Art and Science of Writing about Clinical Outcomes

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Disclosures

- NONE

Outline

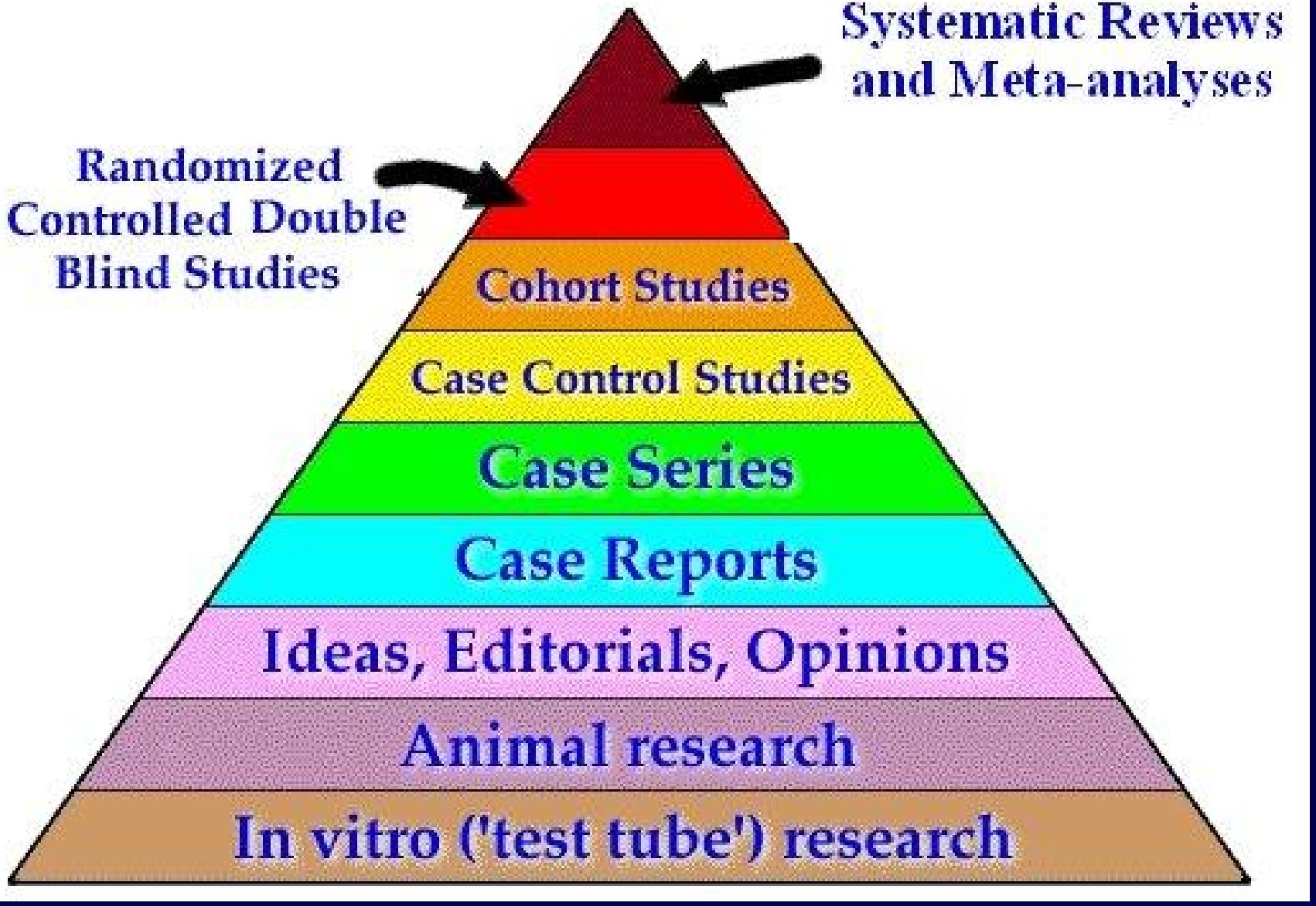
- Overview of General Concepts
- Preparing Sections of a Manuscript
- Manuscript Submission

