Managing the study
(Part 1)

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It seems that we have a very good study design in our hands...

Is that all that we need?

The value of study management and conduct

The best study design can be destroyed if it is not complimented with appropriate study conduct

The value of study management and conduct

- Sample collection:

Assembly of patients, records or studies

- Avoiding bias during study execution

Randomization procedures
Allocation concealment
Blinding
Proper application of the assigned treatment
Proper assessment of the outcomes
Retaining patients: follow-up
Contamination
Co-intervention

Gathering the evidence:
Assembly of patients, records or studies

The process of collecting the proper evidence is crucial for reaching valid conclusions

Gathering the evidence
Patient recruitment

Who will recruit patients?

How will patients be recruited?

From **Where** will patients be recruited?

Gathering the evidence

Patient recruitment: *Who will recruit patients?*

Patient recruitment represents one of the most challenging tasks in clinical studies

It demands:

- Understanding the need for conducting the study
- Knowledge and accurate interpretation of the protocol
- Understanding of the methodological perspective of the study
- Commitment
- Skills of interpersonal communication

Gathering the evidence

Patient recruitment: *Who will recruit patients?*

Good candidates for patient recruiters

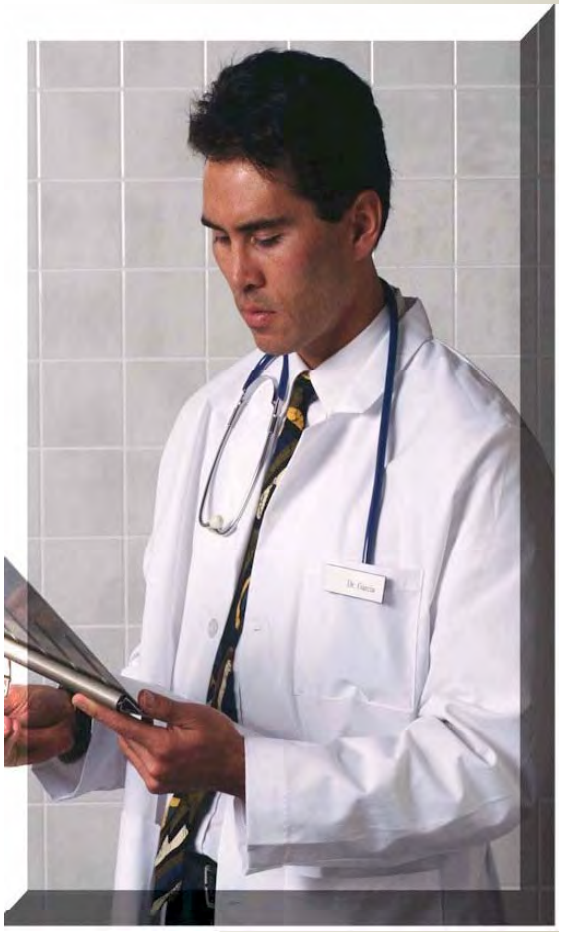
- Physicians or Nurses that have past experience in patient recruitment
- Persons that work in teaching or University affiliated hospitals or medical centers – Research oriented physicians or nurses
- Persons referred by other successful recruiters

Gathering the evidence

Patient recruitment: *Who will recruit patients?*

Not so good candidates for patient recruiters

- Physicians or Nurses that are actively involved in many different research projects – Recruiting competition
- "Contract researchers" – Physicians that have lost their motivation and enthusiasm
- Physicians with strong personal beliefs regarding the treatment modalities evaluated

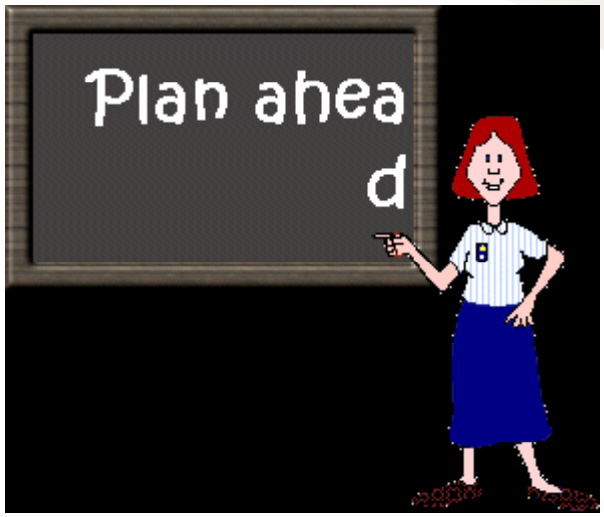


Gathering the evidence

Patient recruitment: *How will patients be recruited?*

Patient recruitment plan:

- Accrual rate
- Interim goals
- Flexibility
- Alternatives
- Active monitoring



It is almost certain that every physician will overestimate the number of patients that can be recruited at a certain period of time

Gathering the evidence

Patient recruitment: *How will patients be recruited?*

Why a prospective patient might not be recruited :

- Ignorance ***(Doesn't know about the study)***
- Unwillingness ***(Doesn't want to be in the study)***
- Not suitable ***(Doesn't satisfy the eligibility criteria)***
- Already taken ***(Is enrolled in a similar study)***

Gathering the evidence

Patient recruitment: *How will patients be recruited?*

Overcoming obstacles

- Media campaigns, radio and TV announcements, newspaper and magazine articles directed at the population of prospective patients
- Direct contact with all the physicians-potential referrers in a given area
- Reinforcing the recruiting efforts of your study investigators
- Let eligible patients know that they can satisfy their own needs while helping others

Gathering the evidence

Patient recruitment:

From where will patients be recruited?

