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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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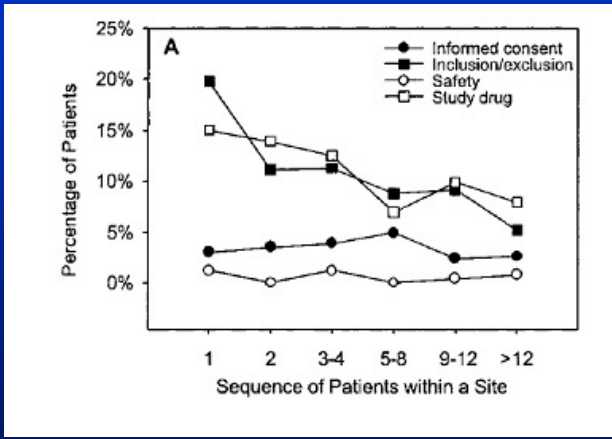
Outline

- 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.**



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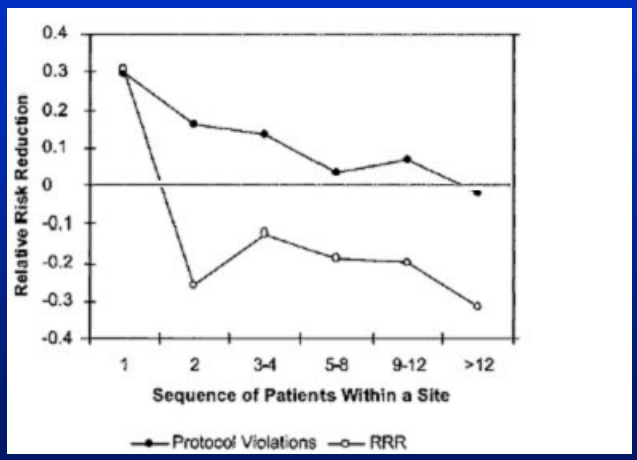
Introduction

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



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Introduction

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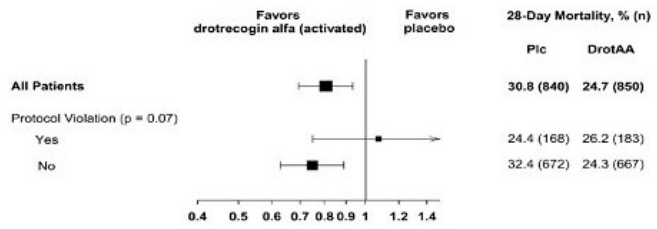

Figure 1. Relative risk of death for PROWESSS subgroups. The relative risk for the overall trial is displayed for reference. For each subgroup, the point estimate of relative risk is displayed with the 95% confidence interval (*CI*). The size of the symbol is proportional to the subgroup size. *Plc*,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

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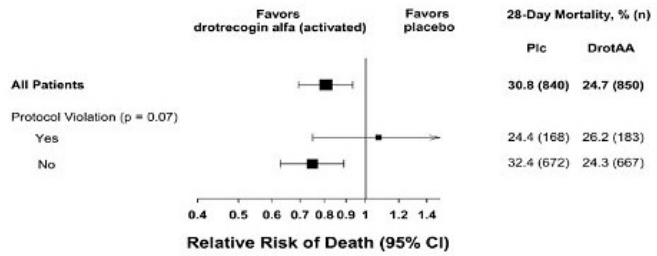

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Laterre PF, Macias WL, Janes J, Williams MD, Nelson DR, Girbes AR, Dhainaut JF, Abraham E. Influence of enrollment sequence effect on observed outcomes in the ADDRESS and PROWESS studies of drotrecogin alfa (activated) in patients with severe sepsis. *Crit Care.* 2008 Sep 11;12(5):R117. [Epub ahead of print]

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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.

Pablos-Méndez A, Barr RG, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. JAMA. 1998 Jan 21;279(3):222-5.

