La revisioni sistematiche come strumento di orientamento per la ricerca

How systematic reviews can inform the direction and content of new research

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University of Glasgow
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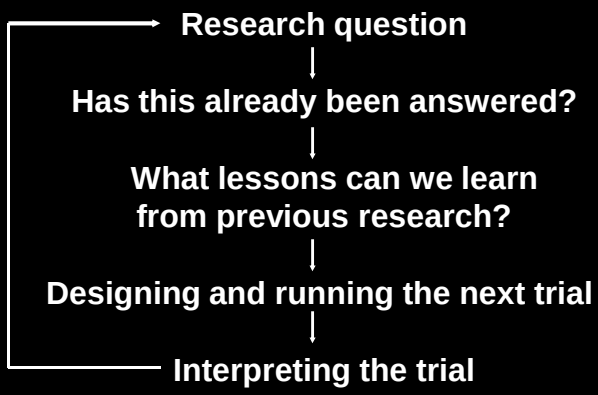
How systematic reviews can inform the direction and content of new research

- Background
- Cycle of research
  - Use of systematic reviews to identify and prioritise research topics
  - Systematic reviews and research design
- Are we using systematic reviews to plan research?
- Conclusions

How systematic reviews can inform the direction and content of new research



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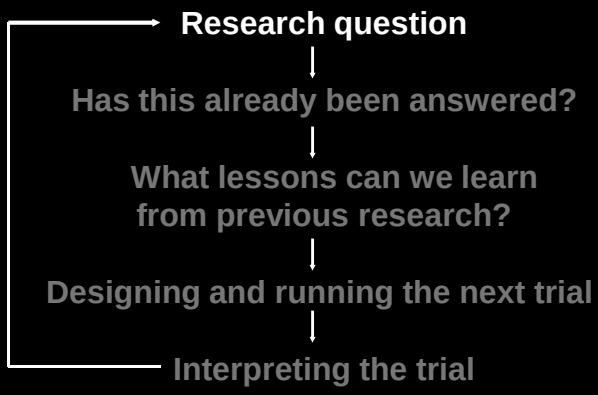

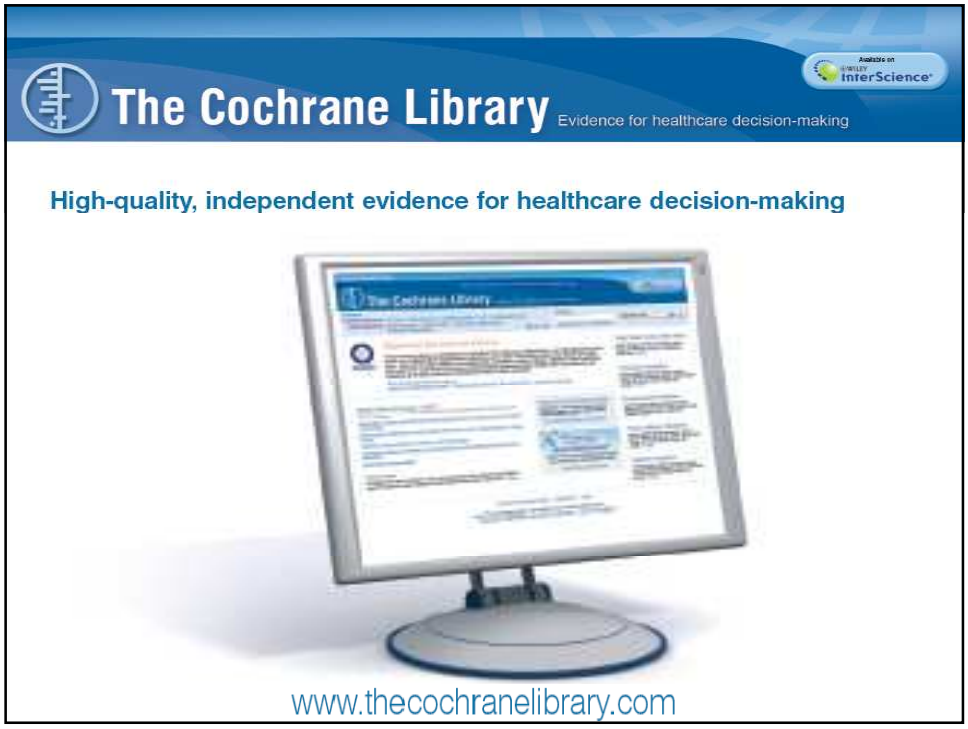

Identifying and prioritising new research questions

- In the UK research agencies such as National Institute of Healthcare Research and Health Technology Assessment use the “implications for research” section of Cochrane reviews as part of planning future research priorities

Atrial fibrillation

Treatments for prevention of embolism

Drug treatment	Benefits	Hazards
Oral anticoagulation (warfarin)	60-70% risk reduction	Bleeding (1-7% pa)
Aspirin (75-300mg)	25% risk reduction	Bleeding (0-3% pa)
Warfarin plus antiplatelet agent	Same as warfarin	More bleeding than warfarin
Oral thrombin inhibitor	Same as warfarin	Liver hazards

Atrial Fibrillation *(Preventing stroke / Primary prevention in high risk individuals)*

Further Research Required?

Trials

Further exploratory research / trials should:

Investigate

- Benefit versus risk of oral anticoagulant therapy in atrial fibrillation patients (i.e. >75 years), particularly when compared with antiplatelet therapies, and administered in a primary care setting.
- The extent to which sustained reduction in blood pressure reduces the risk of stroke in AF patients is unknown and may influence optimal antithrombotic prophylaxis.
- Whether aggressive blood pressure management could obviate the need for anticoagulation in some atrial fibrillation patients.
- The effect of vitamin K antagonists (e.g. warfarin) compared with novel oral anticoagulants that work through other mechanisms (e.g. ximelagatran and others) in patients with atrial fibrillation.

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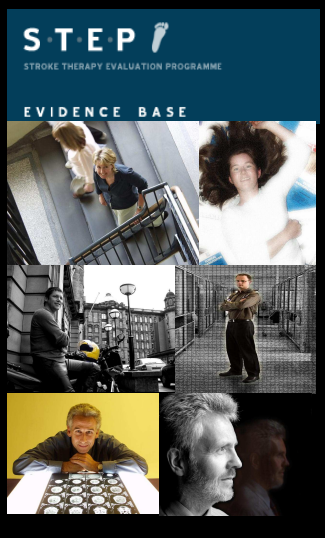
Birmingham Atrial Fibrillation Trial in the Aged (BAFTA)

- People aged 75 years or older with AF who were treated with warfarin had half the number of strokes as did those who were treated with aspirin (Hazard ratio 0.48; 0.28-0.80)

- The safety of warfarin was similar to that of aspirin (Hazard ratio 0.96;0.53-1.75)

