Sensible Clinical Trials: Industry Perspective

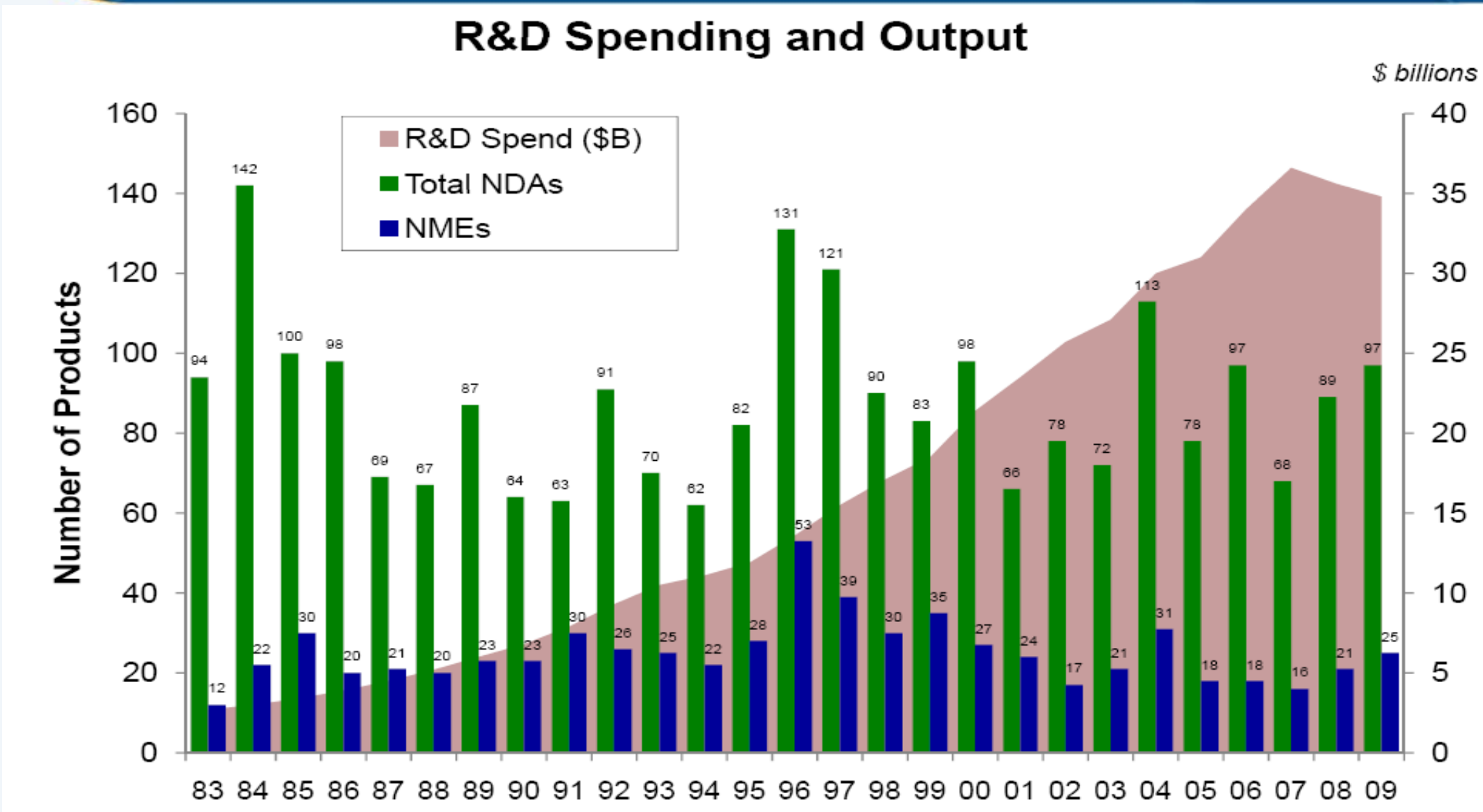
Stephen Pyke, GSK

May 2012, Toronto, Canada

Overview

- Motivation for Change: Low Productivity
- Late Development: Operational Efficiency
- Open Issues

