Interventions
5. Outcomes
6. Effect size measure
7. Nature of Effect

Subject Selection

- Based on:
  - inclusion/exclusion criteria
  - recruitment procedures

- Common selection pressures:
  - Homogeneity
    - Reduces variability
  - Higher risk for the outcome
    - Increases power
  - Lower risk for adverse outcomes
    - Increases likelihood of finding benefit
  - Convenience
    - Decreases scope

Subject Selection (2)

- Selection pressures come at a cost
  - Reduced Generalizability!

- *Where were the participants recruited from (primary care / referral center)?*
- *Do the inclusion and exclusion criteria make sense?*
- *What proportion of the screened population was recruited?*
- *Is my patient similar to the study population?*
- *Is the treatment feasible in my clinical setting?*
- *Will potential benefits of treatment outweigh potential harms of treatment for my patient?*

1. Key Question: *Is it reasonable to extend the result to the patients I see?*

Randomization

- Several methods
  - Computer-based, sealed envelopes, random number tables
- Need to avoid gaming
  - Treating every other patient is problematic
  - Should be independent of investigators
- Can increase likelihood of balance
  - "Blocked" randomization

Key Question: *Were the groups similar at the start of the trial?*

The Spine Patient Outcomes Research Trial (SPORT)

S[illegible]n

L2-3/L3-4	16 (7)	16 (7)
L4-5	80 (34)	85 (35)
L5-S1	136 (59)	138 (57)
Herniation type		
Protruding	59 (25)	67 (28)
Extruded	156 (67)	157 (65)
Sequestered	17 (7)	15 (6)
Posterolateral herniation	182 (78)	195 (81)
SF-36 score, mean (SD)¶		
Bodily pain	27.1 (18.5)	26.7 (17.4)
Physical function	39.7 (24.9)	39.2 (25.7)
Mental component summary	46.3 (12.1)	45.5 (11.9)
Oswestry Disability Index, mean (SD)#	47.5 (21.4)	46.3 (20.6)
Sciatica indices, mean (SD)#		
Frequency	15.8 (5.5)	15.4 (5.5)
Bothersomeness	15.4 (5.1)	15 (5.3)
Satisfaction with symptoms: very dissatisfied	184 (79)	185 (77)
Patient self-assessed health trend		
Problem getting better	42 (18)	48 (20)
Problem staying about the same	108 (47)	112 (47)
Problem getting worse	82 (35)	79 (33)

Abbreviation: SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey.
*All between-group differences nonsignificant at the ≥.05 level.
†Receiving workers' compensation, social security compensation, or other compensation, or application(s) pending.
‡Calculated as weight in kilograms divided by the square of height in meters.
§Indicates problems related to stroke, diabetes, osteoporosis, cancer, fibromyalgia, chronic fatigue syndrome, post-traumatic stress disorder, alcohol, drug dependency, heart, lung, liver, kidney, blood vessel, nervous system, hypertension, migraine, anxiety, stomach, bowel.
‖The diagnoses for approximately 97% of patients were evaluated with magnetic resonance imaging and 3% with computed tomography.
¶Higher score indicates less severe symptoms. Range, 0-100.
#Lower score indicates less severe symptoms. Range for Oswestry Disability Index, 0-100; for sciatica indices, 0-24.

"Computer-generated random treatment assignment based on permuted blocks (randomly generated blocks of 6, 8, 10, and 12) within sites occurred immediately after enrollment via an automated system at each site, ensuring proper allocation concealment."

Weinstein, J. N. et al. JAMA 2006;296:2441-2450

Blinding

- Knowledge of treatment may lead to bias
  - Subject may over- or under-rate benefits
  - Investigator may do the same
  - Subjects may seek out other treatments
- Placebo control or sham surgery may be required
- If blinding subject is not feasible
  - evaluator can be blinded (single-blind) or more objective outcome used

2. Key Question: *Could knowledge of treatment have altered results?*

Interventions

- Should be replicable
  - Benefit of multicenter studies

- Control intervention should isolate the most important components
  - Only differences between the care between groups should be those intrinsic to the treatments being compared

3. Key Question: *Were the groups treated equally, apart from the experimental treatment?*

Outcomes


Multiple Sclerosis
Brain inflammation
MRI changes
Attacks
QOL/Mortality
Surrogate
Patient related