Mant et al Lancet 2007

Stroke rehabilitation
Evidence for practice



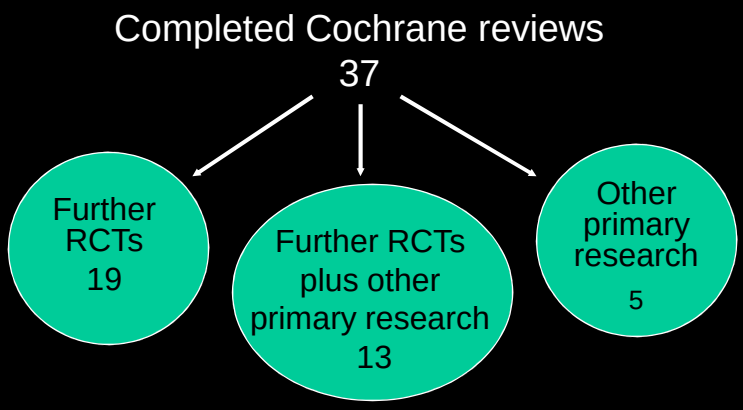
- Project to map out current evidence in stroke rehabilitation
- Consulted a range of people (stakeholders) to identify important research “topics”
- Explored the amount of Cochrane Library evidence available to answer these topics

Recommendations for further secondary research (systematic reviews)

Systematic review cover of topics	Number of topics	Examples
Wholly covered by systematic reviews	7	Attention deficits, memory, neglect /inattention, depression, aphasia, dysarthria, apraxia of speech
Partly covered by systematic reviews Large numbers(>100) RCTs	4	Balance, gait, high tone / spasticity and upper limb problems
Partly covered by systematic reviews Small numbers of RCTs	28	
No completed systematic reviews	36	

Stroke rehabilitation

Cochrane review recommendations for further research



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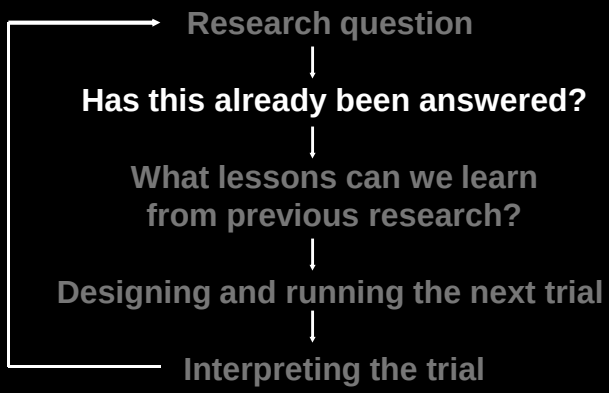


Treatments for subarachnoid haemorrhage

Example of misleading non-systematic review by an expert

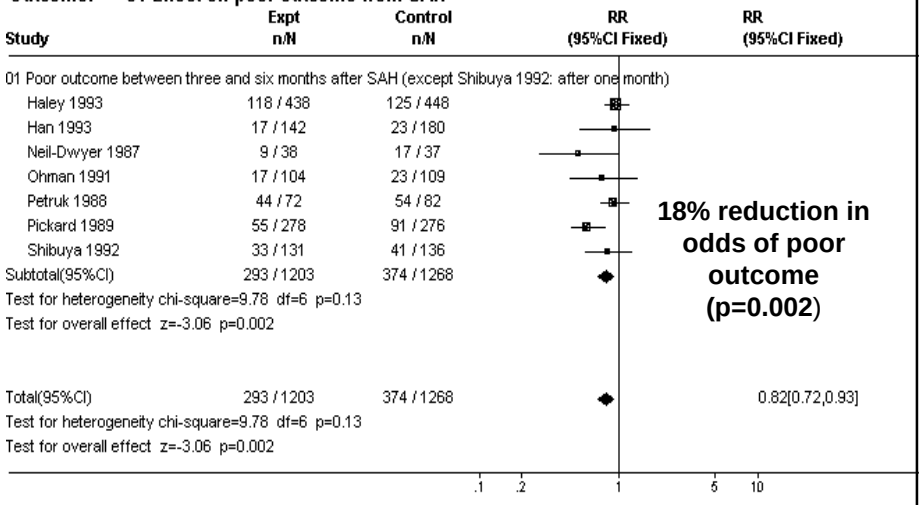
- "The effect of calcium antagonists after SAH are unclear"
- "Antifibrinolytics may be beneficial … to reduce rebleeding"

(Kopitnik et al, JNNP 1993)

If you do a SYSTEMATIC review of the trials, you reach very different conclusions!

Calcium antagonists ARE effective after SAH

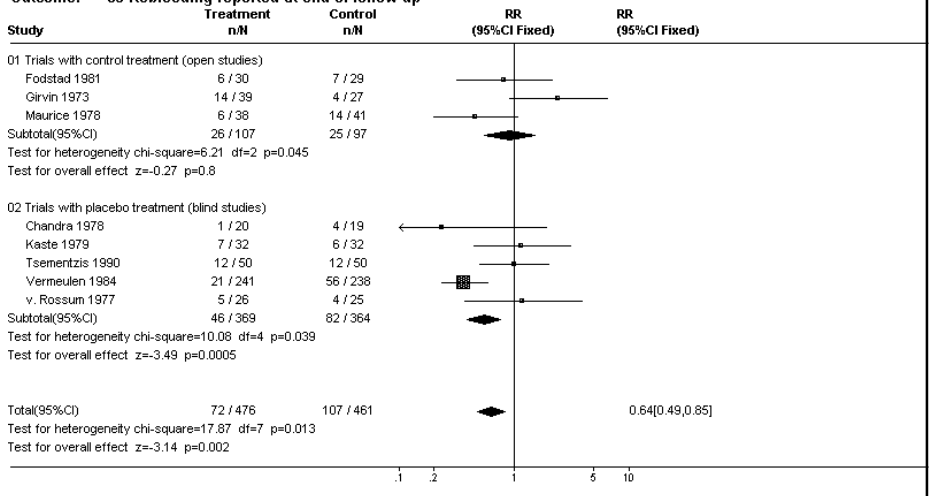
Comparison: 01 Calcium antagonists versus placebo control: all trials
Outcome: 01 Effect on poor outcome from SAH



18% reduction in odds of poor outcome (p=0.002)

Antifibrinolytics DO reduce rebleeds after SAH

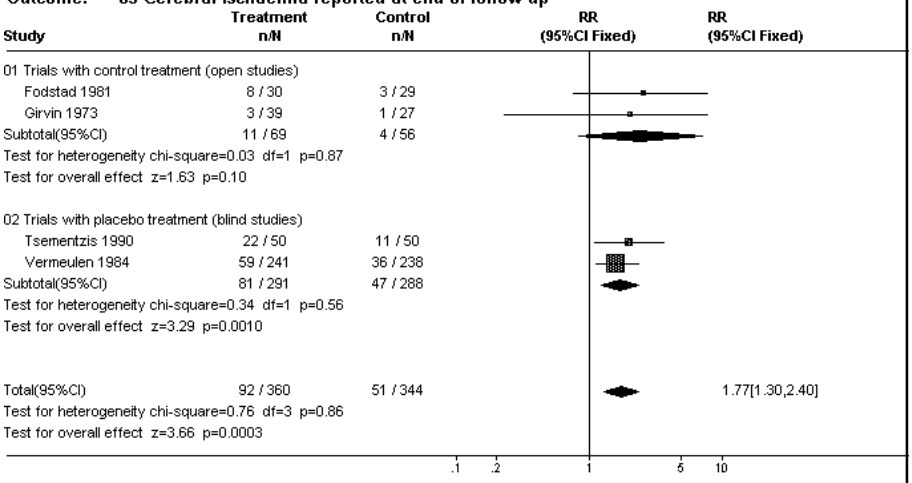
Comparison: 01 Antifibrinolytic treatment versus control treatment with or without placebo
Outcome: 03 Rebleeding reported at end of follow up



But….

