An introduction to Quality by Design

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Criteria for a good trial

* Ask an IMPORTANT question

* Answer it RELIABLY

Quality

"Quality" is the absence of errors that matter to decision making

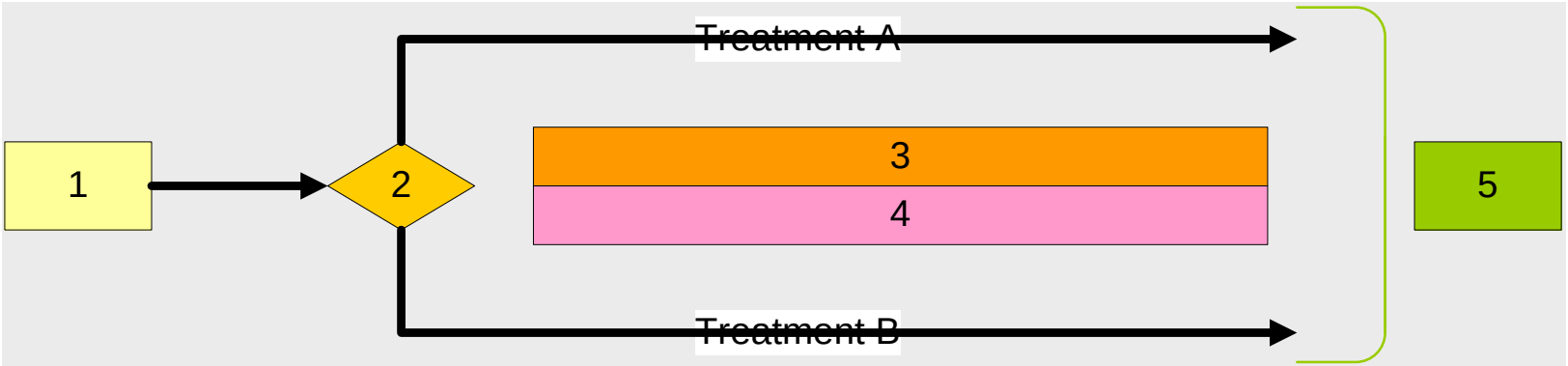
(i.e. errors that have a meaningful impact on patient safety or interpretation of results)

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
  * Detect true effects (efficacy, safety)
* Wider environment
  * participants in other trials
  * public health (including patients not in trials)
  * physical environment

Reliable assessment of treatment effects



1	Recruitment
2	Randomization with Allocation Concealment
3	Compliance with allocated treatment
4	Capture of relevant events in appropriate detail
5	Analysis by allocated treatment

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

* Inclusion criteria
  * relevant to target population
  * at sufficient risk of the key outcomes
  * (not the same as participant characterization)
* Exclusion criteria
  * human subjects protection
    * focus on comorbidity, concomitant medication, consent
    * avoid unnecessary criteria
* Uncertainty principle
  * if uncertain whether the treatment is indicated (or contra-indicated), randomize
* Feasible
  * must fit with routine care: clinicians are busy, patients are sick

Compliance

* Clinical need always overrides research idealism
* Non-compliance
  * Active group stops active treatment
  * Active group starts other treatment (e.g. effective comparator)
  * Control group starts active treatment (unusual in IND studies)
* Impact on results
  * less difference between randomized groups
  * conservative for superiority assessments
  * counter-conservative for non-inferiority / safety assessments

Impact of non-compliance

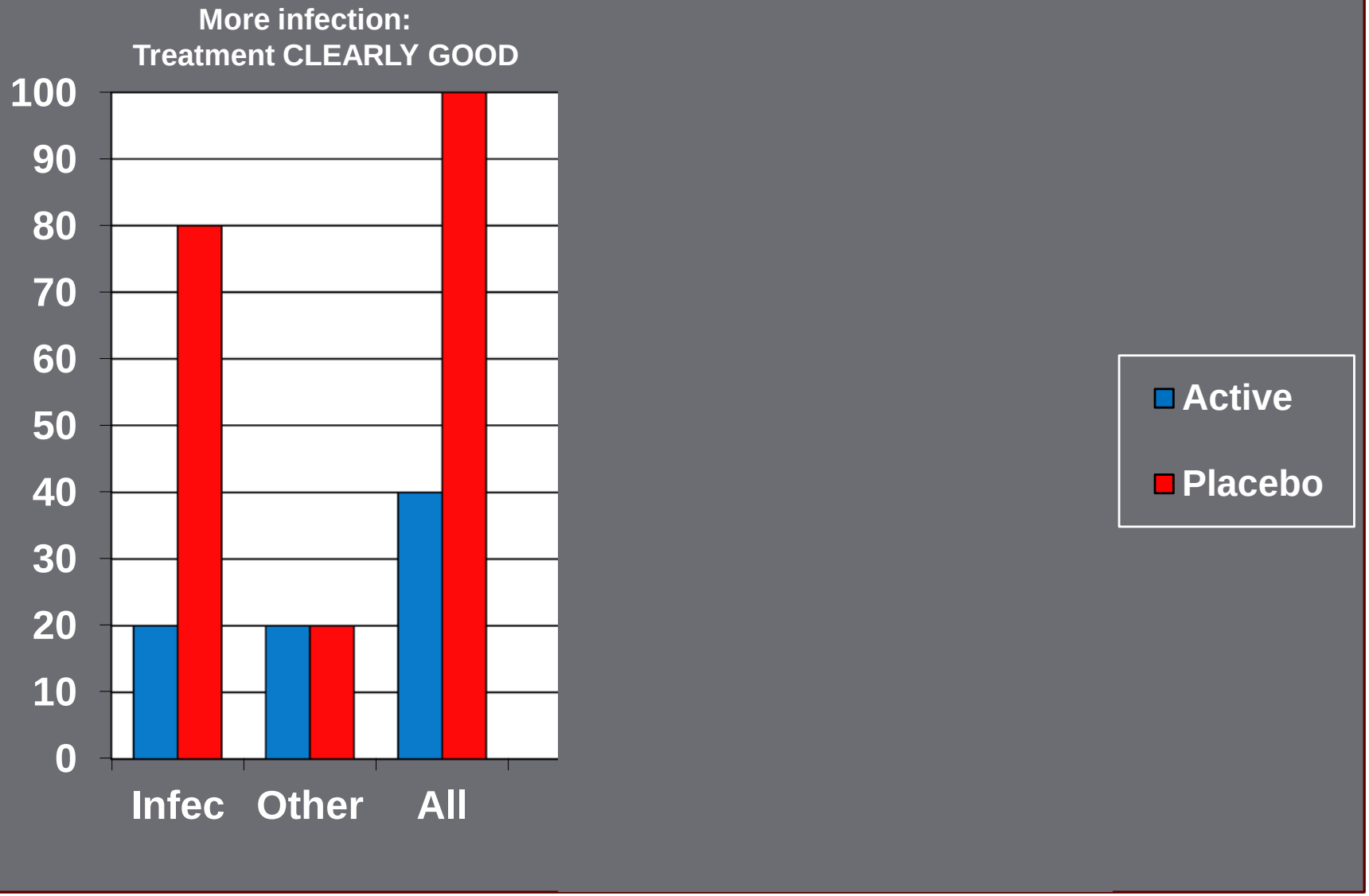
Treatment effect on biomarker	Anticipated relative risk reduction	Active (n=4000)	Control (n=4000)	Power at p=0.01
1.0	20%	480 (12.0%)	600 (15.0%)	91%

