What are the key drivers for quality?

Dr Martin Landray
University of Oxford

Need for reliable evidence from clinical trials

* Essential for appropriate decision making concerning the benefits and risks associated with clinical interventions.

* Decisions made in the absence of reliable evidence (either because relevant trials have never been performed or because those that have been performed were poorly designed or conducted) may harm individual patients and public health.

Criteria for a good trial

* Ask an IMPORTANT question

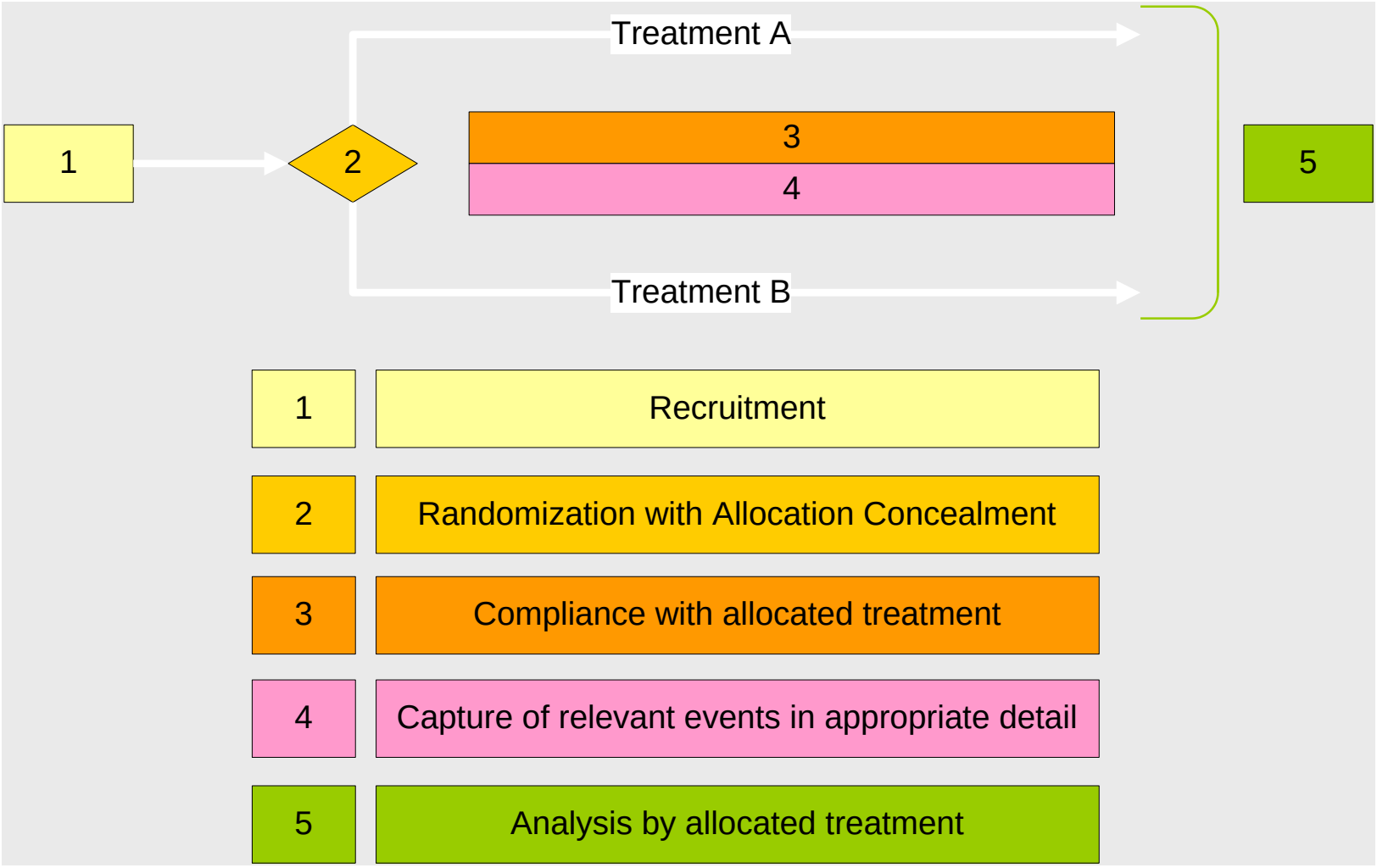
* Answer it RELIABLY

High quality clinical trials

Avoid errors that matter to decision making

* Human subjects protection
  * appropriate information & consent at each stage
  * safe administration & monitoring of investigational products
  * safe study procedures & investigations
* Reliability of results
* Wider environment
  * participants in other trials
  * public health (including patients not in trials)
  * physical environment