Antifibrinolytics INCREASE cerebral ischaemia, so no net benefit

Comparison: 01 Antifibrinolytic treatment versus control treatment with or without placebo
Outcome: 05 Cerebral ischaemia reported at end of follow up



Has the research question already been answered?

- In the UK, research agencies such as Medical Research Council and NIHR now require systematic reviews of available evidence in the justification section of a major grant application
- Increasing use of systematic reviews of pre-clinical data (such as animal experiments)

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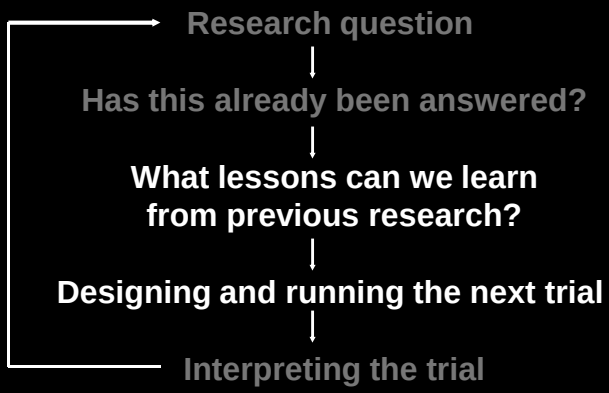


Role of systematic reviews at different stages of a trial

- Planning
  - Initial thoughts on the trial question
  - Design: selection of primary outcome
  - Sample size calculations
  - Methods of improving follow-up response
- During the trial
- After the trial has finished

Clots in Legs or sTockings after Stroke (CLOTS)

Trial 1 - Does early and routine application of compression stockings reduce the risk of above knee deep venous thrombosis in the weeks after an acute stroke?

Thigh length stockings**

**

Measuring outcome: Systematic review of methods to increase response to follow-up questionnaires

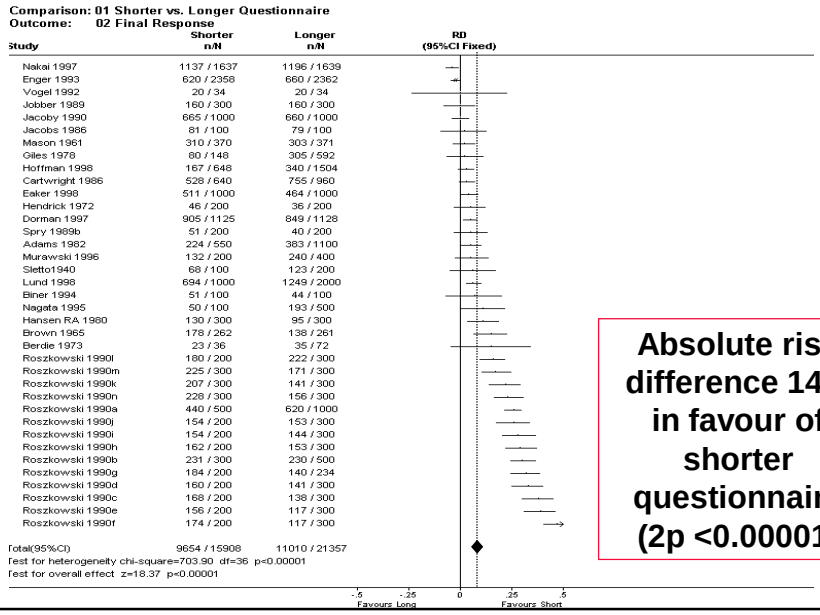
Systematic review of 372 randomised trials including > 250,000 people, evaluating 98 different ways to increase response to postal questionnaires

Some interventions were tested on a very large scale (a total of 93,000 subjects!)

Identified many determinants of questionnaire response rate

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

Short or long questionnaire?: effect on % response



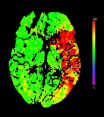
Absolute risk difference 14% in favour of shorter questionnaire (2p <0.00001)

During the trial. Update the systematic review of trials of your intervention to:

- Ensure trial still ethical
- Inform investigators
- Help advertise trial to new centres
- Deal with critics: trial still justified
- Inform Data Monitoring Committee, who will need to review the accumulating data from your trial in the context of an updated SR of all completed trials

Example of IST3

Thrombolysis for ischaemic stroke

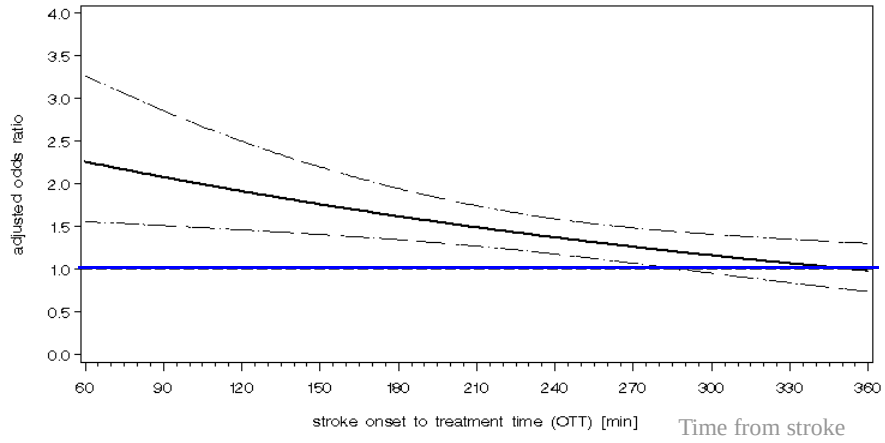


- Promising but hazardous treatment for a minority of stroke patients
- Restricted licence from EU for use in selected patients up to 3 hours after stroke
- Third International Stroke Trial (IST3) exploring other patient groups up to 6 hours
- Recent trials question of ethical position of IST3

rtPA in acute stroke

Global good outcome at day 90

Benefit



Time from stroke

rtPA in acute stroke

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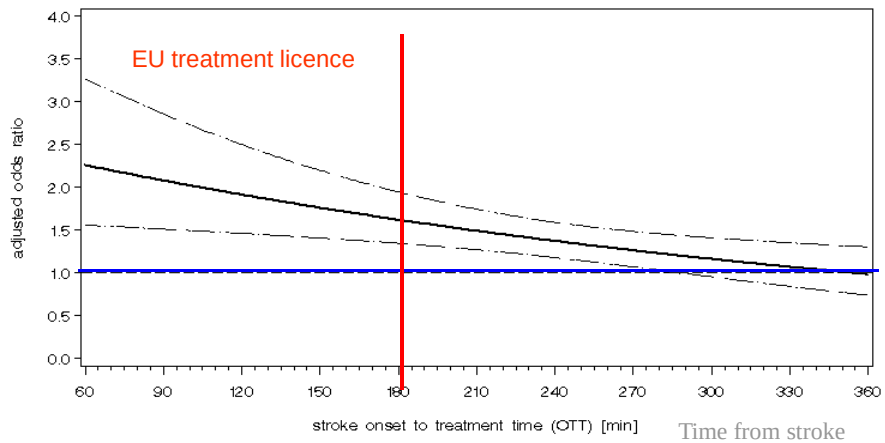