Quantitative Clinical Research

- Observational
  - studies that do NOT specifically involve any intervention or experiment

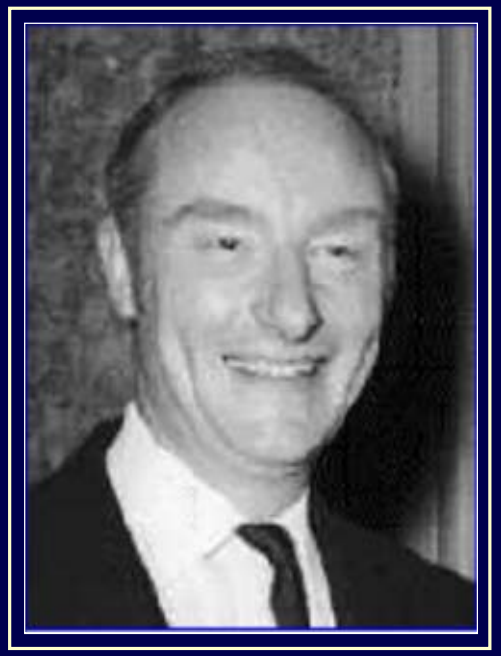
- Experimental
  - studies that entail manipulation of the study factor (exposure)
  - randomization of subjects to treatment (exposure) groups

Treatment Effectiveness Evidence Pyramid



A Recognized Challenge

"*There is no form of prose more difficult to understand and more tedious to read than the average scientific paper!*"



-Dr. Francis Crick, 1994
The Astonishing Hypothesis

Key Challenges

- Many papers are poorly constructed and written
  - Some scientists have not learned good manuscript writing techniques
  - Others do not enjoy writing, and do not take the time or effort to ensure that the prose is clear and logical
- Authors are typically so familiar with the material that it is difficult to step back and view it from the point of view of a reader not familiar with the science
  - Peer review is therefore critical

Top 10 Avoidable Reasons Manuscripts Rejected

1. Wrong journal, format, preparation
2. Disorganized study design
3. Defective tables, figures
4. Poor organization throughout, writing, spelling
5. No hypothesis or problem statement
6. No or insufficient conclusion
7. Overinterpretation of results
8. Article unfocused, too verbose and long
9. Inappropriate statistical methods; methods not sufficient to repeat study
10. Poorly written abstract/title

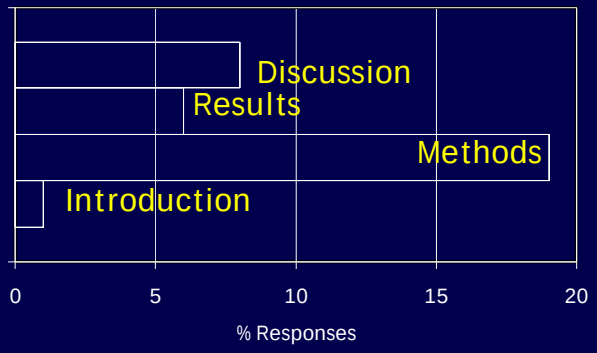
Byrne DW, Publishing Medical Research Papers, Williams and Wilkins, 1998

Manuscript Segments

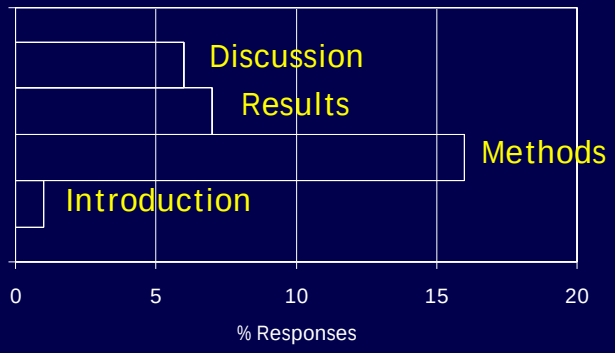
- Title/title page
- Abstract
- Introduction
- Methods
- Results
- Discussion
- (Conclusion)

