Interventional trials

EM Critical Appraisal Day
13th July 2016

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Queen Mary
University of London
Levels of Evidence

<table>
<thead>
<tr>
<th>Box 2. SIGN classification for grading evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
</tr>
<tr>
<td>1+</td>
</tr>
<tr>
<td>1−</td>
</tr>
<tr>
<td>2++</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2+</td>
</tr>
<tr>
<td>2−</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial; SIGN: Scottish Intercollegiate Guidelines Network

Belsey 2009. What is EBM?
Critical appraisal

Population

Intervention

Comparator

Outcome(s)

Study design
## Effect measures

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome – yes</th>
<th>Outcome - No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>No</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Risk ratio = \( \frac{a/[a+b]}{c/[c+d]} \)

Odds ratio = \( \frac{a/b}{c/d} \) or \( \frac{ad}{bc} \)
PARAMEDIC trial

<table>
<thead>
<tr>
<th></th>
<th>30-day survival</th>
<th>30-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUCAS-2</td>
<td>104</td>
<td>1548</td>
</tr>
<tr>
<td>Manual</td>
<td>193</td>
<td>2626</td>
</tr>
<tr>
<td>compressions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk ratio = \( \frac{104}{104+1548} \) / \( \frac{193}{193+2626} \) = 0.92

Odds ratio = \( \frac{104}{1548} \) / \( \frac{193}{2626} \) = 0.91
Absolute vs. relative risk

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*
## Absolute vs. relative risk

<table>
<thead>
<tr>
<th></th>
<th>Mortality</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGDT</td>
<td>92</td>
<td>347</td>
</tr>
<tr>
<td>Standard care</td>
<td>86</td>
<td>370</td>
</tr>
</tbody>
</table>

\[ AR = \frac{92}{92+347} - \frac{86}{86+370} = 0.02 \]

\[ RR = \frac{92}{92+347} / \frac{86}{86+370} = 1.11 \]

Or, \[ RR = AR / CER = 0.02 / 0.19 = 11.0\% \]

\[ NNT (H) = \frac{1}{AR} = \frac{1}{0.02} = 50 \]
Interpreting an observation

Effect

- True observation
- Confounding
- Bias
- Chance
Confounding

Exposure

Confounder

Outcome
Bias

- Selection bias
- Observer bias
- Information bias
- Recall bias
Randomisation...
Allocation concealment ≠ blinding
Blinding reduces observer bias
Who was blinded?

- **Single:** Either researcher or subject is blinded.
- **Double:** Both researcher and subject blinded.
- **Triple:** Researcher, patient and statistician blinded.

.......Open study group allocation.
Intention to treat analysis

Figures from: The Drs guide to critical appraisal Gosall and Gosall
Sample size

- Larger samples ➔ more precise estimates
- Greater precision = narrow confidence intervals
- Two approaches:
  1. Estimation of a measure with a specified precision
  2. Based on hypothesis test or demonstrating a specified significance level
Error

Type I error

• Probability of rejecting null hypothesis when it is true

Type II error

• Probability of not rejecting the null hypothesis when it is false
Power

- Probability that a hypothesis test will give a statistically significant result if an effect truly exists
- $1 - \text{type II error rate}$
- Chosen \textit{a priori}
- \textit{Usually} 80%
Primary outcome

Composite outcome?
A single-centre observational cohort study of admission National Early Warning Score (NEWS)∗

Tom E.F. Abbotta,∗, Nidhi Vaidb, Dorothy Ipc, Nicholas Crond, Matt Wellse, Hew D.T. Torrancea, Julian Emmanuela,f

We aimed to compare NEWS to the Patient at Risk Score (PARS), the existing early warning score in use at our hospital (Table 1). We chose two outcome measures: a composite of mortality and critical care unit (level two or three care) escalation within the first 48 h of the admission, and hospital length of stay. This composite outcome measure has previously been used in similar studies and will capture all patients suffering cardiac arrest at our institution.9,10,13

Trial registration

**Browse Studies**

- Cancer
- Circulatory System
- Digestive System
- Ear, Nose and Throat
- Eye Diseases
- Genetic Diseases
- Haematological Disorders
- Infections and Infestations

**ISRCTN registry**

http://www.isrctn.com

https://clinicaltrials.gov

Queen Mary
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www.qmul.ac.uk
Standard outcome measures....

Core Outcome Measures for Perioperative and Anaesthesics Care (COMPAC)

Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions

A statement from the ESA-ESICM joint taskforce on perioperative outcome measures

Ib Jammer, Nadine Wickboldt, Michael Sander, Andrew Smith, Marcus J. Schultz, Paolo Pelosi, Brigitte Leva, Andrew Rhodes, Andreas Hoeft, Bernhard Walder, Michelle S. Chew and Rupert M. Pearse

# Levels of Evidence

**Box 2. SIGN classification for grading evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tr>
<td>1++</td>
<td>High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1−</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
</tr>
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</table>
| 2++   | High-quality systematic reviews of case-control or cohort studies  
High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal |
| 2+    | Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal |
| 2−    | Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal |
| 3     | Non-analytic studies; for example, case reports, case series |
| 4     | Expert opinion |

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Belsey 2009. What is EBM?
P-value vs. confidence interval

Figure: Effects of corticosteroid allocation on deaths from all causes and severe disability within 6 months by injury severity and time since injury. Risk ratios are plotted (black squares with area proportional to the amount of statistical information in each subgroup) comparing outcome in participants allocated corticosteroids to that in those allocated placebo, with 99% CI (horizontal lines ending with an arrow head when the confidence interval extends beyond the scale). Result for all patients and 95% CI is represented by a diamond, with risk ratio and 95% CI stated alongside. Risk ratios greater than unity represent increased mortality or disability with corticosteroid allocation. GCS-Glasgow Coma Score at randomisation.

Two trials

The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

Lancet 2011; 377: 1096–101

Amiodarone, Lidocaine, or Placebo in Out-of-Hospital Cardiac Arrest

The NEW ENGLAND JOURNAL of MEDICINE

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Population

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