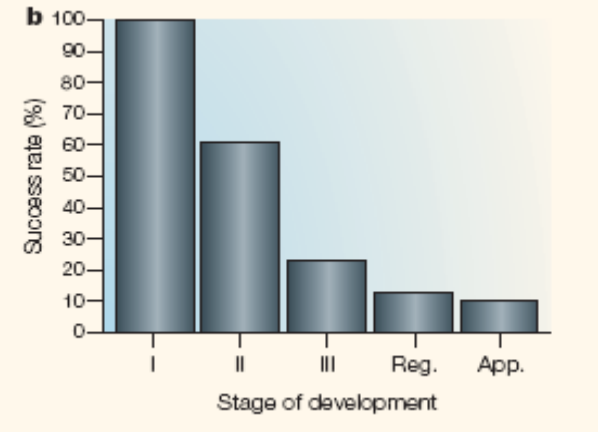
Two decades of futility



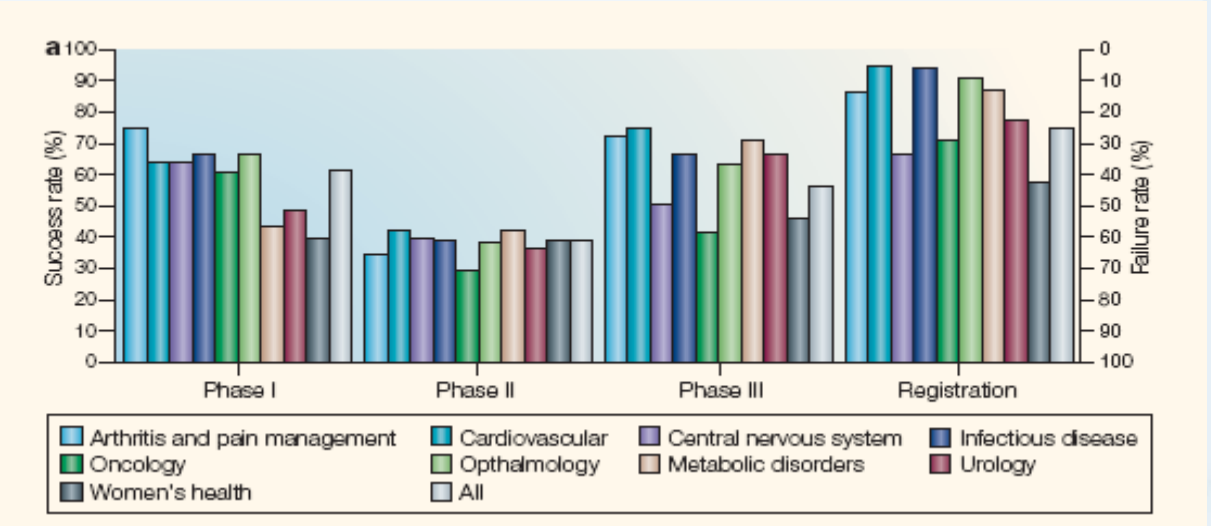
* Parexel; Defined Health analysis; FDA website; Phrma.org website; Includes Pharma Domestic Spend

The legacy of a doomed strategy

- **Industrialisation of discovery and development**
  - Conceit: More in, more out
- **In fact**
  - Number into the funnel increased
  - Number out unchanged / fell
  - Quality of candidates fell
  - High, costly Ph 2/3 failure rates continued