What kind of population do we need?

- Patients referred by general practitioners?
- Outpatient clinic in a tertiary hospital/ "clinical excellence center" : *Highly selected patients, not representative of the milder forms of the disease or exposure*
- Patients admitted in the clinic?

  Patients with a specific clinical spectrum - Patients with severe morbidity
- Community:

  Wide spectrum of the condition under investigation
  Community specific bias: Socioeconomic level, race, education

Diversifying patient demographics

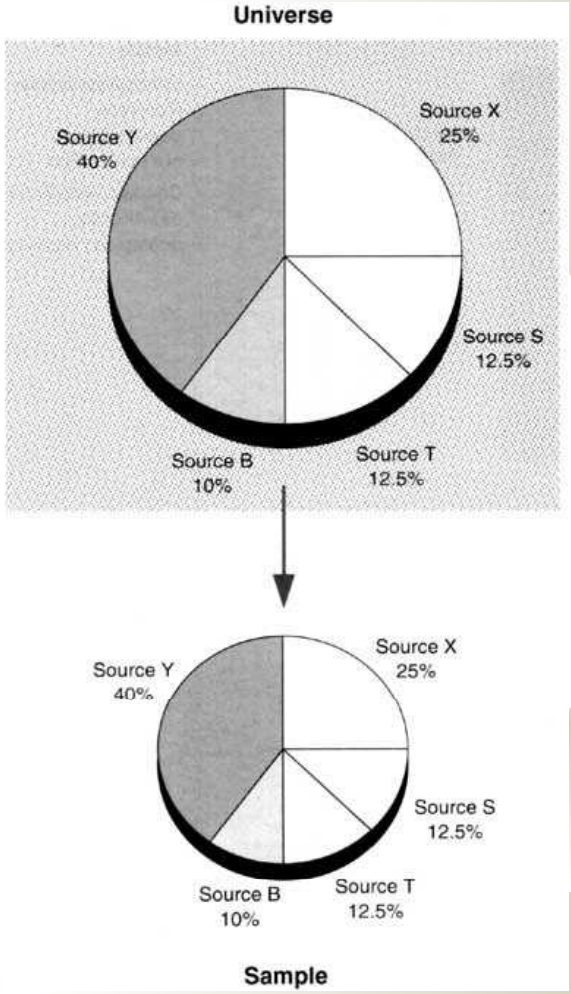
Gathering the evidence

Patient recruitment:

From where will patients be recruited?

REMEMBER:

to be able to extend results the sample must be representative of the population, i.e. all types of subjects included in the population must be ***proportionally*** *represented in the sample*



Gathering the evidence

Patient recruitment:

From where will patients be recruited?

Avoid Selection Bias

Target all eligible women and record all refusals*
(Consecutive accrual)

It may be helpful to obtain some baseline clinical details about them in order to explore any major differences between participants and non-participants, which could affect the external validity of the trial

Gathering the evidence
Records

In retrospective studies (such as case-control studies) retrieval of patients' records is necessary

Gathering the evidence
Records

Important parameters

Where to look:

Records from hospital archives, from registries etc.

What to look for:

Records from **all patients** satisfying the eligibility criteria (Consecutive accrual)

Gathering the evidence
Studies

Where to look?

- Bibliographic Databases
- Relevant Journals
- Unpublished and Ongoing studies

Gathering the evidence

Studies

Where to search?

Bibliographic Databases

- MEDLINE (>16 million articles/ 1950-present)
- PubMed (MEDLINE + Citations not indexed in MEDLINE)
- EMBASE (> 11 million articles/ 1974-present)

Of the 4,800 journals indexed in EMBASE, 1,800 are not indexed in MEDLINE. Similarly, of the 5,200 journals indexed in MEDLINE, 1,800 are not indexed in EMBASE.

Gathering the evidence

Studies

Where to search?

Bibliographic Databases

- SCOPUS (16,500 peer-reviewed journals and 3.6 million conference papers)
- Web of Science (>10,000 journals and >110,000 conference proceedings)

Gathering the evidence

Studies

Where to search?

Other Subject-Specific Bibliographic Databases

- Biological Abstracts / BIOSIS Previews
- International Pharmaceutical Abstracts
- Cumulative Index to Nursing and Allied Health (CINAHL)
- PsycINFO

Gathering the evidence
Studies
Where to search?

<u>Other sources of studies</u>

- Handsearching of relevant journals *(especially those not indexed in bibliographic databases)*
- Conference abstracts or proceedings
- Other reviews, guidelines and reference lists as sources of studies
- Web searching (such as Google Scholar)

Gathering the evidence

Studies

Where to search?

Other sources of studies

Unpublished or Ongoing trials

Registries:

- National and international trials registers

(www.clinicaltrials.gov, WHO ICTRP etc)

- Pharmaceutical industry registries

For more information you can visit:
http://www.cochrane-handbook.org/

Gathering the evidence

Studies

How to search?

Search strategy

3 major components – 3 major concepts

All relevant to the hypothesis to be tested

Gathering the evidence
Studies - How to search?

Is the addition of rLH associated with the probability of live birth in patients undergoing ovarian stimulation for IVF?

Concept 1: Independent variable → addition of rLH
Keywords: recombinant luteinizing hormone OR rec LH or rLH or Luveris...

