Single-Arm Studies in the Regulatory Process

Gianluca Baio

g.baio@ucl.ac.uk

(Joint work with Anthony Hatswell and Nick Freemantle)

Key Advances in Clinical Trials

International Clinical Trials Day

UCL Institute of Clinical Trials and Methodology, 19 May 2017

Outline of presentation

1. **Single-arm/uncontrolled trials**
   - **Do we really need RCTs?**
   - **Some examples**
2. Single-arm trials in the regulatory context
   - **FDA vs EMeA**
3. Conclusions

Outline of presentation

1. Single-arm/uncontrolled trials
   - Do we really need RCTs?
   - Some examples
2. **Single-arm trials in the regulatory context**
   - FDA vs EMeA
3. Conclusions

Outline of presentation

1. Single-arm/uncontrolled trials
   - Do we really need RCTs?
   - Some examples
2. Single-arm trials in the regulatory context
   - FDA vs EMeA
3. **Conclusions**

Do we **really** need RCTs?

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 apprach 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

Department of Obstetrics and Gynaecology, Cambridge University, Cambridge CB2 2QQ
Gordon C S Smith *professor*
Department of Public Health, Greater Glasgow NHS Board, Glasgow G3 8YU
Jill P Pell *consultant*
Correspondence to: G C S Smith
gcss2@cam.ac.uk

BMJ 2003;327:1459–61

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

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

Smith, G. C. S. and Pell, J. P. (2003). BMJ, 327(7429), 1459-1461. doi: 10.1136/bmj.327.7429.1459.

Do we **really** need RCTs?

- Uncontrolled studies are acceptable where change in a condition can clearly be attributable to the therapy, placebo response is minimal, prognosis bleak, and there is no acceptable control arm[1]
  - The background disease is important — relapsing/remitting diseases would be inappropriate, as are time-to-event endpoints
  - The endpoint must also be "**hard/objective**"
    - May be we mean: *"As little arbitrary and as much consistently measureable as possible"?*

[1] Food and Drug Administration (2007). *Guidance for industry — Clinical trials endpoints for the approval of cancer drugs and biologics*

Do we **really** need RCTs?

- Uncontrolled studies are acceptable where change in a condition can clearly be attributable to the therapy, placebo response is minimal, prognosis bleak, and there is no acceptable control arm[1]
  - The background disease is important — relapsing/remitting diseases would be inappropriate, as are time-to-event endpoints
  - The endpoint must also be "**hard/objective**"
    - May be we mean: *"As little arbitrary and as much consistently measureable as possible"?*

- Just because we don't have an RCT, doesn't mean we are any less sure of what we know[2]
  - Chromosome 21 and Down's syndrome
  - Aspirin in Reye's syndrome
  - Laser therapy for "Port Wine" birthmarks
  - Imatinib in Chronic Myeloid Leukaemia
  - ...

[1] Food and Drug Administration (2007). *Guidance for industry — Clinical trials endpoints for the approval of cancer drugs and biologics*

[2] Rawlins, M. (2012). *OHE Annual Lecture 2012*.

Uncontrolled studies — **some** examples

- 'Rate Ratio' (RR) criterion[3]
  - Treated and untreated observations from the same pool + RR **very large** (eg exceeding 10)
  - $\text{RR} = \dfrac{\text{amount of time with the condition}}{\text{amount of time for the intervention to take effect}}$
  - Example: 10 years with a birthmark, 3 months lazer therapy to remove it, so $\text{RR} = 10/0.25 = 40$ ($\Rightarrow$ "overwhelming evidence")

[3] Glasziou P et al. (2007). *BMJ*, 334(7589) 349-351

Uncontrolled studies — **some** examples

- 'Rate Ratio' (RR) criterion[3]
  - Treated and untreated observations from the same pool + RR **very large** (eg exceeding 10)
  - $\text{RR} = \dfrac{\text{amount of time with the condition}}{\text{amount of time for the intervention to take effect}}$
  - Example: 10 years with a birthmark, 3 months lazer therapy to remove it, so $\text{RR} = 10/0.25 = 40$ ($\Rightarrow$ "overwhelming evidence")
- Historical controls
  - Relatively large statistical literature[4] [5]
  - Use data for comparators (most likely placebo) from past studies
  - Exchangeability + **discounting of evidence**
  - Suitable modelling necessary (eg "Robust meta-analytic approach")