Outcomes (2)

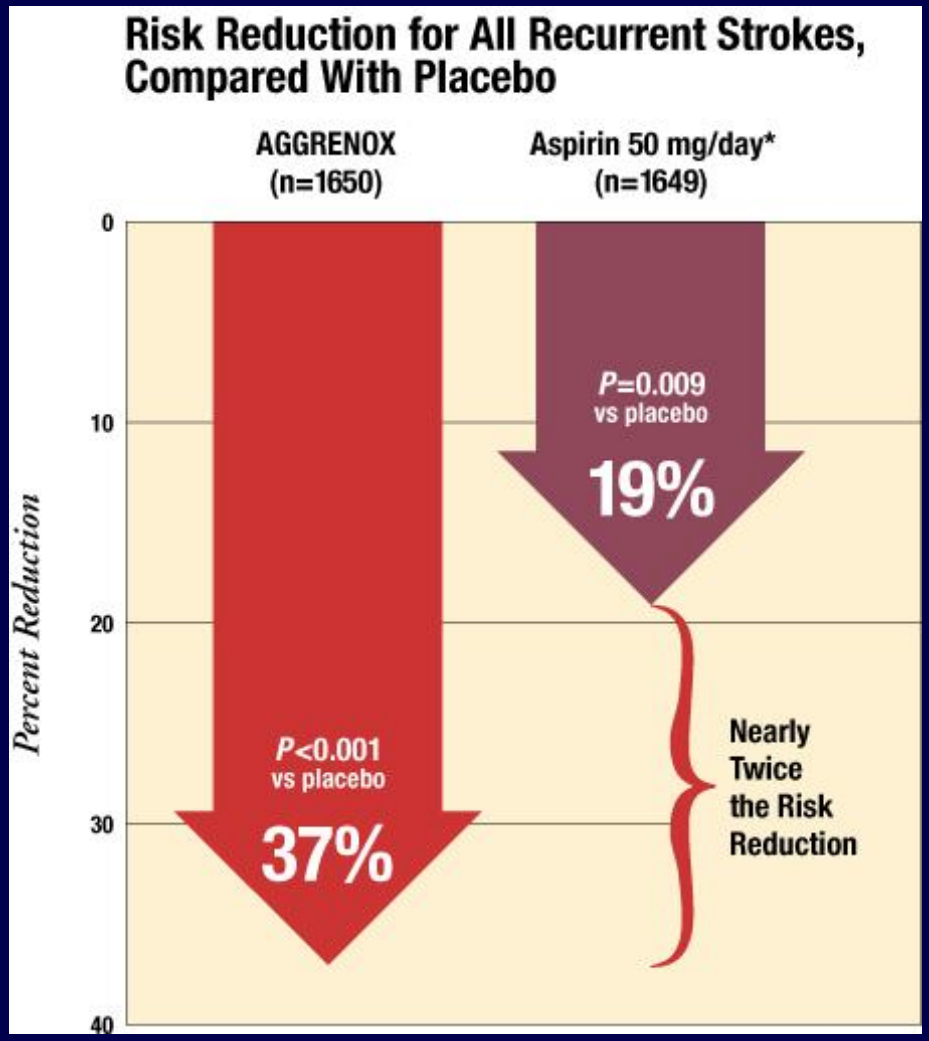
- Single primary outcome
- Composite secondary outcome

