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What can available RCTs evaluating monitoring strategies tell us about the design and analysis of future trials?

Jac Dinnes, Alice Sitch, Jenny Hewison, Doug Altman, Jon Deeks

Biomarker Pipeline

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Methodology workstream

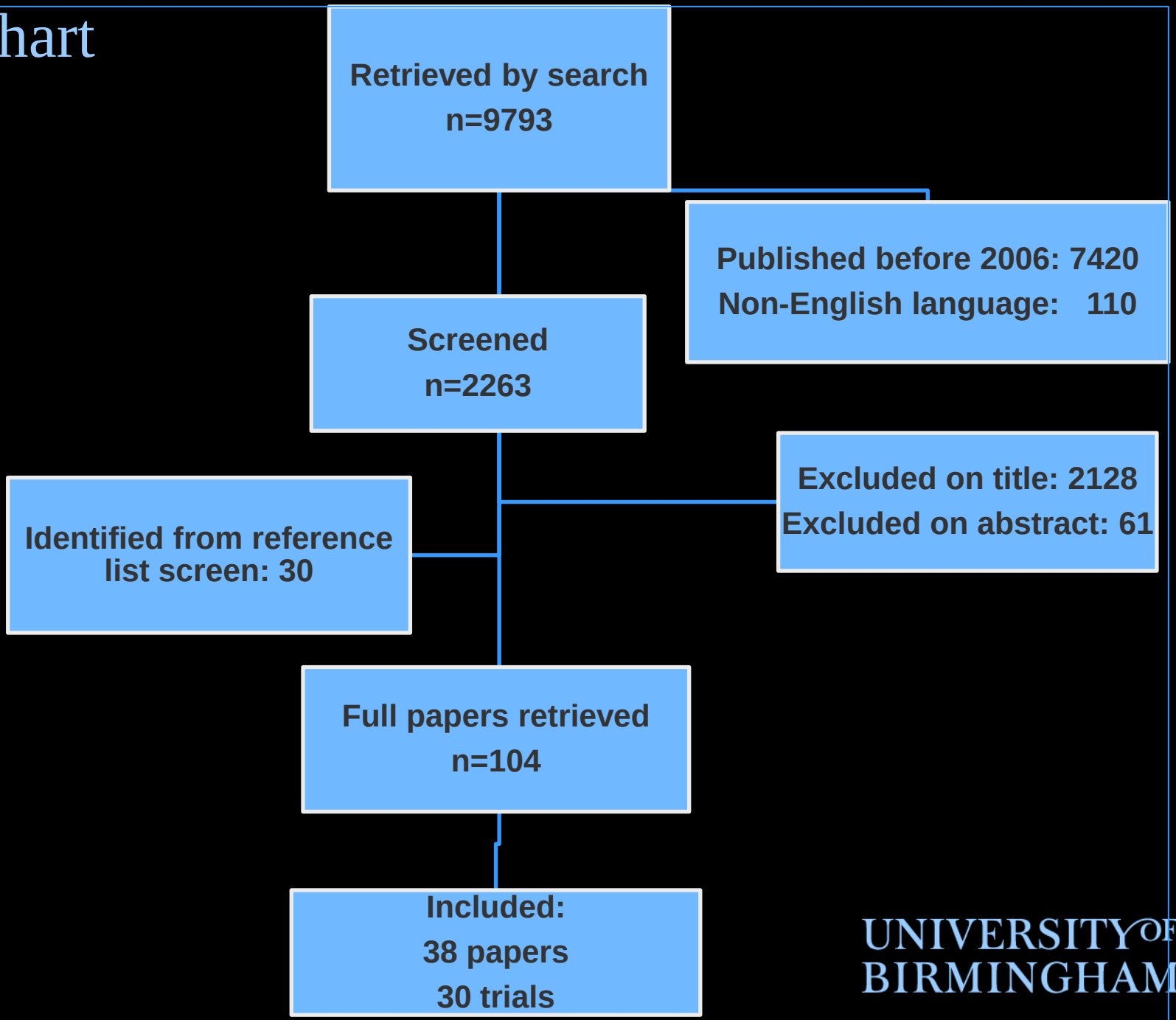
- **Monitoring** - the scheduled, repeated use of a test or tests over time to allow:
  - treatment titration to keep a marker under predefined limits
  - timely decisions about the management of a disease or condition that is likely to progress or recur

- **Aim** – to develop a framework defining the minimum evidence required to justify and guide the introduction of biomarkers for monitoring

Methods

- **Objective**
  - to get a picture of the type of monitoring regimes that have been evaluated in RCTs
  - to highlight potential issues for design and analysis of future trials
- **Literature search**
  - Searched CENTRAL database using keywords (monitor* or serial* or surveill*) in the title or abstract
- **Inclusion criteria**
  - RCTs published 2006-2011
  - ‘Formal’ monitoring regime
  - Aim of monitoring fits definition (monitoring for some event, such as disease progression or recurrence)

Flowchart



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Trial information

Publication type	n	%
Full trial report	19	63%
Interim analysis only (all trials stopped)	5	17%
Protocol only (2 stopped)	6	20%
Number of patients randomised		
Mean (range)	587 (73, 4439)	
Length of follow-up (months)		
Mean (range)	40 (3, 240)	