Not to check these assumptions may have adverse public health implications

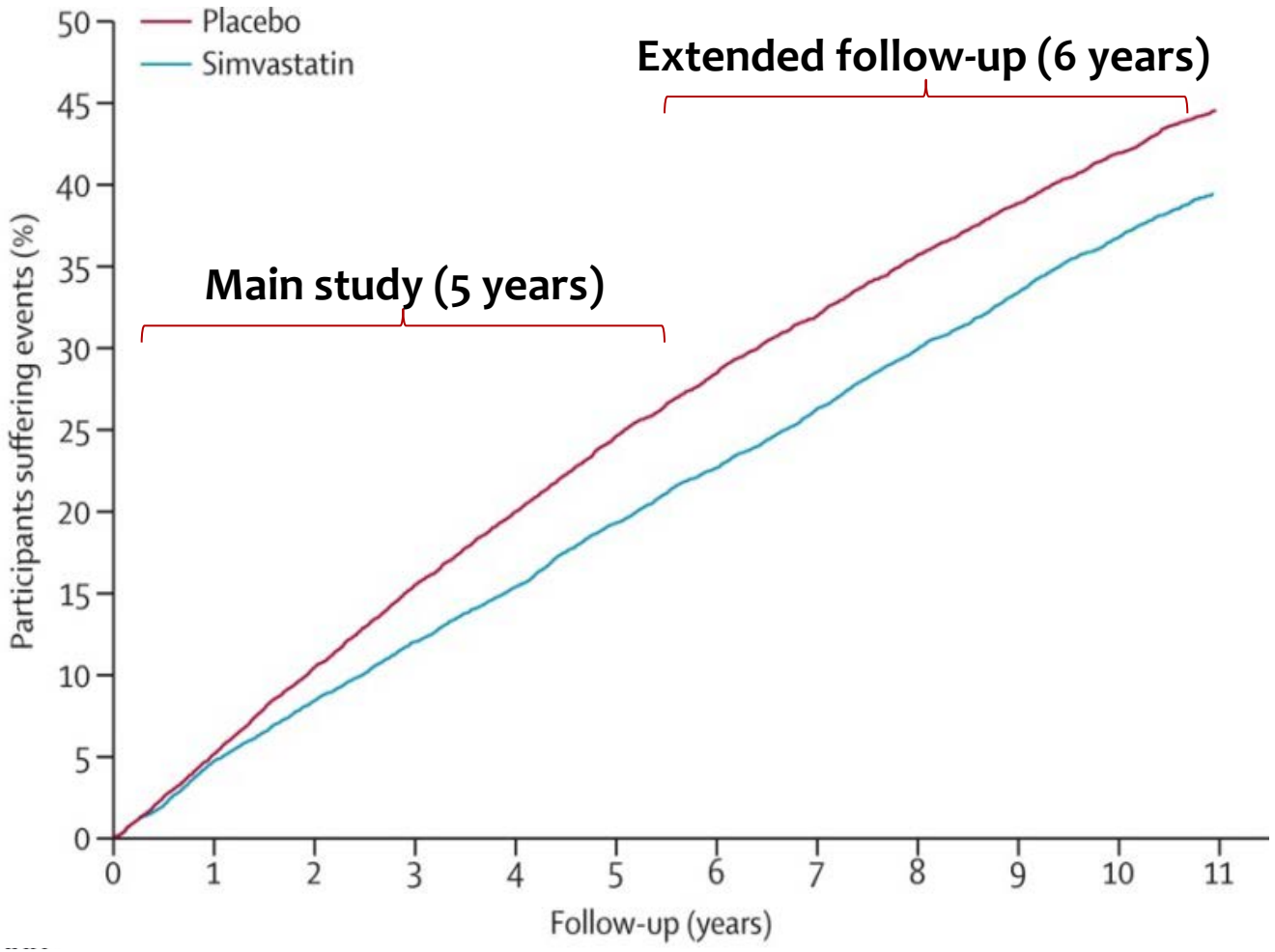
Sufficient numbers of relevant events

* 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

Size of effect on all-cause mortality depends on proportions of infection & other deaths