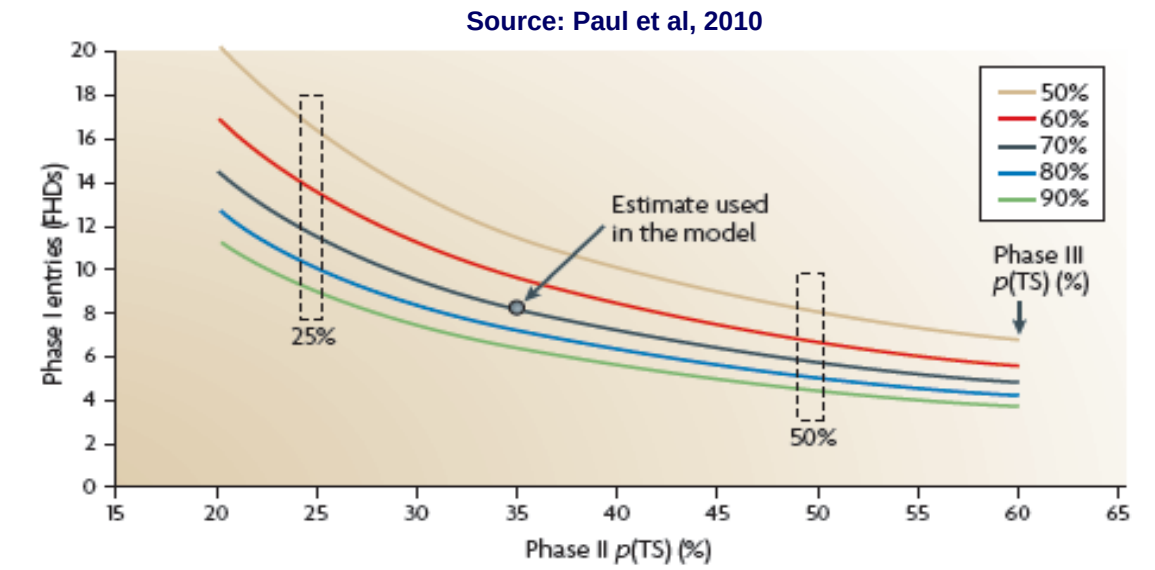


Source: Kola & Landis, 2004



Industry attrition in Ph 2

Source: Paul et al, 2010



- **Pipeline output particularly sensitive to shifts in pr(s) in ph 2**
  - Attrition in Ph 2
  - 65% failure in 2004 ► ~80% failure in 2010?

- **Why**
  - Shift to greater focus on unprecedented mechanisms?

Root cause of failure in Ph 2

- **PK**
  - Poorly absorbed drugs less often an issue
- **Safety**
  - Improved pre-clinical screens ► substantially reduced
- **Efficacy / Differentiation**
  - Now the major cause of Ph 2 attrition