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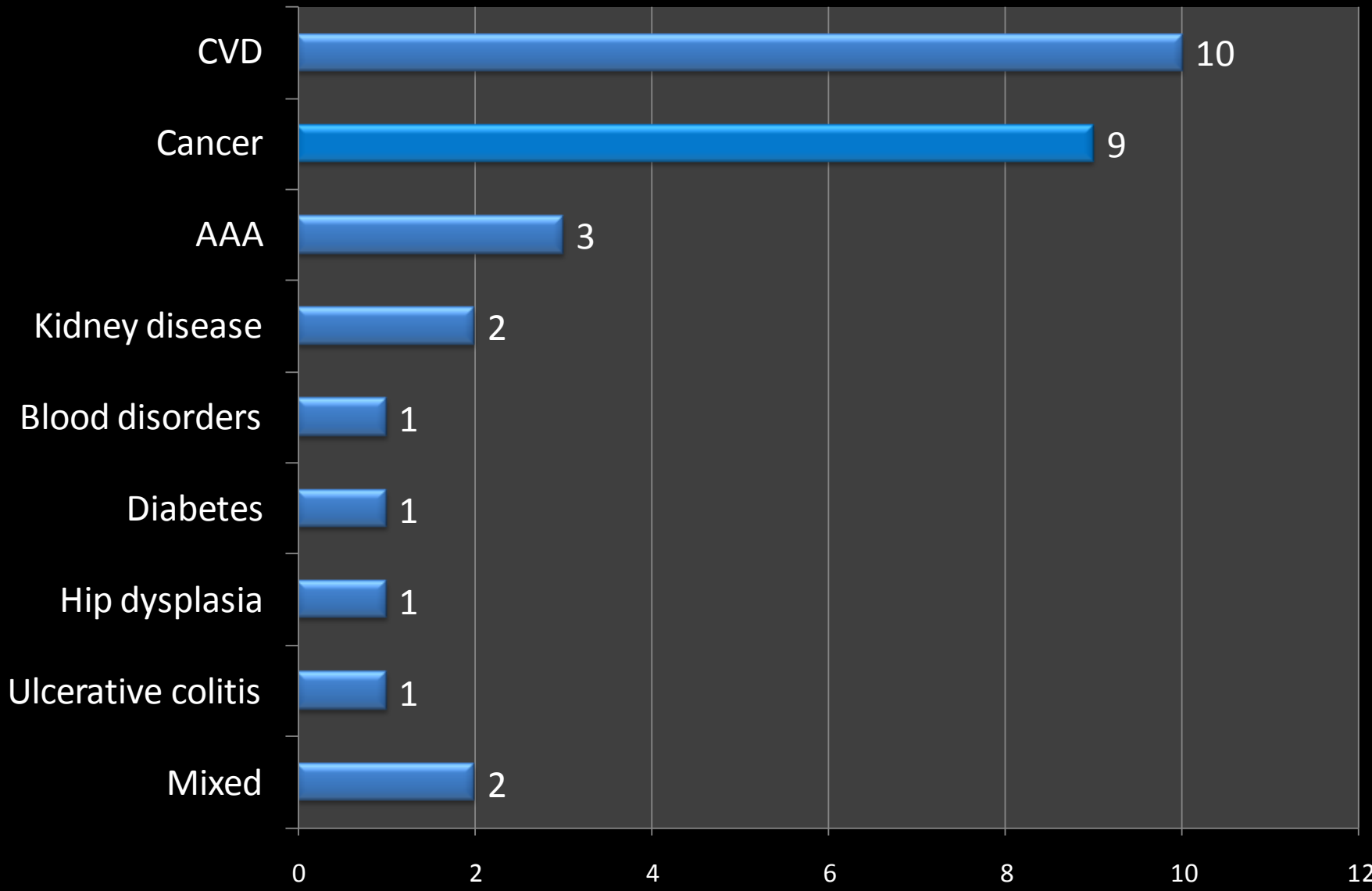
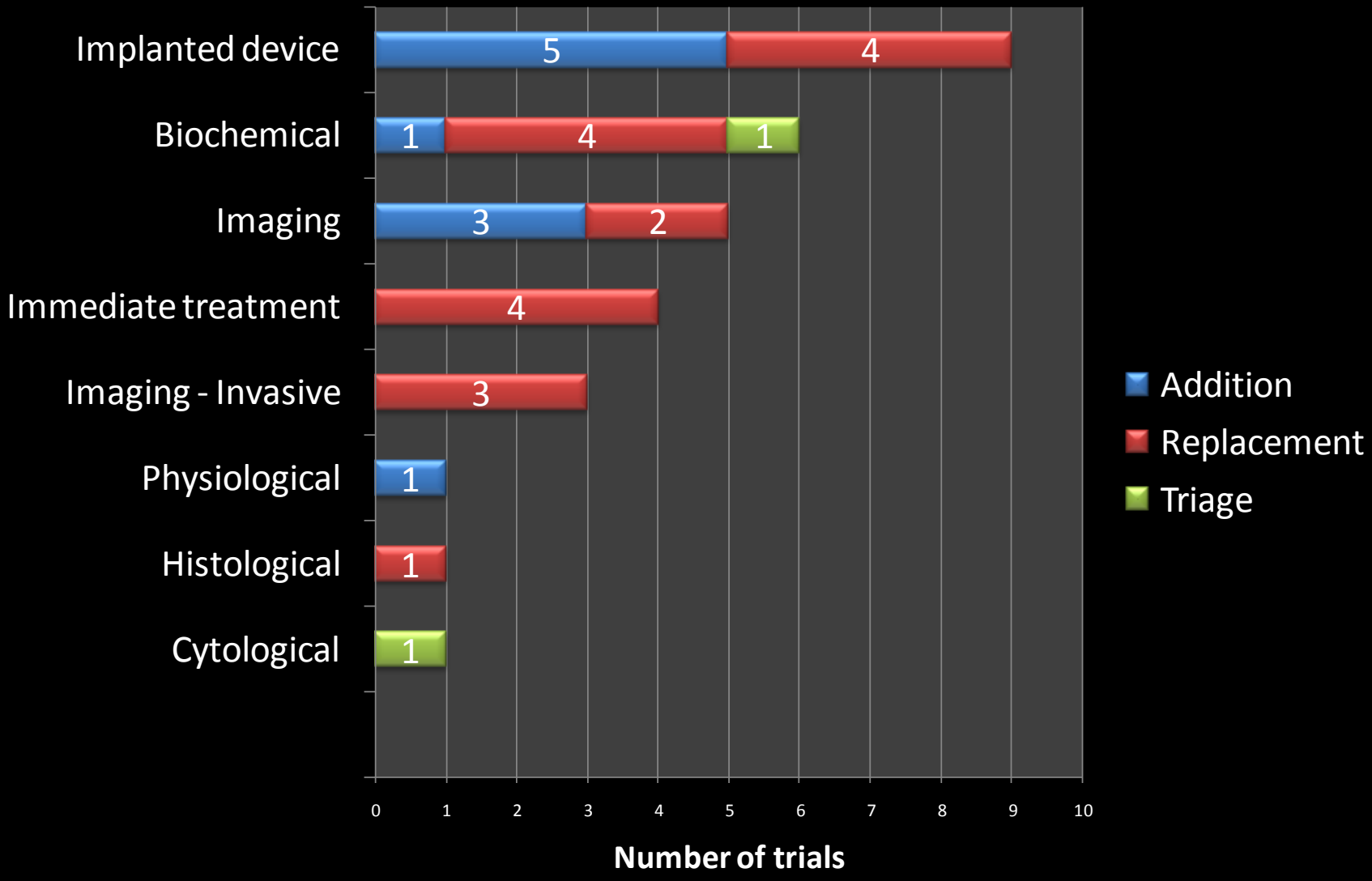
Clinical indication