Prolonged follow-up of participants after the MRC/BHF Heart Protection Study



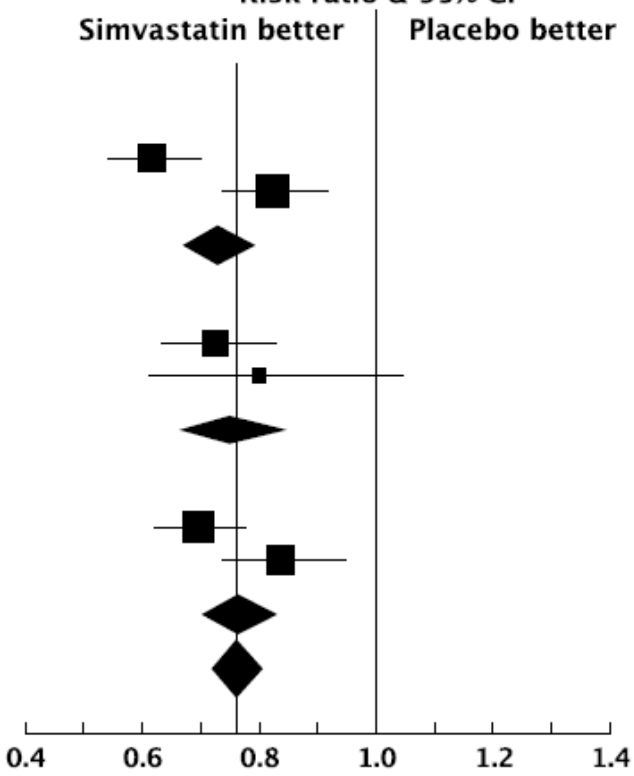
Avoid undue emphasis on data points

Reliable RESULT ≠ Accurate DATA

Accurate DATA ≠ Reliable RESULT

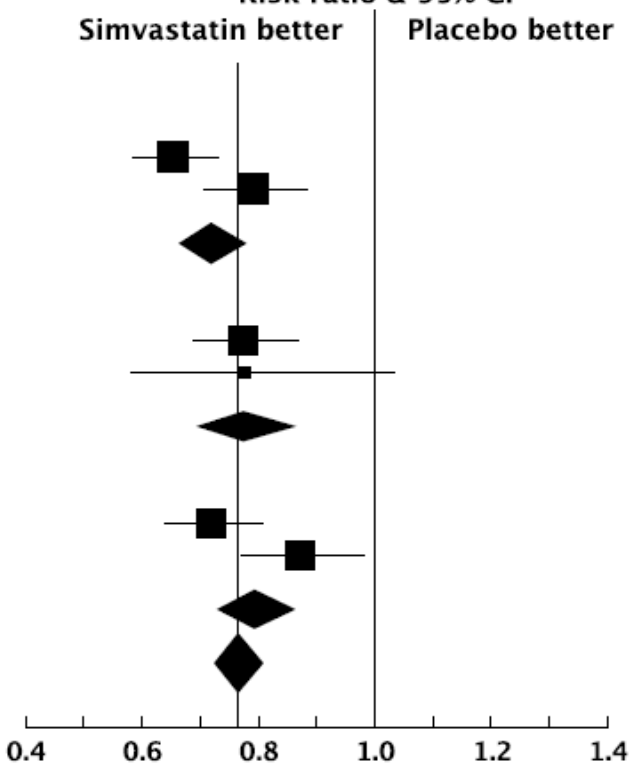
HPS: Effects of simvastatin-allocation on ADJUDICATED major vascular events