Editors' Responses to Key Qs

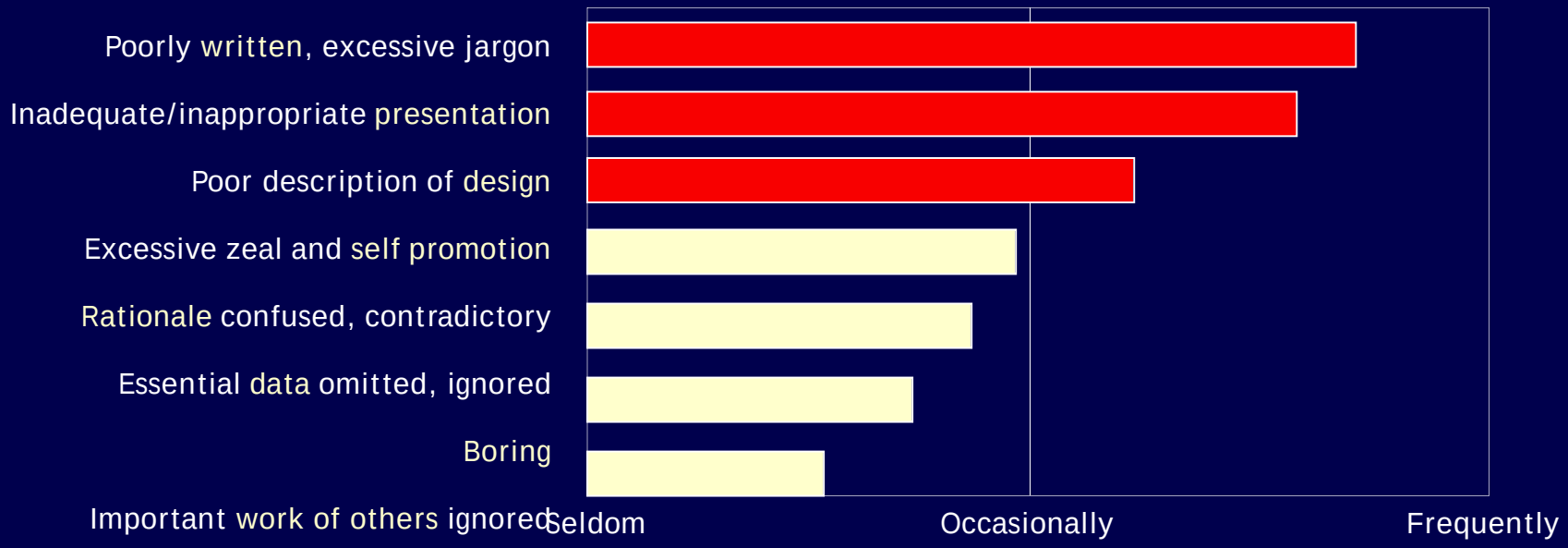
1. What section contains the most flaws?



