How to do (and publish) trials in neurological disorders. Trials in acute disorders like stroke and head injury

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Teaching Course
'How to do and publish clinical trials'
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Disclosures

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- Lecture fees from BI, Bayer paid to Department.
- Member of DSMB for RELY (BI), REVEAL (Merck), STABILITY/SOLID (GSK) trials

Learning objectives. Identify key problems and solutions in clinical trials of treatments for the acute phase of stroke and head injury

- Define the question
- Systematic review of the evidence
- Choose the outcome
- Plan sample size
- Randomisation and allocation concealment
- Efficient data collection and follow-up systems
- Analyse and report the trial

Please raise your hand if:

- You have worked on a randomised clinical trial (e.g. by recruiting patients)

- You would like to set up a research trial of your own

Large-scale investigator-led clinical trials in acute stroke and head injury

Acute ischaemic stroke	n
Aspirin, Heparin: IST-1	19,435
Aspirin: CAST	20,000
i.v. rt-PA: IST-3	3,035
IPC to prevent DVT: CLOTS-3	2,876
Subarachnoid haemorrhage	
Clip vs coil: ISAT	2,143
Intracerebral haemorrhage	
Intensive BP lowering: INTERACT-2	2,839
Head injury	
Corticosteroids: CRASH-1	10,008

Frame your question: (PICO)

Patient (eg acute phase of stroke)

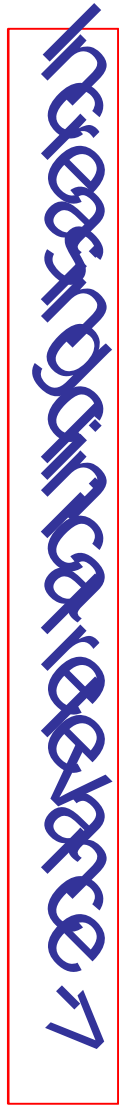
Intervention (drug, procedure etc)

Comparison (placebo, open control, standard therapy etc)

Outcome (death, stroke, disability)

What outcome to measure?

Measurement	Example
Physiology	BP, Cholesterol, intracranial pressure
Pathology	size of cerebral infarct,
Impairment	muscle strength, conscious level
Event	stroke, pulmonary embolus
Function	GOS, mRS, Quality of Life (EQ5D, SF36)
Death	



Example question

P: in the first hours after head injury,

I: do high-dose corticosteroids

C: compared with routine care

O: reduce risk of death or disability?

Do a systematic review before any new trial

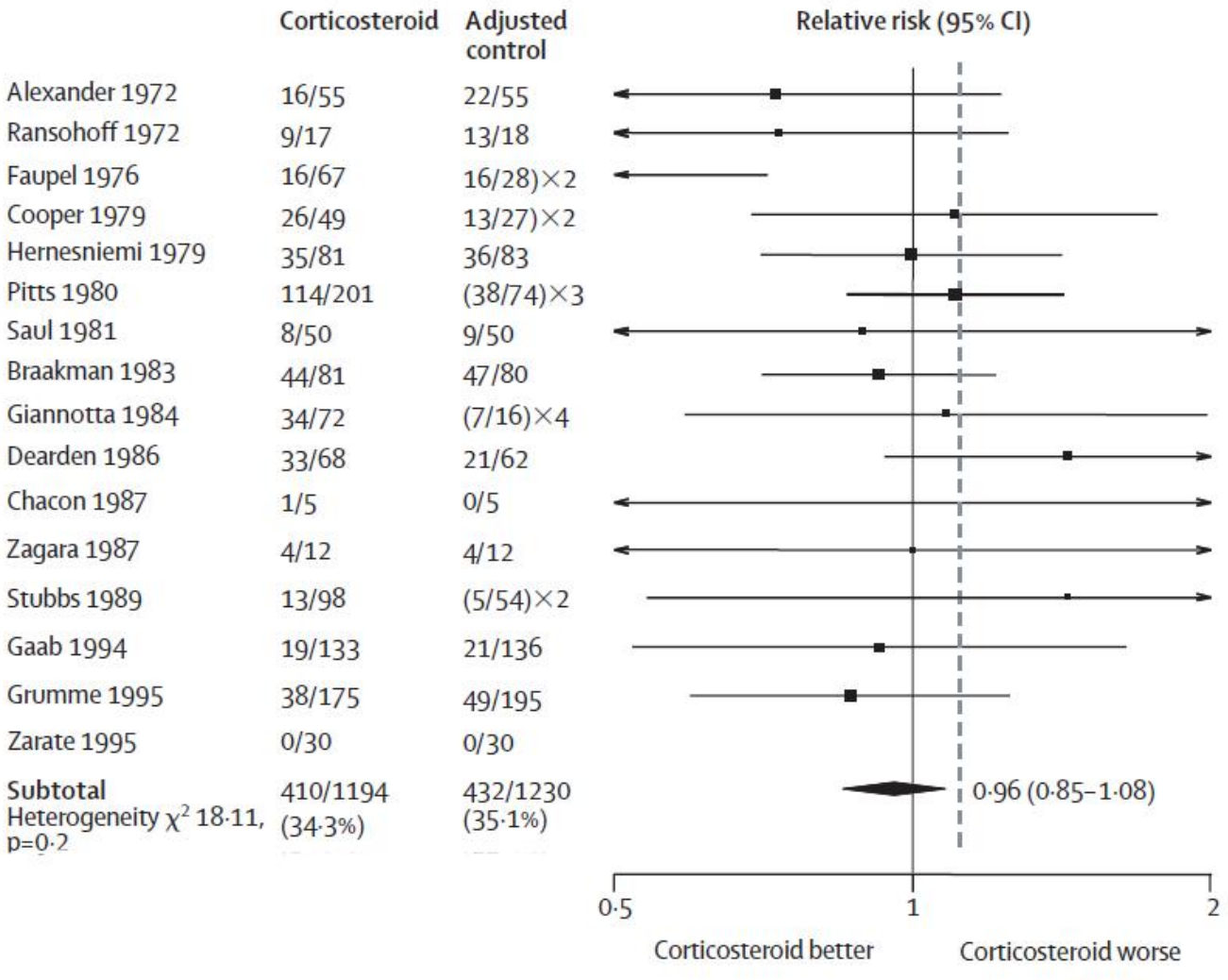
Is the study necessary? A systematic review

- of animal experiments - are pre-clinical data +ve?
- of previous clinical trials – did they answer the question?
  - YES: new trial not ethical
  - NO: trial needed