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)**

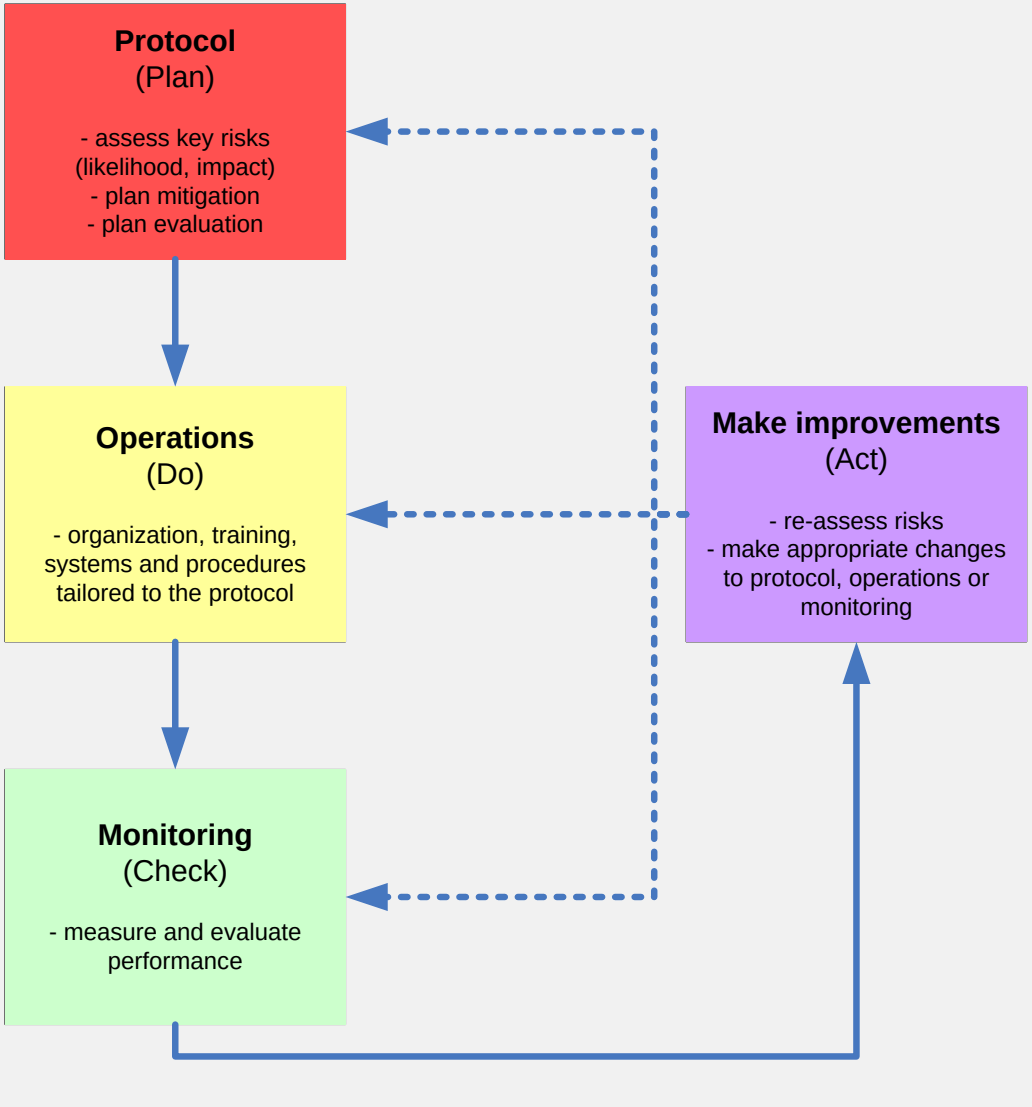


HPS: Effects of simvastatin-allocation on UNADJUDICATED major vascular events

Type of event	Simvastatin allocation: Simvastatin (n=10269)		Placebo (n=10267)		Risk ratio & 95% CI
					Simvastatin better | Placebo better
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)**



Quality by Design (QbD)



Landray et al *DIJ 2012*

Some examples from cardiovascular field

ISIS2: Design

Population	Acute myocardial infarction
Sample size	17,187
Intervention	Streptokinase vs. placebo Aspirin vs. placebo
Compliance	Not recorded
Follow-up	5 weeks
Primary outcome	Vascular mortality
Year of completion	1988

ISIS2: Principles

"By far the most important determinant of the success of ISIS is the extent to which, in those busy hospitals where the majority of acute MI patients are actually admitted, the responsible physicians and nurses choose to enter their patients.

Hence, the extra work must be – and is – absolutely minimal."

ISIS2: Protocol & procedures

* Eligibility
  * Signs or symptoms suggestive of definite or suspected acute myocardial infarction
  * <24 hours since onset of episode of pain that led to admission
  * No *clear* contra-indication to, or indication for, immediate streptokinase or aspirin, *in the view of the responsible physician*
* Randomization
  * By telephone - 9 questions plus site and patient identifiers
* Follow-up data collection
  * Discharge form
  * Pre-randomization ECG

PATIENT IDENTIFIERS (Please PRINT):
(for central monitoring of certified causes of death)

Hospital: .....

Surname/Family name: .....

All given name(s): .....

Date of birth: day: ...../ month: ...../ year: .....

Address: .....

.....

.....

Maiden name: .....
(if available)

Family doctor: .....
(if available)

ISIS 2

Second International Study of Infarct Survival
NOTIFICATION OF DISCHARGE OR PRIOR DEATH

OR: PATIENT STICKER,
IF **ALL** DETAILS PROVIDED

TICK ✓ PRE-TREATMENT CHARACTERISTICS

- ☐ Female
- ☐ Previous myocardial infarction
- ☐ Previous diabetes

TICK ✓ ANY DEVIATIONS FROM TRIAL TREATMENT

- ☐ **STREPTOKINASE/PLACEBO** infusion interrupted, or not given
- ☐ **ASPIRIN/PLACEBO** calendar pack interrupted, or not given

TICK ✓ APPARENT SIDE-EFFECTS OF STREPTOKINASE/PLACEBO INFUSION

- ☐ Significant hypotension during, or just after, infusion
- ☐ Anaphylactic shock
- ☐ Rigor
- ☐ Rash
- ☐ Other (specify, eg. respiratory distress) .....

TICK ✓ MAIN EVENTS (FATAL OR NOT) AFTER RANDOMISATION, AND ENTER DATE (FIRST) OCCURRED

	day / month / year	
☐ "Major" bleed (transfused)	...../...../.....	and site(s).....
☐ "Minor" bleed (not transfused)	...../...../.....	
☐ Cardiac rupture	...../...../.....	
☐ Reinfarction	...../...../.....	
☐ Ventricular fibrillation	...../...../.....	
☐ Other cardiac arrest	...../...../.....	
☐ Stroke, probable cerebral haemorrhage	...../...../.....	Likely residual disability (if alive):
☐ Stroke, infarct or unknown type	...../...../.....	☐ Non-significant/ ☐ Moderate/ ☐ Severe
☐ Discharge alive from hospital	...../...../.....	
☐ Death in hospital	...../...../.....	and underlying cause, if **not** cardiac:

.....

