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Academic Authorship Programme

- Key issues in getting published -
the study design and write-up

Editors of Human Reproduction Journals

12

1 July 2012
Istanbul, Turkey

Academic Authorship Programme: Key issues in getting published – the study design and write-up

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Organised by
the Editors of Human Reproduction Journals

Contents

Learning objectives

After attending the course the participant should be familiar with the principles of study design – including those for treatment and diagnostic test studies. Considerable focus will be devoted to the key components of a manuscript, with practical exercises designed to equip participants with the knowledge required to prepare their work for publication.

Course format

There will be just four lectures; the rest of the day being devoted to small-group exercises with feedback to all participants following each exercise.

Target audience

Young clinicians and scientists, people at the onset of the writing phase of their academic career, and all those who wish to familiarize themselves with present day ideas about designing a study and publishing its outcome.

Scientific programme

09:00 – 09:10	Introduction to the Course – **John Collins (Canada)**
09:10 – 09:40	Principles of study design: treatment studies – **Edgardo Somigliana (Italy)**
09:40 – 10:30	Group work on study design + report to group – **Edward G. Hughes (Canada)**
10:30 – 11:00	Coffee Break
11:00 – 11:30	Principles of study design: diagnostic test studies – **Madelon van Wely (The Netherlands)**
11:30 – 12:30	Group work on study design + report to group - **Edward G. Hughes (Canada)**
12:30 – 13:30	Lunch break
13:30 – 14:00	Key components of a manuscript – **Hans Evers (The Netherlands)**
14:00 – 15:00	Group work on title, abstract, tables and figures + report to group - **Edward G. Hughes (Canada)**
15:00 – 15:30	Coffee Break
15:30 - 16:00	Winning the publications game – **André van Steirteghem (Belgium)**
16:00 – 17:00	Group work on organization of manuscript and report of group work - **Edward G. Hughes (Canada)**
17:00 – 17:10	Conclusions of the Course – **Steve Hillier (United Kingdom)**

Principles of study design
Treatment studies

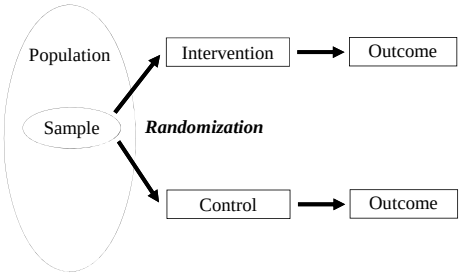
Dr. Edgardo Somigliana, M.D., Ph.D
Fondazione Cà Granda, Ospedale Maggiore Policllinico
Milan, Italy

No conflict of interest to declare

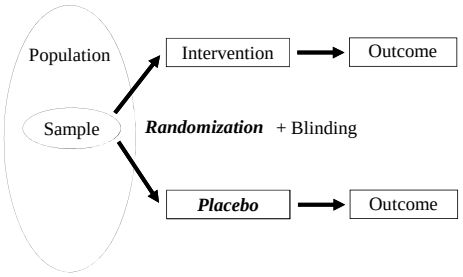
Principles of study design
Treatment studies

Randomized
Controlled Trial
RCT

RCT: Basic Trial Design



RCT: Basic Trial Design



RCT: Basic Trial Design

- ❖ Rationale
- ❖ Basic designs
- ❖ Participants
- ❖ Intervention
- ❖ Blinding
- ❖ Outcomes
- ❖ Adherence
- ❖ Follow-up

RCT: Rationale

Why *do* a randomized blinded trial
- minimize confounding
- minimize co-interventions
- minimize biased outcome ascertainment

Why *not do* a randomized trial
- major ethical issues
- narrow research question
- expensive
- long time from idea to paper

→ Generally reserved for mature questions

RCT: Rationale

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

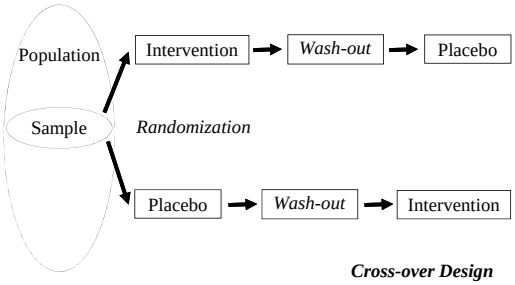
RCT: Rationale

- Participants are assigned to treatment groups by chance with a known probability
- Random number table or computer
- Tamper-proof system
  - ordered, sealed envelopes
  - centralized system (phone, fax, web)