2. What section responsible for outright rejection?

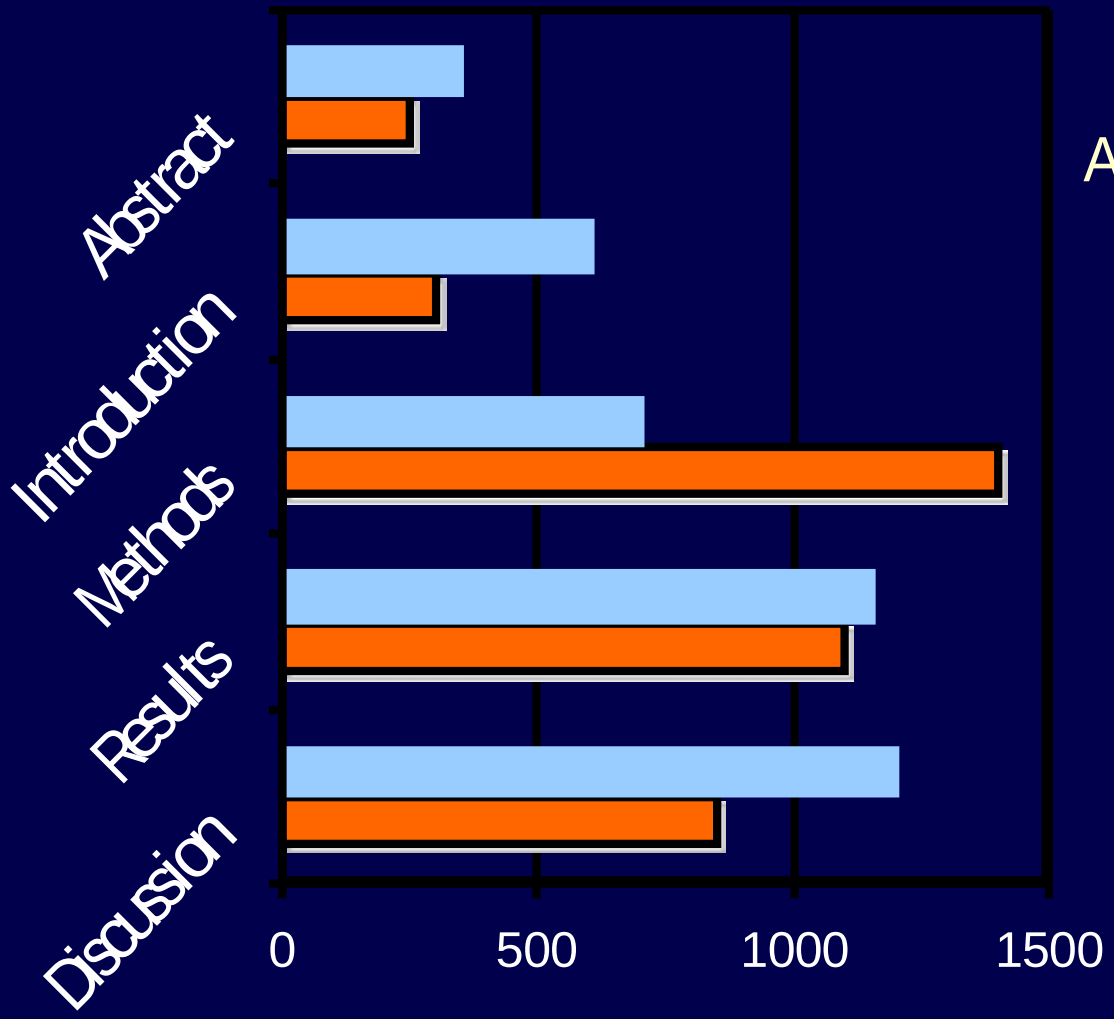


3. How frequently do Editors encounter these manuscript problems?



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

Sections Unbalanced



Article of ~ 3650 words

Originally Submitted Version
Final Accepted Version

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

General Suggestions

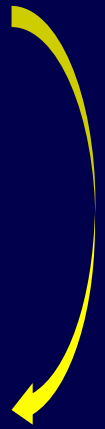
- Use the present tense when referring to work that has already been published
- Use past tense when referring to your own study
- Use the active voice as much as possible
- Avoid complex sentence structure; use simple and clear English
- Keep in mind that the paragraph is the essential unit of thought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

The Title (1)

- First reviewed by Journal Editors before abstract
- What is the single most important point of this study?
  - Start with a short descriptive *working* title
- Write last—your findings and conclusions may alter your title
- One approach - make a list of the most important keywords
  - Think of a title that contains these words
  - The title could state the conclusion of the paper
  - Avoid abbreviations, chemical formulas, proprietary names or jargon
  - Avoid the use of the word “using”
- Avoid unnecessary title phrases
  - *“A Study of… A Study to Determine Results of… An Innovative Method… Contributions to (of)… Investigations on (concerning, about)… Observations on… A Trial Comparing…”*

Title (2)

- Short, Specific, Relevant, Descriptive
  - Not declarative! *"Lazarus arise! Life and Death Issues in Intensive Care"*
  - Should describe main findings or purpose of study
  - *"Comparison of MRI and CT for Detection of Acute Intracerebral Hemorrhage"*
  - *"Extracranial Thrombotically Active Carotid Plaque as a Risk for Ischemic Stroke"*
  - *"End-of-Life Care Issues for Critically Ill Patients in Intensive Care Hospitals"*



- Title Page
  - List authors, degrees, affiliations
  - Corresponding author (usually 1st or last)
  - Funding sources

Abstract (1)

- "*The abstract is the single most important part of a manuscript, yet the most often poorly written*"

- 1st Impression to journal editor and the reader!