TICK ✓ TREATMENT IN HOSPITAL

- ☐ Steroids prior to streptokinase/placebo infusion
- ☐ Subcutaneous heparin
- ☐ Intravenous heparin
- ☐ Oral anticoagulant
- ☐ Intravenous beta-blocker
- ☐ Non-trial aspirin
- ☐ Other anti-platelet agent(s)

TICK ✓ DRUGS ON DISCHARGE

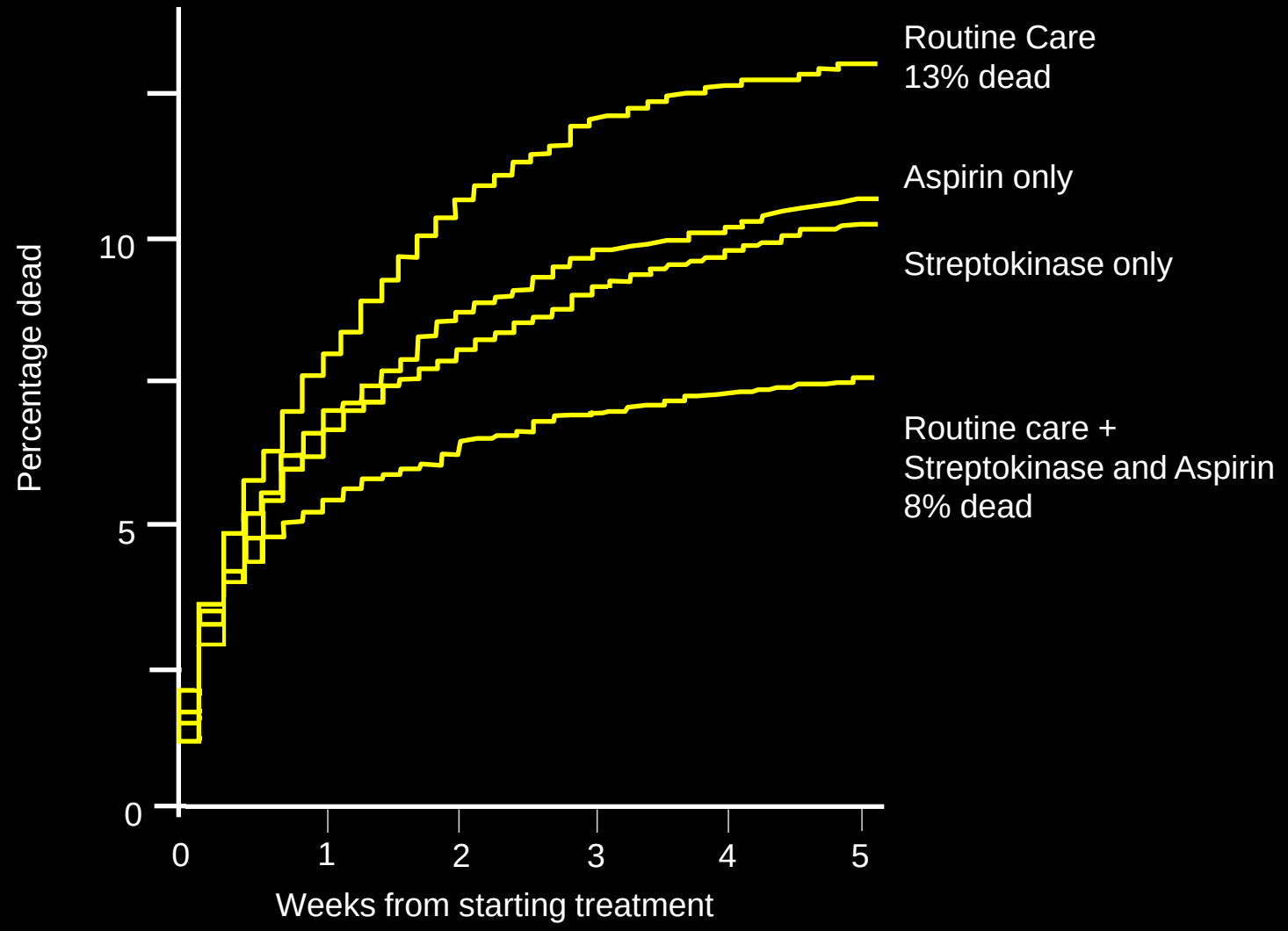
- ☐ Oral anticoagulant
- ☐ Non-trial aspirin
- ☐ Other anti-platelet agent(s)
- ☐ Beta-blocker

NAME OF PERSON COMPLETING FORM (please PRINT):.....

PLEASE SEND: — TOP COPY OF THIS FORM (retain bottom green copy)
— AND PRE-RANDOMISATION ECG (original or good photocopy)
TO: ISIS-2, FREEPOST, OXFORD OX2 6BR, UK (no stamp required within UK)

THANK YOU VERY MUCH

Second International Study of Infarct Survival (ISIS-2)