- ASA/ER-Dipyridamole v. ASA

Stroke: p=0.006

Death: p=0.78

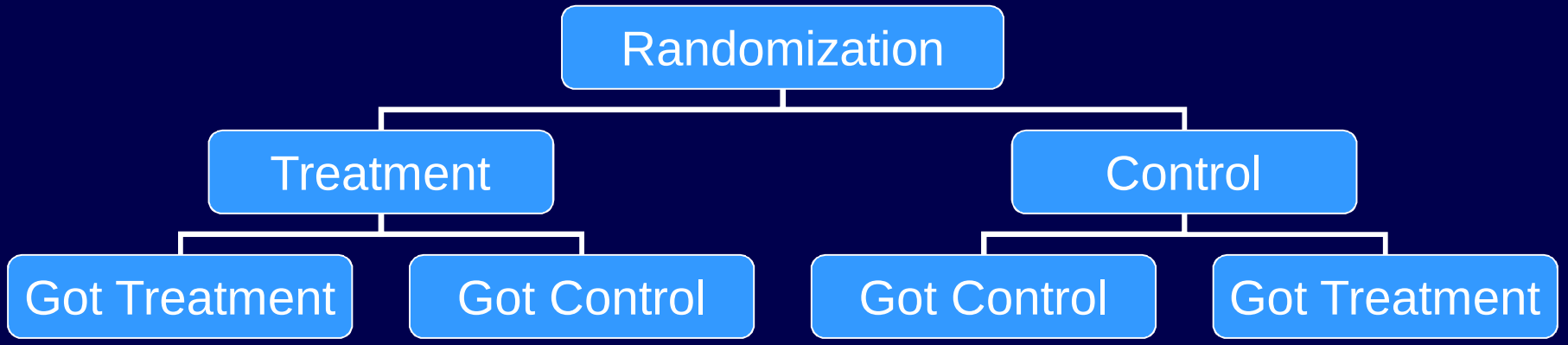
Stroke/Death: p=0.056



ESPS-2 Study. Journal of Neurological Sciences 1996.

Outcomes (3)

- Intention to treat



- Switching may be related to prognosis

Key Question: Were all patients analysed in the groups to which they were randomized?

Treatment Effect

Key Qs to Ask

- **Is there a treatment effect?**
- **What are the possible causes of the treatment effect?**
  - **Bias - Is there SPAM (Selection, Performance, Attrition, Measurement)?**
  - **Placebo**
  - **Chance**
  - **Real effect**
- **How large is the treatment effect?**
  - Relative risk reduction (may obscure comparative absolute risks)
  - Absolute risk reduction: is this clinically significant?
- **How precise is the treatment effect?**
  - What are the confidence intervals?
  - Do they exclude the null value?

    (e.g., is the result statistically significant– magnitude of Chi-square or F-value)

Effect Measures

- "Effect Size" vs. P-values

- Relative vs. Absolute effect sizes
  - Relative risk (RR) and RR reduction (RRR)
  - Absolute risk reduction (ARR) and Number needed to treat (NNT)

Effect Size vs. P-values

- Effect size
  - How big is the difference between the groups?
- P-value
  - How big is the difference compared with what might be expected by chance alone?

P-values

Very dependent on sample size

- Small sample size
  - *clinically significant effects can be missed*
- Large sample size
  - *statistically significant* effects might NOT be *clinically significant*

Clopidogrel for MI/Stroke Prevention

- CAPRIE: RCT, N=19,185
- ***"Long-term administration of clopidogrel to patients with atherosclerotic vascular disease is more effective than aspirin"***
- P=0.043
- Effect size
  - After 1.9 years - event rate 5.83% on aspirin vs. 5.32% on clopidogrel

*CAPRIE Steering Committee, LANCET, 348:1329, 1996.

Effect Size: Relative vs. Absolute

(Dichotomous Outcome Variables)

1. RR = Relative Risk
   - ***Risk in intervention group/Risk in control group***
2. RRR = Relative Risk Reduction
   - *1-RR*
3. ARR = Absolute Risk Reduction
   - ***Risk in control group - Risk in intervention group***
4. NNT = Number Needed to Treat
   - *1/ARR*

Effect Size: Relative vs. Absolute

Example 1: Intervention group: 15%, Control group 20%

- RR = 15%/20% = 0.75
- RRR = 1-0.75 = 0.25
- ARR = 20% - 15% = 5%
- NNT = 20

Effect Size: Relative vs. Absolute

Example 2: Intervention group 5%, Control group 15%

- RR = 5%/15% = 0.33
- RRR = 1-.33 = 0.67
- ARR = 15% - 5% = 10%
- NNT = 10

Relative Risk Reduction:

Does Not Discriminate Treatment Effect Size

Control Event Rate	Experimental Event Rate	Relative Risk Reduction
0.16	0.10	37.5%
0.016	0.010	37.5%
0.0016	0.0010	37.5%

Note: a reduction in event rate from 16% to 10% provides the same RRR as a reduction in event rate from 0.16% to 0.10%

Absolute Risk Reduction:

Does Discriminate Treatment Effect Size

Control Event Rate	Experimental Event Rate	Relative Risk Reduction	Absolute Risk Reduction
0.16	0.10	37.5%	6%
0.016	0.010	37.5%	0.6%
0.0016	0.0010	37.5%	0.06%

Number Needed to Treat:

Good Measure of Clinical Relevance

CER	EER	RRR	ARR	NNT
0.16	0.10	37.5%	6%	16.7
0.016	0.010	37.5%	0.6%	167
0.0016	0.0010	37.5%	0.06%	1667

Number Needed to Treat:

For various CER's and RRR's

Prevalence	RRR				
	50%	40%	30%	20%	**10%**
0.9	2	3	4	6	**11**
0.3	7	8	11	17	33
0.1	20	25	33	50	100
0.01	200	250	333	500	1000
0.001	**2000**	2500	3333	5000	10000

Note: A small RRR for a condition with a high prevalence is more clinically important than a large RRR for a condition with a low prevalence

Heart Protection Study:

How large was the treatment effect?

Outcome	RR	RRR	ARR	NNT
Death	0.87	0.13	1.8%	55
CV Event	0.76	0.24	5.4%	18

5 years

HPS Investigators. Lancet 2002

Heart Protection Study:

Cost of Treatment Effect

Can be calculated from **NNT** (5 years)

- Costs ($25 x 12 x 5 x 55) $82500 to defer one death
- Costs ($25 x 12 x 5 x 18) $27000 to prevent / defer one major vascular event

HPS Investigators. Lancet 2002

Key Questions for Interpreting Randomized Trials

1. Subject selection
   - *Is it reasonable to extend results to my patients?*
2. Randomization
   - Were groups similar?
3. Blinding
   - *Could loss of blind have affected outcome?*
4. Interventions
   - *Is the comparison isolating the key component?*
5. Outcomes
   - *Is the endpoint relevant/appropriate?*
6. *Effect size measure*
   - *Is it clinically relevant?*
7. *Nature of Significant Effect*
   - *Is it real?*

Section Main Conclusions

- Consider key elements carefully
  - Patient selection, randomization, blinding, interventions, and outcomes
- Effect size measures
  - OR, RR, and RRR most relevant for assessing causality
  - ARR and NNT are most relevant for clinical decisions
  - OR, RR, RRR often favored because they look more impressive, but they can be misleading

Publishing Trial Results

Clinical Trial Registration I

- *"The registration of all interventional trials is a scientific, ethical and moral responsibility"*
  - *World Health Organization*

- Required by law in the United States
  - Efficacy trials for IND studies for serious diseases or conditions (FDA)

- Required by the International Committee of Medical Journal Editors (ICMJE) for publishing clinical trial research

- ICMJE Clinical trial definition (2007)
  - Research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes

Clinical Trial Registration II

- Increases transparency and strength/validity of scientific database
- Alleviates selective data presentation of clinical trials in medical literature (publication bias)
- Increases public awareness and access to trials
- Assigns trial identifier

Clinical Trial Registration III

ICMJE Policy

1. Which trial should be registered if you plan to publish the results in a medical journal?

2. Which registration database should you choose?

3. Which data do you have to register?

4. Which journals subscribe to the ICMJE trial registration policy?

Which Trial should be Registered if You Plan to Publish the Results in a Journal?

- ***All* clinically directive trials which test any clinical hypothesis about health intervention and its outcomes**

- No need for registration
  - Phase 1 trials
  - Trials investigating disease biology
  - Trials providing preliminary data

- *Best answer to doubts about reporting – register it!*

Which Registration Database should You Use?

- Must be accessible to the public at no charge
- Must be open to all prospective registrants (meaning that investigators are able to register without restriction by geographic location, academic affiliation, patient demographics, or clinical condition)
- Must be managed by a not-for-profit organization
- There must be a mechanism to ensure the validity of the registration data
- Should be electronically searchable
- Must include all data from the minimal data set

Various Registration Databases

- NLM Clinical Trials database
  - http://www.clinicaltrials.gov
- International Standard Randomised Controlled Trial Number, UK
  - http://isrctn.org
- Australian Clinical Trials Registry
  - http://www.actr.org.au
- University Hospital Medical Information Network, Japan
  - http://www.umin.ac.jp
- Dutch Cochrane Centre
  - http://www.trialregister.nl/trialreg/index.asp
- WHO International Clinical Trials Registry Platform (ICTRP)
  - International norms and standards for trial registration

