Asia Pacific Critical Care Congress,
Sydney, Australia,

Use of a formal study run-in phase to reduce
recruitment errors in a multi-centre
randomised controlled trial:
Is quality better than quantity?

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Outline

• Discuss the impact protocol violations may have on estimates of treatment effectiveness

• Investigate the role of a formal run-in phase on minimising protocol violations
Introduction

- Protocol violations tend to occur early in the trial and decrease as enrolment progresses.

Introduction

- Treatment effects may not become apparent until protocol violations are minimised.

Introduction

- Protocol violations may mask treatment effectiveness.

Figure 1. Relative risk of death for PROWESS subgroups. The relative risk for the overall trial is displayed for reference. For each subgroup, the point estimate of relative risk is displayed with the 95% confidence interval (CI). The size of the symbol is proportional to the subgroup size. Pct, placebo; DrotAA, drotrecogin alfa (activated). Breslau-Day interaction p value is displayed for each subgroup.


What can we do to minimise protocol errors?

- A study *run-in phase* can be used to reduce enrolment of inappropriate patients.

- Used to exclude noncompliant subjects.

What can we do to minimise protocol errors?

• A study run-in phase can be used to reduce enrolment of inappropriate patients.
• Used to exclude noncompliant subjects
• May increase overall power of the trial if only ‘compliant’ subjects are enrolled.


Purpose

H₀: To determine whether a formal study run-in phase can effectively reduce other types of recruitment errors.
**Purpose**

H$_0$: To determine whether a formal study run-in phase can effectively reduce other types of recruitment errors.

**Context**

An NH&MRC funded multi-center clinical trial to be conducted in 30+ sites throughout ANZ.

**Methods**

- Prior to recruiting their first patient, participating centres were required to submit de-identified potentially eligible patients to a study web site during a formal run-in phase.
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Methods

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- The run-in web site did not allocate patients to treatment or control groups.
- Information captured allowed key eligibility criteria to be assessed.
- Appropriateness of enrolment was fed-back to the participating centre.
- Each site was required to identify consecutive truly eligible patients before being allowed to start the trial.
Results

- 32 hospitals submitted 199 potentially eligible patients during the run-in phase.
  - 32 of 199 did not meet key eligibility criteria
  - 16% recruitment error rate
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- As of June 2008, 409 patients had been enrolled in the trial.
  - 4 of 409 did not meet key eligibility criteria
  - 1% recruitment error rate

significantly lower (p<0.001) than run-in phase

Published benchmarks?

- Run-in phase / Live
  - 16% recruitment error rate vs 1% recruitment error rate
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  - 9.4% (159/1690) recruitment error rate (9.4% vs 1%, p<0.001)


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  - 16% recruitment error rate vs 1% recruitment error rate
- PROWESS
  - 9.4% (159/1690) recruitment error rate (9.4% vs 1%, p<0.001)
- INTERCEPT
  - 16.5% (77/464) recruitment error rate (16.5% vs 1%, p<0.001)


Conclusions

Excessive protocol violations may:
- mask effective treatment benefits and
- cause trials be stopped early

A formal study run-in phase:
- can significantly reduce overall protocol violation rates
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*We strongly recommend a formal run-in phase for all trials.*