→ Balances baseline characteristics of the groups

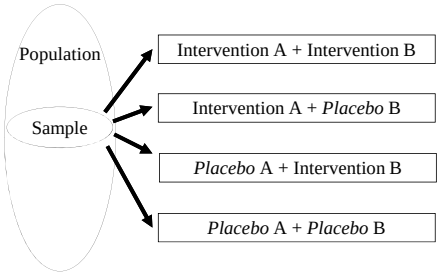
- eliminates confounding due to measured and unmeasured factors
- provides an unbiased comparison between groups

RCT: Alternative Trial Designs



Cross-over Design

RCT: Alternative Trial Designs



Factorial Design

RCT: Participants

Inclusion criteria to maximize:
- Rate of outcomes
- Likely benefit from intervention
- Generalizability
- Ease of recruitment

Exclusion criteria
- Intervention unsafe
- Intervention unlikely to be effective
- Unlikely to adhere to the intervention
- Unlikely to complete follow-up
- Practical problems

Practice Parsimony

Preserve Generalizability

RCT: Choice of intervention

Maximize:
- ❖ Effectiveness *(highest tolerable dose)*
- ❖ Safety *(lowest effective dose)*
- ❖ Generalizability
- ❖ Trial design/conduct (recruitment, compliance, blinding)

Combination of interventions

Advantages:
- Maximize benefit
- Generalizable to clinical practice

Disadvantage :
- Which is effective?

RCT: Choice of Control

Placebo: usually best, but might not be possible or might be unethical

Active therapy for control: to be used if accepted standard available. Advantage of answering clinical question but may require larger sample size and can't tell if better then placebo

Equivalence study: if secondary benefits or cheaper
Be careful to under-powered trials. Absence of difference would mean that control treatment is better.

RCT: Blindness

Maintains balanced groups during follow-up
Eliminates

- *biased outcome ascertainment*
- *biased measurement of outcome*
- *Co-interventions*

Participants use other therapy or change behavior
Medical providers treat participants differently
Two types: *Non-differential* - decreases power
Differential - causes bias

RCT: Blindness

Single blind: Participants are not aware of treatment
Double blinded: Both participants and investigators unaware.

May be *impossible* (surgery, exercise, diet, education)
May be *possible but* dangerous, painful, cumbersome

Difficult even for drugs
Identical placebo difficult to prepare
Drug may smell, taste, fell different
Drug may cause side effects
Test results may unblind
Participants may taste drug

RCT: Blindness

What to do if you can't blind?

- ❖ Be courageous
- ❖ Do the best you can
  - – minimize differential cointervention
  - – blind those measuring outcome
  - – use "hard" outcomes
- ❖ Measure degree of unblinding (*ask participants and investigators to guess treatment*)

RCT: Adherence

Intervention cannot work if it isn't used

Measure adherence

- – Intervention (*pill count, diaries, biologic measure, measuring device in dispenser*)
- – visits
- – study measurements

Choose subjects likely to adhere

Intervention easy and safe

Visits easy and enjoyable

Measurements easy, safe and painless

Never discontinue participants

RCT: Outcome

Efficacy Outcomes: Primary
Secondary
Surrogate
Composite

How to proceed:

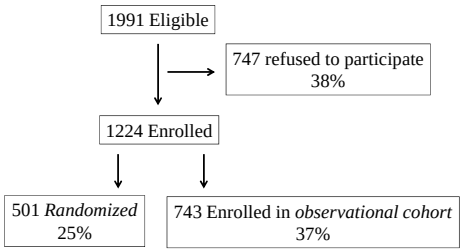
- ❖ Measure all outcomes
- ❖ Pick *one* primary outcome (estimate sample size)
- ❖ Make all the rest secondary

High quality RCTs

- Tamper-proof *randomization*
- *Blinding* of participants, study staff, lab staff, outcome ascertainment and adjudication
- Adherence to study intervention
- Complete *follow-up*
- *Adequate power*