Reliable assessment of treatment effects



Impact of errors on the reliability of results

* **Random Errors**
  * affect the precision of estimates (adding "noise" and reducing statistical power), but will not introduce bias in either direction

    [Note: For equivalence assessments, random errors are counter-conservative]

* **Systematic Errors**
  * lead towards a particular decision

Key features for reliable assessment of moderate treatment effects

- Proper randomization
  - no foreknowledge of likely treatment allocation
- Relevant outcomes
  - sufficient numbers
  - recorded with appropriate accuracy
  - adequate timescale
- Appropriate follow-up
  - meaningful treatment difference
  - minimize post-randomization withdrawals
  - minimize loss to follow-up (e.g. after 1st event occurs or study treatment stops)
- Unbiased ascertainment and analysis of study outcomes
  - focus on robustness of result, not precision of data points
  - comparisons with the randomized control group (except for assessing big effects on rare events)
  - avoid emphasis on subgroups and on non-randomized "on-treatment" analyses

Facilitating recruitment

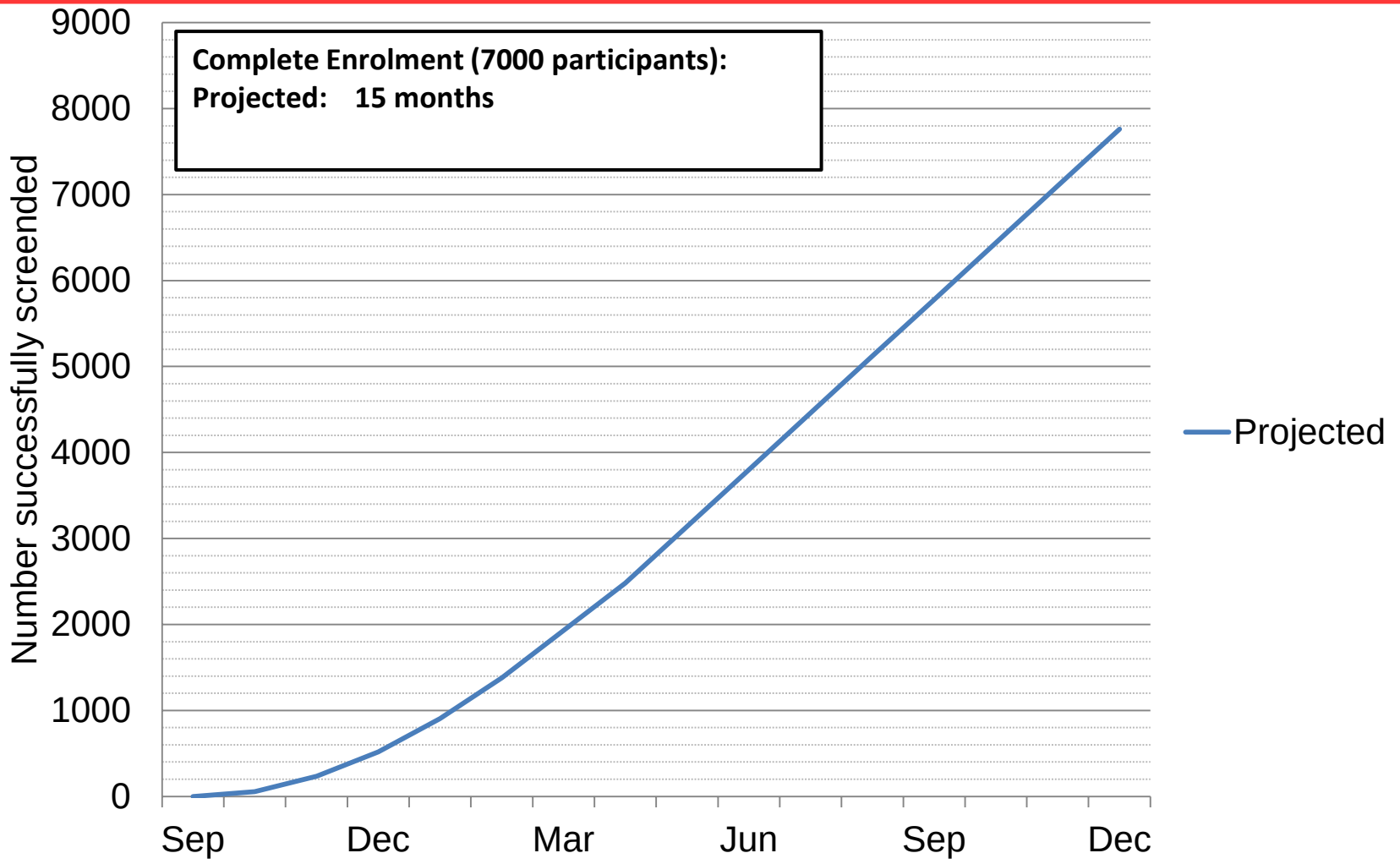
* Protocol
  * Inclusion criteria
    * relevant to target population
    * at sufficient risk of the key outcomes
    * differentiate from participant characterization
  * Exclusion criteria
    * human subjects protection
      * focus on comorbidity, concomitant medication, consent
      * avoid unnecessary criteria (if you don't study it, you'll never know)
* Operations
  * Site selection
  * Pre-screening