Trial planning & conduct

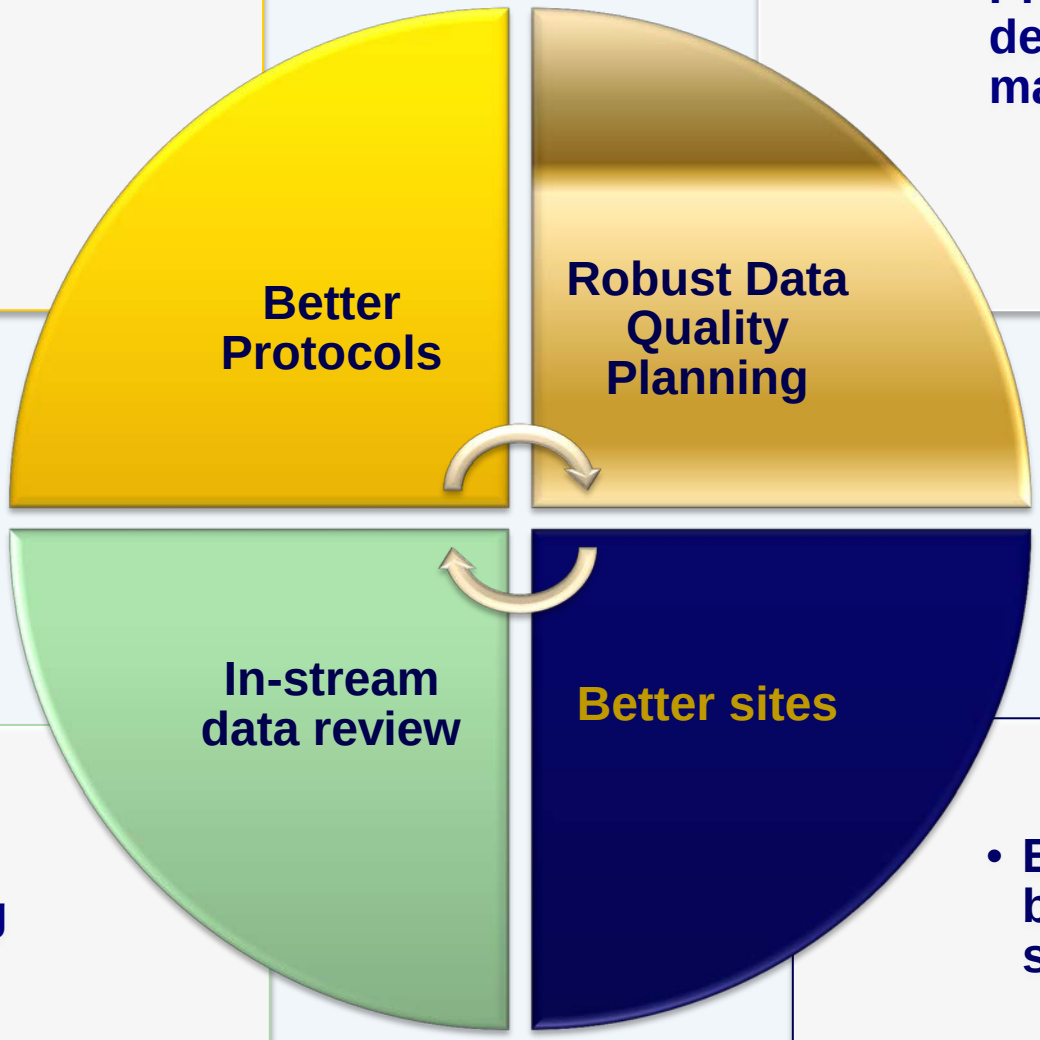
Quality by design

Risk-based approach

Operational excellence

- Facilitated clinical reviews

- Protocol deviations management

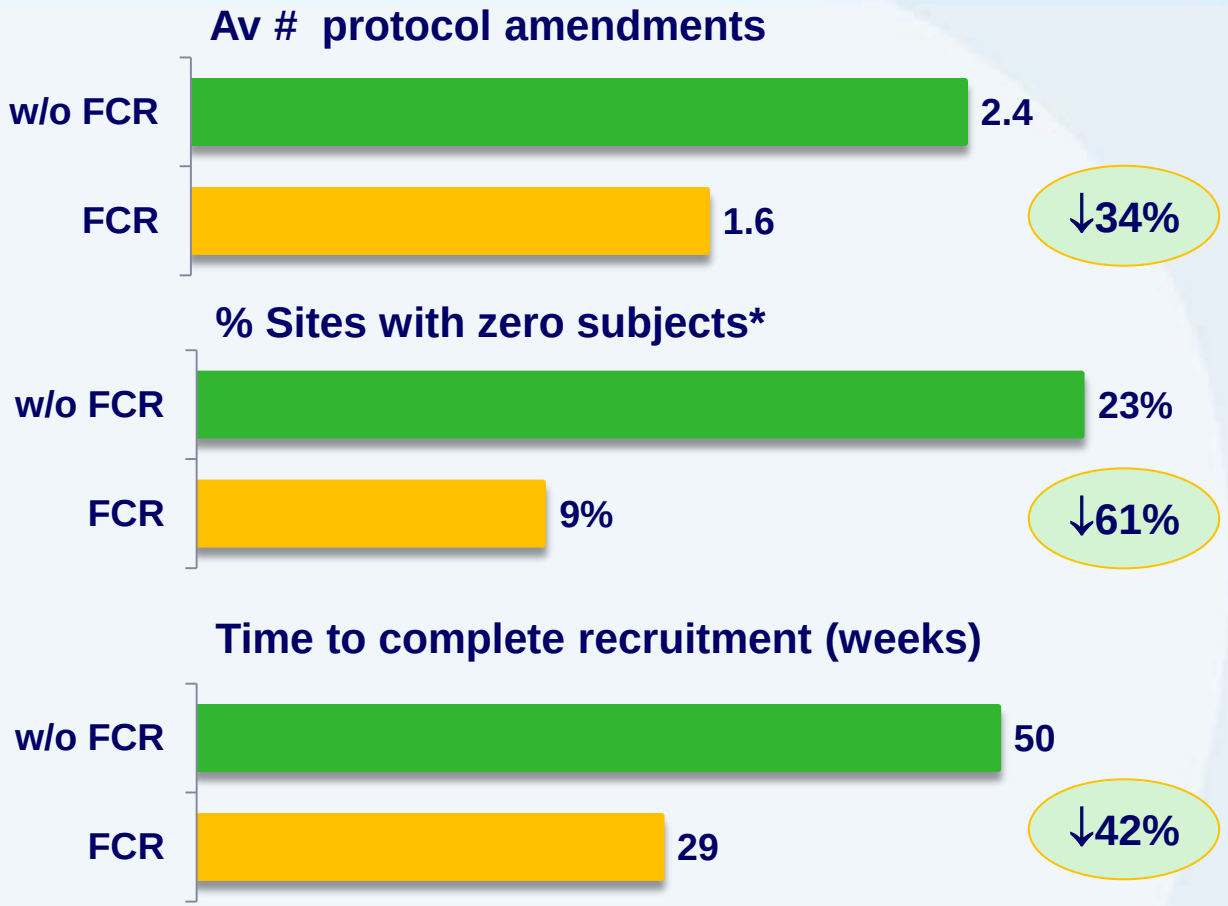


- Adaptive Monitoring

- Evidence-based site selection

Facilitated Clinical Review

- **Studies with FCR**
  - Fewer amendments
  - Fewer unproductive sites
  - Completed faster



66 studies (R&D funded, phase II-IV, interventional) achieved Last Subject First Visit (LSFV) between Jan 2011 and Dec 2011.

* Data taken from site level, study values w/out FCR: 18% and w/ FCR: 8%

Protocol deviations

- **Prepare trial analysis plan early: identify deviations likely to impact**
  - Subject rights, safety, well-being
  - Study conclusions
- **Train key personnel**
  - Study team
  - Site-based staff
- **Identify means of identifying and communicating deviations**
  - Central monitoring
  - Central / programmed data checks
  - Simpler monitoring visit report to highlight active management of deviations