Experimental strategies by proposed role



Monitoring comparison

Type of comparison		
Immediate Rx vs surveillance	4	13%
Comparison of one test versus another	9	30%
Standard follow-up plus new test vs standard follow-up	9	30%
Alternative follow-up vs standard follow-up	5	17%
Alternative follow-up plus new test vs standard follow-up	3	10%
Purpose of monitoring		
More/earlier Rx; improved outcome	17	57%
Delay/avoid treatment; same outcome	4	13%
Reduce testing; same outcome	9	30%

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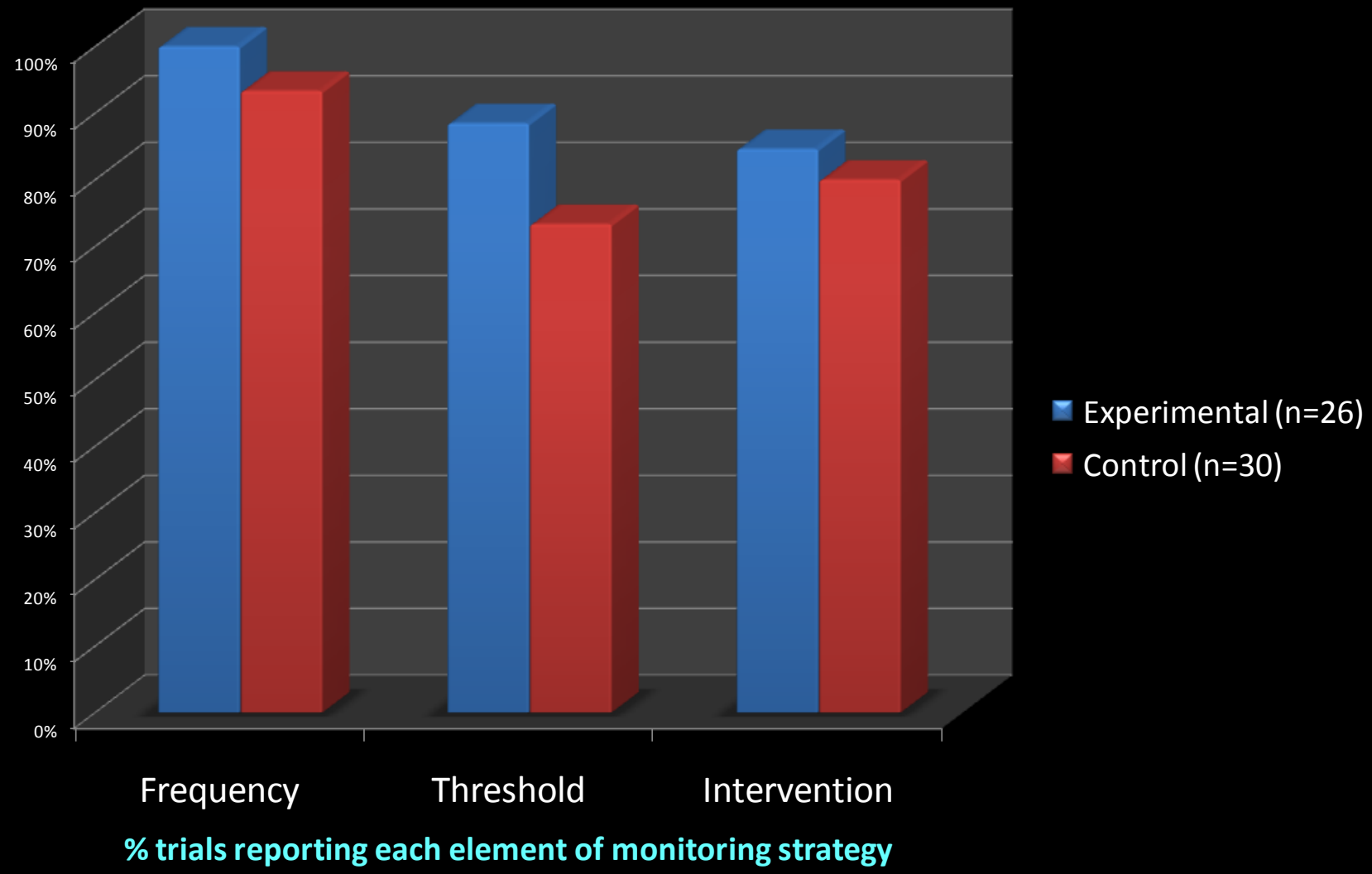
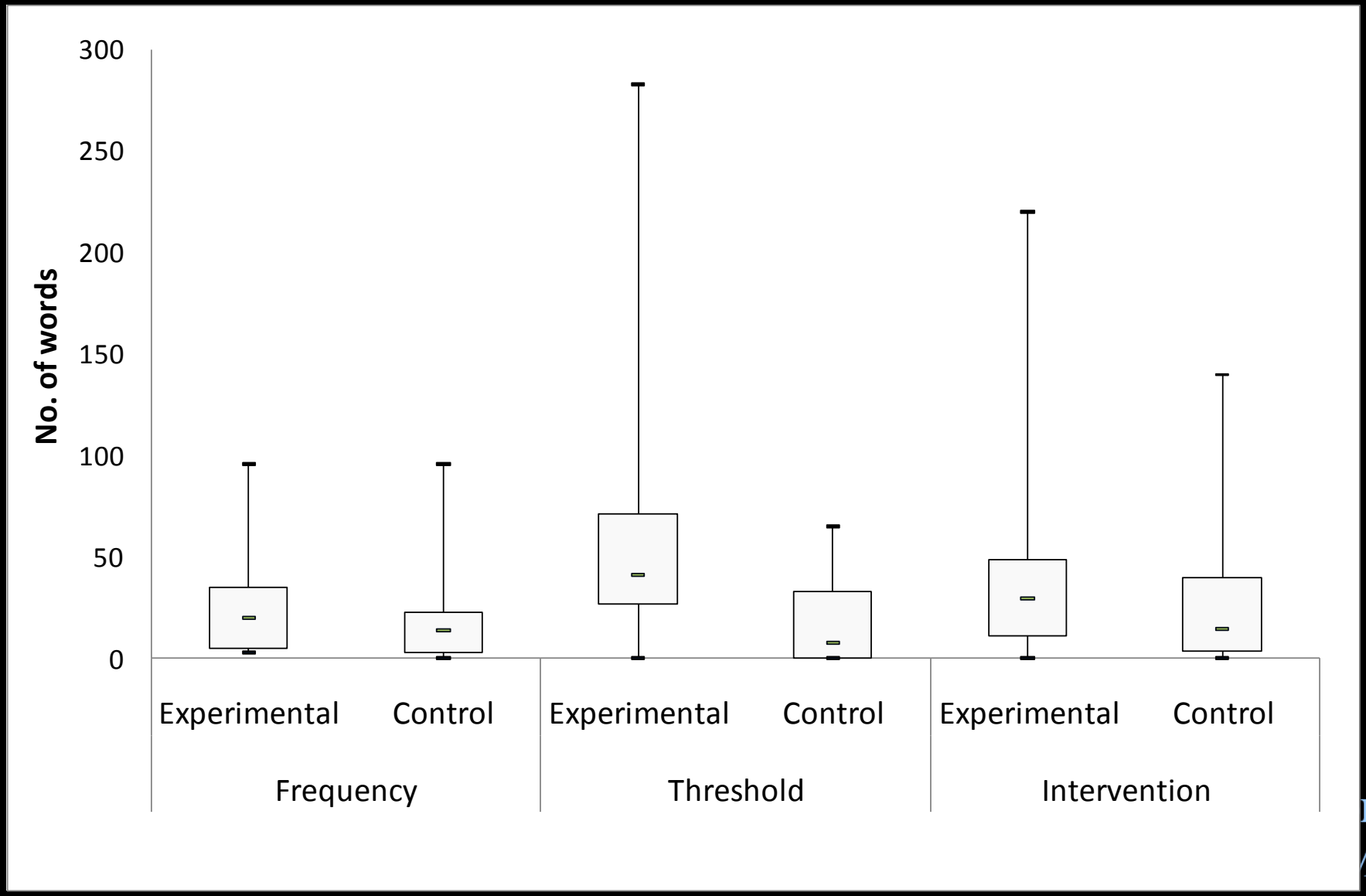
How well was the monitoring strategy described?