Clinical Trial Registration III

www.clinicaltrials.gov

- Eligibility:
  - All clinical studies (observational or interventional)
  - Approved by Institutional Review Board
  - Conforming to appropriate national health authority
- Timing:
  - At any time, but may be required before patient enrollment
- Requirements:
  - Description
  - Patient recruitment information
  - Location and contact description
  - Administrative information

A Study to Assess the Safety and Efficacy of Alefacept in Kidney Transplant Recipients

This study is not yet open for participant recruitment.

Verified by Astellas Pharma Inc, December 2007

Sponsored by:	**Astellas Pharma Inc**
Information provided by:	Astellas Pharma Inc
ClinicalTrials.gov Identifier:	NCT00543569

Purpose

A study to assess the safety and efficacy of Alefacept in de novo kidney transplant patients.

Condition	Intervention	Phase
De Novo Kidney Transplantation	Drug: Alefacept Drug: tacrolimus Drug: basiliximab Drug: mycophenolate mofetil Drug: steroids	Phase II

ChemIDplus related topics: Tacrolimus Mycophenolate Mofetil Tacrolimus anhydrous Alefacept

U.S. FDA Resources

Study Type: Interventional

Which Data do You have to Register (I)?

Unique trial number

•Unique trial number will be established by primary registering entity (the registry)

Trial registration date

•Date of registration will be established by primary registering entity

Secondary Ids

•May be assigned by sponsors or other interested parties

Funding source(s)

•Name of organization(s) that provided funding for the study

Which Data do You have to Register (II)?

Primary sponsor

- Main entity responsible for performing the research

Secondary sponsor(s)

- Secondary entities responsible for performing the research

Responsible contact

- Public contact person for the trial person for patients interested in participating

Research contact person

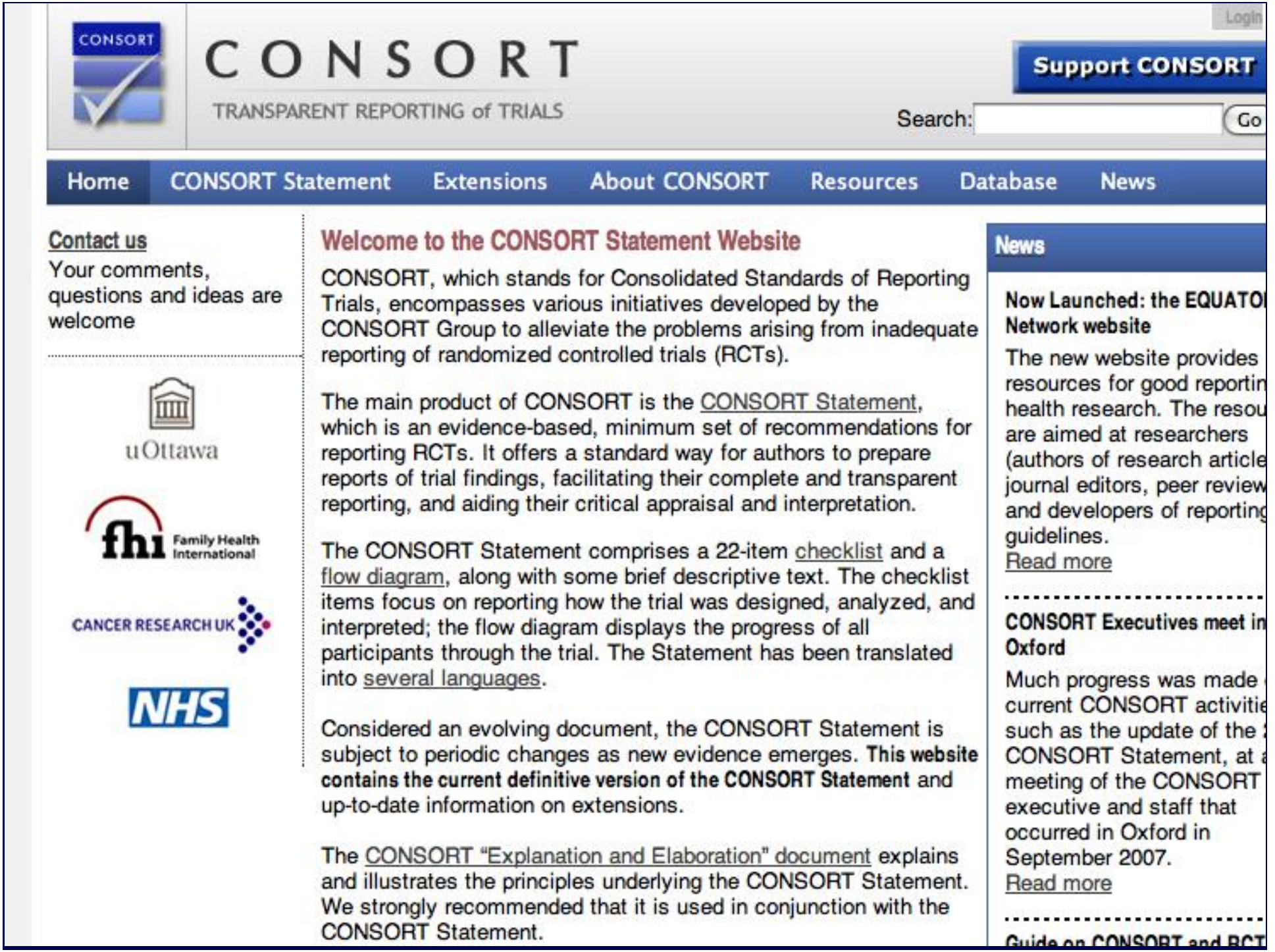
- Person to contact for scientific inquiries about the trial