[3] Glasziou P et al. (2007). *BMJ*, 334(7589) 349-351

[4] Pocock SJ. (1976). *Journal of Chronic Disease*; 29:175-88

[5] Schmidli H et al. (2014). *Biometrics*, 70: 1023-1032

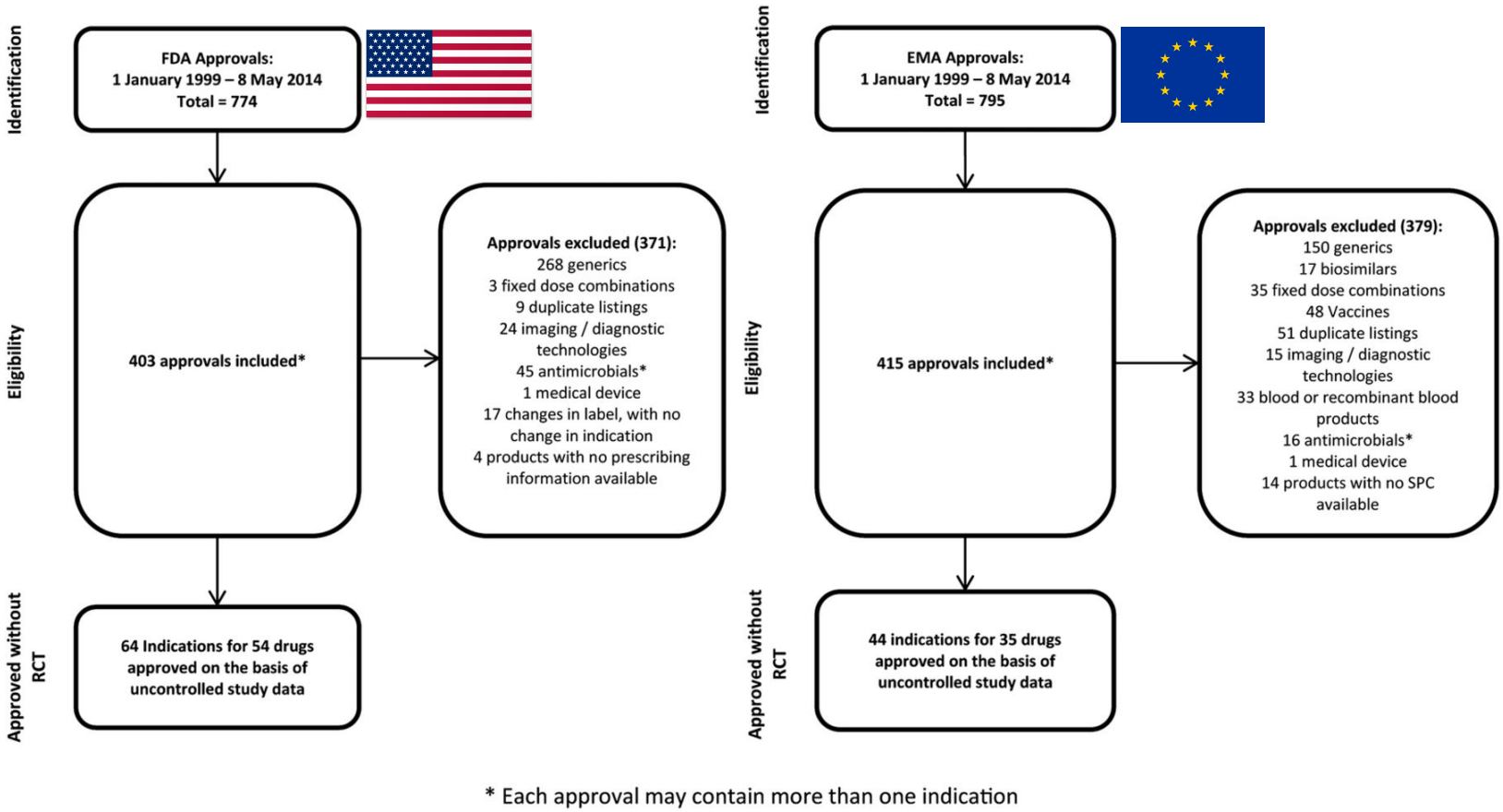
What are we talking about, then?...

- But how many drugs obtaining market authorisation based on single arm trials are there?[6]
  - Newly approved indications
  - FDA vs EMeA (January 1999 to May 2014)

[6] Hatswell AJ et al. (2016) *BMJ Open* 2016;6:e011666

What are we talking about, then?...