RECRUITMENT:
Large-scale recruitment & restricted site numbers

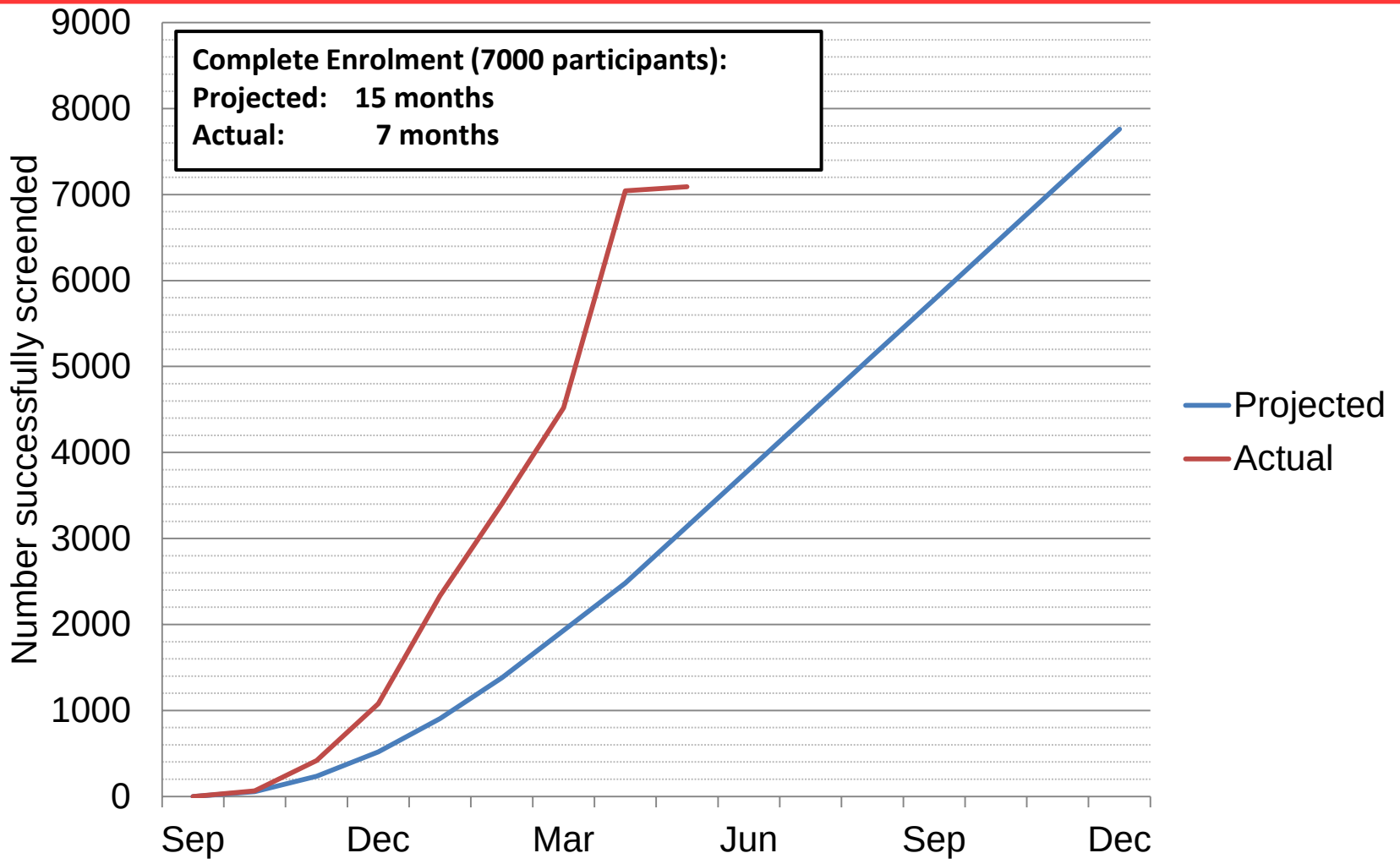
- Pre-screening to identify potentially eligible individuals
- Use of electronic data records (where available)