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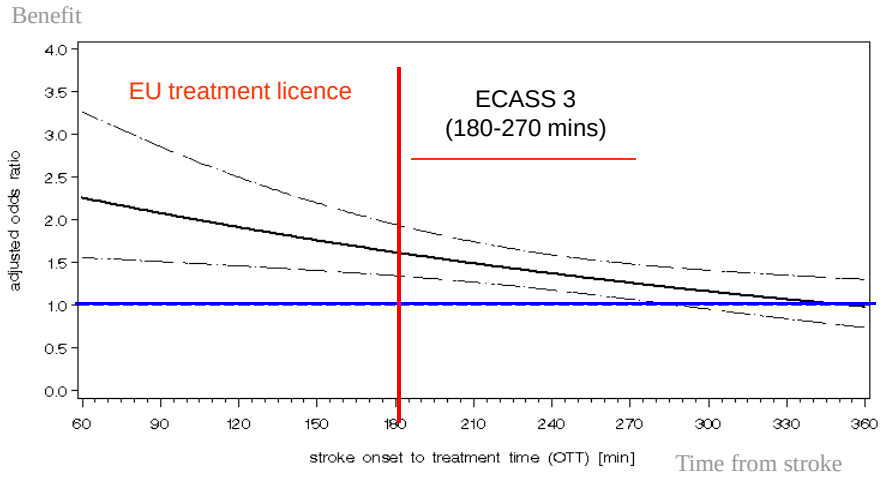

rt-PA trials in acute stroke
2003 versus 2008

	Symptomatic ICH (incl fatal)	Death	Death or Dependency
2003 n=2955	3.1 (2.3-4.2)	1.2* (0.9-1.5)	0.8* (0.7-0.9)

* significant heterogeneity

rt-PA trials in acute stroke 2003 versus 2008

	Symptomatic ICH (incl fatal)	Death	Death or Dependency
2003 n=2955	3.1 (2.3-4.2)	1.2* (0.9-1.5)	0.8* (0.7-0.9)
2008 n=3977	3.1 (2.3-4.0)	1.1 (1.0-1.4)	0.8* (0.7-0.9)

* significant heterogeneity

Systematic review of thrombolysis in stroke: What's new in 2008?

No information on

- Patients >80 years
- Stroke subtype
- Stroke severity
- Antithrombotic drugs pre or post

Justification for IST3

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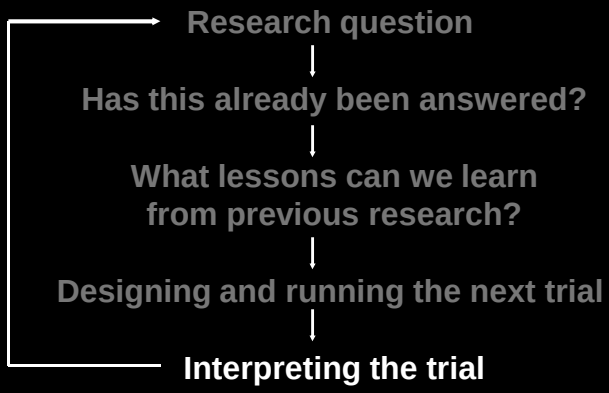

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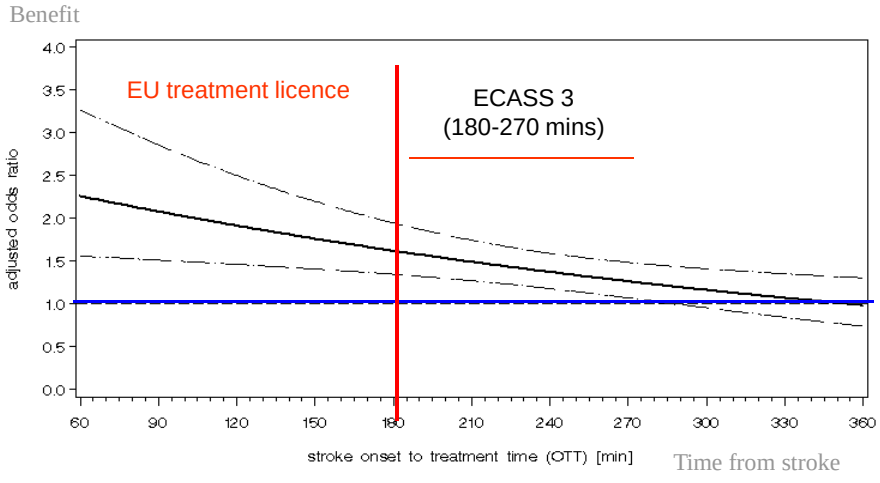

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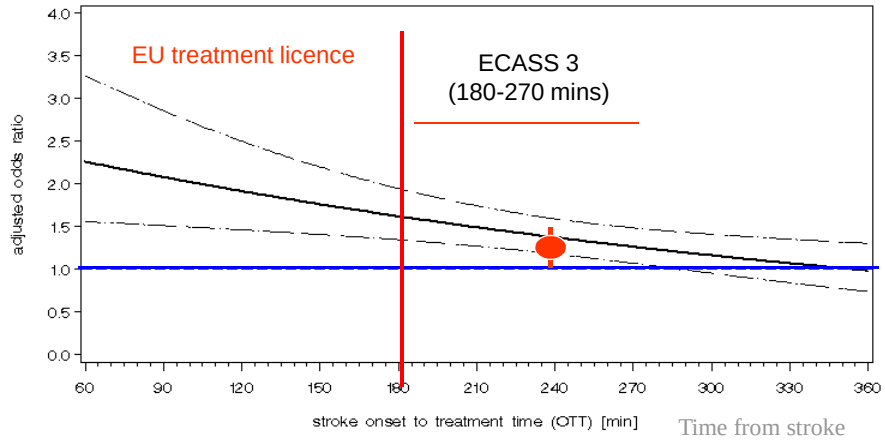
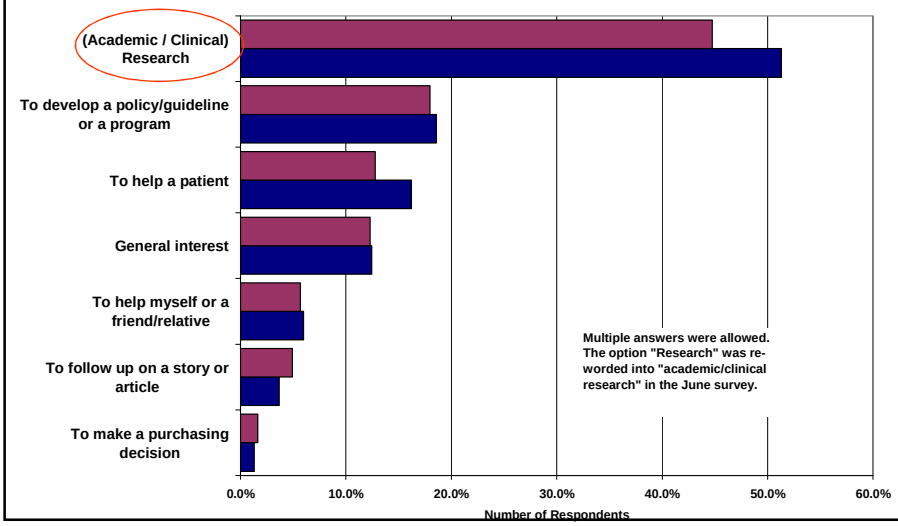