- But how many drugs obtaining market authorisation based on single arm trials are there?[6]
  - Newly approved indications
  - FDA vs EMeA (January 1999 to May 2014)



[6] Hatswell AJ et al. (2016) *BMJ Open* 2016;6:e011666

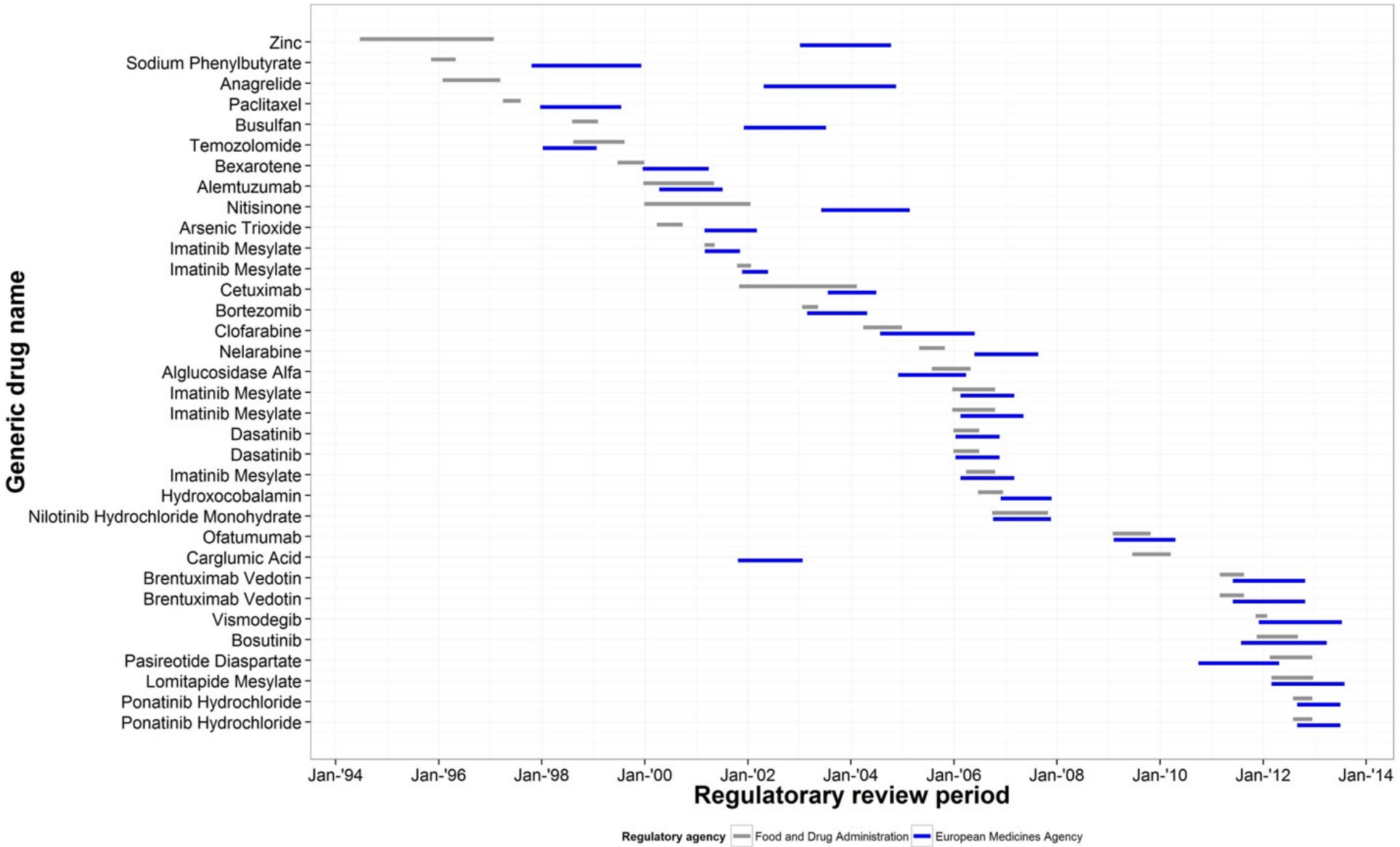
Comparison of FDA and EMeA approval times

- **44** comparable applications made to both agencies
  - FDA: approved 43, rejected 1
  - EMeA: approved 35, rejected 9
  - Most of the applications in **oncology**
- Companies submitted to the FDA first
  - 28/34 submitted first to the FDA
  - **Mean delay to EMA submission: 7.4 months**