- Write it after completion of the main paper

- Do NOT be vague—be substantive and brief
  - *NOT "The implications are summarized"*
  - *INSTEAD Summarize the implications!*

- Do NOT give any information or conclusion that is not stated in the main paper

*Dickersin K et al. *BMC Medical Research Methodology* 2007, **7**:44

Abstract (2)

- **Background** *(1-2 sentences)*
  - What is the major problem/question that prompted the study?
- **Objective** *(1 sentence)*
  - What is the purpose of the study?
- **Methods** *(At least 2 sentences)*
  - How was the study done?
- **Results** *(At least 2 sentences)*
  - What are the most important findings?
  - Clear summary
- **Conclusion** *(1-2 sentences)*
  - What is the most important conclusion drawn? (and what is the clinical relevance of the results?)
  - State clearly with essential *qualifications*

Introduction (1)

- Convinces (or not) the reader whether your study…
  - Has merit and asks important research questions
  - Is focused and supported by relevant recent citations
  - Is ultimately important to human health and human disease

- You will better focus your introduction AFTER you construct your findings (results) and consider them (discussion)

- The research question is the most important part of your introduction

Introduction (2)

1. What is the general problem or current situation? 1 paragraph
   - *What is the existing state of knowledge of this topic?*

2. What is the specific problem or controversy? 1 paragraph
   - *Why did you carry out this research (specific STUDY purpose or rationale)?*

3. What are your hypotheses/questions, and how will you answer them? 1 paragraph
   - *What are you going to do (Objectives, Aims) and what do you expect to find?*

Give only strictly pertinent references

Save detailed comparisons with previous studies for Discussion

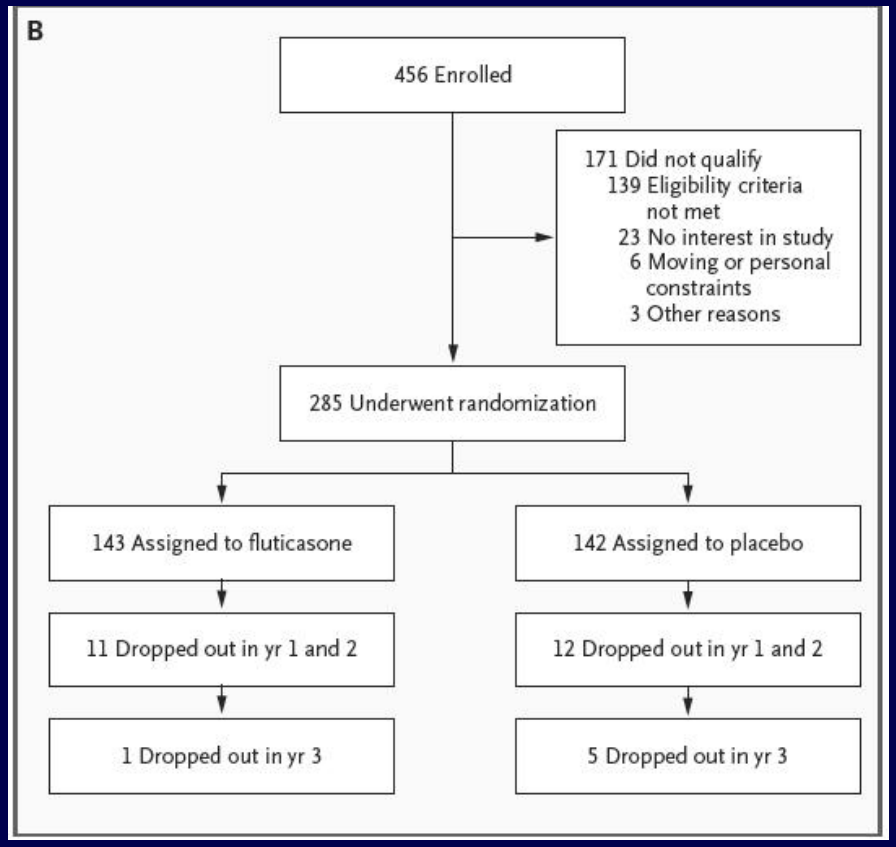
Methods (1)

