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Single-arm trials in cancer drug evaluation

Problem statement

EMA workshop on single-arm trials in cancer drug evaluation, EMA, London, 30 June 2016

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Statement

Randomised active and placebo-controlled trials are generally required;

- Most orphan drugs and paediatric indications submitted for regulatory approval are based on randomised controlled trials that follow generally accepted rules and guidance.

What if (adequately powered) randomised controlled trials are not feasible? "Single-arm trials" as the basis for approval…

- Population too small (rare cancer, stratified medicine,…)?
- Compelling evidence of efficacy in (phase II) exploratory trials?

Current approach: case-by-case, often results-driven.

Can we develop a more systematic approach?

"Dramatic effect" (ICH E10)

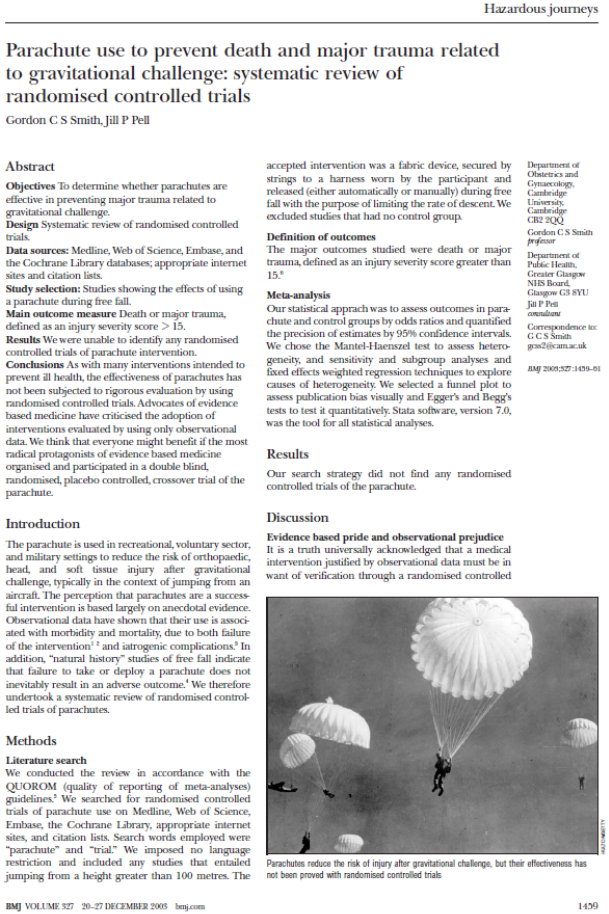
Use of the external control design is restricted to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable;

Start with externally controlled trial and switch to RCT (or stop) if effect not dramatic;

What is the threshold for "dramatic"?

Based on what parameter?

Can we operationalise the concept?



Hazardous journeys

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.
Design Systematic review of randomised controlled trials.
Data sources: Medline, Web of Science, Embase, and the Cochrane Library databases; appropriate internet sites and citation lists.
Study selection: Studies showing the effects of using a parachute during free fall.
Main outcome measure Death or major trauma, defined as an injury severity score > 15.
Results We were unable to identify any randomised controlled trials of parachute intervention.
Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Introduction

The parachute is used in recreational, voluntary sector, and military settings to reduce the risk of orthopaedic, head, and soft tissue injury after gravitational challenge, typically in the context of jumping from an aircraft. The perception that parachutes are a successful intervention is based largely on anecdotal evidence. Observational data have shown that their use is associated with morbidity and mortality, due to both failure of the intervention[1 2] and iatrogenic complications.[3] In addition, "natural history" studies of free fall indicate that failure to take or deploy a parachute does not inevitably result in an adverse outcome.[4] We therefore undertook a systematic review of randomised controlled trials of parachutes.

Methods

Literature search

We conducted the review in accordance with the QUOROM (quality of reporting of meta-analyses) guidelines.[5] We searched for randomised controlled trials of parachute use on Medline, Web of Science, Embase, the Cochrane Library, appropriate internet sites, and citation lists. Search words employed were "parachute" and "trial." We imposed no language restriction and included any studies that entailed jumping from a height greater than 100 metres. The accepted intervention was a fabric device, secured by strings to a harness worn by the participant and released (either automatically or manually) during free fall with the purpose of limiting the rate of descent. We excluded studies that had no control group.

Definition of outcomes

The major outcomes studied were death or major trauma, defined as an injury severity score greater than 15.[6]

Meta-analysis

Our statistical approach was to assess outcomes in parachute and control groups by odds ratios and quantified the precision of estimates by 95% confidence intervals. We chose the Mantel-Haenszel test to assess heterogeneity, and sensitivity and subgroup analyses and fixed effects weighted regression techniques to explore causes of heterogeneity. We selected a funnel plot to assess publication bias visually and Egger's and Begg's tests to test it quantitatively. Stata software, version 7.0, was the tool for all statistical analyses.

Results

Our search strategy did not find any randomised controlled trials of the parachute.

Discussion

Evidence based pride and observational prejudice

It is a truth universally acknowledged that a medical intervention justified by observational data must be in want of verification through a randomised controlled

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Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Approaches to externally controlled trials (ICH E10)

Detailed information (individual patient data regarding demographics, baseline status, concomitant therapy, and course on study);

Should be as similar as possible to the population; use similar timing and methodology Selection of the control group before comparative analyses;

Pre-specify matching on selection criteria and adjustments;

Study group should be substantially superior to the most favourable control to conclude efficacy.

Can we be more specific?

Early access *v.* complete information

How does approval based on single-arm trials affect subsequent decisions?

High unmet need, early (conditional) approval with high uncertainty are frequent in oncology;

- ***Need to communicate uncertainty to inform shared decision making***
- ***How to improve contribution to health technology assessment (HTA)***

Early dissemination of results, early approval → window of opportunity for RCTs reduced

- ***Single-arm trials may be the only acceptable option for some patients***

The evolution of "non-RCT evidence" **Focus on opportunities**

- Evidence can be based on a diverse family of data sources and methodologies complementing (not replacing) RCTs.
- We now have a resource that was not available to the RCT pioneers in the mid-20th century: rich data on past and current patients from observational studies and RCTs.
- We are now starting to develop the methodology and skill set to make use to the resource – to overcome the "non-randomised stigma"?

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