An Overview of the Different Aspects of a Clinical Trial

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Hierarchy in Science

- Clinical Practice Guidelines / Health Technology Assessment
- Systematic Review / Meta-Analysis
- Randomized Controlled Trial
- Controlled Clinical Study
- Retrospective / Prospective Cohort
- Case Report / Case Series
- Expert Opinion

BE BRAVE.
Even if you’re not, pretend to be.
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Case reports

- Identify needs – hypothesis generating
- Identify new drug side effects but also potential novel uses
- Identify rare diseases and rare manifestations of diseases
- Important educational role
- Highlight extremely unusual and novel findings
- No causality – Associations may have other explanations
Case reports

THE LOWERST LEVEL OF EVIDENCE OR MAYBE THE FIRST LINE OF EVIDENCE
Case reports

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Observational studies

To test the association of a risk factor with an outcome

- Cohort study
- Case-control study
- Cross-sectional study
Cohort studies

Study begins here

Measure exposure and confounder variables

Study population

Factor present

Factor absent

Future

Present

https://lo.unisa.edu.au

time

no disease
disease
no disease
disease

https://lo.unisa.edu.au
Cohort studies

Merits:

• There is temporal relationship between exposure and outcome

• Investigate several outcomes for each exposure

• It is possible to perform matching limiting confounders role

• Easier and cheaper than a RCT

• Good to measure incidence of an outcome

Limitations:

• Expensive

• Outcome could take time to occur

• Definition of outcome/exposure can change over the time

• No randomization

• Blinding/masking
### Case-control studies

<table>
<thead>
<tr>
<th>Factor Present</th>
<th>Cases (disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor Absent</td>
<td>Study population</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factor Present</th>
<th>Controls (no disease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor Absent</td>
<td></td>
</tr>
</tbody>
</table>

Study begins here

[https://lo.unisa.edu.au](https://lo.unisa.edu.au)
Case-control studies

• **Assumption:** non-cases are representative of the source population of cases.

**Merits:**

• Suitable to investigate rare diseases/outcomes

• Can be not really expensive

**Limitations:**

• Not suitable for calculating frequency measures

• Not appropriate for rare exposures

• Selection and recall biases
Cross-sectional studies

Study only exists at this point in time

Study population

No Disease

factor present

factor absent

Disease

factor present

factor absent

https://lo.unisa.edu.au
Cross-sectional studies

Merits:

• Quick
• Cheap
• Study of several diseases / exposures at the same time
• Assess the prevalence of a disease
• Public health planning

Limitations:

• Temporal ambiguity
• Possible measurement error
• Not suitable for rare conditions
• Survivor bias
Causality: cause-effect relationship?

Storks deliver babies

Storks Deliver Babies (p. 0.008), Matthews, R, Teaching Statistics. Volume 22, Number 2, Summer 2000
Causality: cause-effect relationship?

land area

storks

birth rate
Confounders

positive confounding: the effect seems stronger
negative confounding: the effect seems weaker
Causality: cause-effect relationship?

Drink a lot of strong coffee

Rohit S Loomba et al. Circulation. 2012; 126: A14459
Causality: cause-effect relationship?

- Smoking and other confounder
- Coffee
- Cardiovascular mortality

Rohit S Loomba et al. Circulation. 2012; 126: A14459
ADJUSTED FOR KNOWN CONFOUNDERS BUT NOT FOR UNKNOWN OR UNMEASURED CONFOUNDERS
Interventional studies
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Strongest Evidence

Study Level Data

Subject Level Data

Weakest Evidence
Interventional studies: RCTs are the gold standard

Randomization in interventional trial: avoids all confounders
Adjustment for confounders in observational trial: avoids known confounders
19% eligible in a real-world population
Figure 1. Screening, Randomization, and Follow-up.
The median duration of the valsartan run-in phase was 15 days (interquartile range, 12 to 22). One patient completed the valsartan run-in phase and underwent randomization without entering the sacubitril–valsartan run-in phase. The median duration of the sacubitril–valsartan run-in phase was 19 days (interquartile range, 15 to 23). One patient completed screening and entered the sacubitril–valsartan run-in phase without having entered the valsartan run-in phase.
Interventional studies: RCTs are the gold standard

Is the study population representative of the source population → Can results be translated to the general population of patients?

**Strict**
- well defined study population makes the effect more predictable (internal validity)
- safer due to exclusion of high-risk patients
- difficult to recruit patients, increasing cost, time of recruitment and risk of the failure of the study

**Broad**
- increases external validity
- facilitates recruitment of patients

Already selection of study site (e.g. tertiary centre) restricts patient selection!
Meta-analyses

A quantitative statistical analysis of several separate but similar experiments or studies in order to test the pooled data for statistical significance.

Why a meta-analysis?