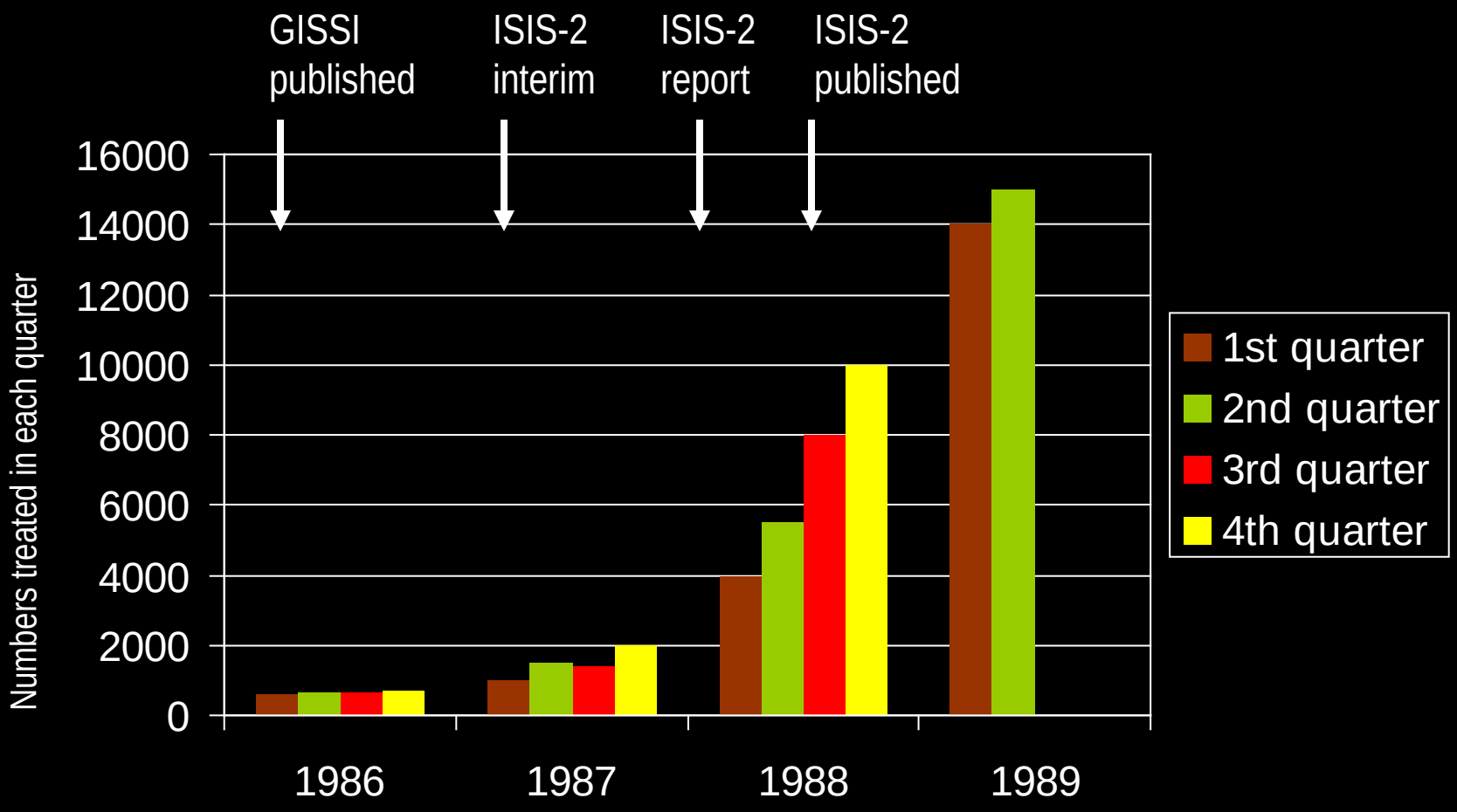
ISIS-2 Lancet 1988

Moderate effects can influence medical practice

	1987	1989
Antiplatelet	9%	84%
Fibrinolytics	2%	68%
Beta-blockers (oral)	25%	31%
Nitrates (oral)	23%	27%

BHF survey of physician treatment policies for acute MI (n=982)

Impact of large-scale randomized trials on sales of streptokinase in England & Wales



A large, streamlined trial to assess reliably the clinical effects of lowering LDL-cholesterol among patients with chronic kidney disease

SHARP: Design

Population	Chronic kidney disease
Sample size	9,536
Intervention	Ezetimibe/simvastatin vs. placebo
Compliance	62% average net compliance 33 mg/dL ↓LDL-C
Follow-up	Median 4.9 years
Primary outcome	Major atherosclerotic event
Year of completion	2010

SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Special features of design

- Largest randomized trial in kidney patients
- Non-restrictive inclusion criteria yield widely generalizable results for CKD populations
- Included CKD patients in stages 3-5 (both pre-dialysis and dialysis)
- Focus on outcomes that are sensitive to LDL lowering (ie, major atherosclerotic events)
- Combination of moderate-dose statin plus ezetimibe yielded large LDL-C reduction, but it was also well-tolerated by CKD patients