Time from stroke

The Cochrane Library Evidence for healthcare decision-making



Conclusion

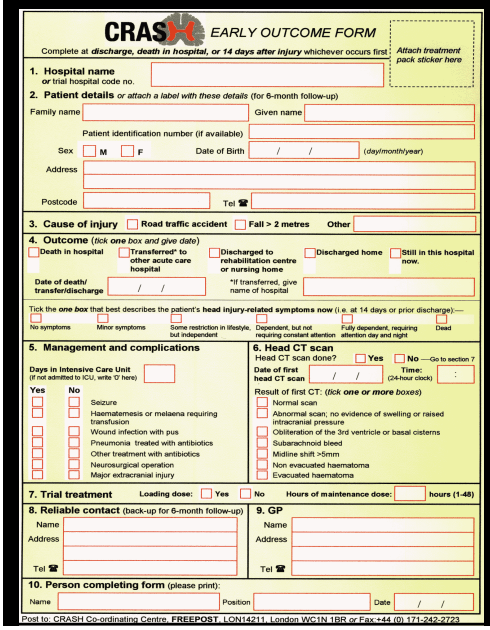
- Systematic reviews are a key component of the whole clinical trial cycle from planning to reporting
- The Cochrane Collaboration supports this process
  - Methodological support
  - Publication/dissemination (Impact factor 4.5)
- The Cochrane Library contains a wealth of methodological information
  - effects of interventions
  - implications for research
  - to aid trial design

The Cochrane Collaboration

Preparing, maintaining, and disseminating systematic reviews of the effects of health care

Thank you for your attention

7 day form, completed by doctor, from hospital notes



CRASH EARLY OUTCOME FORM

Complete at ***discharge, death in hospital, or 14 days after injury*** whichever occurs first

Attach treatment pack sticker here

1. Hospital name or trial hospital code no.

2. Patient details *or attach a label with these details* (for 6-month follow-up)

Family name | Given name

Patient identification number (if available)

Sex ☐ M ☐ F | Date of Birth / / (*day/month/year*)

Address

Postcode | Tel ☎

3. Cause of injury ☐ Road traffic accident ☐ Fall > 2 metres Other

4. Outcome (*tick **one** box and give date*)

☐ Death in hospital ☐ Transferred* to other acute care hospital ☐ Discharged to rehabilitation centre or nursing home ☐ Discharged home ☐ Still in this hospital now.

Date of death/ transfer/discharge / / | *If transferred, give name of hospital

Tick the ***one box*** that best describes the patient's **head injury-related symptoms now** (i.e. at 14 days or prior discharge):—

☐ No symptoms ☐ Minor symptoms ☐ Some restriction in lifestyle, but independent ☐ Dependent, but not requiring constant attention ☐ Fully dependent, requiring attention day and night ☐ Dead

5. Management and complications

Days in Intensive Care Unit (if not admitted to ICU, write '0' here)

Yes	No	
☐	☐	Seizure
☐	☐	Haematemesis or melaena requiring transfusion
☐	☐	Wound infection with pus
☐	☐	Pneumonia treated with antibiotics
☐	☐	Other treatment with antibiotics
☐	☐	Neurosurgical operation
☐	☐	Major extracranial injury

6. Head CT scan

Head CT scan done? ☐ Yes ☐ No —Go to section 7

Date of first head CT scan / / | Time: (24-hour clock) :

Result of first CT: (*tick **one or more** boxes*)

☐ Normal scan
☐ Abnormal scan; no evidence of swelling or raised intracranial pressure
☐ Obliteration of the 3rd ventricle or basal cisterns
☐ Subarachnoid bleed
☐ Midline shift >5mm
☐ Non evacuated haematoma
☐ Evacuated haematoma

7. Trial treatment Loading dose: ☐ Yes ☐ No Hours of maintenance dose: hours (1-48)

8. Reliable contact (back-up for 6-month follow-up)

Name
Address
Tel ☎

9. GP

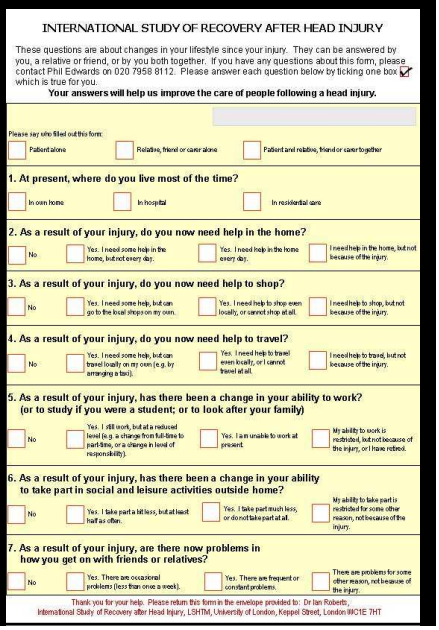
Name
Address
Tel ☎

10. Person completing form (please print):

Name | Position | Date / /

Post to: CRASH Co-ordinating Centre, **FREEPOST**, LON14211, London WC1N 1BR *or* Fax +44 (0) 171-242-2723

6 month questionnaire mailed to patient



INTERNATIONAL STUDY OF RECOVERY AFTER HEAD INJURY

These questions are about changes in your lifestyle since your injury. They can be answered by you, a relative or friend, or by you both together. If you have any questions about this form, please contact Phil Edwards on 020 7958 8112. Please answer each question below by ticking one box ☑ which is true for you.

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

Please say who filled out this form:

☐ Patient alone ☐ Relative, friend or carer alone ☐ Patient and relative, friend or carer together

1. At present, where do you live most of the time?

☐ In own home ☐ In hospital ☐ In residential care

2. As a result of your injury, do you now need help in the home?

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

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

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

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

☐ 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 need help to travel, but not because of the injury.