- Study design or analysis type and period of study
- Condition or disease studied
- Human subjects approval
- Details of sample
  - Number, recruiting methods of study subjects, patients, how organized
- Interventions, outcome measures, statistical analyses
- Include the locations and times that data were collected
- Give enough information to replicate the study
  - Don’t assume only the specialist in your field will read it

Methods (2)

- 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

Methods (3)



Method diagrams communicate schedule of procedures, enrollment, study design, guidelines, algorithms to reduce text and increase comprehension.

Results (1)

- Write after figures and tables are constructed
  - Consider your data critically, allow to speak for self
  - Construct tables, figures and include them in outline
  - Write the results corresponding to order listed in methods
  - Use logical subheadings

- State ALL the findings
  - Whether significant or not
  - Without bias or interpretation
  - Avoid using descriptive terms (e.g. markedly, prominent)
  - Do not include weaknesses, strengths of study, ie don't discuss results

Results confirm or reject your hypothesis: they do not prove anything

Results (2)

- In Tables and Figures, be descriptive, specific
  - Do not repeat the obvious:
    - NO: Results of the cerebral white matter analysis are shown in Table 1
    - YES: *Cerebral white matter lesions increased in group 1 over the first 10 study weeks (Table 1)*

- Present absolute numbers and percentages so reviewers can judge the significance of the findings

- Statistical significance ?= clinical significance

Results (3)

- 3 ways to present results
  - Written description
    - stick to facts---keep simple & focused
    - Adhere to describing comparisons as significant or not
    - Indicate whether summary data are means/medians +/- SD/SEM/CI
  - Table
    - Key table – Baseline Demographics, Clinical Characteristics
    - Title and abbreviations (if specific numbers are essential)
  - Figure
    - Key figure - Study flow chart (number of patients enrolled, eligible, dropped, completed)
    - Title and legend (to show relations between data sets)

- Restrict tables and figures to those needed to explain a key point and to assess its support

- If you choose a figure or table: *do not* restate the data
  - Highlight and interpret key points in text

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*

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

Discussion (1)

- Make it brief but informative!
  - ~20% of total text
  - Don’t restate all the results
- First state the answer to the question posed in the Introduction
- Provide evidence in support of answer
- Describe conflicting results and reasons for such differences
- Establish newness of findings
- Relate observations to other relevant findings

Discussion (2)

- Begin and end with most exciting, convincing and novel results!
  - Put in the middle what is debatable, complicated or boring
- Organize mid-section systematically (e.g. follow order of Results)
- Avoid speculations, recommendations, and suggestions for future studies until the end
- Discuss limitations as well as strengths
  - Design weaknesses
    - cluster in a paragraph before conclusions
  - Methodological problems
    - discuss in the context of specific findings
  - Serious problems:
    - indicate how much they undermine confidence in validity of results (i.e., spin to minimize the damage)

Tables and Figures

- Tables are appropriate for large or complicated data sets that would be difficult to explain clearly in text
- Figures are appropriate for data sets that exhibit trends, patterns, or relationships that are best conveyed visually
- Any table or figure must be sufficiently described by its title and caption or legend, to be understandable without reading the main text of the results section
- Do not include both a table and a figure showing the same information

Tables (1)

This requires a table!