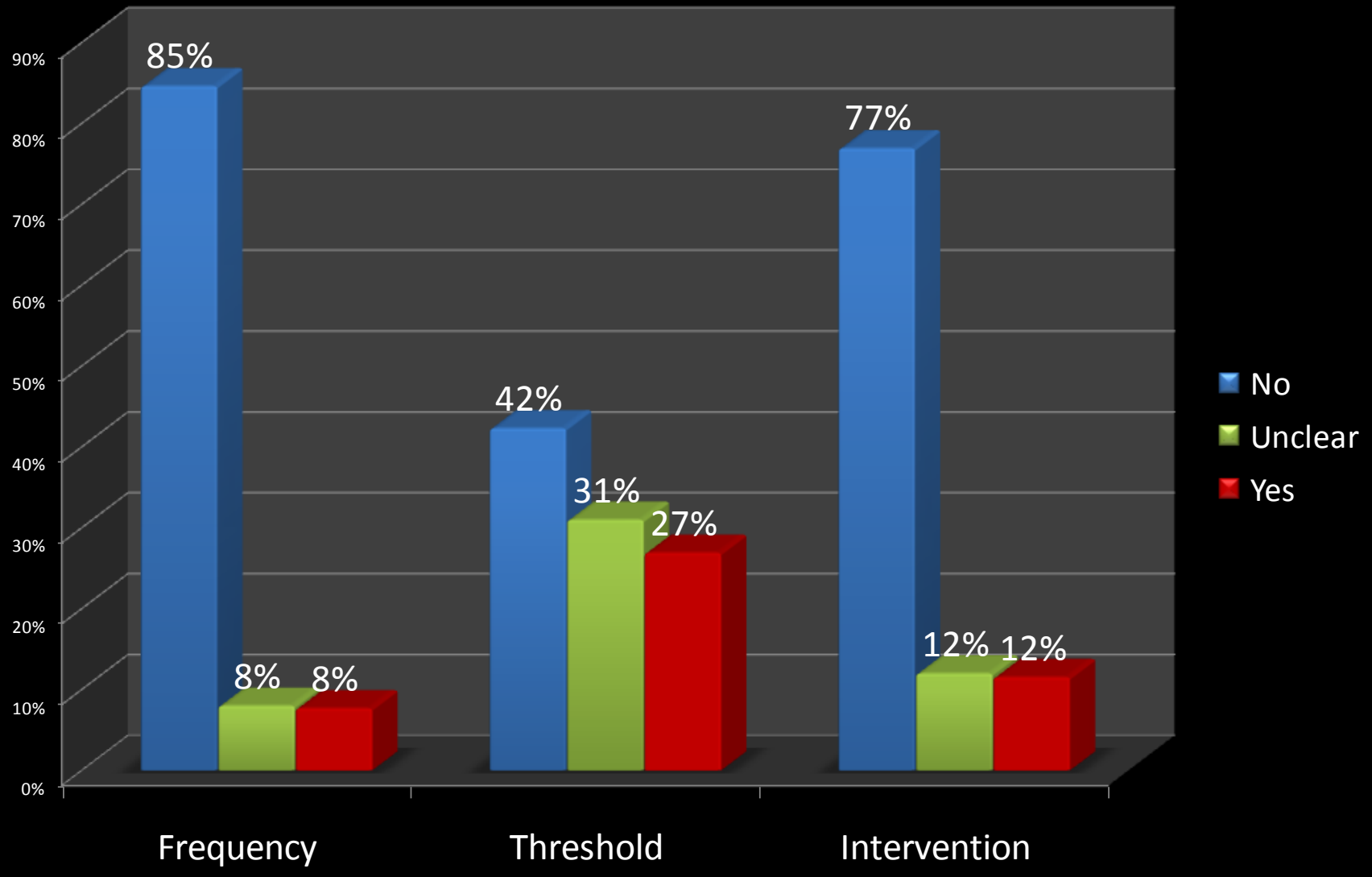


% trials reporting each element of monitoring strategy

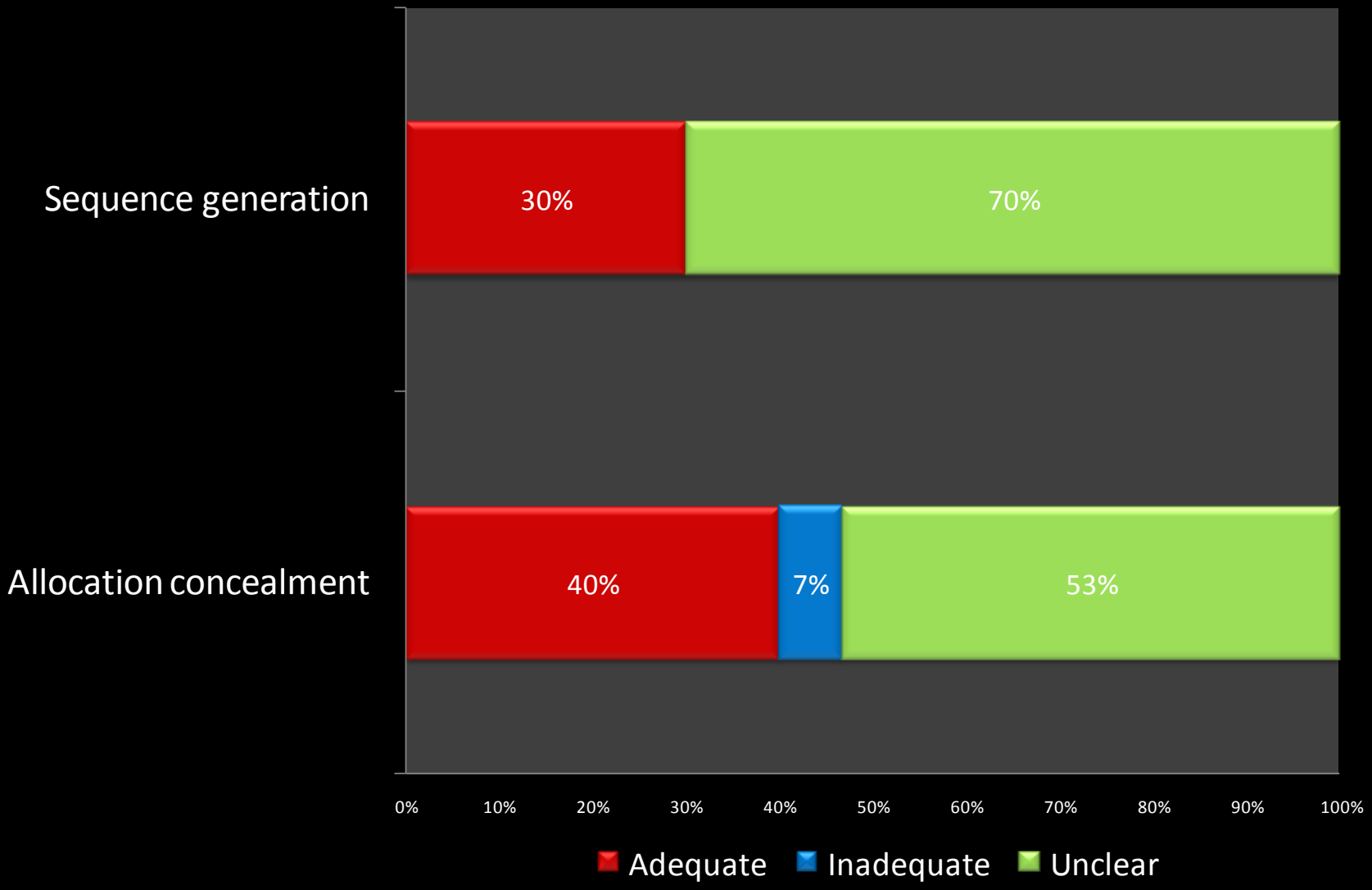
Number of words used to describe strategies



Evidence presented for experimental strategy?