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.

6. As a result of your injury, has there been a change in your ability to take part in social and leisure activities outside home?

☐ No ☐ 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.

7. As a result of your injury, are there now problems in how you get on with friends or relatives?

☐ No ☐ Yes. There are occasional problems (less than once a week). ☐ Yes. There are frequent or constant problems. ☐ There are problems for some other reason, not because of the injury.

Thank you for your help. Please return this form in the envelope provided to: Dr Ian Roberts, International Study of Recovery after Head Injury, LSHTM, University of London, Keppel Street, London WC1E 7HT

The paper reporting your trial result should comply with the CONSORT guideline

- The result of a randomised controlled clinical trial is important, but cannot be viewed in isolation
- The publication reporting your trial results should include an up-to-date systematic review of all trials (i.e. including yours)
- Readers need to know how your trial results relate to those of other published RCTs, and what the totality of the evidence indicates

http://www.consort-statement.org/

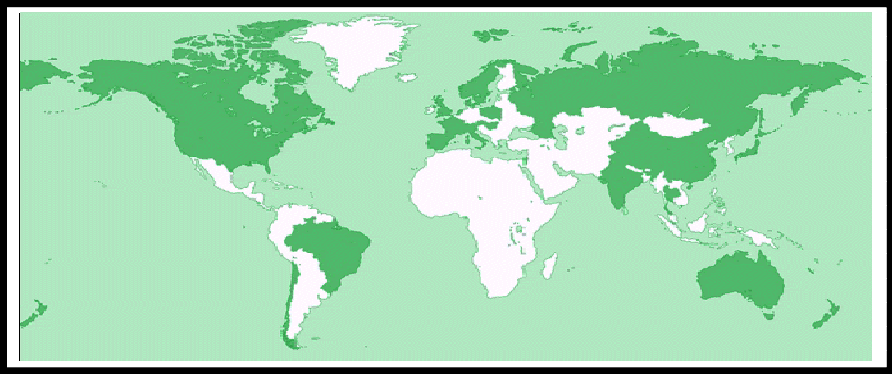
Levels of Evidence

Weakest

- Textbooks & narrative reviews
- One large, good quality randomised trial.
- Systematic review of all relevant randomised trials

Strongest

Cochrane Stroke Review Group: 140 reviewers from 21 countries preparing systematic reviews on the prevention, treatment and rehabilitation of stroke



http://www.dcn.ed.ac.uk/csrg

Conclusions of Cochrane reviews about treatments for acute stroke

Definitely beneficial

– Antiplatelet agents (aspirin)

Unclear who to treat; more trials needed

– Thrombolysis *

– Surgery for intracerebral haematoma

– Defibrinating agents

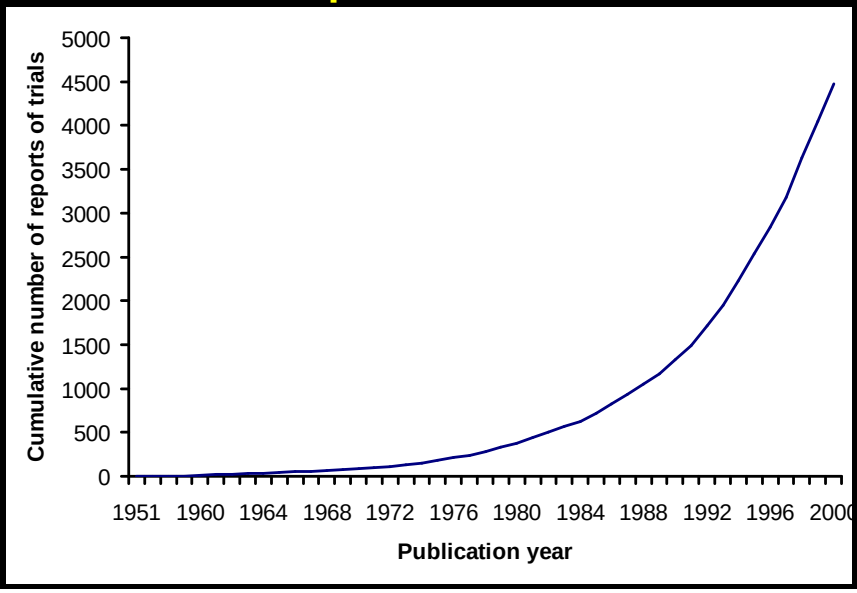
No evidence of net benefit

– Routine anticoagulant use

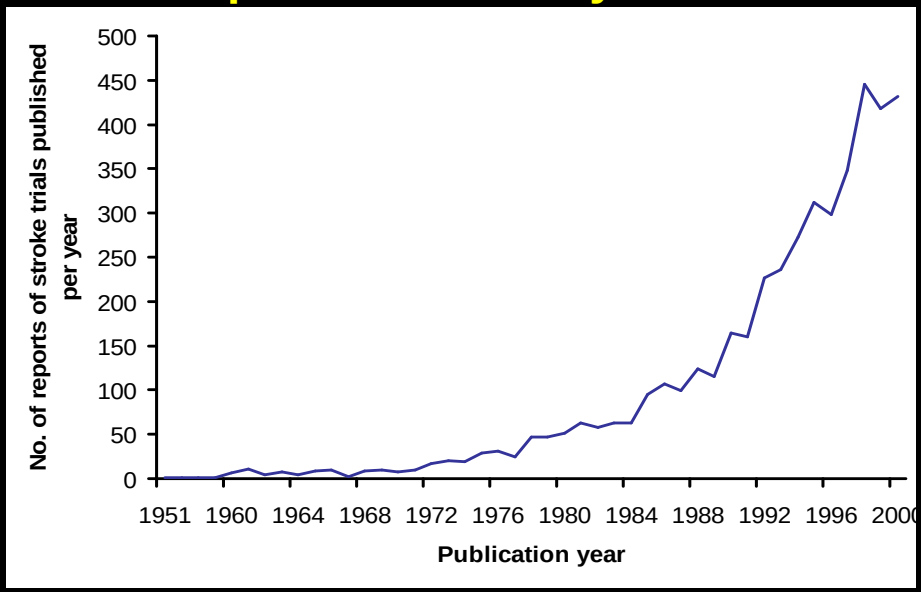
– Anti-oedema agents (glycerol, corticosteroids)

– Neuroprotective agents (calcium antagonists)