Comparison of FDA and EMeA approval times

- **44** comparable applications made to both agencies
  - FDA: approved 43, rejected 1
  - EMeA: approved 35, rejected 9
  - Most of the applications in **oncology**
- Companies submitted to the FDA first
  - 28/34 submitted first to the FDA
  - **Mean delay to EMA submission: 7.4 months**
- The FDA reviewed products faster
  - FDA: 8.7 months vs EMeA: 15.5 months — **a difference of 6.8 months**
  - FDA reviewed 31/34 products faster
- These findings are in line with the literature

Comparison of FDA and EMeA approval times



Comments

- FDA may be more "risk-averse"?
  - Higher approval rates based on uncontrolled studies
  - Differences in pharmaceutical markets and regulatory context (pressure from advertisement, private insurance, ...)
  - Risk vs "unmet medical need"

Comments

- FDA may be more "risk-averse"?
  - Higher approval rates based on uncontrolled studies
  - Differences in pharmaceutical markets and regulatory context (pressure from advertisement, private insurance, ...)
  - Risk vs "unmet medical need"

- Difference in timing of approval despite use of the same evidence
  - FDA extensive use of "accelerated approvals" (results based on a surrogate end point, with confirmatory RCTs conducted subsequently)
  - EMeA less frequently use the equivalent process of "conditional approval"
  - **Main consequence**: patients in Europe (including the UK!) must wait longer for innovative treatments

Comments

- FDA may be more "risk-averse"?
  - Higher approval rates based on uncontrolled studies
  - Differences in pharmaceutical markets and regulatory context (pressure from advertisement, private insurance, ...)
  - Risk vs "unmet medical need"

- Difference in timing of approval despite use of the same evidence
  - FDA extensive use of "accelerated approvals" (results based on a surrogate end point, with confirmatory RCTs conducted subsequently)
  - EMeA less frequently use the equivalent process of "conditional approval"
  - **Main consequence**: patients in Europe (including the UK!) must wait longer for innovative treatments

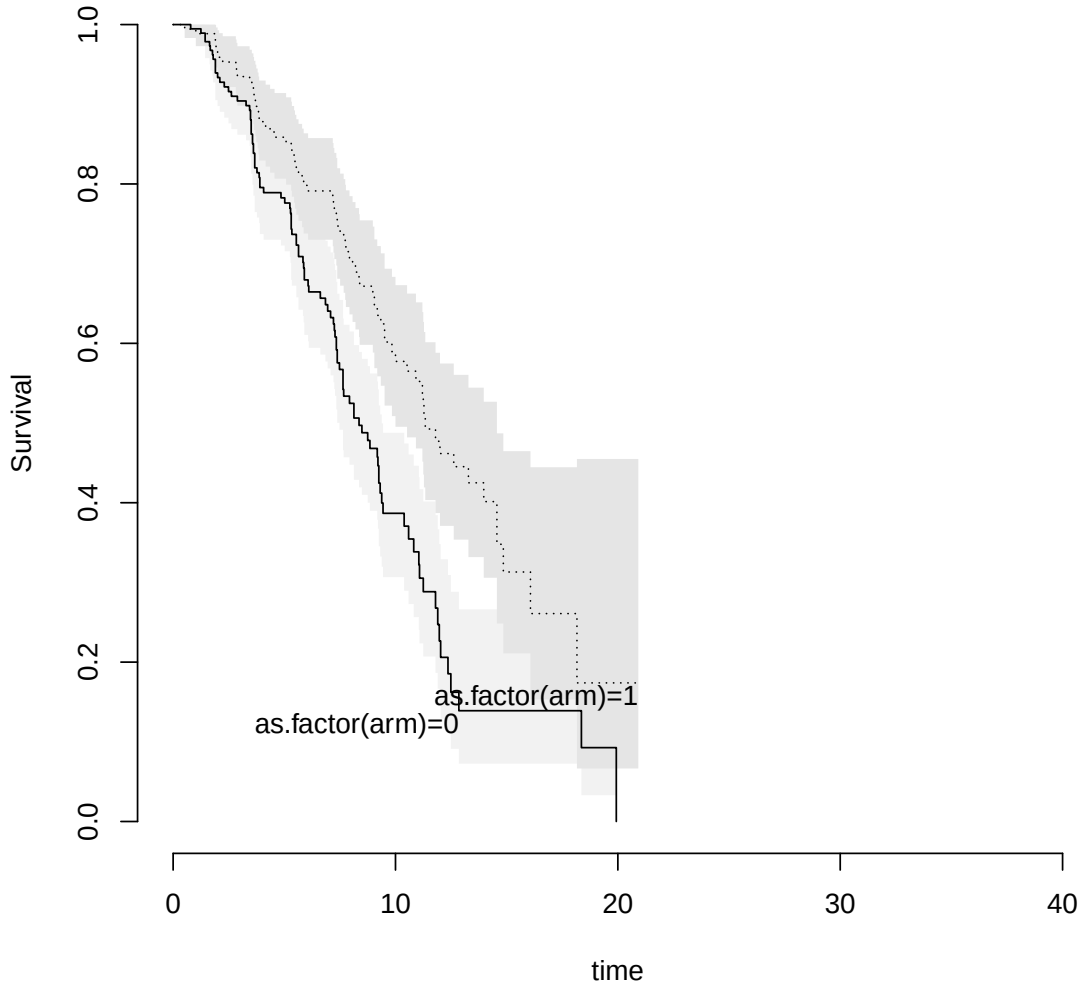
- Companies submit to FDA first
  - Bigger market? Bigger/more responsive staff??