UK Sites	88
Identify	300,000
Invite	230,000
Screen	24,000 (10%)
Consent	16,000 (7%)
Randomized	8,000 (3%)
(per site)	~90

Value of pre-screening



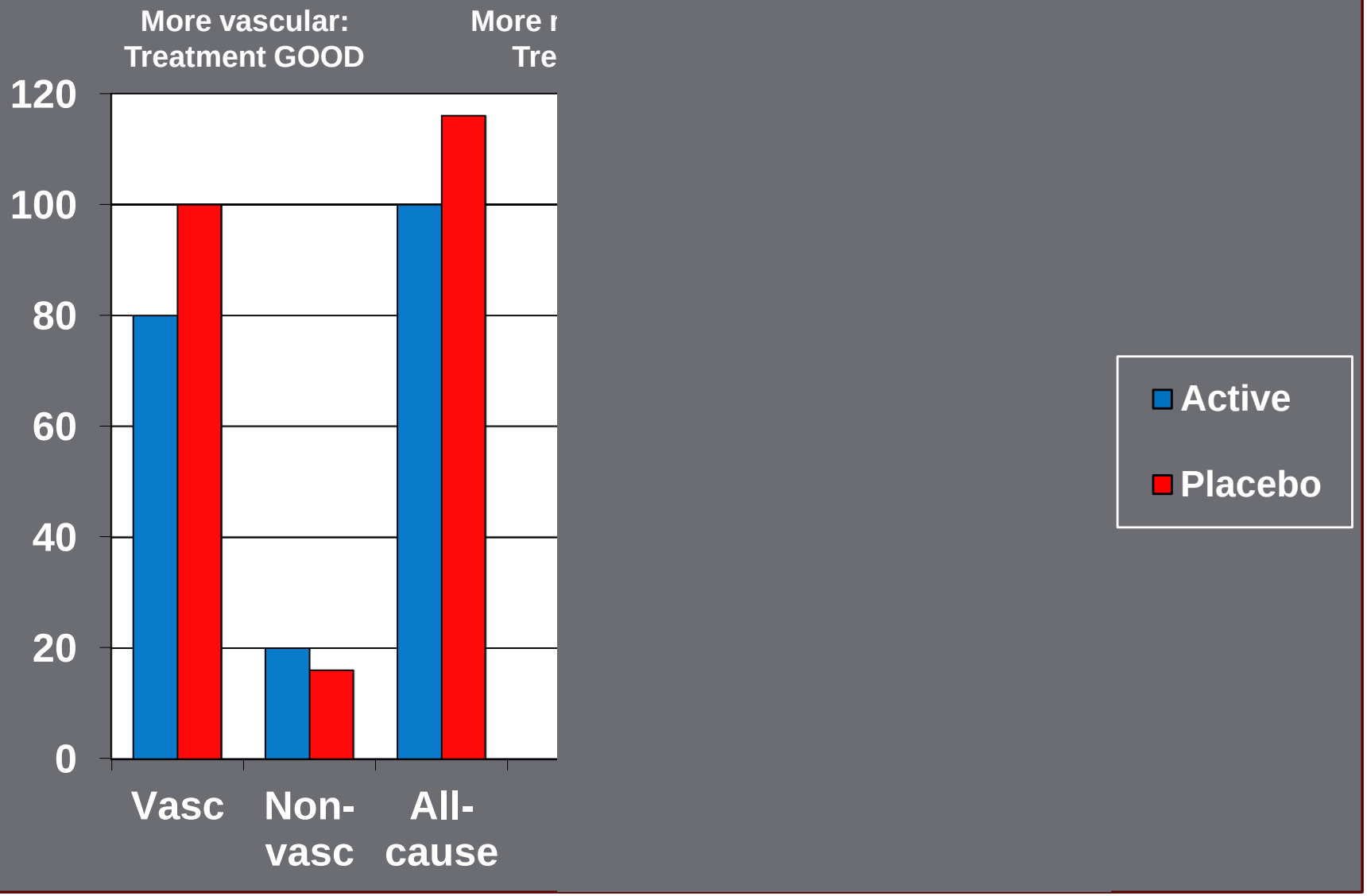
Value of pre-screening



Sufficient numbers of relevant events

* Number of events, not participants, is chief determinant of power
* Composite outcomes that combine events which may involve different directions of effect are less sensitive and generalizable (e.g. total mortality, or total cancer)
* Treatment effects (hazards & benefits) may emerge at different time points

Direction of effect on all-cause mortality depends on proportions of vascular & non-vascular death



Unbiased treatment allocation & follow-up

* No foreknowledge of likely treatment allocation
* Meaningful treatment difference
* Minimize post-randomisation withdrawals (i.e. intent-to-treat)
* Minimize losses to follow-up (e.g. after primary event occurs or study treatment stops)

Biased (i.e. non-randomized) follow-up & analysis

	Active	Placebo	P-value
Randomized	6481	6536	
Not willing/ineligible	117	159	=0.02
Received treatment	6364	6377	
Withdrew consent	343	396	=0.05
Lost to follow-up	367	369	>0.05

Comparison of the 6364 versus 6377 who received treatment described as having been *"Analyzed by intention-to-treat"*

SUVIMAX Arch Intern Med 2004

Impact of non-compliance

Treatment effect on biomarker	Anticipated relative risk reduction	Active (n=4000)	Control (n=4000)	Power at p=0.01
1.0	20%	480 (12.0%)	600 (15.0%)	91%
0.7	14%	516 (12.9%)	600 (15.0%)	54%