Concept 2: Dependent variable → live birth
Keywords: Live birth or delivery or birth or pregnancy

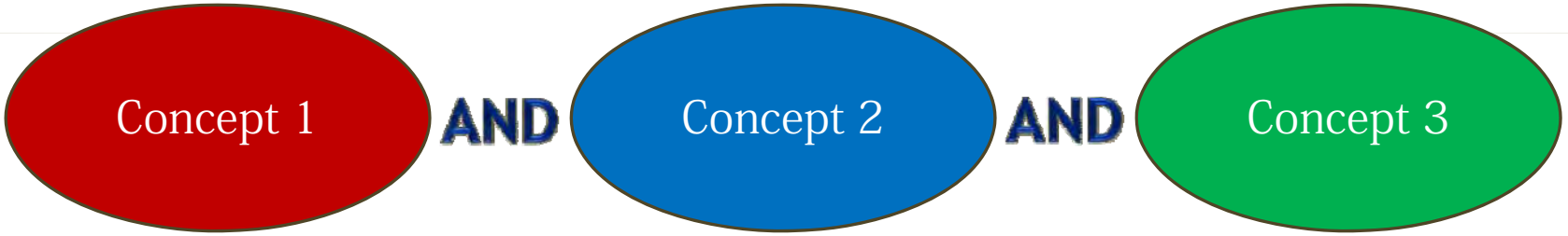
Concept 3: Population studied → patients undergoing IVF
Keywords: in-vitro fertilization OR in-vitro fertilisation OR ovarian stimulation OR IVF

Eligibility criteria will form other concepts:
e.g. if only RCT are to be included then "random*" could be another search term

Gathering the evidence
Studies - How to search?

Is the addition of rLH associated with the probability of live birth in patients undergoing ovarian stimulation for IVF?

Search Strategy:



Our goal is to ensure that no relevant study is missed

Sensitivity

Accuracy

Gathering the evidence
Studies - How to search?

Search fields – Limits

Search field: Each keyword can be searched in various fields

"Title", "Title/Abstract", "Text", "Keywords", "Author"

PubMed and Embase also offer "Limits":

Type of article: "Clinical trial", "Review", "meta-analysis", "Letter" etc
Species: "Human", "animals" etc
Gender: "Female", "Male" etc
Ages: "All child", "All Adult" etc

Tip: Once you have identified a key article for your search you can also use the **"Related Articles"** or **"Similar Articles"**

Gathering the evidence
Studies - How to search?

Controlled Vocabulary Thesaurus

MEDLINE: MeSH (Medical Subject Heading)

EMBASE: EMTREE

Different researchers may use different words to describe the same concept:

e.g.: poor or low or inadequate or suboptimal or slow or minimal or...

ovarian response

By using the intelligent "Controlled Vocabulary Thesaurus"
of each search engine
it is possible to identify more articles

Gathering the evidence
Tools for better data recording and management

Case Report Form (CRF):

Official clinical data-recording document or tool used in a clinical study

Purpose:

- Collects relevant data in a specific format in accordance with the protocol
- Allows for efficient and complete data processing, analysis and reporting

Design:

- Standardized – Easily Comprehensible
- All info required per protocol should be included in the CRF
- Data not to be analyzed should not be included in the CRF

Gathering the evidence
Tools for better data recording and management

Designing CRF:

- Optimize for all potential users (different background)
- Collect data required by regulatory agencies (e.g. IRB, FDA)
- Be clear and concise with your data questions
- Avoid duplication
- Request minimal (if any) free text responses
- Provide units to ensure comparable values
- Provide instructions to reduce misinterpretations

Gathering the evidence
Tools for better data recording and management

Designing CRF:

- Provide "choices" for each questions
- Use "None" and "Not done"
- Collect data in a fashion that:

  allows for the most efficient computerization
- CRF book needs to be finalized and available before an investigator starts enrolling patients into a study

Ask investigators to review CRF and provide you with feedback

Gathering the evidence

Tools for better data recording and management

Example CRF:

SYMPTOMS AND SIGNS OF CURRENT EPISODE (PLEASE MARK EACH QUESTION)

DERMATOLOGIC:

Erythema migrans (physician diagnosed EM at least 5 cm in diameter)? .....[Y] [N] [?]

RHEUMATOLOGIC:

Arthritis characterized by brief attacks of swelling in one or a few joints? .....[Y] [N] [?]

NEUROLOGIC:

Bells palsy or other cranial neuritis? .....[Y] [N] [?]
Radiculoneuropathy? .....[Y] [N] [?]
Lymphocytic meningitis? .....[Y] [N] [?]
Encephalitis .....[Y] [N] [?]
Antibody to B. burgdorferi higher in CSF than serum? .....[Y] [N] [?] or not tested [ ]

CARDIOLOGIC:

2nd or 3rd degree atrioventricular block? .....[Y] [N] [?]

Other clinical: _____

Date of onset of first symptoms: __/__/__ (mo dy yr) Date of diagnosis: __/__/__ (mo dy yr) Date of report to health agency: __/__/__ (mo dy yr)

OTHER HISTORY

Was the patient hospitalized for the current episode?.....[Y] [N] [?]

Name of antibiotic(s) used this episode? _____Use in days_____

Was the patient pregnant at the time of the illness? .....[Y] [N] [?]

