How to plan and report your study: clinical studies

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Planning

Start with a clear question. Be sure that the methods are adequate to answer the question.

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Planning (example 1):

- Our aim was to compare gentamicin to ciprofloxacin as a single dose before prostatectomy.
- The main outcome was UTI in the week following the operation.
- We randomized patients to the 2 interventions in a 1:1 scheme.
- As both treatments are in use in our hospital in clinical practice we did not ask for patients' consent.
- Our sample size calculation was 200 patients, and we recruited 204.

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Declaration of Helsinki:

- In medical research involving competent human subjects, each potential subject must be **adequately informed** of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study.
- After ensuring that the potential subject has understood the information, the **physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent**, preferably in writing.

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Planning (example 2):

- In Mordor resources are so poor that the great majority of HIV carriers and AIDS patients are not treated with anti-retroviral drugs.
- We have performed a RCT of our new drug vs placebo in HIV carriers.
- The patients gave their written informed consent.
- Primary outcome: the proportion of subjects with undetectable plasma viremia at 12 months.

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Declaration of Helsinki:

- The benefits, risks, burdens and effectiveness of a new intervention must be tested **against those of the best current proven intervention**, except in the following circumstances:
  - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
  - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

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Ethical issues:

- Should be addressed and resolved before starting the study.
- Don't make assumptions: read the Helsinki declaration, GCP rules, take advice with the local research ethics committee.
- When in the slightest doubt, obtain approval of the committee.

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Planning (example 3):

"All eligible patients were included in the study (RCT) during a 2-year study period"

	Pip-Tazo (n = 30)	IMP (n = 32)	p value
Clinical response	14 (46.7)	9 (28.1)	0.130
Relapse	0/14	2/9 (2.2)	0.058
Microbiological response			
Complete response	23/24 (95.8[a])	24/25 (96[a])	1.000
Partial response	1/24 (4.2[a])	1/25 (4[a])	
Surgical intervention			
None	3 (10)	4 (12.5)	0.739
Debridement	5 (16.7)	4 (12.5)	
Ray resection	4 (13.3)	2 (6.3)	
Amputation	18 (60)	22 (68.8)	
Side effects			
Total	9 (30)[b]	3 (9.4)	0.055
Hepatotoxicity[c]	5 (16.7)	1 (3.1)	
Nephrotoxicity[d]	6 (20)	1 (3.1)	
Hematological side effects	2 (6.7)	–	
Other (nausea)	–	1 (3.1)	

Data are given as n (%).

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Saltoglu et al. Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections. Clin Microbiol Infect 2010.

Sample size calculations

- Perform a sample size analysis:
  - Observational studies
  - Non-inferiority/ equivalence/ superiority trials
- For trials:
  - Interim analyses
    - Appropriate adjustments to sample size
  - Stopping rules
    - Highly relevant for trials showing statistically significant differences

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Structured reporting but helpful for planning as well:

- SPIRIT - RCTs
- CONSORT + extensions: randomised controlled trials
- STROBE: observational studies
- STARD: diagnostic accuracy
- ORION: hospital epidemiology
- PRISMA: systematic reviews/ meta-analyses
- MOOSE: meta-analysis of observational studies

Equator network: http://www.equator-network.org/

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Analysis

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Analysis: example 1

- In a cohort of 1011 patients admitted to the hospital, we found 22 carriers of MRSA.
- On univariate analysis, 18 factors were significantly related to carriage.
- These factors were entered into a stepwise logistic regression model.
- The resulting model was highly predictive of carriage, and can be used to reduce the number of screened patients.

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Criteria used to examine logistic regression models in articles reviewed in the *Journal of Clinical Epidemiology* and *American Journal of Epidemiology*

Criterion	Description
Sufficient events per independent variable	The ratio of outcome events to independent variables should be 10:1 or higher. The fewer events per independent variable, the greater the opportunity for the estimates of the regression coefficients to be unreliable; the sample variance of the model coefficients, and confidence intervals will also be less accurate.
Conformity with linear gradient for continuous variables	Articles with continuous or ranked independent variables test to assure conformity with the linear gradient or check on the log-odds scale. This is not an issue for dichotomous predictor variables for which there are only two values and one possible change.
Tests for interactions	Article includes a discussion of interaction terms and why they were either included or not included. If interactions are included, then the significance of the interaction is reported.
Collinearity	Explicit tests for collinearity are undertaken and reported. Some software packages may include automatic checks for collinearity — if so the fact the collinearity was examined is reported.
Validation	Model validation is discussed and validation procedure reported if appropriate, e.g., split-sample methods, cross validation, bootstrapping or other resampling methods.
Statistical significance	Statistical tests of significance are applied to each variable's coefficients and to the entire model.
Goodness-of-fit, Discrimination measures	Summary goodness-of-fit measures or discrimination statistics (ROC curves) are reported describing how well the entire model matches the observed values.
Selection of independent variables	Article explains how variables were selected for inclusion into the model? Variables may be chosen based on earlier research; sometimes they are selected by virtue of significant association in a bivariate analysis with the outcome variable.
Coding of variables	Study provides an appropriate description of the coding for independent variables. The coefficient for an independent variable depends on how that variable is coded. The effect of the coding on the interpretation of the regression coefficients is especially important when interaction terms are reported.
Fitting procedure	Procedure for entering variables into the model is explicitly stated, with description of appropriateness of method selected (e.g., forward inclusion, backward elimination, best-subset, or specified a priori, either collectively or in "hierarchically" grouped subsets).