Evidence-based site selection

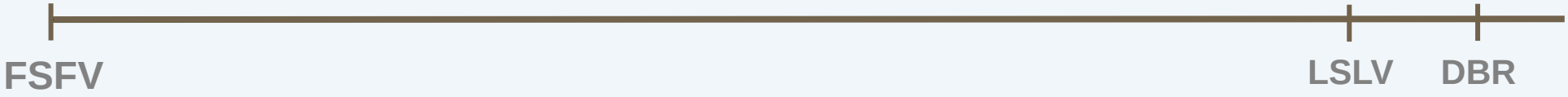
- **Review company databases for past performance**
  - Recruitment
  - Patient data quality
  - Query response speed
  - Protocol deviation rates

	% opened sites zero subjects recruited
2006	29%
2007	22%
2008	20%
2009	20%
2010	12%

Adaptive Site Monitoring

On-site visits → **On-site and off-site engagements**

Establish confidence in site quality → **Frequency, type based on site performance and need**



- Significant change in monitoring practice
- GSK Rolled out 2010-11
- Will take time to fully realize benefits
- Positive internal QA assessment trends
- Positive feedback from staff and site staff

Image review: BICR vs. LE

- **Blinded independent central review of radiological images to confirm local evaluation of PFS in trials of anti-cancer therapies**

- **Utility uncertain**
  - Necessary to ensure local evaluation free from bias?
  - Useful as audit tool for sample-based review?