Where was the patient most likely exposed? County _____State_____

Gathering the evidence
Tools for better data recording and management

Study data extraction sheet (SDES):

- Based on the same principles as the CRF
- Standardization
- All info needed per protocol should be recorded in the SDES
- Available for review from all authors
- Easy to identify discrepancies between Data Extractors

Gathering the evidence
Tools for better data recording and management

CRF & SDES:

Electronic forms of CRF and SDES become increasingly available

However,

Always keep hard copies of the CRFs and SDES

- *Hardware failures*
- *More difficult to temper with*

Avoiding bias during study execution

or else... how to avoid spurious findings

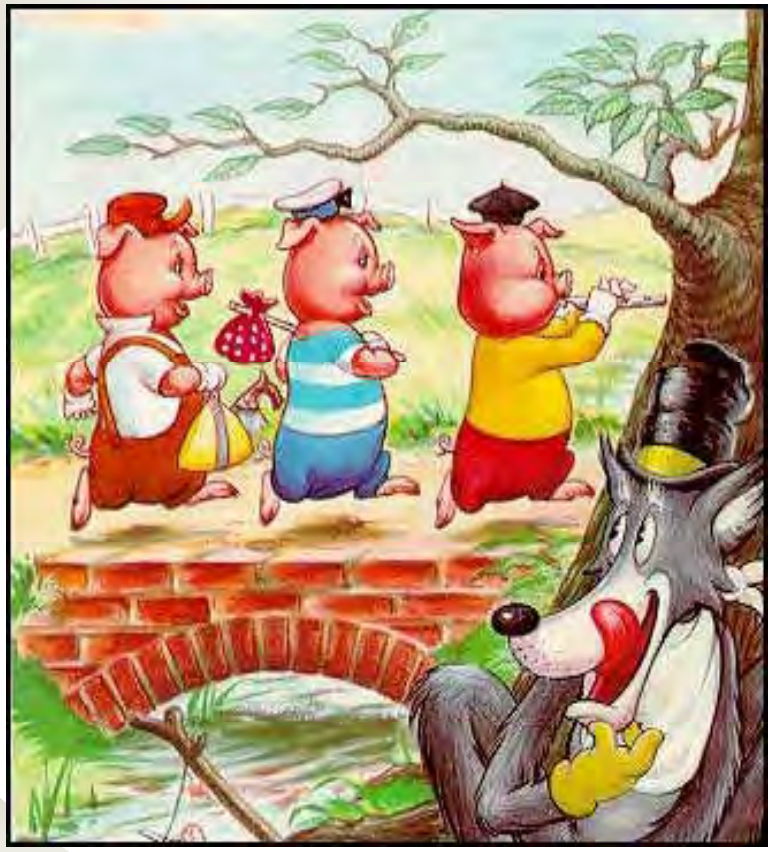
Avoiding bias during study execution

Bias:

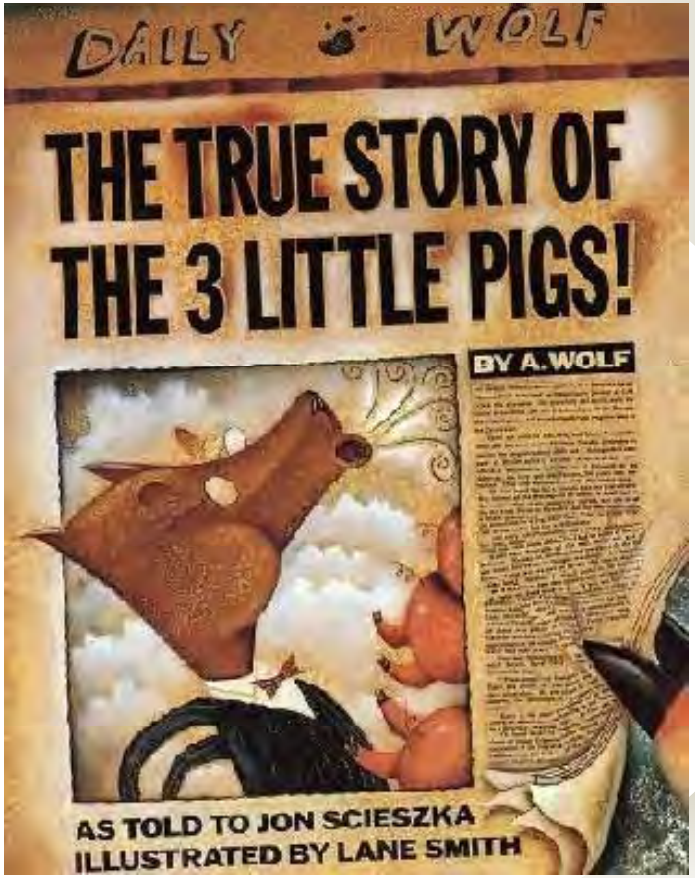
How two people tell a different story
referring to **the same facts**

Avoiding bias during study execution

Bias:



The story of the 3 innocent little pigs and the big **BAD wolf**….



….or maybe not???

Bias: a researcher's worst nightmare

Bias in medical research:

"any factor or process that tends to deviate the results or conclusions of a study systematically away from the truth"

Sackett DL, J Chronic Dis, 1979

Bias: a researcher's worst nightmare

Most important types of Bias in medical research:

Selection bias, defined as a non-random imbalance among treatment groups of the distribution of factors capable of influencing the end-points, that is, of sub-experimental factors (including prognostic factors)

Assessment bias (or ascertainment bias), defined as a non-random imbalance among treatment groups in the way subjects are followed and assessed during the course of the study

Analysis bias, defined as a distortion in favor of one of the treatments, intervening during the data analysis

Performance bias, defined as a non-random imbalance among study groups in the treatment they receive besides the examined intervention

Bias: a researcher's worst nightmare

How can we protect our study from bias?

Randomization

the assignment of subjects to treatments
with a predefined probability and by chance

Why?