Trial validity - randomisation



Bourge et al, Randomized controlled trial of an **implantable continuous hemodynamic monitor** in patients with advanced heart failure: the COMPASS-HF study. J Am Coll Cardiol 2008; 51: 1073-79

The COMPASS-HF (Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure) study was a prospective, multicenter, randomized, single-blind, parallel-controlled trial of 274 New York Heart Association functional class III or IV HF patients who received an implantable continuous hemodynamic monitor. Patients were randomized to a Chronicle (Medtronic Inc., Minneapolis, Minnesota) (n = 134) or control (n = 140) group. All patients received optimal medical therapy, but the hemodynamic information from the monitor was used to guide patient management only in the Chronicle group. Primary end points included freedom from system-related complications, freedom from pressure-sensor failure, and reduction in the rate of HF-related events (hospitalizations and emergency or urgent care visits requiring intravenous therapy).

Described as single-blind; patient blinding maintained by

- Transmitting ICHM data weekly
- Standardised clinician communication scripts
- Pre-determined call schedules for control patients

The 2 safety end points were met with no pressure-sensor failures and system-related complications in only 8% of the 277 patients who underwent implantation (all but 4 complications were successfully resolved). The primary efficacy end point was not met because the Chronicle group had a nonsignificant 21% lower rate of all HF-related events compared with the control group (p = 0.33). A retrospective analysis of the time to first HF hospitalization showed a 36% reduction (p = 0.03) in the relative risk of a HF-related hospitalization in the Chronicle group.

Rustin et al, **Early** versus **delayed treatment** of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomised trial. Lancet 2010; 376:1155-63

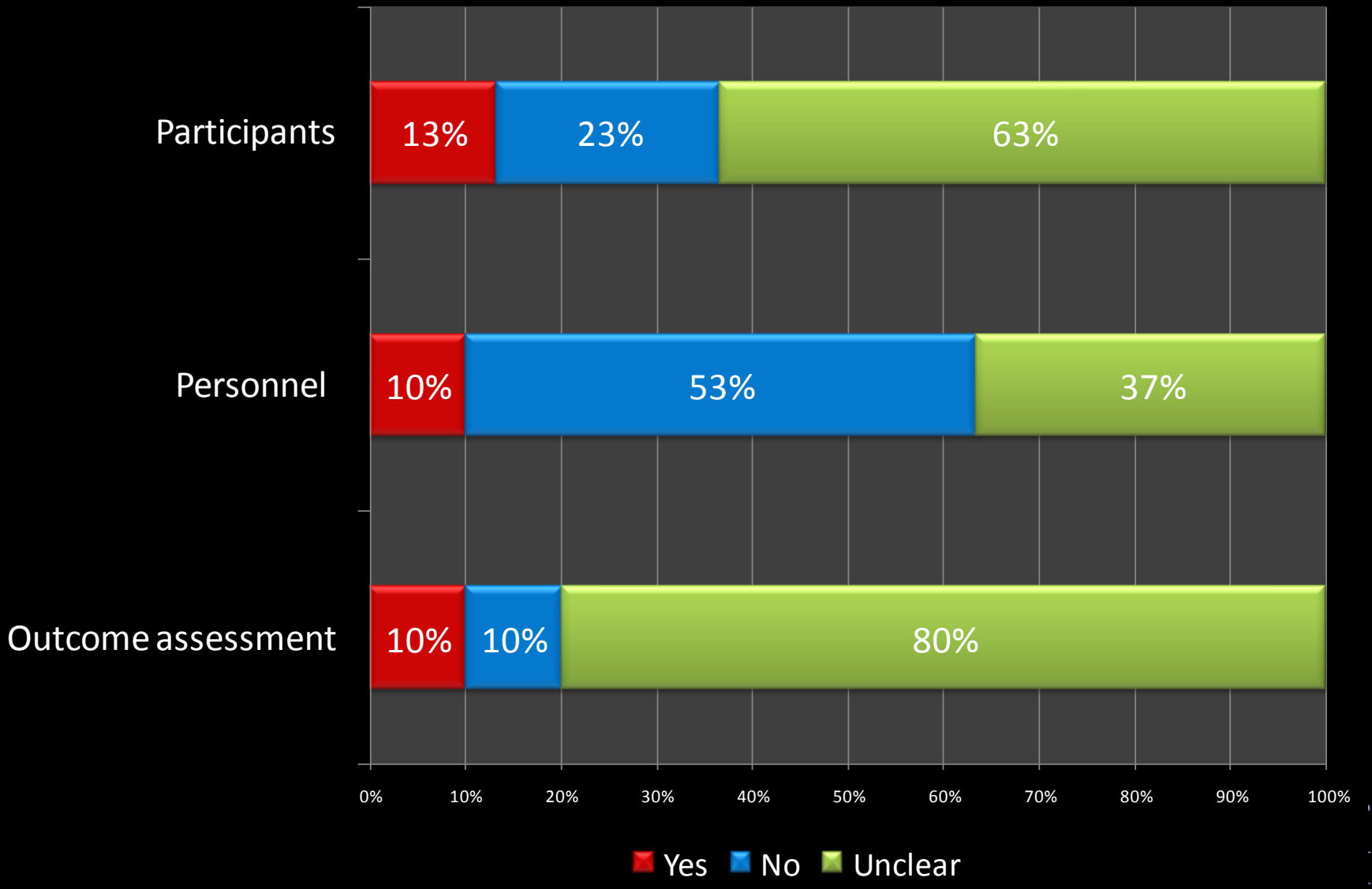
Methods Women with ovarian cancer in complete remission after first-line platinum-based chemotherapy and a normal CA125 concentration were registered for this randomised controlled trial. Clinical examination and CA125 measurement were done every 3 months. Patients and investigators were masked to CA125 results, which were monitored by coordinating centres. If CA125 concentration exceeded twice the upper limit of normal, patients were randomly assigned (1:1) by minimisation to early or delayed chemotherapy. Patients and clinical sites were informed of allocation to early treatment, and treatment was started as soon as possible within 28 days of the increased CA125 measurement. Patients assigned to delayed treatment continued masked CA125 measurements, with treatment commencing at clinical or symptomatic relapse. All patients were treated according to standard local practice. The primary outcome was overall survival. Analysis was by intention to treat. This study is registered, ISRCTN87786644.