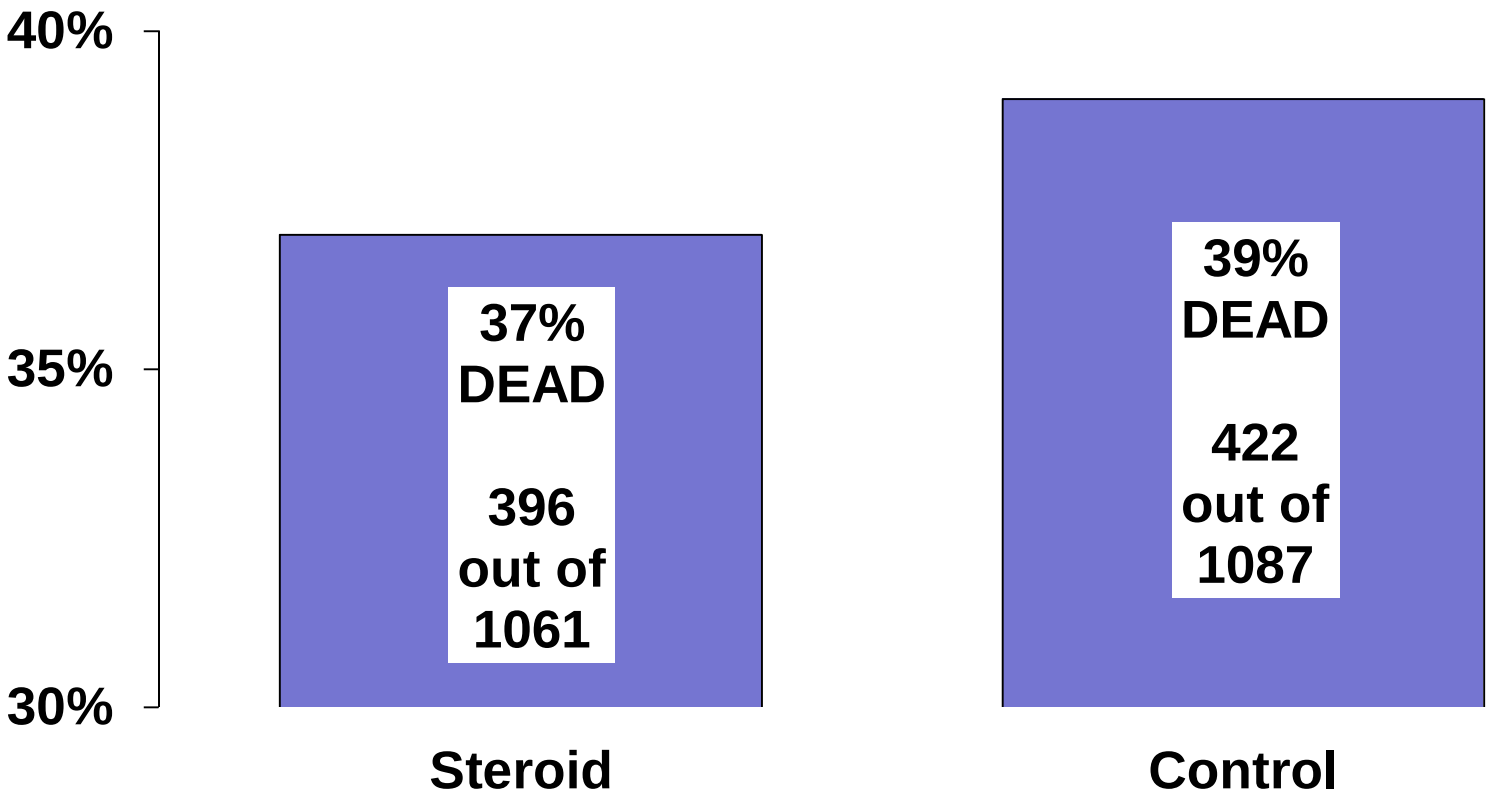
It can help the design of a new trial:

- Identify the methodological problems in prior trials to avoid in new trial
- Estimate treatment effect -> ensure sample size calculation realistic

Systematic review of randomised trials of corticosteroids for head injury



Mortality in the completed randomised trials of steroids in head injury



2% absolute difference in deaths =
20 per 1000 treated avoid death

Hypothesis and sample size

- Steroids -> reduce risk of death after traumatic brain injury
- Null hypothesis = there will be no difference between the two groups
- You specify the parameters of your ‘test of significance’,
  - the Type I error (?ð a
  - the expected difference between groups; and
  - the risk of falsely concluding that there is no such effect (Type II error, ?”, 1-power)

Calculate a sample size

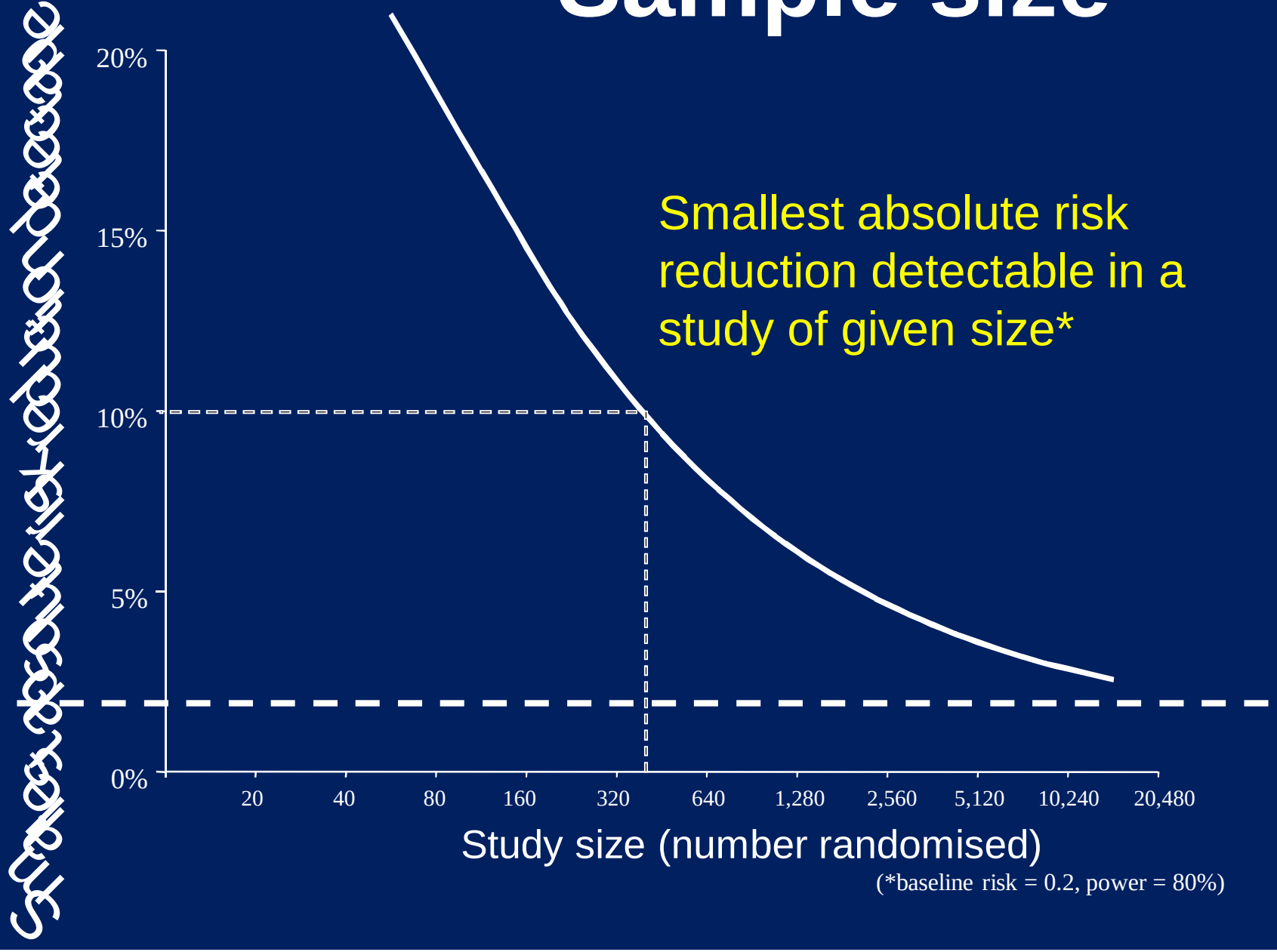
- Trial of drug vs control
- Baseline risk with standard care:
- Risk of death without treatment = 20%
- Select power = 80%
- How big a treatment effect do aim to detect?:

  20% -> 10%? Improbably large effect

  20% -> 15%? Large effect

  20% -> 18%? Moderate effect – worthwhile (and similar to systematic review estimate)= 2% absolute difference

Sample size



(*baseline risk = 0.2, power = 80%)

What does this mean?

- Effects on major outcomes are often only moderate
- Small studies may
  - Fail to detect moderate but worthwhile effects
  - Falsely suggest benefit where none exists
- Large numbers are needed if trials are to provide reliable estimates

CRASH: Corticosteroid Randomisation After Significant Head Injury 1998 to 2005

A large efficient placebo controlled trial, among 20,000 adults with head injury and impaired consciousness, of the effects of a 48-hour infusion of corticosteroids on death and neurological disability

www.crash.lshtm.ac.uk/

Lancet 2004; 364: 1321–28, Lancet 2005; 365: 1957–59

Trial protocol

Methods for randomisation, allocation concealment and follow-up

Treatment allocation has two aspects:

- **Allocation sequence**: determines what treatment the next patient entering the trial will receive
- **Allocation concealment**: ensures the clinician who recruits the patient cannot find out what the next treatment will be and so avoids selection bias. Not the same as blinding!!!

Methods for randomisation: pro & con

‘Central’

- Telephone or web-based access call to central trial office; enter baseline data in computer, system informs doctor of treatment allocation
- Concealment 100%,
- Baseline data complete100%

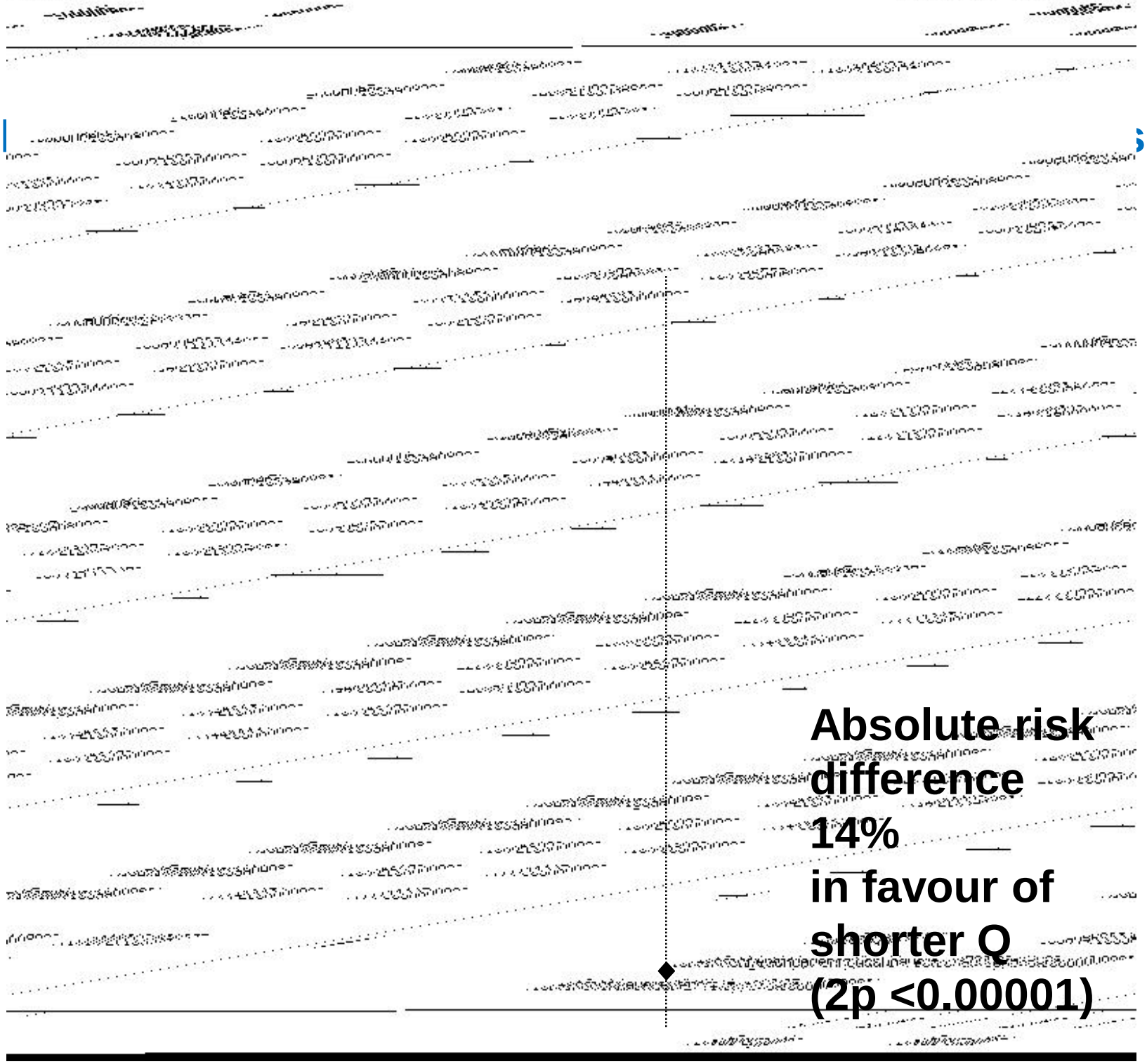
‘Local’

- Open sealed envelope or take next numbered box of treatment
- Risk that concealment is < 100%
- Risk patients recruited but not registered and of incomplete baseline data:

Follow up: response rates to postal questionnaires higher with:

- incentives, especially if unconditional
- shorter 'user-friendly' questionnaires
- providing a second copy of the questionnaire
- university sponsorship
- follow-up contact
- personalised questionnaires
- coloured as opposed to blue or black ink
- use of stamped as opposed to franked envelopes
- first class outward mailing

Edwards PJ, Methods to increase response rates to postal questionnaires. Cochrane Database of Systematic Reviews.


Absolute risk difference
14%
in favour of shorter Q
(2p <0.00001)

Simple clinical follow-up data for CRASH = One page A4 postal questionnaire at six months

Response rate in the 10,000 randomised patients was 99.6% (vs 80% in previous head injury trials)

INTERNATIONAL STUDY OF RECOVERY AFTER HEAD INJURY

...uestions are about changes in your lifestyle since your injury. They can be answered by you, a friend, or by you both together. If you have any questions about this form, please contact Nin Ritchie on 020 7299 4142. Please answer each question below by ticking one box ☑ you.