Bias: a researcher's worst nightmare

Why randomize?

eliminates selection bias
for both known and unknown factors
(confounders)
capable of influencing the response to treatments

it allows the
frequentist approach to statistical inference

(The foundation of the frequentist approach to statistical inference is the assumption that the sample is extracted randomly from the population)

Bias: a researcher's worst nightmare

How to randomize?

Randomization is carried out through lists of random numbers*

* 0577445292
* 3721208915
* 0374227859
* 1016442935
* 2283885502
* 5497964383
* 2380852827
* 0221757791
* 1726275631
* 6485059716

**A list of random numbers is a sequence of numbers which follow one another without any discernible order or trend, i.e. each number has the same probability of appearing at any position of the list*

Bias: a researcher's worst nightmare

How to randomize?

Randomization lists are generated

by specialized computer software

(also available in the World Wide Web)

Bias: a researcher's worst nightmare

Types of randomization

Simple randomization

Each patient has the same probability of receiving each of the study treatments

Example: Lets assume we are conducting a RCT comparing two types of gonadotrophins: ***A vs. B***

Subject	Allocated treatment
1	A
2	B
3	A
4	A
5	B
6	B
7	B
8	A

Bias: a researcher's worst nightmare

Types of randomization

Simple randomization

Bear in mind that there is also a small (but existing) probability that a randomly generated sequence could "appear" to be not so random

Subject	Allocated treatment
1	A
2	B
3	A
4	B
5	A
6	B
7	A
8	B

Subject	Allocated treatment
1	A
2	A
3	A
4	A
5	B
6	B
7	B
8	B

Bias: a researcher's worst nightmare

Types of randomization

Randomization in blocks

Randomization sequence is regenerated for every block of patients which could be of a fixed or variable size

- To obtain numerically balanced groups (especially in small studies)
- To obtain a constantly balanced recruitment, that is, a similar size of the treatment groups throughout the enrolment process (helpful when interim analyses are planned or routine treatment of recruited patients, other than the intervention examined, changes with time)

Bias: a researcher's worst nightmare

Randomization in blocks

Block randomization using a fixed block size of 4

Block	Subject	Treatment
1	1	A
	2	B
	3	B
	4	A
2	5	A
	6	B
	7	A
	8	B
3	9	B
	10	B
	11	A
	12	A
4	13	B
	14	A
	15	A
	16	B
5	17	B
	18	A
	19	B
	20	A

Bias: a researcher's worst nightmare

Randomization in blocks

Block randomization using a variable block size of 4 or 6

Block	Subject	Treatment
1	1	B
	2	B
	3	A
	4	B
	5	A
	6	A
2	7	A
	8	B
	9	B
	10	A
3	11	A
	12	A
	13	B
	14	B
4	15	A
	16	B
	17	B
	18	B
	19	A
	20	A

Bias: a researcher's worst nightmare

Randomization in blocks

Disadvantages:
the researcher may be able to guess the sequence, even in the presence of blinded treatments (especially when using blocks of small fixed size)

Example:
Assume that one of the two treatments is known by its pharmacological properties to be associated with tachycardia.
If the researcher has knowledge that randomization has been performed using blocks of four, then knowing the patients who presented tachycardia can lead him to a good guess regarding the next allocation

Bias: a researcher's worst nightmare

Simple randomization and randomization in blocks

Randomization does not ensure homogeneous groups in all potential prognostic factors
(especially is small studies)

Randomization ensures that potential imbalances between groups have resulted by pure chance

How can I ensure that the groups will be homogeneous for specific important parameters?

Bias: a researcher's worst nightmare

Stratified randomization

Stratified randomization ensures constant balance between groups in a limited number of predetermined factors (confounders) that could affect the groups response to treatment (e.g. age, gender, previous medical history etc.)

Bias: a researcher's worst nightmare

Stratified randomization

Example:

Stratum	Age	Male Factor	AFCs	Randomization
1	< 35 years	Positive	< 9	ABBA, BBAA, BABA, AABB…
2	≥ 35 years	Negative	< 9	ABAB, ABBA, BABA, BBAA…
3	< 35 years	Negative	< 9	AABB, BBAA, ABAB, ABBA…
4	≥ 35 years	Positive	< 9	ABBA, BABA, AABB, ABAB…
5	< 35 years	Positive	≥ 9	AABB, BBAA, ABAB, ABBA…
6	≥ 35 years	Negative	≥ 9	ABBA, BBAA, BABA, AABB…
7	< 35 years	Negative	≥ 9	BBAA, BABA, BAAB, AABB…
8	≥ 35 years	Positive	≥ 9	BABA, AABB, BBAA, ABBA…

Bias: a researcher's worst nightmare

Stratified randomization

As the number of prognostic factors increases (n),

randomization becomes more difficult

to implement in real-life

(strata=2^n)

especially in small studies

Bias: a researcher's worst nightmare

Dynamic randomization or minimization

- the allocation to each treatment group is decided based on the distribution among treatment groups of pre-established prognostic factors at the time a new patient is to recruited (minimizes imbalance)

Bias: a researcher's worst nightmare

Dynamic randomization or minimization

- it allows for imbalance correction on-the-fly
- It requires previous knowledge of the distribution of the prognostic factors in the two groups up to that point
- It is not considered truly random
- Some randomness can still be achieved through the use of a "biased coin" randomization procedure

Bias: a researcher's worst nightmare

Randomization in unequal groups

- Allocation ratio is usually 1:1
- Certain situations call for different allocation ratios (3:2, 2:1, 3:1, etc.)

e.g. Randomize more patients to new treatment (assess the safety profile)

Drawback:

- Reduced power

R=1:1
Power: 95%

R=3:2
Power: 92.5%

Bias: a researcher's worst nightmare

How NOT to randomize

- Alternate sequence (A-B-A-B-A-B-A-B-A-B…)
- Based on final digit of Social Security Number or other Identification Numbers (odds=A, even=B)
- Based on Week Days etc.