Where do we go next?

- Market authorisation vs reimbursement
  - Particularly in European health care settings

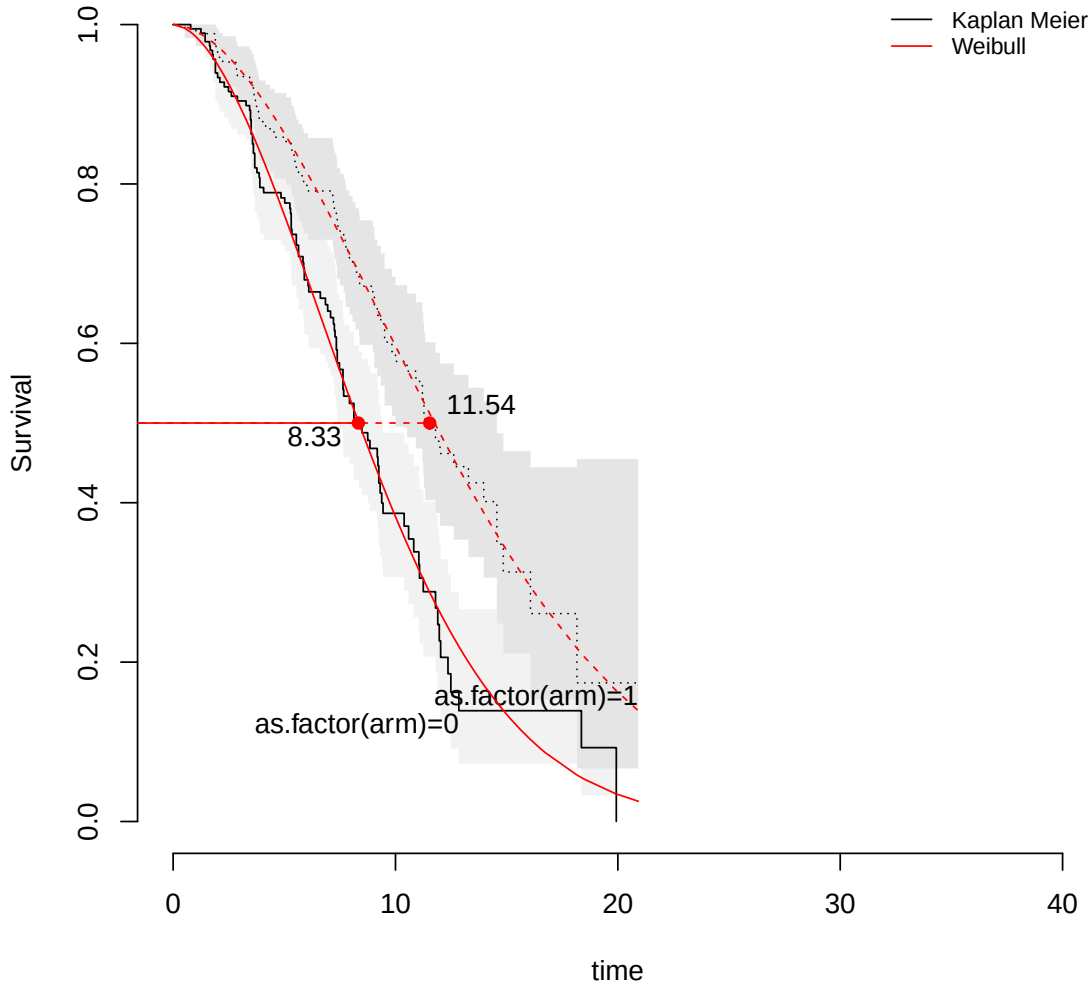
Where do we go next?

