

## Annals of Internal Medicine

- **88,000 subscribers**
  - The largest specialty journal
  - 50% general internists
  - 25-75% of subspecialists receive it
  - International readers
- **24 issues per year**
- **2000+ manuscripts per year**
  - One-third from abroad
  - Accept 8% of original research articles
- **Impact factor:**
  - Fourth among all large-circulation, general medicine journals (after NEJM, JAMA, and Lancet)

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## Outline

- **Peer review and manuscript selection**
- **Common shortcomings of manuscripts**
- **Desirable elements of a research project**

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## Annals editorial staff

- Senior Editors: 3.5 FTE
- Associate Editors: 7 x 20%
- Statisticians: 5 (1.0 FTE)
- Managing Editor
- Manuscript representatives: 3
- Others: 4
  
- Editorial Budget: \$2M

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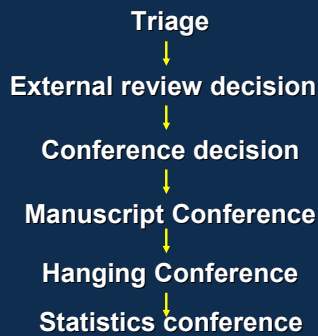
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## The review process at Annals



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Milestone	day	# MS
Editor screens -> Deputy Ed.	0	1000
DE → Associate Editor	1	1000
AE decides to get ext. review	7	500
2-3 people agree to review	21	500
AE receives reviews	42	500
AE decides to send to MS conf	49	350
Ed. and DE decide → MS conf	52	250
Conference decision		
Provisional accept	55	80
Re-invite	55	20
Stat review → letter to author	70+	90

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## Two types of acceptance

- **Provisional (PR)**
  - PR letter (+ statistician's letter)
  - Revision (usually mild)
  - Final acceptance
- **Re-invite**
  - Eventually accept 85%
  - Reject and re-invite
  - Re-invite letter spells out key issues that must be resolved for us to take the article
  - Revision and re-analysis (often extensive)
  - Re-review (maybe) and re-discussion at conference (maybe)
  - PR letter

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## Editorial decision criteria

- **Potential to change patient care**
  - Does the evidence support the conclusions? (“is it true”)
  - How does it advance the field (“is it new”)
  - How will it affect patient care?
- **Conference discussion centers on these three issues**

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## What makes a manuscript easy to review?

- **It answers these questions**
  - “is it true”
    - Does the evidence support the conclusions?
  - “is it new”
    - How does it advance the field?
  - How will it affect patient care?

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## Discussion at Manuscript Conference: Factors that lead to acceptance

- **Hot topic**
- High impact disease
- **Unexpected but believable findings**
- First report
- **Large effect size, narrow confidence interval**
- Complements recently accepted article
- **A good vehicle for an editorial on important subject**
- High level of public interest in topic

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## Discussion at Manuscript Conference: Factors that lead to rejection

- **Fatal flaw**
- Many non-fatal problems with study design and execution
- **Secondary report of major study adds little**
- Nothing to distinguish it from previous work
- **Small effect size, wide confidence interval**
- Hot issue but recently resolved
- **Already published a lot on this topic recently**

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## “Is it new?”

- **Introduction:**
  - Establish the context: show clearly the gap that the research will fill
- **Discussion:**
  - state early and clearly how the principal finding advances the field
  - cite the findings of previous work.
    - Consider using an evidence table to summarize previous work and yours

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## “Is it true?”

- **External validity: “to whom do the conclusions apply?”**
  - Describe how you formed the study cohort
    - Source population, recruiting, inclusion, exclusion
    - Use a figure to describe cohort formation
  - Describe the intervention carefully
  - Be clear on what the study is to prove
    - Efficacy: Does it work? proof of principle
    - Effectiveness: does it work in the real world?

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## “Is it true?”

- **Internal validity: “Do the data support the conclusions?”**
  - State clearly the primary hypothesis and outcome measure
    - Distinguish from secondary hypotheses and exploratory analyses
  - Account for loss of patients.
  - Adjust for known confounders and test for effects of potential unmeasured confounding (sensitivity analysis)

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## Are the conclusions true?