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Reporting

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Be clear (1):

- Avoid very long sentences.
- Reduce use of acronyms to minimum.
- Write an informative and clear Abstract.
- Don't spare details in your description of the methods.
- Ask a colleague (not necessarily very knowledgeable in the materia) to read it for clarity.
- If you are not a native English speaker, ask a colleague who is to read it for style and language.

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Be clear (2):

- Use the structured discussion format suggested by Docherty and Smith, *BMJ 1999;318:1224–5*. The discussion would include in this order:
  - Statement of principal findings
  - Strengths and weaknesses of the study
  - Strengths and weaknesses in relation to other studies, discussing particularly any differences in results
  - Meaning of the study: possible mechanisms and implications for clinicians or policymakers
  - Unanswered questions and future research

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Be concise:

- Leave out (mainly in the Introduction) details that are well known to your audience.
- Avoid repetitions in the Introduction and Discussion.
- Avoid repetitions in the text of the Results and Tables or Figures. As a rule, results should be described in detail in tables and figures; and only important details emphasized in the text.
- Limit yourself to a very short review of the field; and mainly discuss your results.
- Limit yourself to conclusions that are based directly on your results.

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Be informative:

- Supply actual numbers (nominator and denominator) and not only percentages; certainly not only p values. Be sure to do it in the Abstract as well.
- Make use of confidence intervals.
- Use guidelines for structured reporting

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In summary:

- Take care of problems at the planning stage: write a detailed protocol.
- Use guidelines for structured reporting.
- When writing your report:
  - Be clear
  - Be informative
  - Be concise

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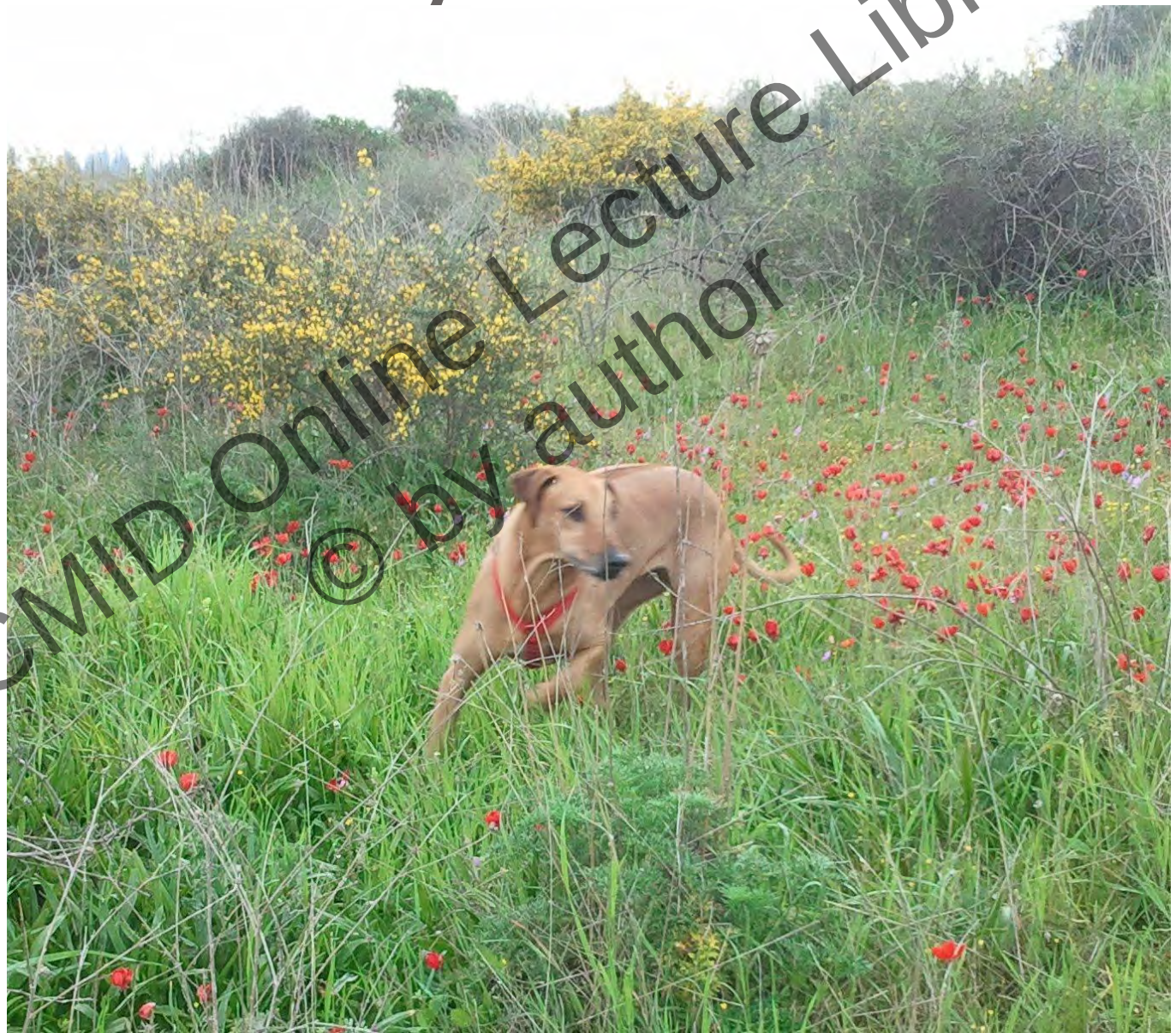
Thank you



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