Masked CA125 – CA125 ↑-- pts randomised:

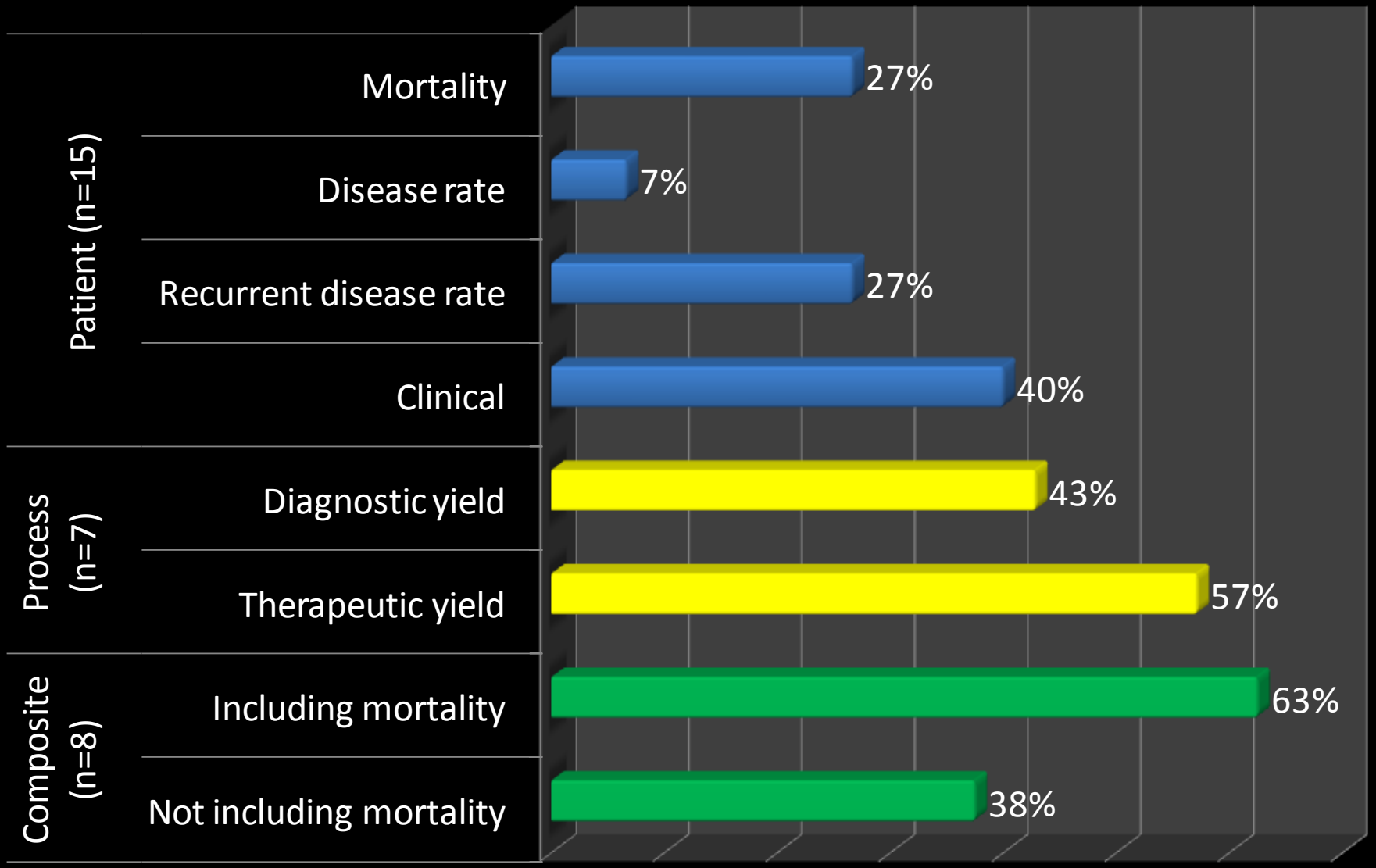
- Immediate chemotherapy
- Continue masked CA125 until clinical relapse
  - 'non-disclosure' of results rather than blinding

Findings 1442 patients were registered for the trial, of whom 529 were randomly assigned to treatment groups and were included in our analysis (265 early, 264 delayed). With a median follow-up of 56·9 months (IQR 37·4–81·8) from randomisation and 370 deaths (186 early, 184 delayed), there was no evidence of a difference in overall survival between early and delayed treatment (HR 0·98, 95% CI 0·80–1·20, p=0·85). Median survival from randomisation was 25·7 months (95% CI 23·0–27·9) for patients on early treatment and 27·1 months (22·8–30·9) for those on delayed treatment.