The SPORT Trial

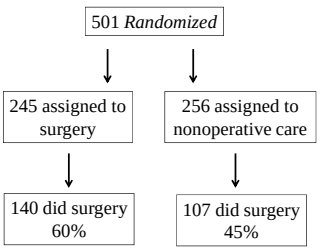
Surgical vs non-operative treatment for lumbar disk herniation



Weinstein et al., 2006

The SPORT Trial

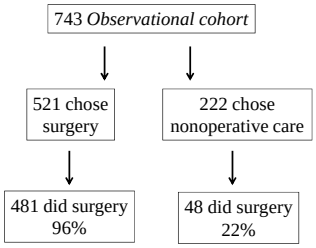
Surgical vs non-operative treatment for lumbar disk herniation



Weinstein et al., 2006

The SPORT Trial

Surgical vs non-operative treatment for lumbar disk herniation



Weinstein et al., 2006

The SPORT Trial

Surgical vs non-operative treatment for lumbar disk herniation

Randomized study: Benefit in both arms, no significant differences between groups

Observational cohort: Benefit in both groups, but surgery better

→ Surgery better in motivated patients, but conclusions exposed to bias due to patients' preferences.

Weinstein et al., 2006

Alternatives to RCTs

- ❖ Patients Preference Trial
- ❖ Time point series
- ❖ Case series
- ❖ Case report

Never give up…
The perfect study does not exist but all studies can be informative!

References

Solomon et al. Should we be performing more randomized controlled trials evaluating surgical operations? Surgery 1995:118:459-67

McCullog et al. Randomized trials in surgery: problems and possible solutions. BMJ 2002;324:1448-51

Weinstein et al. Surgery versus nonoperative treatment for lumbar disk herniation. The Spine Patients Outcome Research Trial (SPORT): A randomized trial JAMA 2006;296:2441-50

Weinstein et al. Surgery versus nonoperative treatment for lumbar disk herniation. The Spine Patients Outcome Research Trial (SPORT) Observational cohort JAMA 2006;296:2451-9

Preference Collaborative Review Group. Patients' preferences within randomized trials: systematic review and patient level metanalysis. BMJ 2008;337:a1864

Principles of study design: diagnostic test studies

Madelon van Wely, PhD

Center for reproductive medicine, AMC-UVA, Amsterdam

Financial/commercial disclosure: none

Learning objectives

- What is important when designing a diagnostic study
- How to use the results of diagnostic tests
- How to interpret the results in practice

What is diagnosis?

- Increase certainty about presence/absence of disease
- Disease severity
- Monitor clinical course
- Assess prognosis – risk/stage
- Plan treatment e.g., location
- Stall for time!

Importance of diagnosis

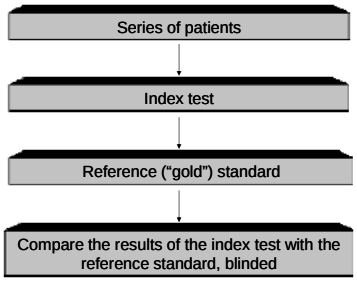
- 2/3 malpractice claims against GPs in UK
- 40,000-80,000 US hospital deaths from misdiagnosis per year
- Adverse events, negligence cases, serious disability more likely to be related to misdiagnosis than drug errors
- Diagnosis uses <5% of hospital costs, but influences 60% of decision making

Diagnostic Errors—The Next Frontier for Patient Safety

JAMA, 2009, vol 301 (10), pp 1060

Appropriate diagnostic studies needed

Basic structure of diagnostic studies



Dealing with diagnostic tests: 3 easy steps

1. Will the results be valid?	• Appropriate spectrum of patients? • Does everyone get the gold standard? • Is there an independent, blind or objective comparison with the gold standard?
2. Presentation of results?	• Sensitivity, specificity, predictive values • Likelihood ratios • ROC curve
3. Will the study help me look after my patients?	• Can I do the test in my setting? • Do results apply to the patients I see? • Will the result change my management? • Costs to patient/health service?

Valid results: A*ppropriate spectrum* of patients?

- Ideally, test should be performed on group of patients in whom it will be applied in the real world clinical setting
- **Spectrum bias** = study uses only highly selected patients…….perhaps those in whom you would *really* suspect have the diagnosis

Valid results: A*ll* patients have the gold standard?