Purpose

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

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Context

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

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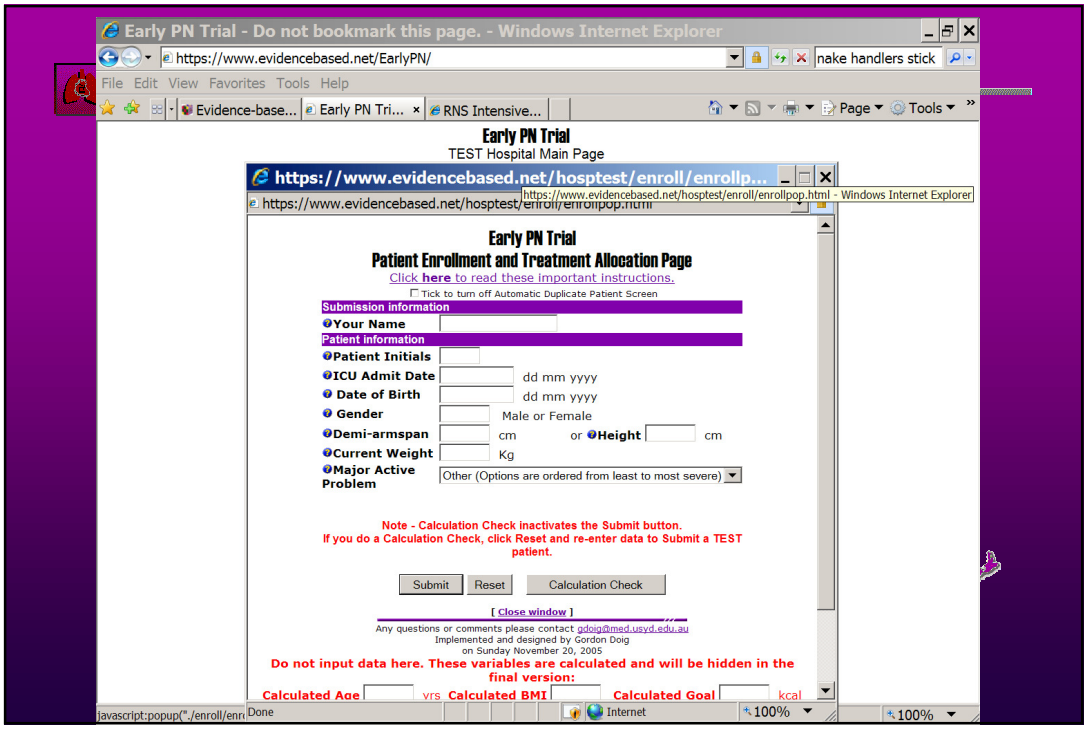
- The run-in web site did not allocate patients to treatment or control groups.
- Information captured allowed key eligibility criteria to be assessed.
- Appropriateness of enrolment was fed-back to the participating centre.
- Each site was required to identify consecutive truly eligible patients before being allowed to start the trial.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Note - Calculation Check inactivates the Submit button.
If you do a Calculation Check, click Reset and re-enter data to Submit a TEST patient.
Submit
Reset
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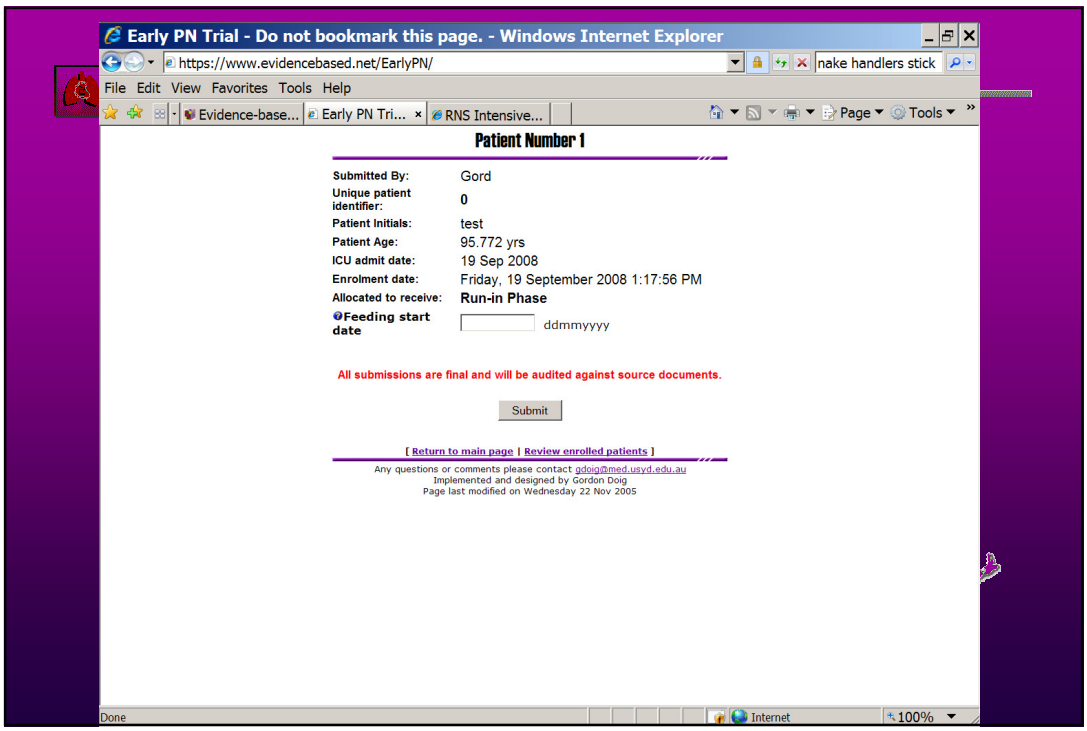
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Submitted By: Gord
Unique patient identifier: 0
Patient Initials: test
Patient Age: 95.772 yrs
ICU admit date: 19 Sep 2008
Enrolment date: Friday, 19 September 2008 1:17:56 PM
Allocated to receive: Run-in Phase
Feeding start date