Cumulative total number of reports of stroke trials published 1951-2000



Number of reports of stroke trials published each year



Archie Cochrane, the ‘father’ of Evidence-Based Medicine, said, in 1972

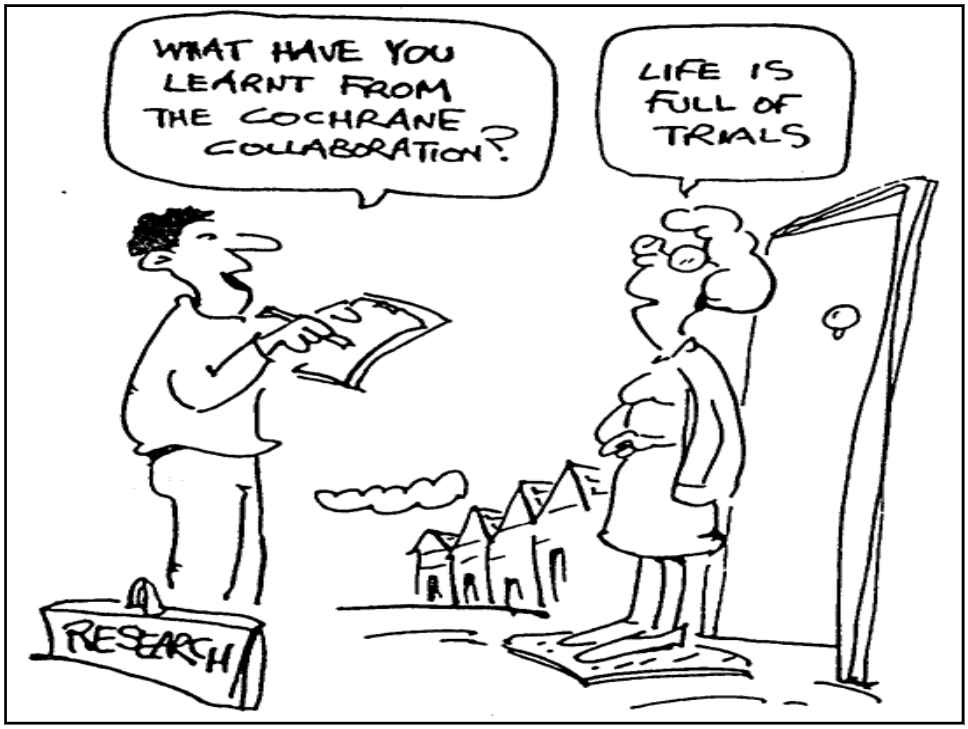
"It is surely a great criticism of our profession that we have not organised a critical summary, by speciality or sub-speciality, adapted periodically, of all relevant randomised controlled trials."

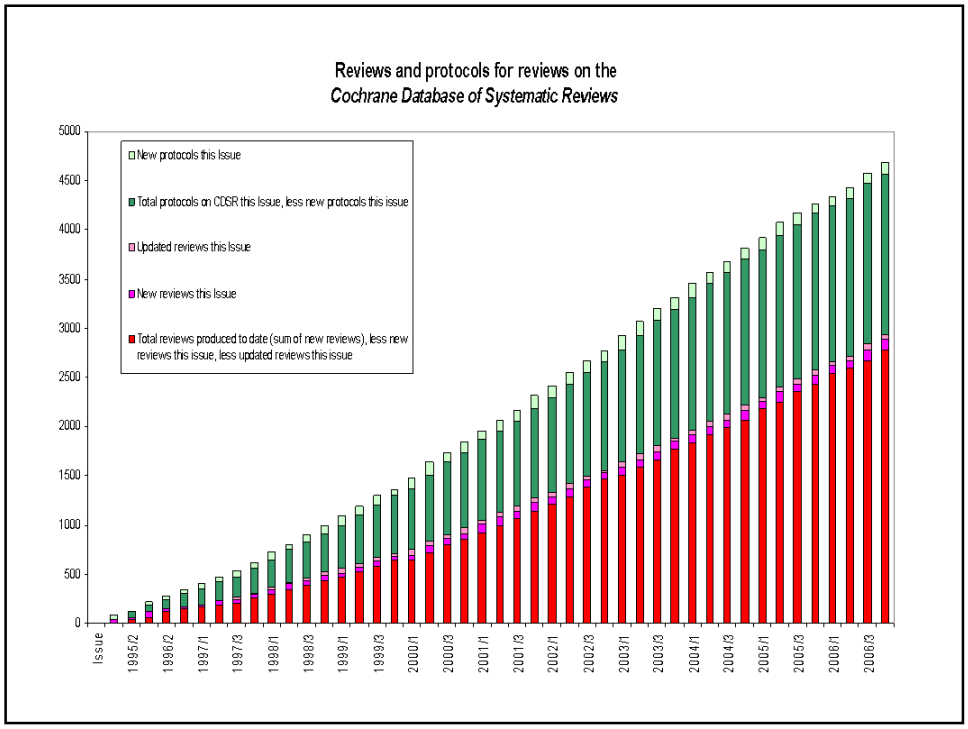
The Cochrane Collaboration

Is an international organisation that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions. It is a not-for-profit organisation.

Cochrane Stroke Review Group

- 140+ reviewers from 21 countries.
- 18 volunteer hand-searchers searching 41 specialist journals and conference proceedings in 5 languages. 24 translators working in 16 languages.
- 48 Systematic reviews (+ 27 protocols) on stroke treatment, rehabilitation & secondary prevention.
- The abstracts of the completed stroke reviews are available free of charge at the Cochrane Stroke Group's web site: http://www.dcn.ed.ac.uk/csrg/.




Reviews and protocols for reviews on the
Cochrane Database of Systematic Reviews
New protocols this Issue
Total protocols on CDSR this Issue, less new protocols this issue
Updated reviews this Issue
New reviews this Issue
Total reviews produced to date (sum of new reviews), less new reviews this issue, less updated reviews this issue
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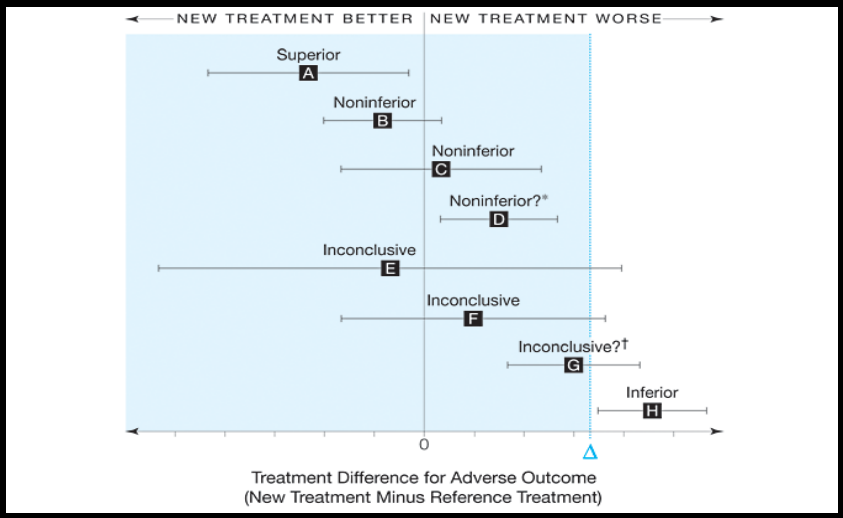
The joys of Collaboration

Possible Scenarios of Observed Treatment Differences for Adverse Outcomes (Harms) in Noninferiority Trials



Piaggio, G. et al. JAMA 2006;295:1152-1160.