- Ideally all patients get the gold /reference standard test
- **Work-up bias** = only **some** patients get the gold standard…..perhaps the ones in whom you really suspect have the disease

Valid results: *Comparison* with the gold standard?

- Ideally, the gold standard is independent, blind and objective
- **Observer bias** = test is very subjective, or done by person who knows something about the patient

Presentation of results: 2 by 2 table

		Disease: present	Disease: absent
Test	+	True positives (a)	False positives (b)
	-	False negatives (c)	True negatives (d)

Presentation of results: 2 by 2 table - sensitivity

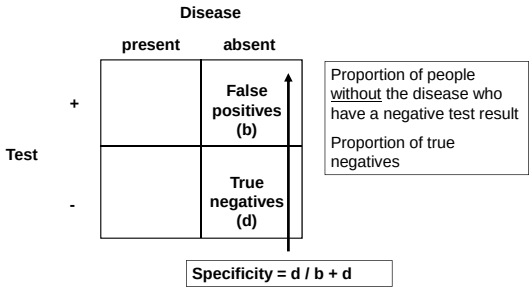
		Disease: present	Disease: absent
Test	+	True positives (a)	
	-	False negatives (c)	

Proportion of people with the disease who have a positive test result

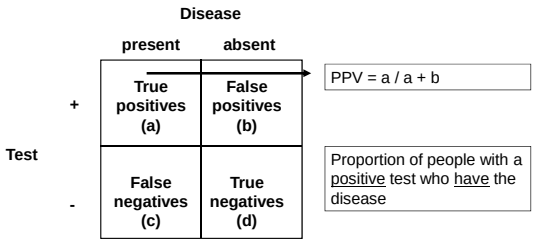
Proportion of true positives.

Sensitivity = a / a + c

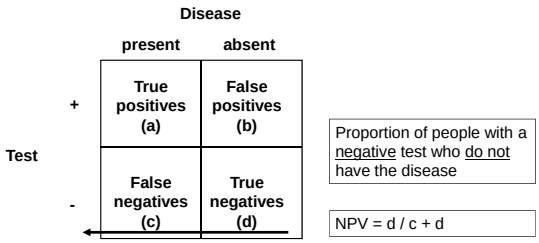
Presentation of results: 2 by 2 table - specificity



Presentation of results
2 x 2 table - positive predictive value



Presentation of results
2 x 2 table - negative predictive value



Presentation of results

- PPV and NPV only apply to patients with the same prevalence as the patients where the values were generated from
  - Are not very useful!
- Sensitivity and specificity are not affected by prevalence
  - Beware of clinical differences!
    - Prevalence of gynecological diseases in general practice low
    - Prevalence in clinic is high, likely also greater disease burden

Presentation of results: Likelihood ratios

- Positive likelihood ratio (LR+)

  How much more likely is a positive test to be found in a person with the disease than in a person without it?

  LR+ = sens/(1-spec) = ratio of true positives to false positives

- Negative likelihood ratio (LR-)

  How much more likely is a negative test to be found in a person without the condition than in a person with it?

  LR- = (1-sens)/(spec) = ratio of true negatives to false negatives

Presentation of results
2 x 2 table - positive likelihood ratio

How much more often a positive test occurs in people with compared to those without the disease

		Disease: present	Disease: absent
Test	+	**True positives (a)**	**False positives (b)**
Test	-	**False negatives (c)**	**True negatives (d)**

LR+ = a/a+c / b/b+d

or

LR+ = sens/(1-spec)

Presentation of results
2 x 2 table: negative likelihood ratio

		Disease present	Disease absent
Test	+	True positives (a)	False positives (b)
	-	False negatives (c)	True negatives (d)

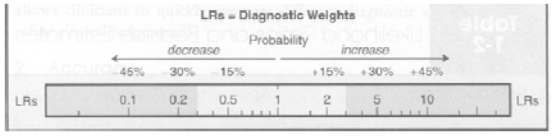
How less likely a negative test result occurs in people with the disease compared to those without the disease

LR- = c/a+c / d/b+d

or

LR- = (1-sens)/(spec)

How to interpret likelihood ratios?