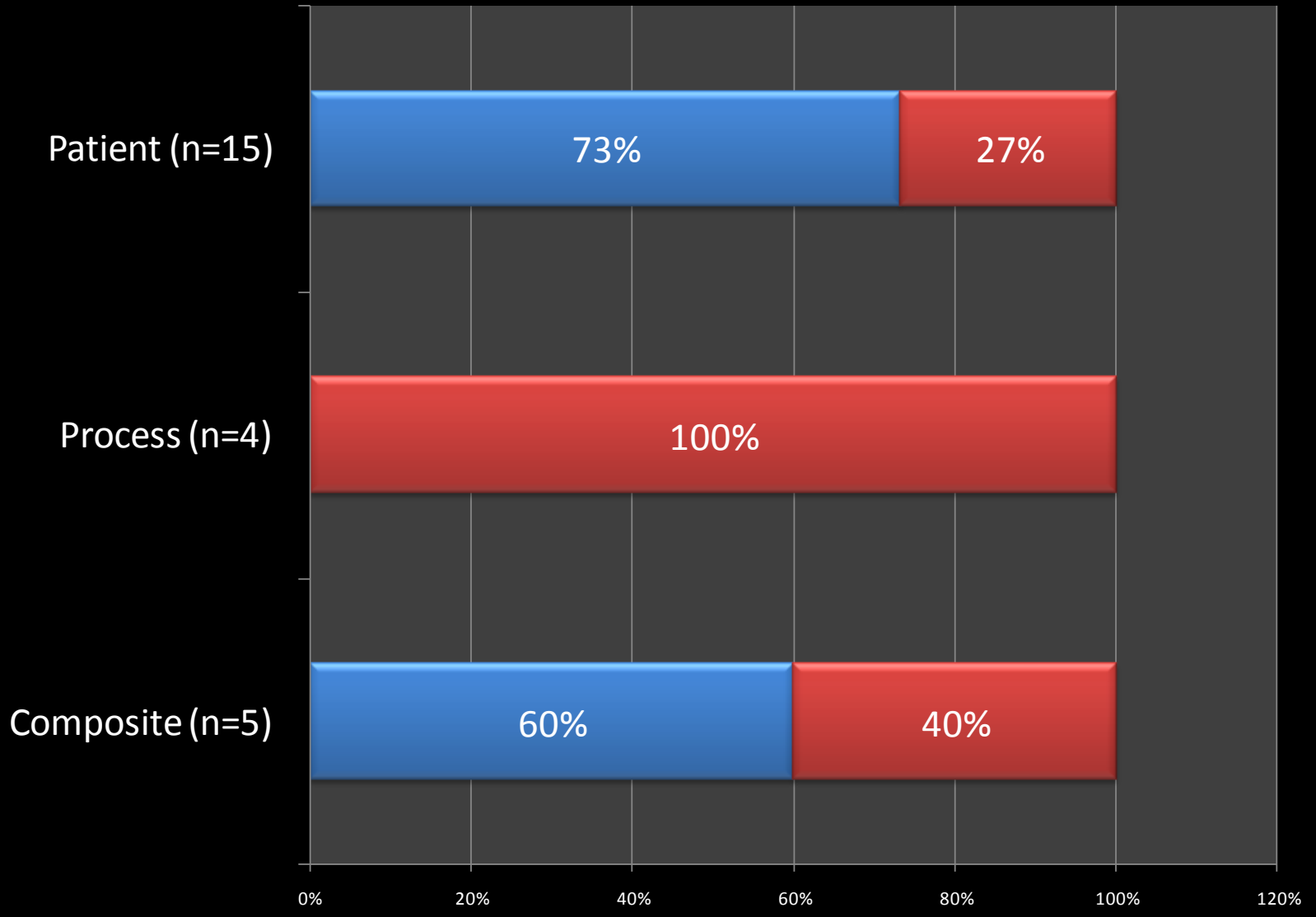
Trial validity – Blinding reported?



% trials reporting each type of primary outcome



Was the primary result statistically significant? (n=24)



Conclusions

- **Lessons**
  - Not many trials around
  - Trial reporting could be better
  - Thinking to do around blinding
  - Further investigation of observed vs predicted effects

- **Future work**
  - Identify bigger sample of trials

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Rosendahl et al, Immediate treatment versus sonographic surveillance for mild hip dysplasia in newborns. Pediatrics 2010; 125: e9-16

Newborns with mild hip dysplasia randomised:

- Immediate abduction treatment
- Sonographic surveillance

The same pediatric radiologist performed the majority (80%) of follow-up ultrasound examinations, and 2 other pediatric radiologists performed the remainder. All treated infants had their abduction splinting device removed before entering the radiology department for imaging. In addition, parents were instructed not to discuss their child's treatment with the radiologists to ensure that the radiologists were blinded to the intervention assigned.

All AI measurements were repeated by a fourth experienced radiologist (Dr Aase) who was blinded to the study group and previous findings and had not been involved in ultrasound assessments. On the basis of the AI, the hips were classified as normal (AI within 1 SD), acetabular ossification delay (1 SD < AI < 2 SD), or dysplasia

At 12 months,
difference in mean inclination angle:
0.1 (95%CI: -0.81, 0.91)

TOMBOLA Group. Cytological surveillance compared with immediate referral for colposcopy in management of women with low grade cervical abnormalities: multicentre randomised controlled trial. BMJ 2009; 339: b2546

Interventions Cytological screening every six months in primary care (n=2223) or referral for colposcopy and related interventions (n=2216). All women were followed for three years, concluding with an exit appointment at which colposcopic examination was undertaken. Colposcopists assessing outcome at this appointment were blinded to randomisation.

Results The cumulative incidence of cervical intraepithelial neoplasia grade II or worse was 79 per 1000 person years in the colposcopy arm and 58 per 1000 person years in the cytological surveillance arm (relative risk 1.37, 95% confidence interval 1.19 to 1.57).

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