In these cases the recruiting physician can predict to which group will the next patient be allocated

These methods are considered quasi or pseudo-randomization methods

Bias: a researcher's worst nightmare

Is the generation of a proper randomization plan enough against selection bias?

No, if someone took a sneak peek

Bias: a researcher's worst nightmare

The value of allocation concealment

- Even a flawless randomization plan is useless if the sequence that has been generated is known to recruiting physicians (and/or patients)
- Selection bias might infiltrate since physicians might categorize specific patients as "eligible" or "ineligible" based on this knowledge

Allocation concealment is considered at least equally important with randomization and specific measures should be employed for its implementation

Bias: a researcher's worst nightmare

The value of allocation concealment

Trials that use inadequate or unclear allocation concealment tended to yield ***40%*** *larger estimates of effect compared with those which used adequate concealment*

Schulz et al., 1995, JAMA
Juni P, Altman D and Egger M., 2001, BMJ

Bias: a researcher's worst nightmare

Deciphering the allocation concealment scheme

Deciphering the allocation concealment scheme

Schultz and Grimes, 2002, The Lancet

Bias: a researcher's worst nightmare

Common methods to ensure allocation concealment

- Randomization plan should be trusted to someone not participating in the trial, especially in the recruitment process
- Sealed, opaque, sequentially numbered envelopes or containers

(which are opened after the participants name is written on the envelope)

- Central telephone, fax or email service
- Central pharmacy

Bias: a researcher's worst nightmare

Most important types of Bias in medical research:

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Performance bias, defined as a non-random imbalance among study groups in the treatment they receive besides the examined intervention

Bias: a researcher's worst nightmare

How can we protect our study from ascertainment, performance or analysis bias?

Blinding

Not knowing the group in which each patient has been allocated

Bias: a researcher's worst nightmare

Why blinding (or masking) is so important?

It protects from

1) Ascertainment bias, where physician's assessment about patient outcomes are influenced by the knowledge of which treatment they received
2) Performance bias, where physician's management of patients (besides the intervention examined) might be influenced by the knowledge of which treatment they received
3) Analysis bias, where statisticians and data analysts might handle and analyze data differently favoring one or another treatment

Bias: a researcher's worst nightmare

Types of blinding

Single-blinded studies

The patient is unaware of which treatment he/she is taking, while the investigators are aware of the treatment received by each patient

Advantages:

- relatively simple and inexpensive design

Disadvantages

- patients might under- or over-report treatment effects and side-effects, based on some influence or response from the investigators
- investigators may give advice or prescribe additional therapy to the control group if they feel that these patients are disadvantaged in comparison to the active group

Safety studies often have a single-blind design
that allows investigators to detect side-effects more rapidly

Bias: a researcher's worst nightmare

Types of blinding

Single-blinded studies

Blinding of patients can be achieved by concealing the identity of the medication each group receives

- The use of placebo is mandatory when no active treatment is available for comparison
- Tablets, bottles, injections or other drug preparations should be identical and without any marks indicative of their identity
- Under no circumstance during the follow-up of the patient should the treating physicians or nurses provide hints regarding the allocation of the patient

Bias: a researcher's worst nightmare

Types of blinding

Double-blinded studies

The patient and the physicians assessing the outcome of interest are unaware of which treatment the patient has been taking

Advantages:

- Investigator's preconceptions of the treatments used in the study do not influence their judgment of outcome

Disadvantages

- more complex design
- not always easy to implement (e.g. surgical procedures)
- experienced researchers might suspect the allocated treatment based on certain "side effects" of each drug
- the researchers cannot monitor satisfactorily the safety profile of a drug

(a Data Monitoring Safety Board is needed - DMSB)

Bias: a researcher's worst nightmare

Types of blinding

Triple-blinded studies

The patient, the physicians assessing the outcome of interest as well as all members of the project team (such as the statistician, and data manager), and even the DMSB, are unaware of which treatment the patient has been taking

Advantages:

- Analysis bias is minimized

Disadvantages

- extremely more complex design
- the researchers cannot monitor satisfactorily the safety profile of a drug

This design is more appropriate for studies in which the risk of adverse events of the new treatment is low or comparable to the active treatment

Bias: a researcher's worst nightmare

Some notes on blinding

Blinding through assigning different tasks to different researchers

If the assigned treatment must be delivered by a physician then this physician should not be involved in any other aspect of the study