LR<0.1 = strong negative test result

Decrease in likelihood

LR=1 no diagnostic value

No change in likelihood

LR>10 = strong positive test result

Increase in likelihood

Converting LR to post test probability

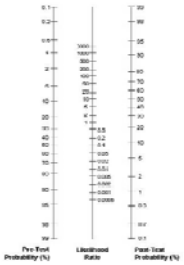
Presentation with a HCG of 3000 IU/L – LR = 15
Prevalence EUG: 5% in a non-symptomatic woman with a history of EUG
Prevalence EUG: 40% if the woman had abdominal pain

Pre test probability (prevalence)	Pre test odds	LR	Post test odds	Post test probability
5%	.05/.95	15	0.79	0.79/1.79 =44%
40%	.40/.60	15	10	10/11=91%

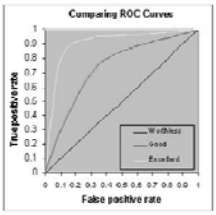
From Mol et al, Human Reprod 1999, 14

Usefulness of LR

- LR can help fine tune the risk of disease for an individual patient
- Can help decide on management



ROC curve



1. Tradeoff between sensitivity and specificity
2. The closer the curve follows the left-hand border and then the top border of the ROC space, the more accurate the test.
3. The closer the curve comes to the 45-degree diagonal of the ROC space, the less accurate the test.
4. The slope of the tangent line at a cut point gives the likelihood ratio (LR) for that value of the test.
5. The area under the curve is a measure of test accuracy.

Further from 0.50, (straight line, where LR =1), the better the test

Will the test apply in my setting?

- Reproducibility of the test and interpretation in my setting
- Do results apply to the mix of patients I see?
- Will the results change my management?
- Impact on outcomes that are important to patients?
- Where does the test fit into the diagnostic strategy?
- Costs to patient/health service?

Practical group assignments

- Pick a diagnostic article
- Rapidly appraise it using the 3 steps
- Explain sensitivity/specificity etc

- Diagnosis: patent or blocked tubes
- Gold standard: diagnostic laparoscopy - not suitable for standard use
- Alternative CAT: Easy, non-invasive, cheap
- Question: Discriminative capacity of CAT
- How would you design this diagnostic study

Key components of a manuscript

The history of science publishing, authorship, attractive titles, scientific language, the message, organization of an article, how do readers read, 18 effective paragraphs, writing assistance, the importance of abstracts in the age of *e*-publishing.

Hans Evers

Writing up biomedical research

- Think of yourself as a reader for a moment.
- What kind of papers do you like to read?
- Short, substantial and clear most likely.
- Well, then, *write* short, substantial and clear papers yourself.

Mimi Zeiger

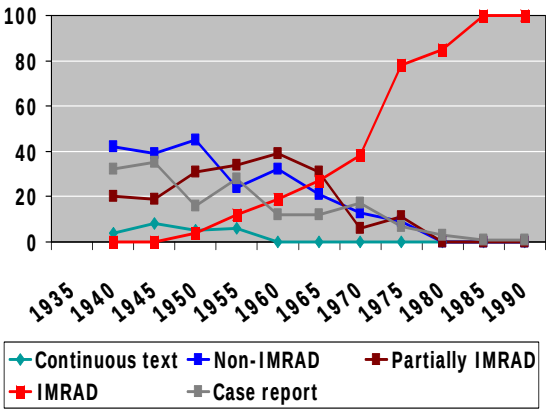
2 questions before deciding to write

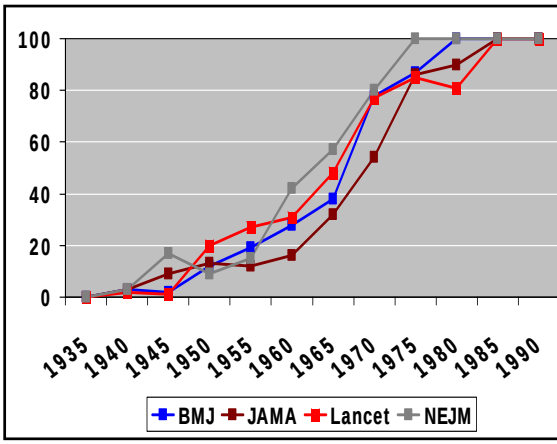
- So what ?
- Who cares ?