- Market authorisation vs reimbursement
  - Particularly in European health care settings
- Particularly for cancer drugs (around 40% of NICE appraisals!), need for **extrapolation** and modelling



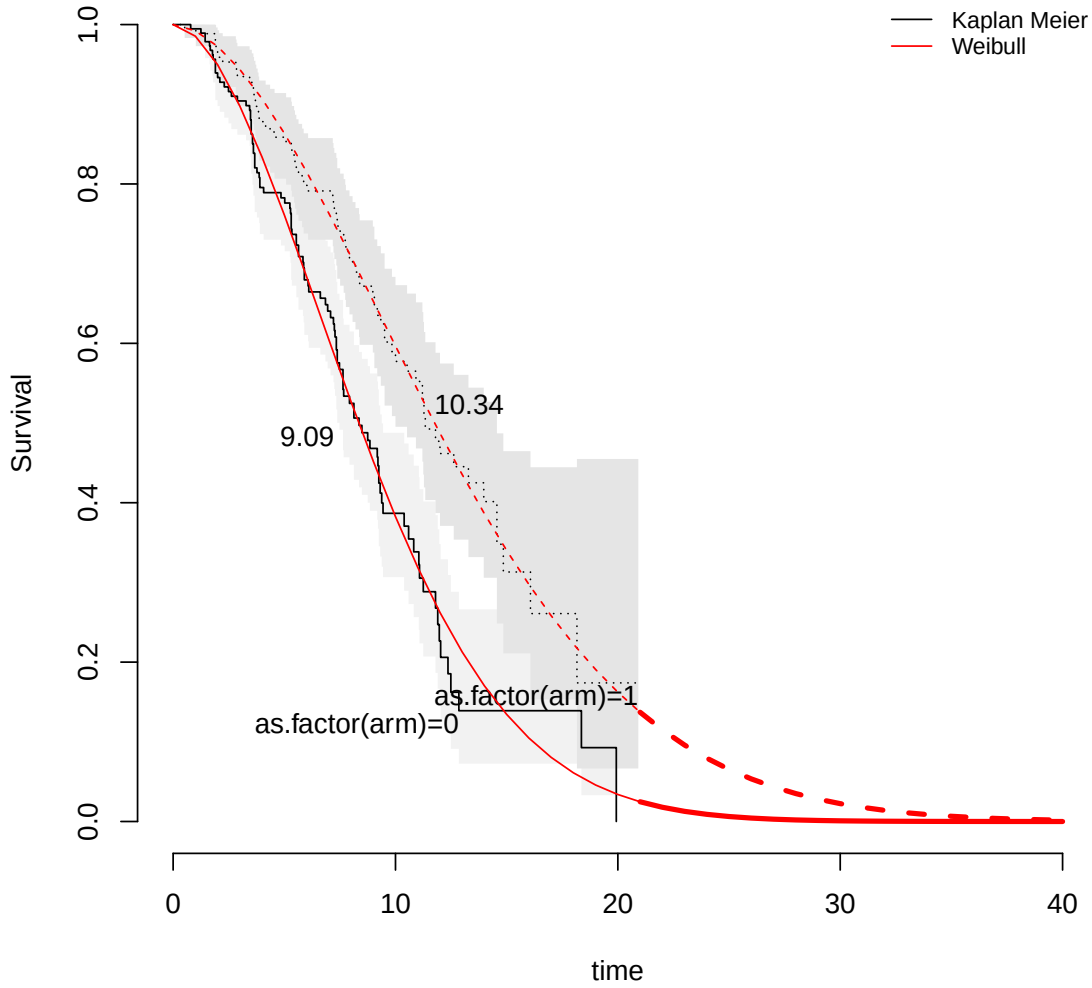
Where do we go next?