ddmmyyyy
All submissions are final and will be audited against source documents.
Submit
[Return to main page | Review enrolled patients]
Any questions or comments please contact gdoig@med.usyd.edu.au
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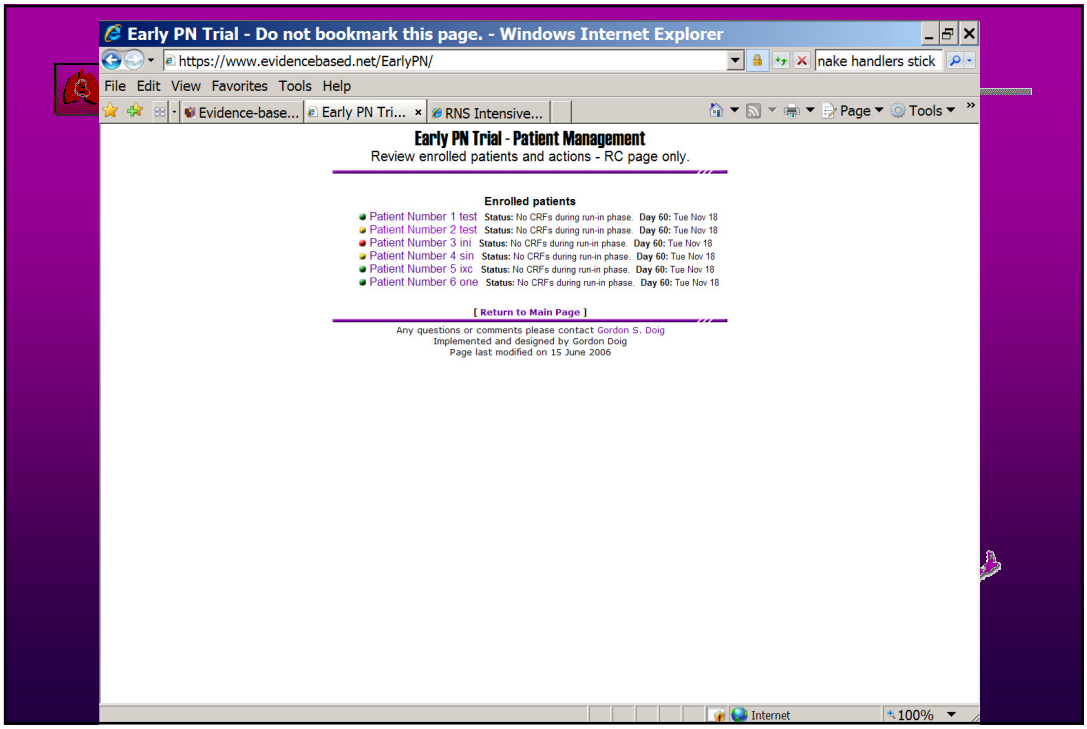

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  - 32 of 199 did not meet key eligibility criteria
  - *16% recruitment error rate*
- As of June 2008, 409 patients had been enrolled in the trial.
  - 4 of 409 did not meet key eligibility criteria
  - *1% recruitment error rate*

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

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Published benchmarks?

- Run-in phase / Live
  - *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)

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Sprung CL, Finch RG, Thijs LG, Glauser MP. International sepsis trial (INTERSEPT): role and impact of a clinical evaluation committee. Crit Care Med. 1996 Sep;24(9):1441-7.

Conclusions

Excessive protocol violations may:

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We strongly recommend a formal run-in phase for all trials.