...swers will help us improve the care of people following a head injury.

Please say who filled out this form:

...elative, friend or carer alone | Patient and relative, friend or carer together | Patient alone

...t of the time?

1. At present, where do you live mos...

In residential care | In own home | In hospital

...elp in the home?

2. As a result of your injury, do you now need h...

...need help in the home | I need help in the home, but not because of the injury | No | Yes: I need some help in the home, but not every day | Yes: ... every day

...

3. As a result of your injury, do you now need help to shop...

...ven | I need help to shop, but not because of the injury | No | Yes: I need some help, but can go to the local shops on my own | Yes: I need help to shop ... locally, or cannot shop at all

4. As a result of your injury, do you now need help to travel?

...d help to travel, but not ...e of the injury | No | Yes: I need some help, but can travel locally on my own (e.g. by arranging a taxi) | Yes: I need help to travel even locally, or I cannot travel at all | I ne... because

5. As a result of your injury, has there been a change in your ability to work? (or to study if you were a student; or to look after your family)

No | Yes: I still work, but at a reduced level (e.g. a change from full-time to part-time, or a change in level of responsibility) | Yes: I am unable to work at present | My ability to work is restricted, but not because of the injury, or I have retired

...esult of your injury, has there been a change in your ability ...art in social and leisure activities outside home?

6. As a r... to take p...

...Yes: I take part a bit less, but at least ...half as often | Yes: I take part much less, or do not take part at all | My ability to take part is restricted for some other reason, not because of the injury | No

...iury, are there now problems in ...nds or relatives?

7. As a result of your inj... how you get on with frie...

...sonal ...e a week) | Yes: There are frequent or constant problems | There are problems for some other reason, not because of the injury | No | Yes: There are occa... problems (less than onc...

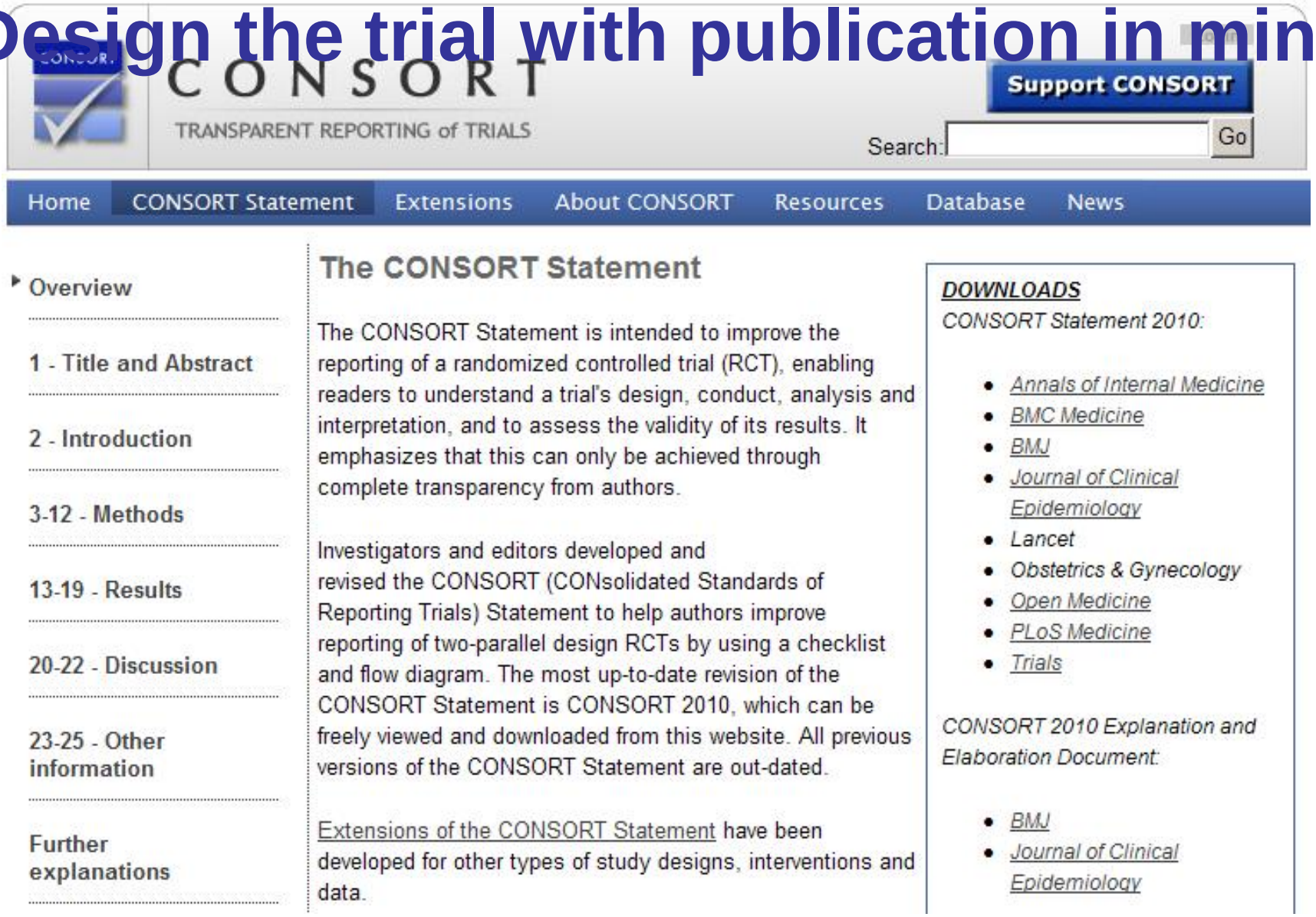
...o. Please return this form in the envelope provided to: ...t Injury, LSHTM, University of London, 49-51 Bedford Square, London WC1B 3DP. Thank you for your help. Dr Ian Roberts, International Study of Recovery after Head...

Keep it simple

- Simplify protocol and procedures
- Reduce data collection/CRF size
  - Ø Better response rate
  - Ø Less data to check
  - Ø Less missing data
- Reduce the work involved for investigators