Title of the study

- Brief title chosen by the research group (can be omitted)

Which Data do You have to Register (III)?

Item	Description
Official scientific title	Name of intervention, condition studied, outcome
Research ethics review	Received appropriate ethics committee approval
Condition	Medical entity being studied
Intervention(s)	Comparison/control intervention(s)
Key inclusion/exclusion criteria	Key patient characteristics that determine patient eligibility
Study type	Randomized vs. non-randomized, type of masking, type of controls, and group assignment.
Anticipated trial start date	Estimated enrollment date of first participant
Target sample size	Total number of subjects the investigators plan to enroll before closing study
Recruitment status	Is this information available (yes/no)?
Primary outcome	Main endpoint study designed to evaluate?
Key secondary outcomes	Description should include time of measurement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fhi Family Health International
CANCER RESEARCH UK
NHS
Welcome to the CONSORT Statement Website
CONSORT, which stands for Consolidated Standards of Reporting Trials, encompasses various initiatives developed by the CONSORT Group to alleviate the problems arising from inadequate reporting of randomized controlled trials (RCTs).
The main product of CONSORT is the CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting RCTs. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.
The CONSORT Statement comprises a 22-item checklist and a flow diagram, along with some brief descriptive text. The checklist items focus on reporting how the trial was designed, analyzed, and interpreted; the flow diagram displays the progress of all participants through the trial. The Statement has been translated into several languages.
Considered an evolving document, the CONSORT Statement is subject to periodic changes as new evidence emerges. This website contains the current definitive version of the CONSORT Statement and up-to-date information on extensions.
The CONSORT "Explanation and Elaboration" document explains and illustrates the principles underlying the CONSORT Statement. We strongly recommended that it is used in conjunction with the CONSORT Statement.
News
Now Launched: the EQUATOI Network website
The new website provides resources for good reportin health research. The resou are aimed at researchers (authors of research article journal editors, peer review and developers of reporting guidelines.
Read more
CONSORT Executives meet in Oxford
Much progress was made current CONSORT activitie such as the update of the CONSORT Statement, at a meeting of the CONSORT executive and staff that occurred in Oxford in September 2007.
Read more
Guide on CONSORT and RCT

CONSORT Guidelines for Reporting of Clinical Trials I

- Title and abstract
- Introduction
- Materials and Methods
- Results
- Discussion
- Flow diagram

CONSORT Guidelines for Reporting of Clinical Trials II

- Scientific background and explanation of rationale
- Specific hypotheses and objectives
- How participants are allocated to interventions, including method used to generate and implement the random allocation sequence
- Eligibility criteria for participants
- Details of the interventions intended for each group
- Statistical methods used to compare groups for outcomes, including how sample size was determined
- Explanation of any interim analyses and stopping rules