• To increase power

• To improve precision

• To answer questions not posed by individual studies and increase generalizability

• To settle controversies arising from apparently conflicting studies or to generate new hypotheses
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Strongest Evidence:
Study Level Data

Weakest Evidence:
Subject Level Data
Registry

- Collects uniform data (clinical, lab, etc)
- Evaluate specified outcomes for a population defined by a particular disease, condition, or exposure

Disease Registry: Includes patients with the disease regardless of drug or device exposure

Product Registry: Includes subjects receiving the drug or device regardless of indication

In principle, no testing of research hypothesis (i.e. cohort study)

Registry: key words

• **Cohort study** – enrolls subjects with something in common (same disease, same treatment, etc.) who are followed up over time.

• **Real-world** - representative of real world patient characteristics (less inclusion and exclusion criteria than in RCTs)

• **Non-interventional**
Non-interventional studies

- the **investigational medicinal products** are used in accordance with the terms of the **marketing authorization** and the **normal clinical practice** of the state concerned;

- the assignment of the subject to a particular therapeutic strategy is **NOT decided in advance**;

- the decision to prescribe the investigational medicinal products is not taken together with the decision to include the subject in the clinical study;

- diagnostic or monitoring procedures in addition to normal clinical practice are not applied to the subjects.
Registries supports RCTs for:

Phenotyping groups of patients to be enrolled in trials

A comprehensive population-based characterization of heart failure with mid-range ejection fraction

Angela S. Koh¹,², Wan Ting Tay³, Tiew Hwa Katherine Teng¹,², Ola Yedin⁴, Linda Bremner⁵, Ulf Dahlof⁶, Gianluigi Savarese⁷, Carolyn S.P. Lam¹,⁸,⁹, and Lars H. Lund⁷,⁸

Intermediate

Resembles HFrEF

Resembles HFpEF
Registries supports RCTs for:

Selecting outcomes and inclusion/exclusion criteria

Reductions in NT-proBNP → better prognosis in EF≥40%

NT-proBNP decreases
HR: 0.46

Savarese et al.
Circ HF 2016

Relationship between NT-proBNP and CV/non-CV events

Savarese et al. JACC HF 2018
Registries for:
Exploring subgroups which have been previously neglected

Association between renin–angiotensin system inhibitor use and mortality/morbidity in elderly patients with heart failure with reduced ejection fraction: a prospective propensity score-matched cohort study

Gianluigi Savarese, Ulf Dahlström, Peter Vasko, Bertram Pitt, and Lars H. Lund

Age>80 years
RASi 80%

HR 0.78 (0.72 – 0.86)
1-year ARR: 11%, NNT: 9

Age≤80 years
RASi 94%

HR 0.81 (0.71 – 0.91)
1-year ARR: 6%, NNT: 17
Registries for:
Fostering implementation of treatments in clinical practice

Risk-adjusted use of therapy over time

- B-blocker RAS: ~83 → 93%
- Aldo antagonist: ~34 → 28%
- ICD CRT: ~2 → 4%
- ~1 → 3%
Registries for:
Testing effectiveness
Registries for:
Post-marketing surveillance

- Evaluate short/long-term effectiveness (day-to-day circumstances)
- Measure/monitor short/long-term safety and tolerability
- Measure and/or improve quality of care
Registries for:
Randomized registry based controlled trials

**RCT**
- Randomized evidence
- Complex regulatory requirements
- Collection of non-essential data
- For-profit CROs
- Multiple ethics approvals
- Complex consent forms
- Many unknowns for power calculation
- In-feasible: (pre)-screening is manual, inefficient and unpredictable
- Enrolment slow
- Trial population unpredictable
- Outcomes assessment manual, inefficient
- Selective → not generalizable to real world
- Expensive to conduct: in HF: 6,000 patients, >$200M, ~$50,000 per patient
- Industry must recoup drug development and trial costs
  → Delivers novel patented expensive therapy: e.g. sacubitril/valsartan: $5-15 per day

**But:**

**RRCT**
- Simplified regulatory procedures
- Focus on essential baseline and outcome data
- Non-profit AROs
- Single ethics approval
- Simplified consent forms
- For power calculation: know eligible sample and event rates
- Feasible: Have lists of existing and know n new eligible patients
- (Pre)-screening is automated, efficient and predictable
- Outcomes assessment automatic
- Non-selective: both efficacy and effectiveness
- Inexpensive to conduct: ~$5M = ~$1,000 per patient
- Non-selective → real world evidence
- Promotes adoption of evidence into practice
- Delivers new use of existing drug: generic HF drug: e.g. spironolactone 10 cents per day

**Registry**
- Efficient enrolment integrated in real-world health care
- Real-world generalizable descriptive and outcomes data
- Epidemiological characterization
- Utilization of evidence based therapy
- Quality reporting, benchmarking
- Quality improvement
- Equality of care
- Risk markers
- Comparative outcomes → Hypothesis generating
- Efficient
- Inexpensive

**But:**

Lack of randomization → NOT comparative effectiveness

Many study designs
Democracy in Science
Thank you

Are you <40 years?

Cardiovascular Pharmacotherapists and Trialists of Tomorrow (CPTT)

A lot of benefits for you!!!