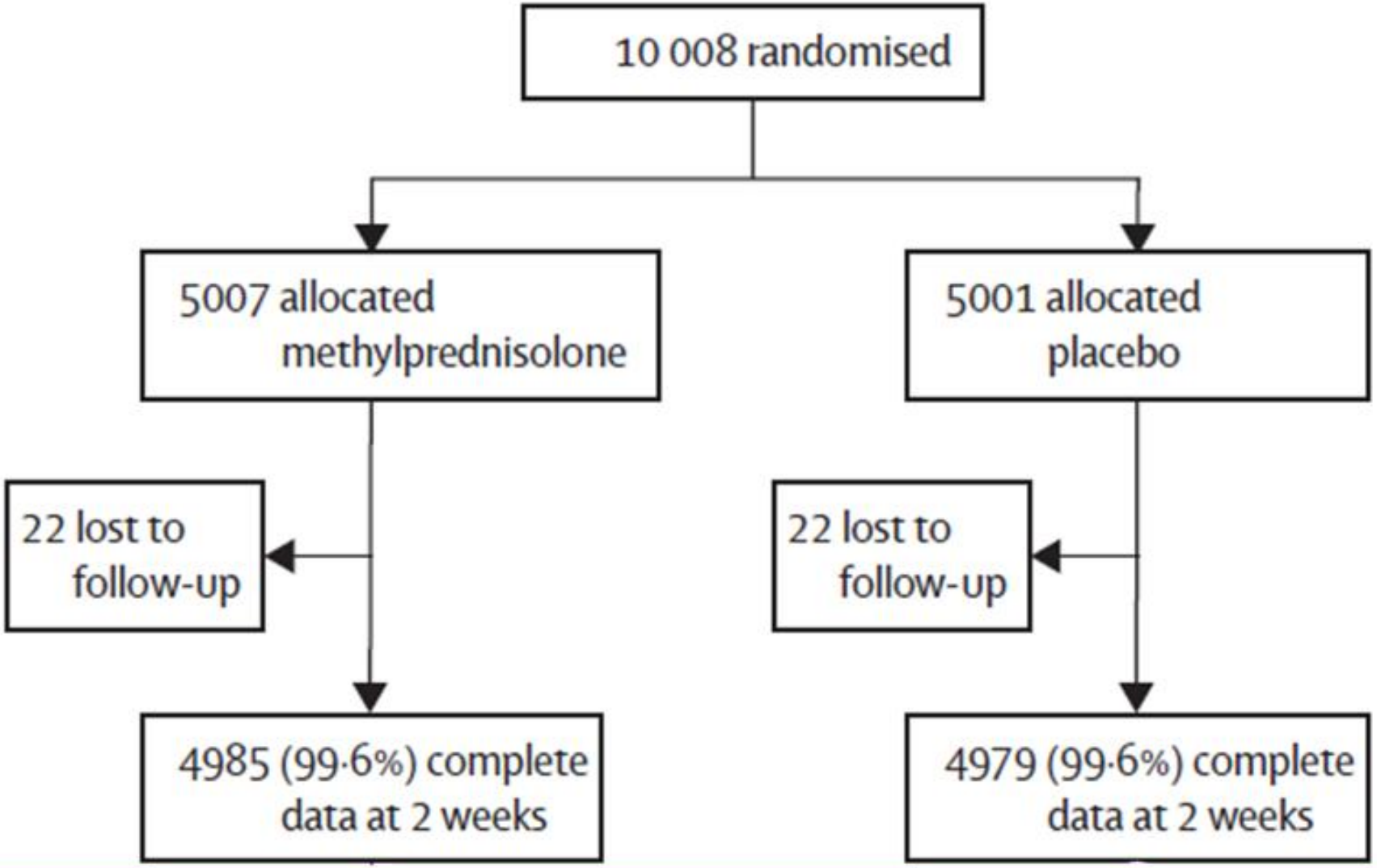
Reporting the trial results

Design the trial with publication in mind



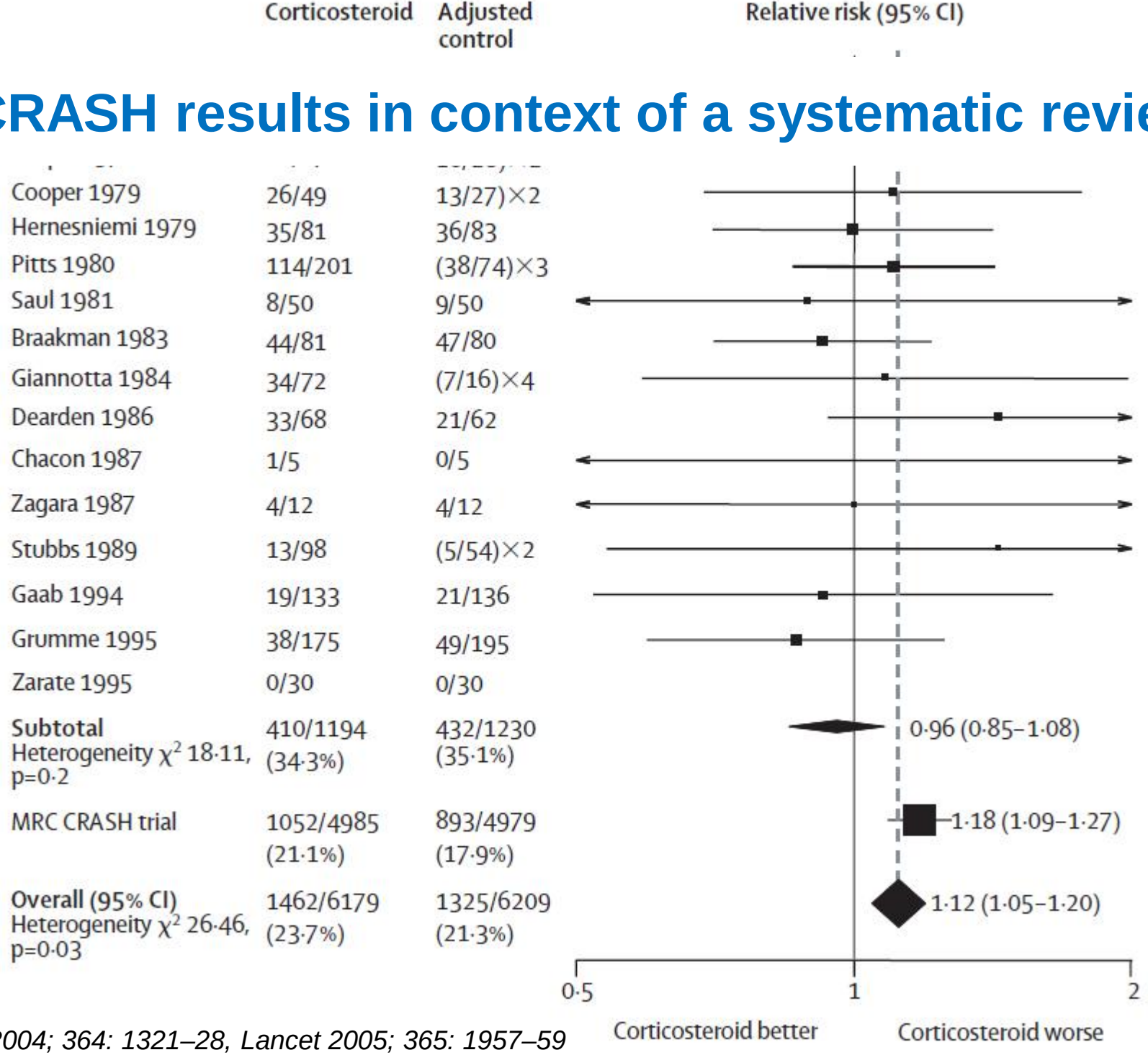
www.consort-statement.org/

CONSORT flow diagram



Lancet 2004; 364: 1321–28, Lancet 2005; 365: 1957–59

CRASH results in context of a systematic review

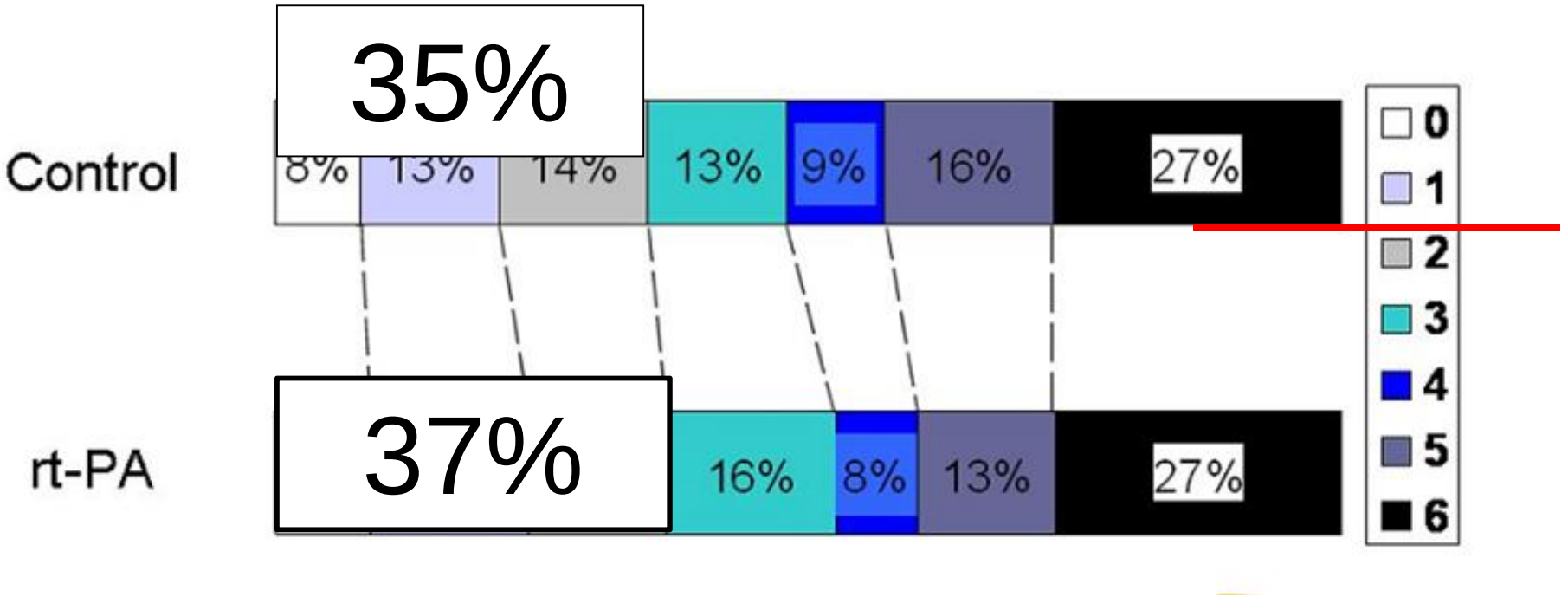


Lancet 2004; 364: 1321–28, Lancet 2005; 365: 1957–59

Analytic method for ordinal scales

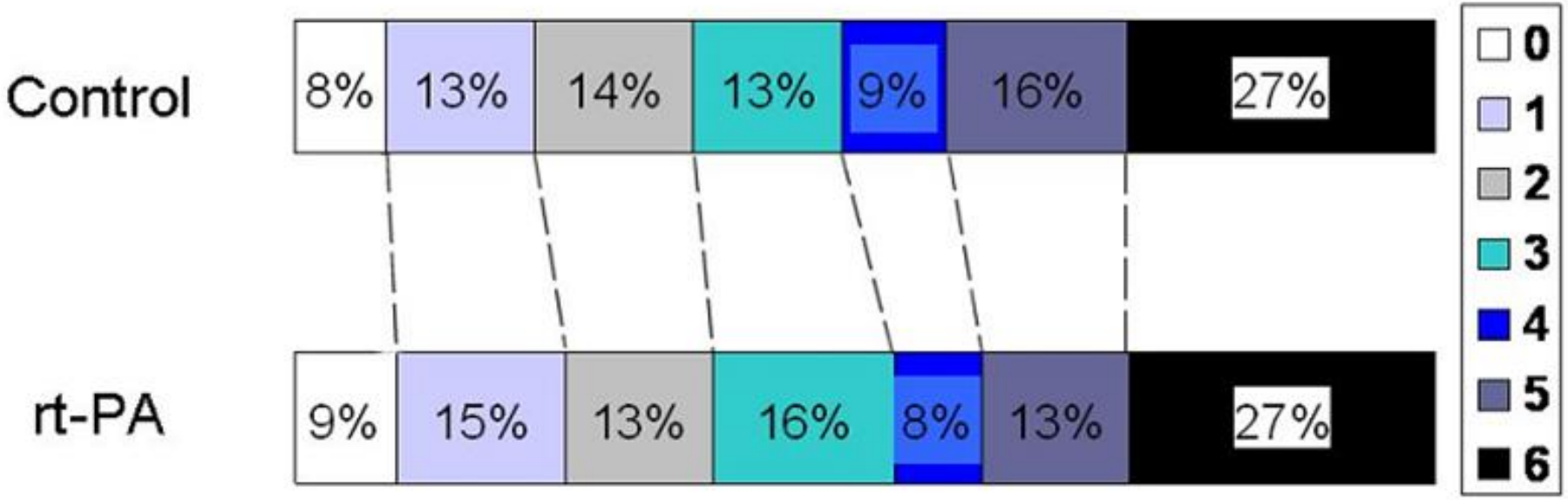
- Oxford Handicap Scale ranges from
  - 0 = no symptoms, to
  - 5 = severe disability
- Dichotomous analysis = compare ‘% dead or dependent’ (OHS 3-6) treatment vs. control; easy to understand, ***statistically inefficient***
- Ordinal analysis uses all the data from the whole scale; ***statistically more efficient***

IST-3 trial of thrombolysis vs control in 3035 patients with acute ischaemic stroke: OHS at 6 months



37% vs 35% alive and independent : NS

Ordinal analysis 6 month OHS



Favourable shift; adjusted common odds ratio 1·27 (95% CI 1·10- 1·47), p=0·001
or, the odds of surviving with less disability were 27% greater for patients treated with rt-PA

Managing and marketing your clinical trial

Turn the protocol into a trial that works: you need the help of a team

A trial management group (TMG)

- Lead clinician = Chief Investigator
- Trial manager
- Statistician
- Experienced trialist / clinical trials unit support
- Expert(s) for advice on specific areas

Trial oversight committees

Trial Steering Committee (TSC): overall supervision

- Recruitment
- Data quality
- Decision to halt recruitment
- Publication/ presentation
- No access to unblinded data

Data Monitoring Committee (DMC)[1,2]

- Independent, expert scientific review of statistical methods and proposed analyses
- Ensure adequate quality in the conduct of the trial and collection of data
- Review of unblinded data (advise TSC only when 'proof beyond reasonable doubt')
- Protection of participants and trial

1. MRC Guidelines for Good Clinical Practice in Clinical Trials.
2. Data monitoring and interim analysis of trials. Health Technol Assess 2005;9(7).