2

The organization of articles

1665	Letter	*"First I saw this, then I saw that"*
1750	Report	Narrative
1850	TED	Theory Experiment Discussion
1972	IMRAD	Introduction Material & Methods Results and Discussion

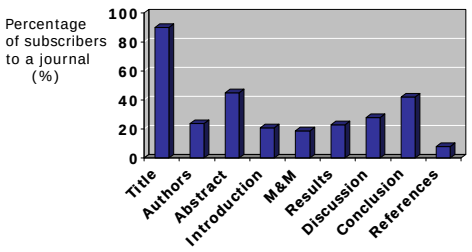




How do clinicians read journals?

1. Grazing 80%
2. Hunting 15%
3. Gorging 5%, and falling

What do grazers read?



6 Questions before starting

Introduction	*Why did you study this problem?*
M&M	*What did you do?*
	How did you do it?
Results	*What did you find?*
Discussion	*What does it mean?*
	How does it relate to previous work in the field?

6

18

Reporting clinical studies effectively in 18 thoughtful paragraphs

Introduction

Paragraph	Text
1. Start	The first sentence should pick up some or most of the words from the title
2. Why	Provide a context and motivation for the investigation
3. What	The last sentence should begin: "The purpose of this study is to …"

Beginning	Example
Purpose	This paper presents an evidence-based approach to diagnosing PID.
Scope	This paper discusses 5 causes of fertilization failure after ICSI.
Viewpoint	Calling ART clinicians 'providers' insults our professionalism.
Quotation	Recently, in Human Reproduction, Edwards reported …
Question	Which is the safest way to perform a laparoscopy?
Argument	The diagnosis of PCOS is not based on ultrasound findings. Is this logical?
Action	Now is the time to reconsider blastocyst transfer.
Case report	The next patient you see may have porphyria. Will you recognize it?
Statistic	1 in 6 high school girls is chlamydia positive.

Introduction

Paragraph	Text
1. Start	The first sentence should pick up some or most of the words from the title
2. Why	Provide a context and motivation for the investigation
3. What	The last sentence should begin: "The purpose of this study is to …"

Material & Methods

Paragraph	Text
4. Subjects	Study design
	Inclusion/exclusion criteria, participants
	Informed consent, IRB approval
	Demographics (if retrospective): table I
5. Procedures	Detail experiment, drugs, equipment
6. Definitions & criteria	Disease criteria, ranking system (give criteria), staging of disease, (in)dependent variables
7. Data collection	Prospective/retrospective
	Validation of data, data quality
	Blinding, intra/interobserver variability
	Gold standard
8. Statistics	Statistical tests in order in which applied
	Sample size, power calculation

Results

Paragraph	Text
9. Subjects	Demographics (if prospective): table I
10. Results	Facts & numbers, no editorializing
11. Presentation	Tables & figures (do not repeat text)
12. Correlations	How well did independent variable (predictor) lead to dependent variable (outcome)?
	Effect sizes of variables
	Comparison to gold standard
	Statistical significance (statement of strength of evidence, not of clinical importance)

Discussion

Paragraph	Text
13. Summarize results	Principal findings, i.e. those that address questions posed in Introduction
	Do not reiterate Results
	Never introduce new data
14. Interpretation of results	Principal findings of paragraph 13 become substrate on which principal conclusions are based
	Too many conclusions dilute the impact of any one
15. Interpretation in context of the literature	Consistent with or departure from current thinking
	Give reasons
	No literature review, focus on relating studies
16. Clinical implications	Clinical study: discuss new insight in disease
	Basic study: discuss pathophysiology
17. Limitations	Be thoughtful & self-critical, discuss validity of findings, practical limits, interpretations

Conclusion

Paragraph	Text
18. So what	Restate principal findings and conclusions
	Emphasize clinical and basic science implications of principal findings
	Indicate logical next step (if any)

Introduction

1. Statement of issue
2. Why this paper is needed
3. Purpose & hypothesis

M&M

4. Subjects
5. Procedures & techniques
6. Definitions & criteria
7. Data collection & validation
8. Statistical tests

Results

9. Descriptive statistics, baseline population comparisons
10. Results, outcome
11. Measures of data validity
12. Statistical analysis

Discussion & Conclusion

13. Principal results
14. Interpretation of principal results
15. Interpretation in context of literature
16. Clinical/pathophysiol. implications
17. Limitations
18. Conclusion, future directions

What IMRAD does not address

- The title
- The authors
- The abstract
- The acknowledgements
- The references

http://www.consort-statement.org/

The CONSORT statement is an important research tool that takes an evidence-based approach to improve the quality of reports of randomized trials.