CONSORT Guidelines for Reporting of Clinical Trials III

- Baseline demographic and clinical characteristics of each group
- Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat."
- For each outcome, a summary of results for each group, and estimated effect size and its precision (*e.g.*, 95% confidence interval)
- Address any other analyses performed, including subgroup analyses, indicating those pre-specified and those exploratory
- All important adverse events or side effects in each intervention group

CONSORT Guidelines for Reporting of Clinical Trials IV

- Interpretation of the results, taking into account…
  - study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes
- Generalizability of the trial findings
- Interpretation of the results in the context of current evidence

CONSORT - Simple Items

- Their “golden rules” for reporting numbers
  for example, numbers less than 10 are written as words (e.g. nine) and larger numbers are written as the number (e.g.12)

- do not use decimal places if the sample size is less than 100

- etc

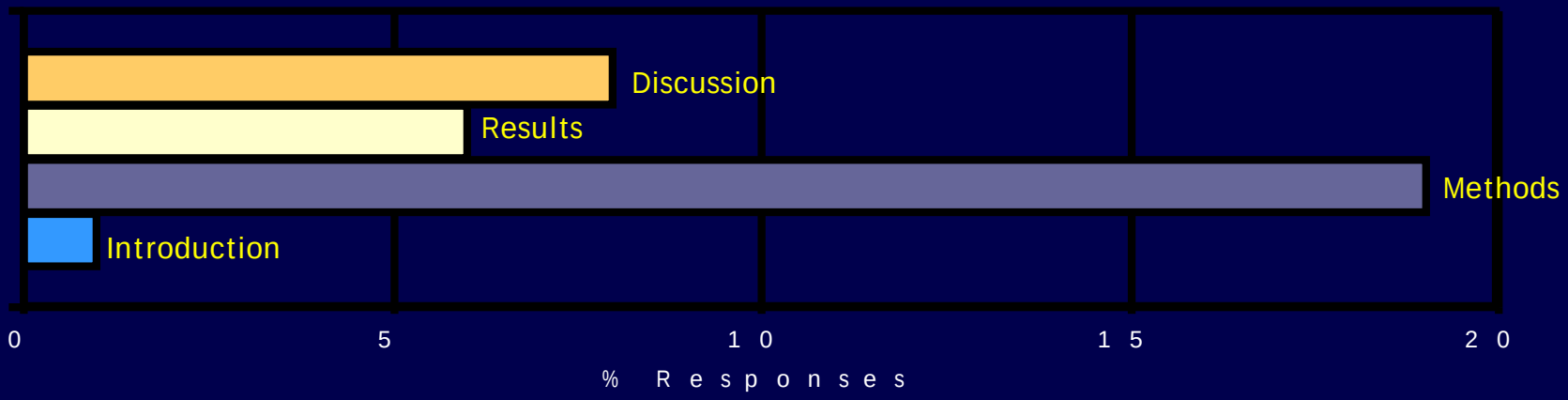
General Suggestions

Manuscript Preparation

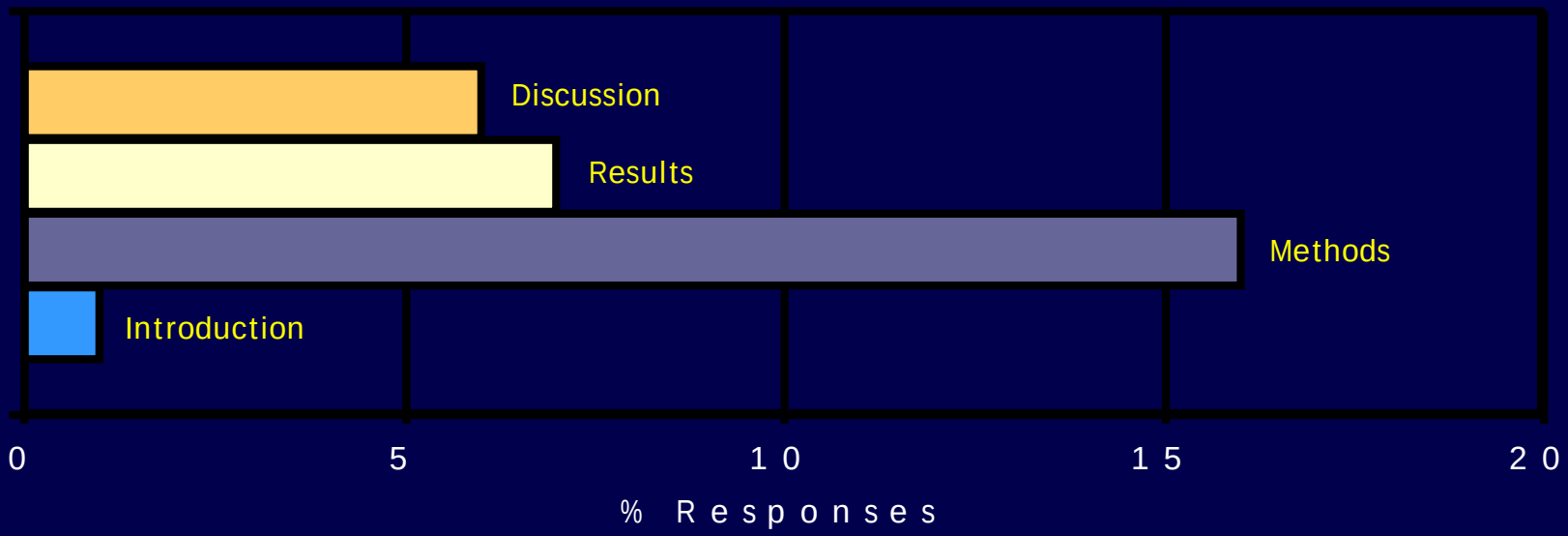
- Use the present tense when referring to work that has already been published
- Use past tense when referring to your own study
- Use the active voice for introduction and discussion
- Use the passive voice for methods and results
- Avoid complex sentence structure; use simple and clear English
- Keep in mind that the paragraph is the essential unit of thought
- Avoid lengthy or unfocused reviews of previous research
- Aim to generally cite one key reference per point

Editors' Responses to Key Qs

1. What section contains the most flaws?



2. What section responsible for outright rejection?



Byrne DW, Publishing Medical Research Papers, Williams and Wilkins, 1998

Methods Section

- First to be written
- Balance between brevity and completeness
  - Sometimes reference an often-used method