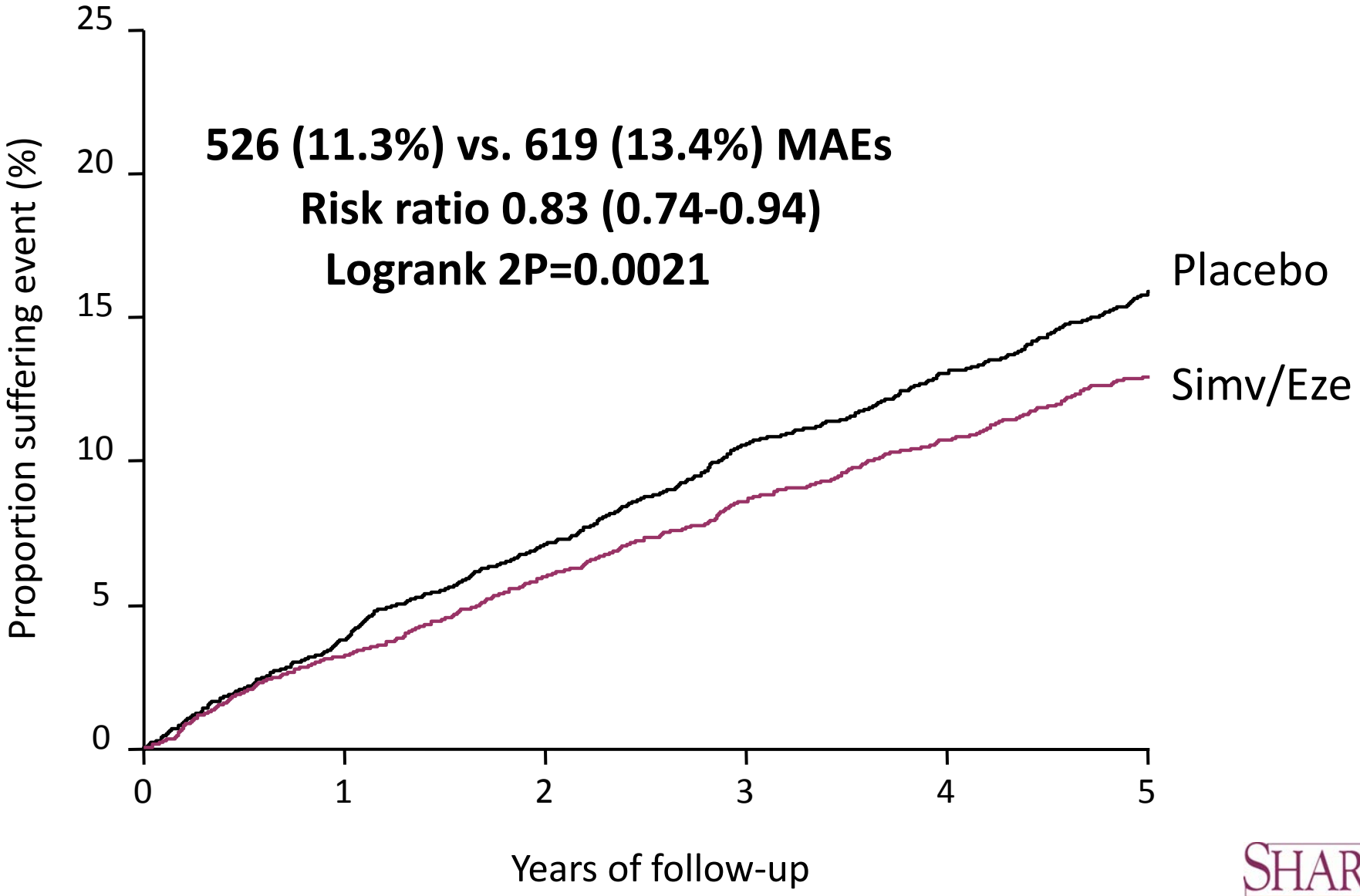
SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Wide inclusion criteria

- History of chronic kidney disease (CKD)
  - Not on dialysis: elevated creatinine on 2 occasions
    - Men: ≥1.7 mg/dL (150 µmol/L)
    - Women: ≥1.5 mg/dL (130 µmol/L)
  - On dialysis: hemodialysis or peritoneal dialysis
- Age ≥40 years
- No history of myocardial infarction or coronary revascularization
- Uncertainty: LDL-lowering treatment not definitely indicated or contraindicated

SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Major Atherosclerotic Events



SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Efficacy and safety

Outcome	Eze/simva	Placebo	RR	95% CI
Major atherosclerotic event	526	619	0.83	0.74-0.94
Vascular death	361	388	0.93	0.80-1.07
Non-vascular death	668	612	1.09	0.98-1.21
Cancer	438	439	0.99	0.87-1.13
Other SAEs	3258	3270	0.98	0.93-1.03

SHARP
STUDY OF HEART AND RENAL PROTECTION

SHARP: Other non-fatal SAEs*

	eze/simva (n=4650)	placebo (n=4620)	RR (95% CI)
Other cardiac	526 (11.3%)	557 (12.1%)	0.94 (0.83 – 1.05)
Other vascular (excl. cardiac)	324 (7.0%)	367 (7.9%)	0.88 (0.76 – 1.02)
Cancer (not incident)	73 (1.6%)	63 (1.4%)	1.15 (0.82 – 1.61)
Other renal	1958 (42.1%)	1966 (42.6%)	0.98 (0.92 – 1.04)
Respiratory	654 (14.1%)	666 (14.4%)	0.98 (0.88 – 1.09)
Liver/Pancreas/Biliary	82 (1.8%)	76 (1.6%)	1.08 (0.79 – 1.47)
Gastrointestinal	957 (20.6%)	988 (21.4%)	0.96 (0.87 – 1.04)
Skin	238 (5.1%)	240 (5.2%)	0.99 (0.82 – 1.18)
Genital & breast	176 (3.8%)	185 (4.0%)	0.94 (0.77 – 1.16)
Psychiatric	68 (1.5%)	62 (1.3%)	1.09 (0.78 – 1.54)
Neurological	220 (4.7%)	222 (4.8%)	0.99 (0.82 – 1.19)
Musculoskeletal	483 (10.4%)	471 (10.2%)	1.02 (0.90 – 1.16)
Hematological	224 (4.8%)	200 (4.3%)	1.12 (0.92 – 1.35)
Eye	184 (4.0%)	179 (3.9%)	1.02 (0.83 – 1.25)
Ear, Nose, Throat	72 (1.5%)	82 (1.8%)	0.87 (0.64 – 1.20)
Endocrine	58 (1.2%)	39 (0.8%)	1.47 (0.99 – 2.19)
Other medical	891 (19.2%)	896 (19.4%)	0.99 (0.90 – 1.09)
Non-medical	340 (7.3%)	333 (7.2%)	1.02 (0.88 – 1.19)
ANY OF ABOVE	**3258 (70.1%)**	**3270 (70.8%)**	**0.98 (0.93 – 1.03)**

***Excludes: MVEs, incident cancer, TIA, hospitalization with angina or heart failure, dialysis access revision, diabetes and hypoglycaemia, dialysis or renal transplantation, pancreatitis, hepatitis, gallstone events, myopathy and rhabdomyolysis**

SHARP
STUDY OF HEART AND RENAL PROTECTION

QbD approach to antibacterial drug development: FOCUS on the IMPORTANT

* Important Question
  * Is this new drug effective (and safe)?