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Results
Discussion
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Competing interests
Authors' contributions
Acknowledgements
References

Research

Highly accessed | Open access

Marketing and clinical trials: a case study

David Francis[1]*, **Ian Roberts**[2], **Diana R Elbourne**[3], **Haleema Shakur**[2], **Rosemary C Knight**[3], **Jo Garcia**[3], **Claire Snowdon**[4,3], **Vikki A Entwistle**[5], **Alison M McDonald**[5], **Adrian M Grant**[5] and **Marion K Campbell**[5]

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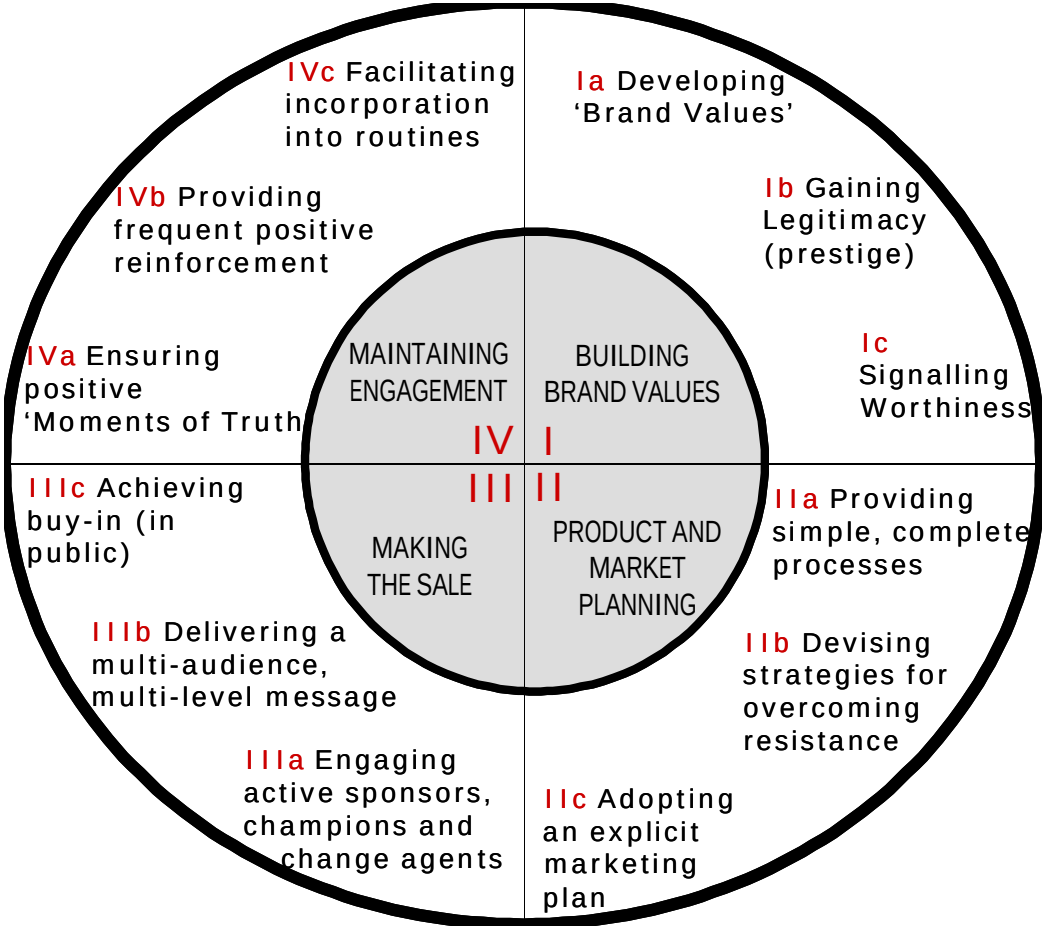
Trials 2007, **8**:37 doi:10.1186/1745-6215-8-37

Marketing clinical trials



Read this article!!! *http://www.trialsjournal.com/content/8/1/37*

Key references 1

(1) Francis D, Roberts I, Elbourne D, Shakur H, Knight R, Garcia J et al. Marketing and clinical trials: a case study. Trials 2007;8(1):37.

(2) Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. Lancet 2001 February 3;357(9253):373-80.

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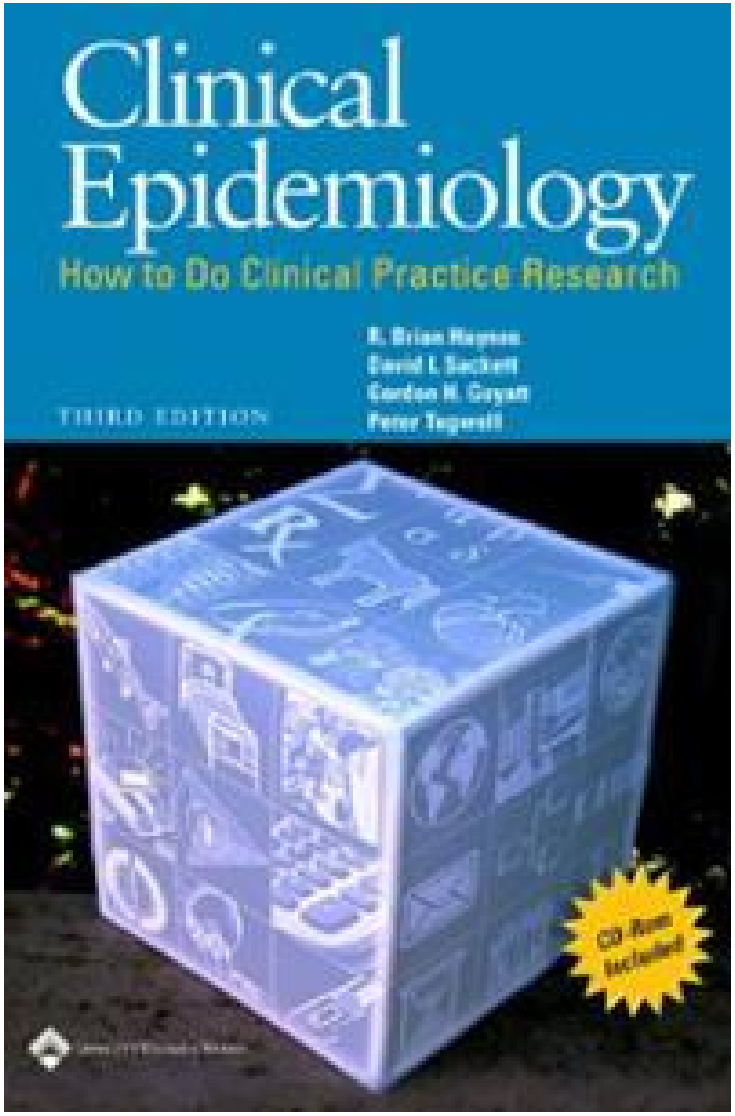


Summary

- Define the question clearly
- Systematically review previous trials
- Choose a clinically relevant outcome
- Ensure the sample size is large enough
- Ensure secure randomisation and allocation concealment
- Simplify data collection and follow-up systems
- Analyse and report the trial according to CONSORT