- **Positive ongoing engagement on this issue with EMA**

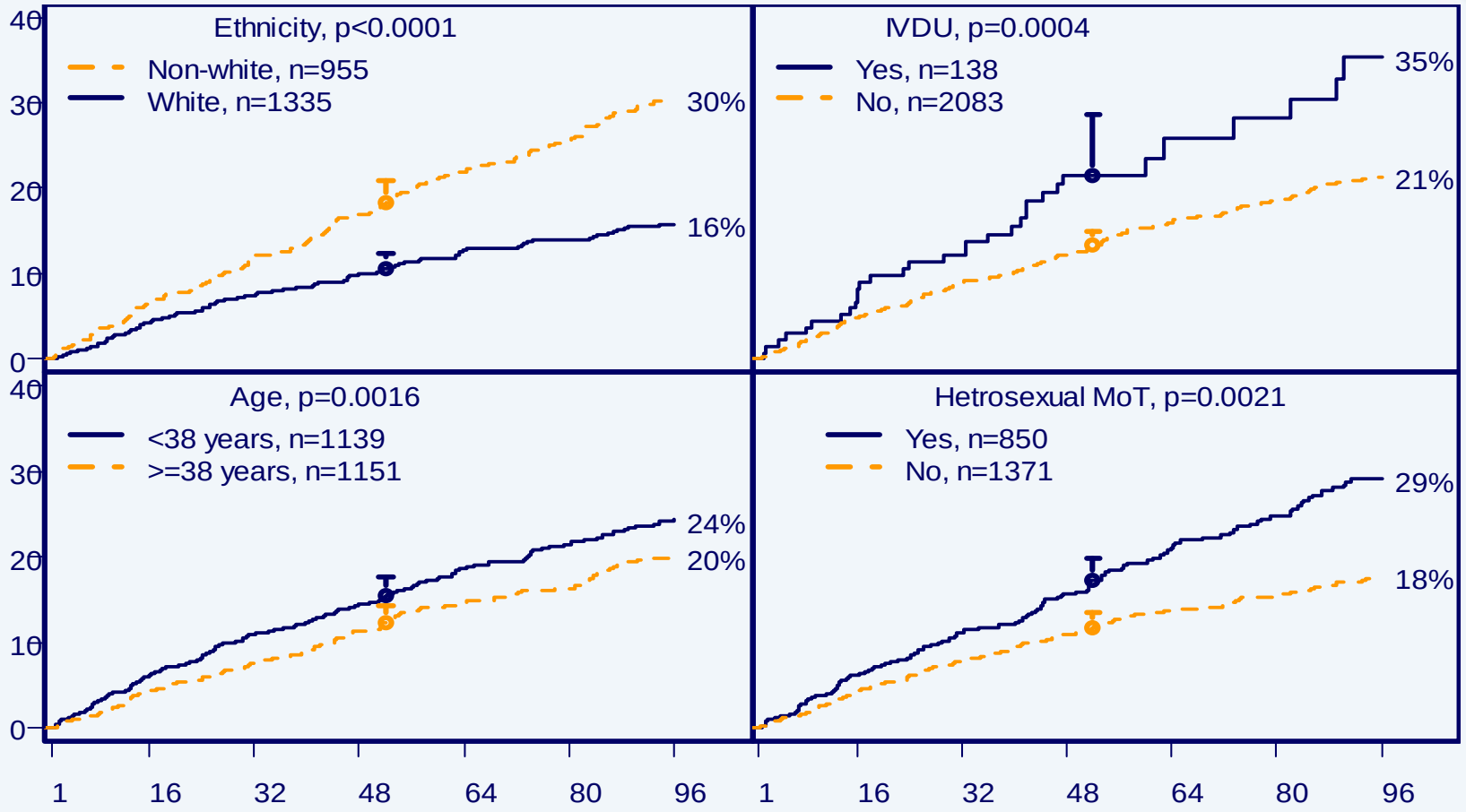
Prevention of avoidable missing data

- **HIV: dropouts classed as treatment failures, regardless of reason**

- **CHMP Guideline: Clinical Development of Medicinal Products for the Treatment of HIV Infection:**
  - "If a non-inferiority margin can be scientifically justified and non-inferiority is a reasonable clinical objective, such studies are acceptable....A low 'lost to follow-up' rate is essential …"

- **Are trial drop-outs avoidable?**
  - Reason for dropout unrelated to treatment
  - Impact on study size, cost: ↑5% response rate = ↓15% trial size

Trial dropout : not-treatment related



Source: Hughes. S. Personal communication

Way forward

- **No change to trial population entry criteria**
- **Target trial retention efforts in identifiable patient subgroups to minimise ‘avoidable’ withdrawals**
- **Preliminary evidence suggests strategy works:**
  - Unavoidable withdrawal rate similar to historic average
  - Avoidable withdrawals more than halved

Thank you