Not to check these assumptions may have adverse public health implications

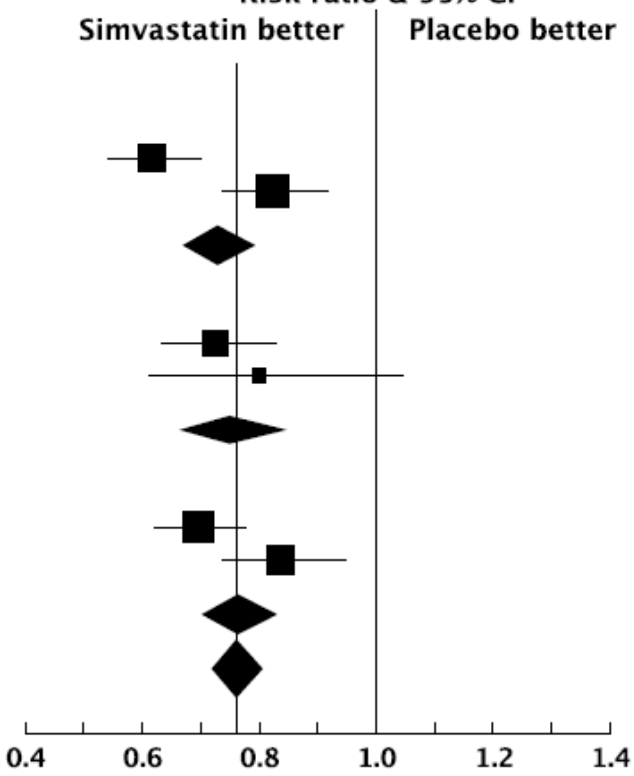
Avoid undue emphasis on data points

Reliable RESULT ≠ High quality DATA

High quality DATA ≠ Reliable RESULT

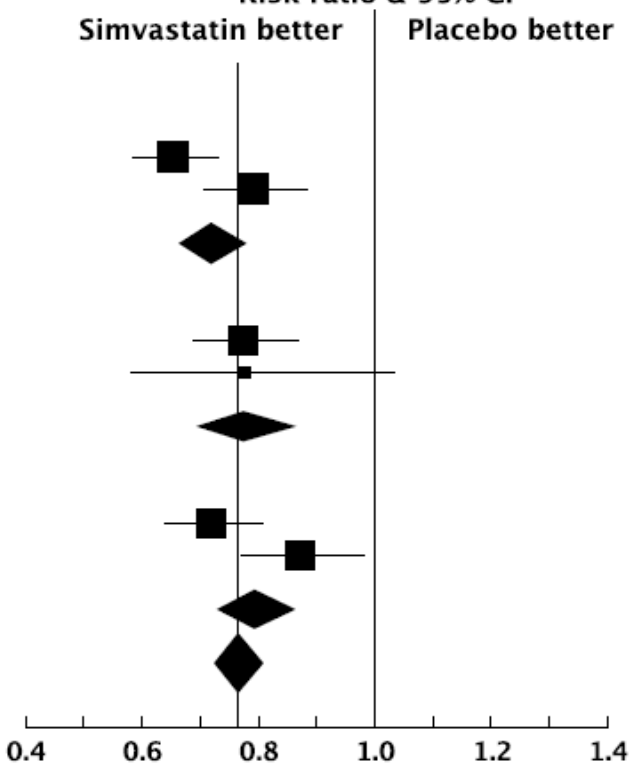
HPS: Effects of simvastatin-allocation on ADJUDICATED major vascular events

Type of event	Simvastatin allocation: Simvastatin (n=10269)		Placebo (n=10267)		Risk ratio & 95% CI
Coranary events					
Non-fatal MI	357	(3.5%)	574	(5.6%)	0.62 (0.54-0.70)
Coronary death	587	(5.7%)	707	(6.9%)	0.82 (0.74-0.92)
Any coronary event	**898**	**(8.7%)**	**1212**	**(11.8%)**	**0.73 (0.67-0.79)**
Strokes					
Non-fatal stroke	366	(3.6%)	499	(4.9%)	0.72 (0.63-0.83)
Fatal stroke	96	(0.9%)	119	(1.2%)	0.80 (0.61-1.05)
Any stroke	**444**	**(4.3%)**	**585**	**(5.7%)**	**0.75 (0.66-0.85)**
Revascularisations					
Coronary	513	(5.0%)	725	(7.1%)	0.70 (0.62-0.78)
Non-coronary	450	(4.4%)	532	(5.2%)	0.84 (0.74-0.95)
Any revascularisation	**939**	**(9.1%)**	**1205**	**(11.7%)**	**0.76 (0.70-0.83)**
ANY MAJOR VASCULAR EVENT	**2033**	**(19.8%)**	**2585**	**(25.2%)**	**0.76 (0.72-0.81)**



