Statistical issues in the design of randomised surgical trials: a practical example of the possible solutions

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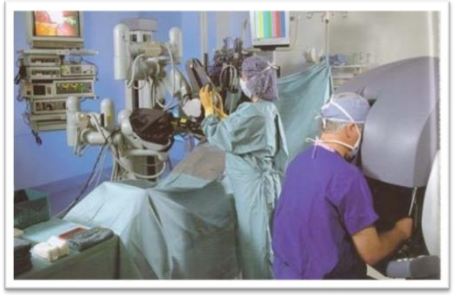
Introduction

Surgical trials have unique design and implementation issues

- Minimise any ‘learning curve’ effect
- Blinding
- Timing of randomisation

Surgical trial example



ROLARR Trial

- International, multi-centre, randomised, superiority trial
- Comparing laparoscopic vs. robotic-assisted surgery for rectal cancer
- 400 patients recruited over 18 months
- 3 year follow-up period
- 30-35 surgeons performing both surgical procedures

ROLARR

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Trial endpoints

Short-term endpoints include:

- Conversion rate to open surgery
- Positive pathological resection margins
- Quality of life (QoL) and health economics

Longer-term endpoints include:

- Local recurrences
- Overall and disease-free survival

Issue 1: Learning curve

- **Surgeons need to be over their initial learning curve**
- **This should:**
  - Minimise the effect of the learning curve on patient outcomes
  - Reduce complexities in the analysis
  - Produce more accurate and generalisable results

Issue 1: Solutions adopted

- **Only include surgeons who have performed at least 30 rectal cancer resections**
  - Minimum of 10 for each procedure
- **Randomisation stratified by surgeon**
- **Collection of time-dependent factors known to influence the learning curve**
- **Collection of quality assurance data**

Issue 1: Why adopted?

- **No evidence to demonstrate the end of the learning curve**
- **Pragmatic decision to balance risks of:**
  - Reducing the number of surgeons involved
  - Introducing a learning curve effect
- **30 rectal cancer resections chosen after discussions with surgeons**

Issue 2: Blinding

- **Double-blinded trials goal standard**
- **Blinding reduces introduction of bias**
- **In surgical trials, blinding**
  - surgical teams generally impossible
  - patients may be feasible

Issue 2: Solutions adopted

- Decision not to blind patients
- Surgical teams and patients aware of surgical procedure performed
- Incorporated objective measures and central blinded assessments
- Intention-to-treat analysis to safeguard against bias

Issue 2: Why adopted?

- Maintenance of blind in practice extremely problematic
- Health-care insurers may require surgical details
- Patients seen by many health-care professionals

Issue 3: Randomisation timing

- Preference for surgery to be as soon as possible after randomisation
- Problematic due to theatre planning

Issue 3: Solution adopted

- Randomisation as close to date of surgery as possible (no more than 28 days prior to planned surgery date)
- Recommend within 14 days of planned surgery date where possible

Issue 3: Why adopted?

- Pragmatic approach
- Difficulties with tighter timelines for some surgeons
- Timings to be monitored by Independent Data Monitoring Committee to allow prompt action

Discussion

- **Surgical trials are complex to design, implement and also analyse**
- **Careful consideration is needed to ensure accurate and unbiased interpretation of results**

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