- Market authorisation vs reimbursement
  - Particularly in European health care settings
- Particularly for cancer drugs (around 40% of NICE appraisals!), need for **extrapolation** and modelling



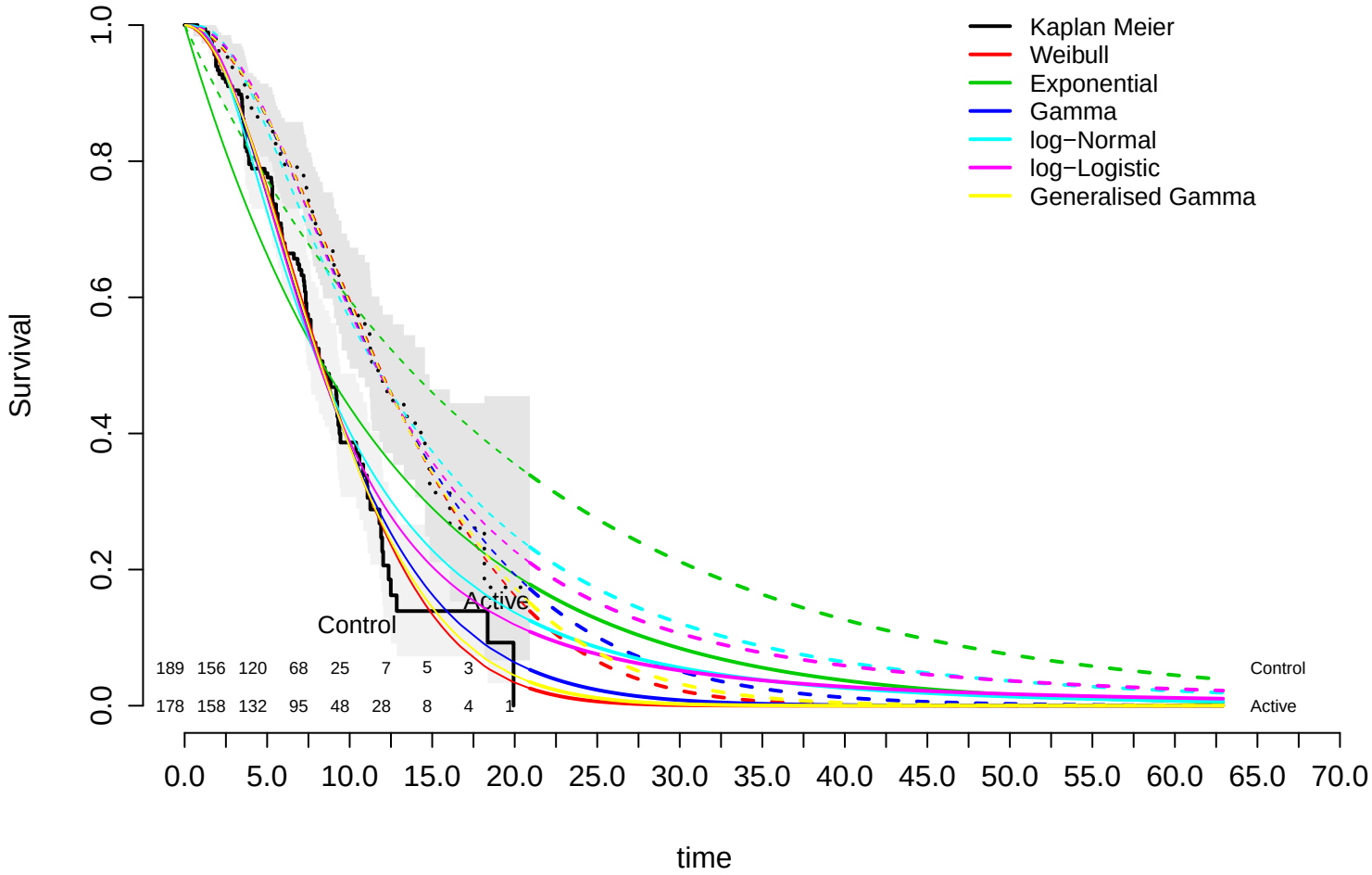
Where do we go next?

- Market authorisation vs reimbursement
  - Particularly in European health care settings
- Particularly for cancer drugs (around 40% of NICE appraisals!), need for **extrapolation** and modelling



Where do we go next?

- Market authorisation vs reimbursement
  - Particularly in European health care settings
- Particularly for cancer drugs (around 40% of NICE appraisals!), need for **extrapolation** and modelling



Thank you!