Writing assistance

CONSORT	Treatment study, RCT
STARD	Diagnostic test study
STROBE	Observational study
QUOROM	Systematic review, meta-analysis of RCT's
MOOSE	Systematic review, meta-analysis of observational studies

http://www.consort-statement.org/

How did I won the publication game?

According to Tim Albert
www.timalbert.co.uk

- 7-9 September 2011 I completed the Train the Trainers Course on Writing a Journal Article from Tim Albert Training
- In 2006 I followed the BMJ Editors' Course run by Tim Albert and Harvey Marcovitch in preparation to become EIC of Human Reproduction

TIM ALBERT TRAINING

Write for publication 3

Motivational quote

'I came on this course with an article that had been rejected by the *BMJ*. When I rewrote it after the course it was accepted by *The Lancet*.'

Write for publication 4

10 steps to publication

1. Game
2. Player
3. Brief
4. Sort
5. Plan
6. Write
7. Rewrite
8. Extras
9. Others
10. Send

Write for publication 5

3. Set the brief

- *Task:* write out message (see form)

Write for publication 6

Setting the brief

- Message

Write for publication 7

- In the middle comes the message
- Top left: Why did we start?
- Top right: What did we do?
- Bottom right: What did we find?
- Bottom left: What does it mean?

- A few months after the Course was the 20th anniversary of the birth of the first ICSI child
- I had the intention to write an editorial in Human Reproduction
- I wrote the editorial while I was on the Course

Message

- Is different from the title
- My message was: “In 20 years more than 2 million children have been born after ICSI (intracytoplasmic sperm injection)

Why did we start?

- Louise Brown was born in July 1978
- IVF is treatment for female-factor and idiopathic infertility
- IVF is not successful for male-factor infertility
- Can we assist the fertilization process?
- Micromanipulation allowed zona drilling, partial zona dissection – inconsistent results
- Few reports on subzonal insertion

What did we do?

- Experimental work in mice: influence of acrosome reaction on SUZI of one sperm
- Successful in mice – approval for human under strict conditions – some success
- SUZI “failed” sometimes and sperm went into the oocyte = sperm entered the oocyte
- This ICSI more consistent results than SUZI and became the assisted fertilization procedure when needed

What did we find?

- ICSI can be used with different spermatozoa: ejaculate, epididymis and testis
- Is for the male what cIVF is for the female
- Standard treatment for male-factor infertility
- Preimplantation Genetic Diagnosis uses also ICSI
- Prospective follow-up of children needed and done

What does it mean?

- Effective treatment for male infertility: majority of patients can be helped
- Two major drawbacks: 1) ICSI is overused and 2) as other ART there are too many multiple pregancies including twins – SET whenever possible
- Clinical research should continue
- Basic research needed to understand infertility

Acknowledgment

- People
- Institutions

- Human Reproduction: 27, 1-2, 2012
- Celebrating ICSI's twentieth anniversary and the birth of more than 2.5 million children – the "how, why, when and where"

Mark your calendar for the upcoming ESHRE Campus events

- Basic Semen Analysis Course in Greek Language
  4-7 September 2012 - Athens, Greece
- Basic Genetics for ART practitioners
  7 September 2012 - Rome, Italy
- Regulation of quality and safety in ART – the EU Tissues and Cells Directive perspective
  14-15 September 2012 - Dublin, Ireland
- Basic Semen Analysis Course in Spanish language
  18-21 September 2012 - Galdakano,Vizcaya
- GnRH-antagonists in ovarian stimulation
  28 September 2012 - Hamburg, Germany
- The best sperm for the best oocyte
  6-7 October 2012 - Athens, Greece
- Basic Semen Analysis Course in Italian language
  8-11 October 2012 - Rome, Italy
- Accreditation of a preimplantation genetic diagnosis laboratory
  11-12 October 2012 - Istanbul, Turkey
- Endoscopy in reproductive medicine
  21-23 November 2012 - Leuven, Belgium
- Evidence based early pregnancy care
  29-30 November 2012 - Amsterdam, The Netherlands

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