e.g. comparison of two different surgical techniques

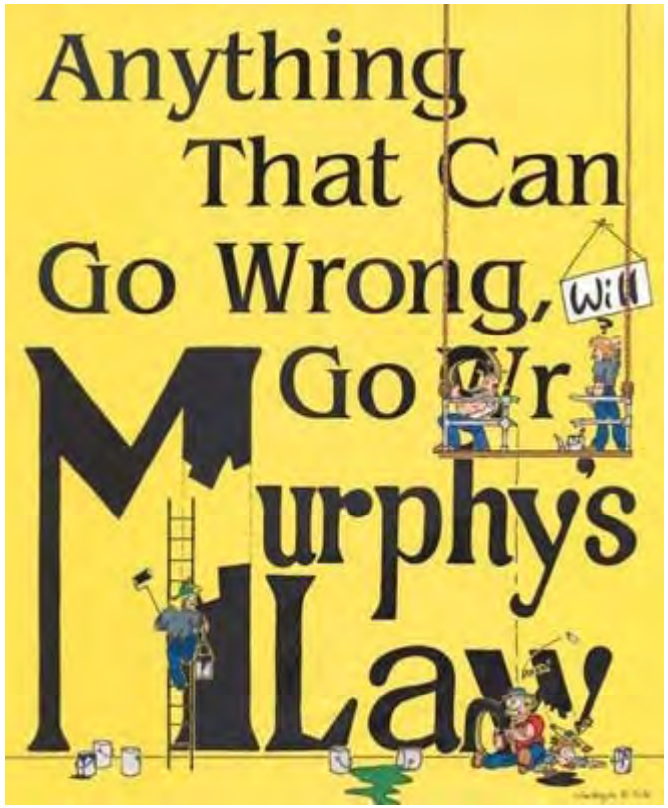
Double-dummy blinding

When the two treatments are administered in different ways, then two identical placebos (dummies) must be administered

e.g. Comparison of daily administered gonadotrophin vs. long-acting gonadotrophin

Bias: a researcher's worst nightmare

During follow-up...



...many things can go wrong

Bias: a researcher's worst nightmare

Key issues during follow-up

Co-intervention:

- Occurs when sympathetic care-givers provide out-of-protocol additional interventions (which are effective) in patients that know to be controls
- Such co-interventions can distort the results of the comparison by underestimating the effect of the actual treatment
- Avoidance of such practices or recording of such incidents allows for a more objective estimation of the treatment effect

Sackett D., 2007, Int J Epidemiol, 36 (3), 664-665

Bias: a researcher's worst nightmare

Key issues during follow-up

Contamination:

- When patients (or treating physicians) realize that they belong to the control/ placebo group and receive (or administer) the experimental treatment often "just to be safe"
- Such contamination can also occur from allocation errors
- Contamination leads to an underestimation of the actual treatment effect of the experimental treatment (when compared to placebo)

Sackett D., 2007, Int J Epidemiol, 36 (3), 664-665

Bias: a researcher's worst nightmare

Key issues during follow-up

Co-intervention and contamination

can be measured and their effect controlled for

given that a proper follow-up protocol has been implemented

e.g. periodic blood sampling from controls for detection of specific drug effects or drug metabolites