HPS: Effects of simvastatin-allocation on ADJUDICATED major vascular events

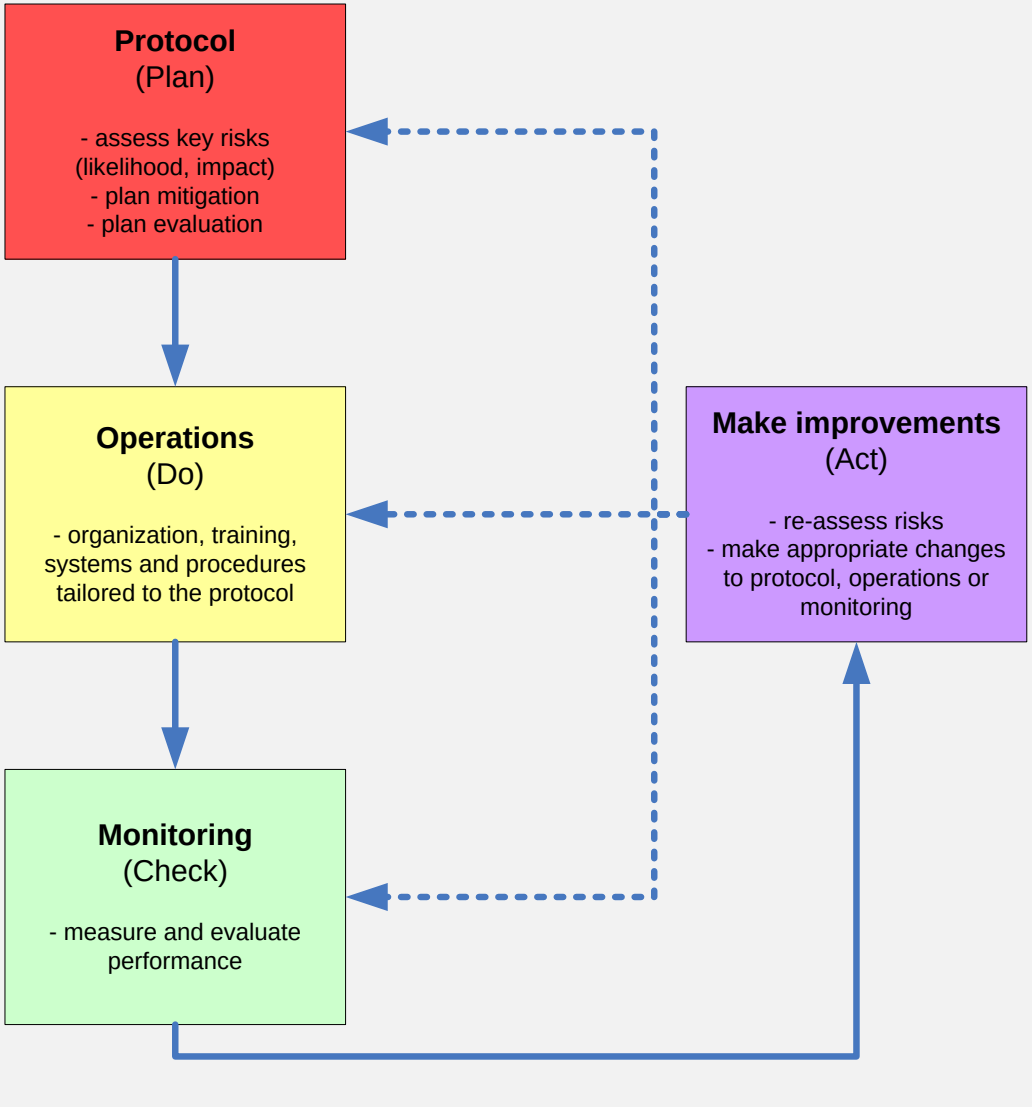
Type of event	Simvastatin allocation: Simvastatin (n=10269)		Placebo (n=10267)		Risk ratio & 95% CI
Coranary events					
Non-fatal MI	492	(4.8%)	743	(7.2%)	0.65 (0.58-0.73)
Coronary death	547	(5.3%)	687	(6.7%)	0.79 (0.71-0.88)
Any coronary event	**988**	**(9.6%)**	**1350**	**(13.1%)**	**0.72 (0.66-0.78)**
Strokes					
Non-fatal stroke	487	(4.7%)	621	(6.0%)	0.77 (0.69-0.87)
Fatal stroke	82	(0.8%)	105	(1.0%)	0.78 (0.58-1.03)
Any stroke	**550**	**(5.4%)**	**700**	**(6.8%)**	**0.77 (0.69-0.87)**
Revascularisations					
Coronary	487	(4.7%)	667	(6.5%)	0.72 (0.64-0.81)
Non-coronary	492	(4.8%)	559	(5.4%)	0.87 (0.77-0.98)
Any revascularisation	**943**	**(9.2%)**	**1166**	**(11.4%)**	**0.79 (0.73-0.86)**
ANY MAJOR VASCULAR EVENT	**2187**	**(21.3%)**	**2765**	**(26.9%)**	**0.77 (0.72-0.81)**



Improve study conduct by better design (not by finding problems retrospectively)

* Practical protocols are more likely to succeed
  * e.g. integration with usual clinical pathways, clear & feasible procedures
* Maximize recruitment & minimize sites/countries
* Select location based on feasibility
* IT can do more than just capture data
* Tailor monitoring/oversight to detect potential issues
* Relevant training & mentor staff based on their role

Quality by Design (QbD)



Landray et al *in press*

Conclusions

* Objective: Improve the availability of reliable information on for important healthcare decisions
* Design quality in to the trial protocol and procedures
* Identify and address risks as trial progresses
* Focus efforts to enhance quality (including monitoring):
  * Appropriate to the setting
  * Proportionate to the risks
  * Foster improvement
* Be open about quality assurance
  * Share management plans and issues identified