- Use headings for clarity and easy reference
- Use figures and tables (e.g., flow diagram)
- Naming things—be consistent
  - Acronyms—spell out first time, use consistently throughout
  - Specialized tests, terms—use identical name in text, figs, tables
- Develop list of frequently used terms
- Present in logical order and your subsequent results should follow that same order

The Draft of the Paper

- Look at the information for Authors (on line)
- Look at a recent issue
  - Format
  - Style
  - Content
- Try to cite recent work in the journal to which you submit (if applicable)

Suggesting Reviewers (at least 5)

- Choose experts (senior and junior)
- Avoid non-experts
- Choose rigorous scientists
- May improve acceptance chances J

Ann R Coll Surg Engl. 2000 Apr;82(4 Suppl):133-5., J Pediatr. 2007 Aug;151(2):202-5., *JAMA.* 2006;295(3):314-317.

What Do Manuscript Reviewers Look For?

- Creativity
- Originality
- Scientific importance
- Relevancy to readership
- Study design
- Interpretation
- Clarity and brevity
- Likely significance after revision
- Ranking

Response to Manuscript Peer Review

- If your paper is rejected
  - Focus on the critiques
  - Address them in a revision for a different journal

- If a request is made for you to submit a revision of your paper
- - State each entire and exact comment followed by your reply
  - Point-by-point response to the comments made
  - Indicate where changes have been made in the manuscript
  - Explain why you disagree with a comment or why you feel suggested changes are not necessary

Conclusions

- Conclusions need to flow from analysis and show clear relevance to the overall pre-specified hypothesis

- Findings should be interpreted in light of…
  - significance
  - current research literature
  - limitations of the study
  - questions, aims, objectives, and theory

O'Leary, Z. (2005) RESEARCHING REAL-WORLD PROBLEMS: A Guide to Methods of Inquiry. London: Sage. Chapter 11.