Sackett D., 2007, Int J Epidemiol, 36 (3), 664-665

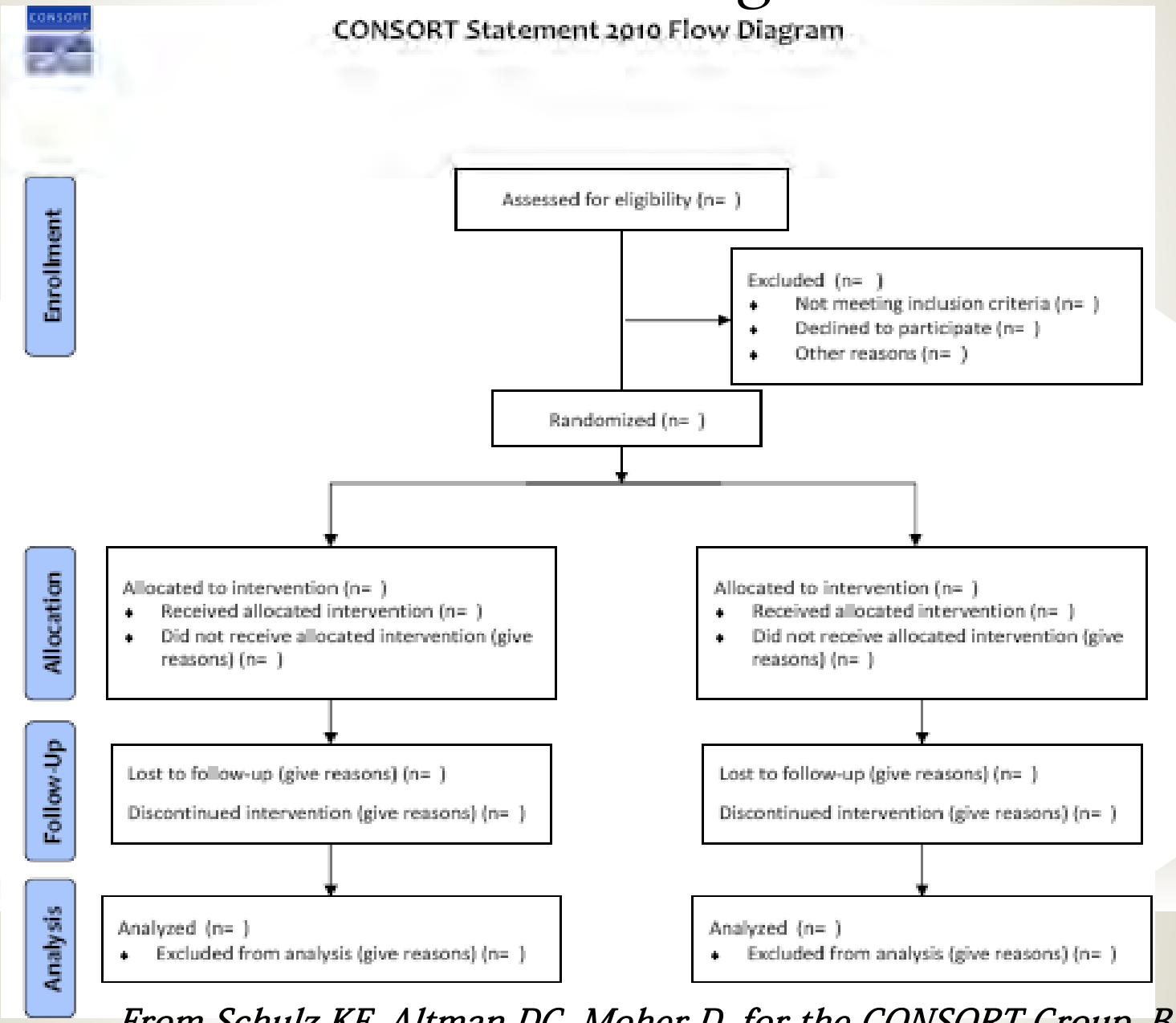
Bias: a researcher's worst nightmare

Follow-up and management of bias

Proper follow-up:

- Predetermined schedule of primary and secondary outcomes assessment (length of observation period, intervals)
- Standardization of assessment procedures and training of physicians
- Limit the time frame of follow-up as much as possible
- Record any post randomization exclusions, drop-outs, protocol deviations, lost-to-follow up, missing data cases etc. **with reasons**

Bias: a researcher's worst nightmare



From Schulz KF, Altman DG, Moher D, for the CONSORT Group. BMJ 2010

Bias: a researcher's worst nightmare

Follow-up and management of bias

Proper follow-up ensures:

- Appropriate evaluation of the comparative effect of the two treatments compared in terms of efficacy (per protocol analysis)
- Appropriate evaluation of side-effects and compliance for each treatment

e.g. even if a drug is more efficacious, it could be a failure due to multiple severe side-effects that lead patients to dropping out

- Appropriate evaluation of the comparative effect of the two treatments compared in terms of effectiveness (intention-to-treat analysis)

Conclusions

The value of study management and conduct

Sample collection:

Proper assembly of evidence

(patients, records or studies)

is crucial for reaching valid conclusions

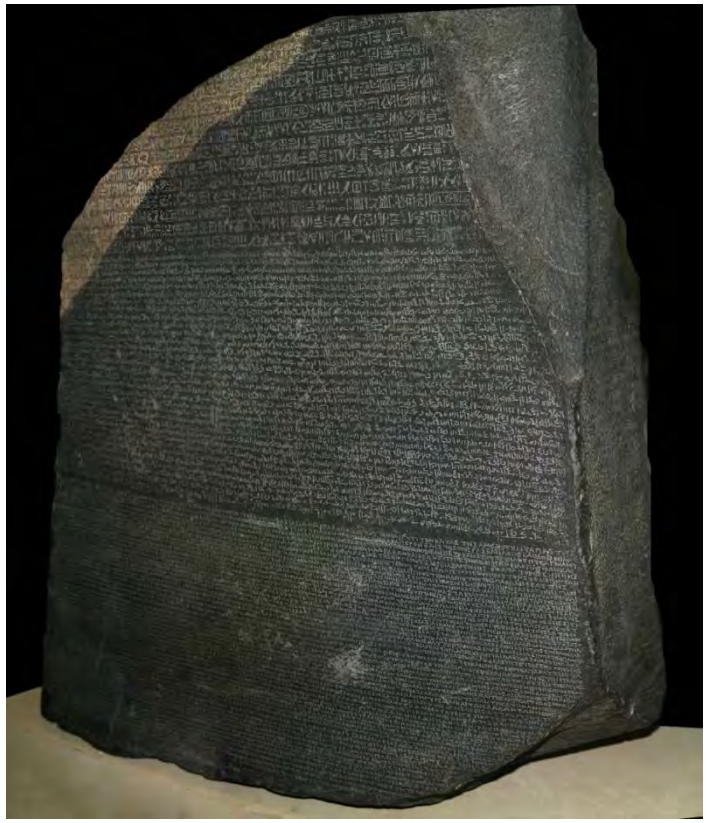
The value of study management and conduct

Defense against bias:

There are various forms of bias that can infiltrate your study and invalidate the results

Randomization, allocation concealment, blinding and proper follow-up minimize the potential bias(-es) and ensure that your data will be one more step towards the truth

Never underestimate your research efforts



Within each patient, within each small study
may lie the Rosetta Stone of information
that will bring us closer to a major scientific breakthrough…

Further reading:

1. The CONSORT statement http://www.consort-statement.org/
2. The Cochrane Handbook for Systematic Reviews of Interventions, http://www.cochrane-handbook.org/
3. A Manager’s guide to the design and conduct of clinical trials, by Phillip Good, John Wiley & Sons, Inc., Hoboken, New Jersey
4. Randomized Controlled Trials, Design, Practice and Reporting, by D. Machin and P. Fayers, John Wiley & Sons, Inc., Hoboken, New Jersey
5. Design and Analysis of Clinical Trials, Concepts and Methodologies, by S-C Chow and J-P Liu, John Wiley & Sons, Inc., Hoboken, New Jersey
6. The Design of Studies for Medical Research, by D. Machin and M.J. Campbell, John Wiley & Sons, Inc., Hoboken, New Jersey
7. Allocation concealment in randomised trials: defending against deciphering, K.F. Schultz and D.A. Grimes, the Lancet, 2002;359:614-618
8. Schulz KF, Chalmers I, Altman DG. The landscape and lexicon of blinding in randomised trials. Schulz KF, Chalmers I, Altman DG, Ann Intern Med 2002; 136: 254 – 59