During the encoding task, significant activation clusters were detected in the left middle frontal gyrus (MFG) extending into the inferior frontal gyrus (IFG) (BA 9/45/47; Talaraich coordinates: −40, 14, 28), left MFG (BA 8; −40, 22, 50), left superior frontal gyrus (BA 6; −24, −8, 64), right IFG (BA 47; 28, 28, −2), left LTL (BA 22; −62, −22, 2), right cerebellum (30, −70, −16) together with right fusiform/lingual gyrus (BA 18; 18, −88, −14), left cerebellum/vermis (−6, −60, −16) (Fig. 1, top row) as well as the left (−30, −12, −18) and right hippocampus (34, −12, −16) (Fig. 2, left panel). During the retrieval task, when performance was not considered, significant activation clusters were detected in the left IFG (BA 47; −28, 24, −4), left MFG/IFG extending into the anterior cingulate cortex (BA 9/44/24; −36, 12, 28), right IFG (BA 44; 56, 16, 24 and BA 47; 36, 20, −10), left supramarginal gyrus (BA 40; −34, −46, 42), right putamen and caudate (16, 10, 2), right cerebellum (36, −74, −18) together with right fusiform/lingual gyrus (BA 18; 28, −90, −6) and vermis (−2, −62, −40) (Fig. 1, middle row) as well as the right hippocampus (26, −4, 22) (Fig. 2, right panel). During retrieval, brain activation related to accurate memory performance was observed in the left LTL (Fig. 1, bottom row), with peak activation in the middle temporal gyrus (BA 21 and 22; −50, −38, −4) extending into the superior and inferior temporal gyri. No activation clusters were detected in the prefrontal cortex, hippocampus, or other MTL structures. No brain regions showed negative correlations with behavioral performance.

Tables (2)

This result does NOT require a table!

Table 1. Effect of aeration on growth of *Streptomyces coelicolor*

Temp (°C)	No. of expt	Aeration of growth medium	Growth[a]
24	5	+[b]	78
24	5	–	0

[a] As determined by optical density (Klett units).

[b] Symbols: +, 500-ml Erlenmeyer flasks were aerated by having a graduate student blow into the bottles for 15 min out of each hour; –, identical test conditions, except that the aeration was provided by an elderly professor.

Manuscript Submission

Factors to Consider in Choosing Journal (1)

- What does the journal publish?
- Topic
- Human vs. animal work
- Clinical vs. non-clinical
- Full articles vs. short communications
- Reviews

Factors to Consider in Choosing Journal (2)

- Most journals do not receive enough good reviews
- Lack of papers on a topic doesn't always mean lack of interest in the topic
- Lack of interest in a topic can sometimes be changed

Factors to Consider in Choosing Journal (3)

- Your audience: national vs. international
- General vs. specialty vs. subspecialty
- Diversity of audience
  - EMG – neurologists vs. physiatrists
  - Child neurologist vs. pediatricians
  - Cerebrovascular diseases: neurologist?
  - Basic scientist? Neurosurgeon? Cardiologist?
- Impact factor
  - Attracts (some) authors

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.

Strategies for Annoying Editors & Reviewers (1)

- Leave traces of a previous rejection
- Show you are not familiar with the journal's Info for Authors and the "look" of a paper in its published form
- Editorialize: "This work is very important"
- Say your paper, case, data are "the first", "unique", "novel"
- Use adjectives and adverbs

Strategies for Annoying Editors & Reviewers (2)

- Ignore a recent paper (or editorial) in the journal
- Repeat material from the Introduction in the Discussion
- Repeat the Results in the Discussion
- Repeat the Tables or Figures in the Results
- Repeat the Abstract in a “Summary” or “Conclusion” at the end of the paper

What Do Reviewers Look For?

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

Response to Review

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

- In the revision for the same journal:

  - 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

- Analyze and present data in manuscript appropriately
- Review relevant literature
- Choose correct journal
- Tell a convincing, concise story stressing the novelty and importance of the findings
- Format the paper as per journal specifications

”What is written without effort, is in general read without pleasure”

- *Samuel Johnson*

(English author, critic, & lexicographer (1709 – 1784)