- **Don’t call a study “negative” when it’s actually “inconclusive.”**
  - Negative =
    - no important effect
    - 95% confidence interval for effect size does not include a clinically important effect
  - Inconclusive:
    - no important effect
    - 95% confidence interval for effect size does include a clinically important effect

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## Are the conclusions true?

- **Avoid a biased presentation or interpretation**
  - Give a balanced account of the findings and their implications.
  - Strive for a cautious tone
  - Let the findings speak for themselves. Don't exaggerate

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## Are the conclusions true?

- **Address the possibility of bias in the presentation or interpretation:**
  - Sponsored research: state clearly who is responsible for
    - the design and conduct of the study
    - the manuscript
    - the decision to publish.
  - Declare conflicts of interest

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## • The Discussion

- Discuss prior work and what your paper adds
- limitations of the research
  - Threats to validity

## • The article

- Keep it short and to the point

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## Discuss potential impact of findings

- **“How might the findings be used?”**
  - in practice
  - in guidelines
  - in policy

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## Some other rules:

- **Short declarative sentences.**
- **Use active voice.**
- **Paragraph structure:**
  - topic sentences, bottom lines, transitions
- **Be concise**
- **Involve a statistician at every stage**
- **Avoid inflaming reviewers and editors**

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## Outline of presentation

- **Peer review and manuscript selection**
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## Common shortcomings

- Inadequate description of cohort assembly
- Underpowered
- Single site
- Inattention to costs of intervention

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## Common statistical errors

- Calling an inconclusive study “negative.”
- Unstable predictive models:
  - too many predictor variables for the number of outcome events
- Combining heterogeneous studies in a meta-analysis
- Step-wise addition of variables to regression model

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## Common statistical errors

- Biased methods for missing values
- Not adjusting for clustering
- Not taking into account measurement error
- Adjusting only for baseline values of covariates that change over time

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## What do editors like to see?

- **A diverse study population that represents the world of clinical practice**
  - Multi-center studies > single center studies
  - Adjust for center effects
- **A large study population →**
  - Narrow confidence intervals → less risk of false-negative or false-positive conclusion
  - Powerful subgroup analyses

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## Some far-out suggestions

- **Cost-effectiveness analysis**
- Using decision analysis to set target enrollment
- **Consider alternatives to RCTs**
- Use decision analysis to choose the key questions to study
- **Studies of chronic disease**
- Characterize patient preferences

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## What is cost-effectiveness analysis?

- “A method designed to assess the comparative impact of expenditures on different health outcomes.” (Garber et al, 1997)

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## What is cost-effectiveness analysis?

- **Cost-effectiveness analysis is comparative.**  
– Innovation vs. usual care

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## The cost-effectiveness ratio

$$C/E = \frac{\text{Cost}_{\text{new}} - \text{Cost}_{\text{old}}}{\text{QALYs}_{\text{new}} - \text{QALYs}_{\text{old}}}$$

**QALYs<sub>new</sub> = quality-adjusted life years of the new intervention**

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## Decision analysis to set target enrollment

- **Parameters for calculating sample size**
  - Variance of endpoint measure
  - **Minimum clinically important effect size**
- **Use of decision analysis**
  - Create decision tree
  - The unknown is the effect size
  - Determine the effect size at which the expected value of treatment = the expected value of don't treat

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## Alternatives to RCTs

- **Observational studies**
  - **Advantages:** cheap, large N, reflects community practice
  - **Disadvantage:** patient and MD preferences determine treatment rather than random assignment → confounders
  - Adjusting for confounders
    - Multivariable regression models
    - Propensity score
    - Sensitivity analysis
- **Non-randomized experiments**
  - Before-after studies

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## Other ways to do RCTs

- **Achieving equipoise:**
  - Preference trial
    - randomize only those indifferent between the treatments
- **Avoiding lengthy exposure to placebo**
  - Randomized withdrawal
    - Randomize responders; endpoint is failure
  - Early escape
    - endpoint is failure rate; remove placebo failures

Reference: Small Clinical Trials. National Academy Press, 2001  
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## Use decision analysis to choose the key questions to study

- **Do a decision analysis of the problem**
  - E.g. surgery vs. medicine for heartburn
- **Do a sensitivity analysis to see what parameters of the model are important to the decision**
- **Do a study to obtain accurate information about the key parameters**

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