Further study: online resources

- Cochrane stroke group website

  http://stroke.cochrane.org/
- Searchable database of stroke trials

  http://www.askdoris.org/cd_t1.asp?opt=2709
- On-line training in systematic reviews
- http://www.cochrane.org/training/authors

Key stroke trials: investigator led & of interventions with limited commercial potential

Stroke prevention

- BP lowering (MRC)
- Aspirin (Canadian, UKTIA),
- Anticoagulants (SPIRIT/ESPRIT, WARSS, EAFT, SPAF, BAFTA)
- Surgery /stents for stroke prevention (ECST, NASCET, VA,ACST, CAVATAS, ICSS, ECST-2)
- Cholesterol reduction (HPS, SEARCH, THRIVE)

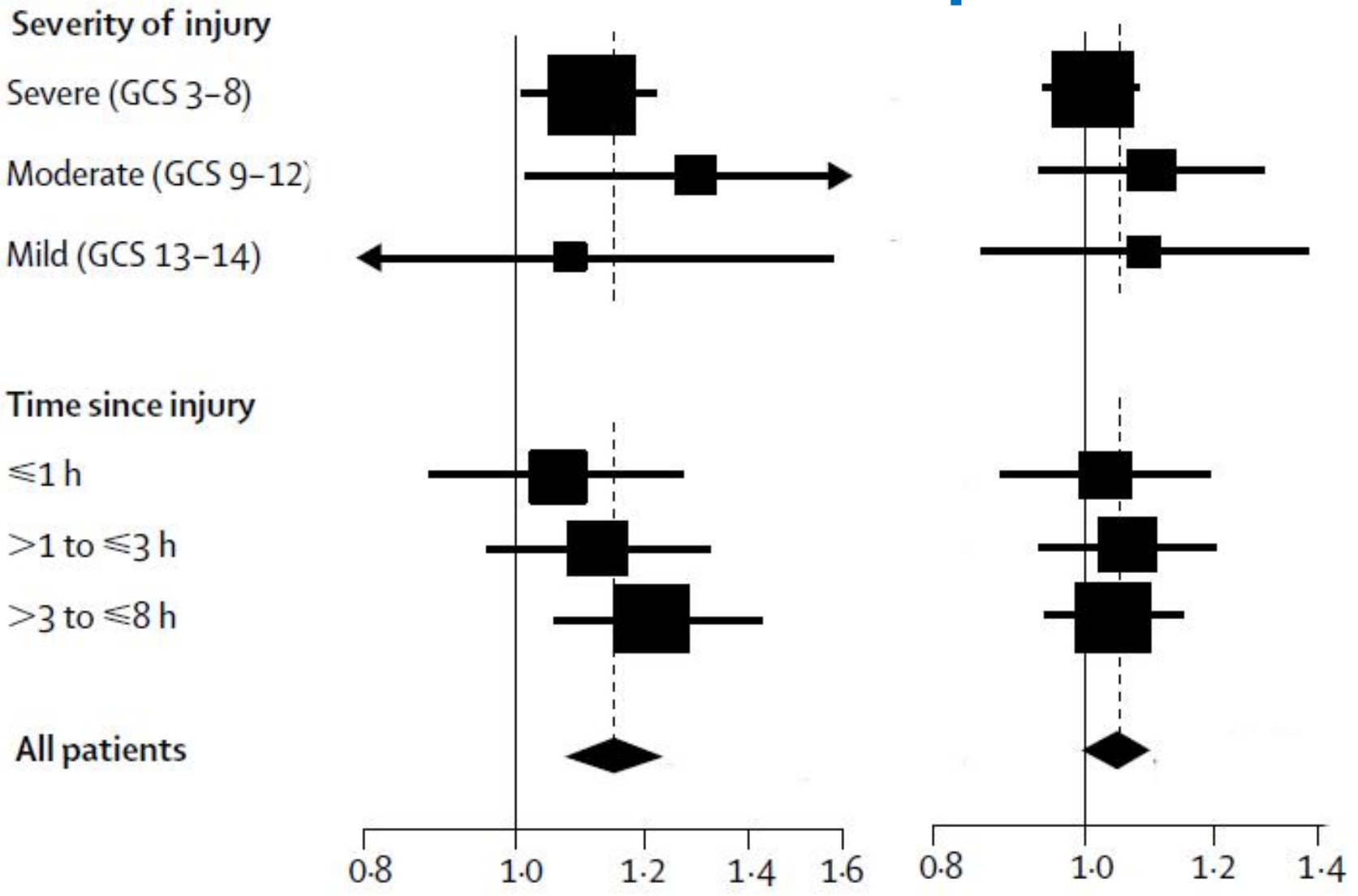
Stroke treatment

- Stroke Units (all)
- Aspirin for acute stroke (IST, CAST)
- Coiling for ruptured aneurysm (ISAT)
- Thrombolysis for acute stroke (NINDS, IST3)

CRASH: 6 months

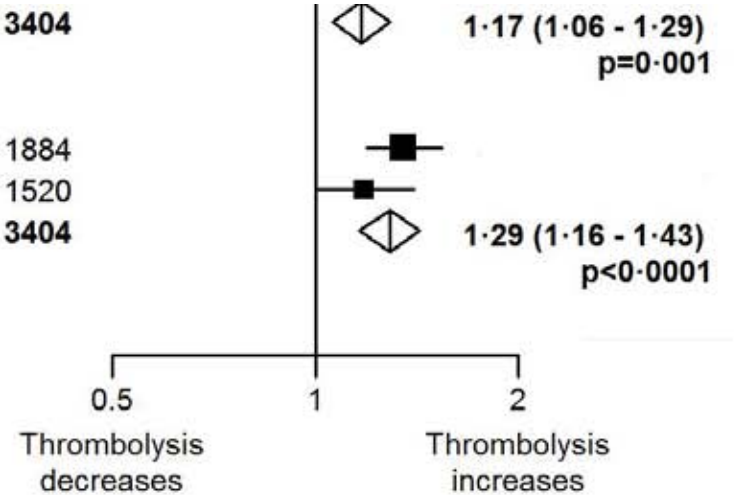
dead

dead or dependent



All rt-PA trials: Outcome at end of follow-up

Endpoint	No. trials	Events (No. patients) Thrombolysis	Control	Odds Ratio (95% CI)
All deaths by the end of follow-up				
All trials before IST3	11	271 / 2033	233 / 1944	
IST3	1	408 / 1515	407 / 1520	
All trials	**12**	**679 / 3548**	**640 / 3464**	**1·06 (0·94 - 1·20) p=0·33**
Alive and independent (mRS 0-2) by the end of follow-up *				
All trials before IST3	9	1057 / 1968	900 / 1884	
IST3	1	554 / 1515	534 / 1520	
All trials	**10**	**1611 / 3483**	**1434 / 3404**	**1·17 (1·06 - 1·29) p=0·001**
Favourable outcome (mRS 0,1) by the end of follow-up *				
All trials before IST3	9	848 / 1968	678 / 1884	
IST3	1	363 / 1515	320 / 1520	
All trials	**10**	**1211 / 3483**	**998 / 3404**	**1·29 (1·16 - 1·43) p<0·0001**



Wardlaw Lancet 2012