* Reliable Answer
  * Feasibility
    * Would I enter myself/relative/patient into this study?
    * Does this require additional work
  * Collect essential information efficiently
    * Avoid the temptation to add extras
    * Avoid errors through careful design
    * Check for errors that matter to decision making (participant safety / reliability of results)

QbD approach to antibacterial drug development: RECRUITMENT

* Inclusion
  * Likely to have relevant diagnosis (HABP/VABP)
  * Likely to have relevant organism
    * i.e. outlook good if treated with an effective agent
  * Likely to have relevant outcome
    * i.e. outlook poor if not treated appropriately

* Uncertainty
  * No definite indication for, or contraindication to, active or comparator treatment

* Feasibility
  * Methods must fit in to routine clinical pathway

QbD approach to antibacterial drug development: COMPLIANCE

* NB: Not possible to mandate against use of effective treatment

* Non-compliance:
  * Discontinuation of active treatment
  * Initiation of other effective treatments in either active or comparator arm
  * Loss to follow-up
    * e.g. after primary event or after stopping study treatment

* Implications:
  * Non-compliance reduces the difference between treatment groups
    * Conservative for superiority assessments
    * Counter-conservative for non-inferiority (including safety) assessments

QbD approach to antibacterial drug development: OUTCOMES & ANALYSIS

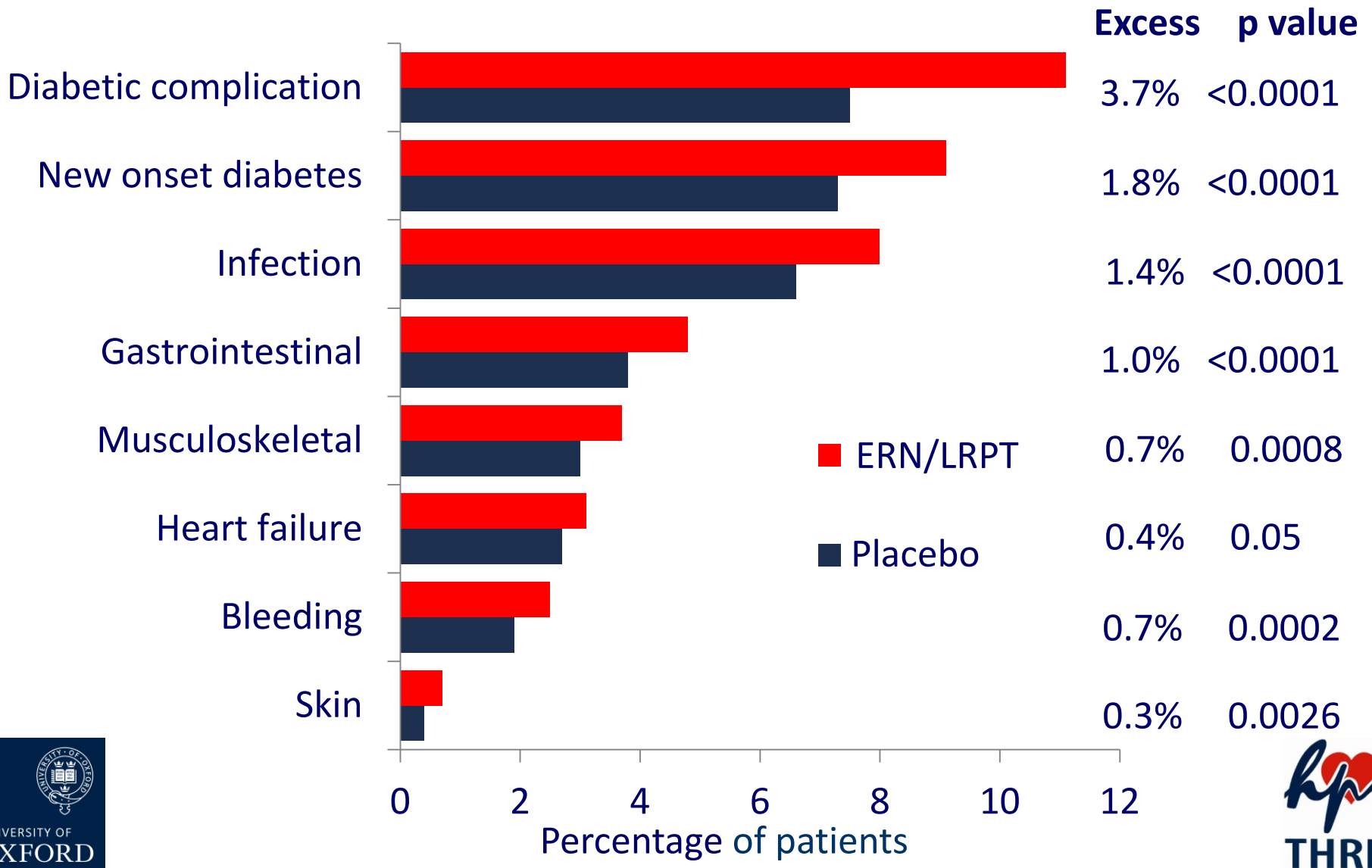
* Choice of outcome must be:
  * Clinically relevant
  * Objective
  * Assessed blind to treatment allocation
  * Likely to be affected by the randomized intervention

* Analysis
  * Intention-to-treat
  * Could be limited to pre-specified sub-group (e.g. based on bacteriology/sensitivities on baseline samples)
  * Avoid sub-group analyses that are
    * (a) underpowered,
    * (b) determined by factors recorded post-randomization, and/or
    * (c) data derived

Summary

* 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

Effect of ERN/LRPT on SERIOUS adverse events (median follow-up 3.9 years)



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