JAMA

Statistics are like a bikini:
what they show is intriguing, but
what they conceal is vital

GRAZIE!

Conclusions of Cochrane reviews about organisation of services and rehabilitation following stroke.

Definitely beneficial

– Organised stroke rehabilitation.

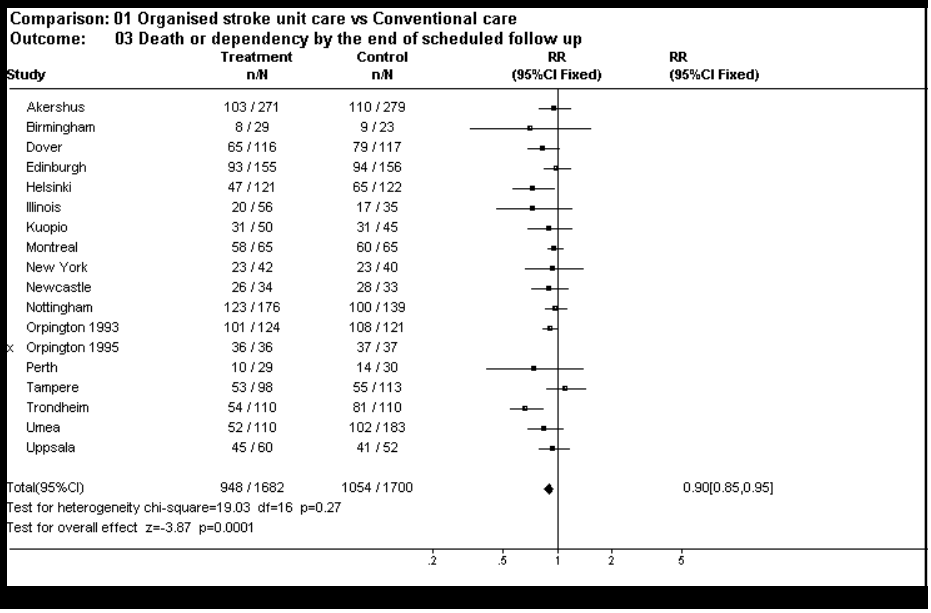
Promising, but more trials needed

– Acute stroke units.
– Early supported discharge from hospital.
– Speech therapy for aphasia.

Work in progress

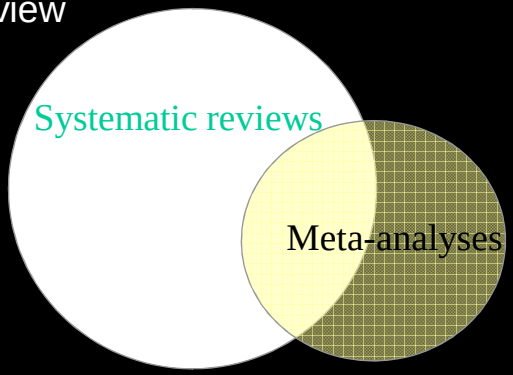
– Interventions for dysphagia.
– Electrical stimulation for shoulder pain.

The benefits of stroke unit care



Systematic reviews and meta-analysis?

Meta-analysis is *optional* part of systematic review



Cochrane review recommendations for further research

- For all 37 topics with associated completed Cochrane reviews, further primary research was recommended, in;
- 19 the associated Cochrane review(s) recommended further RCTs only.
- 13 the associated Cochrane review(s) recommended further RCTs plus ‘other’ primary research,
- 5 the associated Cochrane review(s) recommended ‘other’ primary research but not RCTs
- Thirteen of the 37 topics with at least one completed Cochrane review were judged to have a potentially beneficial treatment effect (ie. judged as “beneficial” or “likely to be beneficial” using the ‘Clinical Evidence’ categorisation). We therefore recommend full-scale RCTS as priority action for these 13 topics.

Recommendations for further secondary research

- **3 Star Priority ***** Four of the 68 topics (balance, gait, high tone / spasticity and upper limb problems) have a large number of known RCTs (>100) and only partly covered by systematic review evidence. Key priorities systematic reviews in order to establish the direction of the existing randomised controlled trial evidence
- **2 Star Priority **** 36 of these 68 topics have no completed systematic reviews. Need to establish if there is any existing evidence of effective treatments.
- **1 Star Priority *** 28 of these 68 topics are partly covered by completed systematic reviews

- Seven topics were judged to be wholly covered by systematic review evidence (attention deficits, memory, neglect/inattention, depression, aphasia, dysarthria, apraxia of speech).

Recommendations for further primary research

- **Priority ***** Randomised controlled trials, with appropriate power, for all topics / interventions for which there is evidence of a possible beneficial effect. Topics categorised as potentially beneficial include stroke unit care, mixed rehabilitation ward care, early supported discharge, information provision with education, occupational therapy, therapy-based rehabilitation services, repetitive task training, physical fitness training, oral protein and energy nutritional supplementation, staff led interventions for oral hygiene, psychotherapy for depression, anti-depressants for emotionalism and piracetam for aphasia. We consider that carrying out primary research relating to these topics / interventions should be a priority as this should provide the greatest potential for an impact on the outcome of individual patients.

A quick look at Clinical Evidence….

Medical treatment in stroke

Beneficial	• Aspirin
Trade off between benefits and harms	• Systemic anticoagulation (unfractionated heparin, low molecular weight heparin, heparinoids, oral anticoagulants, or specific thrombin inhibitors) • Thrombolysis (increased overall mortality and fatal haemorrhages but reduced dependency in survivors; beneficial effects on dependency do not extend to streptokinase)
Unlikely to be beneficial	• Neuroprotective agents (calcium channel antagonists, citicoline, gamma-aminobutyric acid agonists, glycine antagonists, lubeluzole, magnesium, N-methyl-D-aspartate antagonists, tirilazad)
Likely to be ineffective or harmful	• Acute reduction in blood pressure

Clinical Evidence, issue 1 2006

Topic (Topic Tree)
Raised intracranial pressure *(Acute stroke management / Acute neurological complications of stroke)*
Intervention 1
Corticosteroids
Further Research Required?
Exploratory research
Other suggested research activity:
•Factoring in corticosteroid treatment as an additional arm of a large trial of some more promising treatment might be sensible and cost effective. •Given the likely mode of action of corticosteroids in acute ischaemic stroke, patients with large infarcts and much cerebral oedema might be considered the ones likely to benefit, if this treatment were shown to be effective. •Perhaps newer ways of administration such as the use of mega-doses of corticosteroids (eg methylprednisolone 500 - 1000 mg/day) may be more effective on the vasogenic component of the oedema of large infarcts
Research not required as:
The present data do not hold enough promise of clinically worthwhile benefits to advocate a large scale trial.
Intervention 2
Glycerol (an anti-oedema osmotic agent)
Further Research Required?
Trials
Further trials should:
•Test these treatments in large scale randomised controlled trial comparing glycerol with non glycerol treatment, perhaps restricted to patients who have clinical evidence of cerebral oedema, in which the long term effects of treatment on disability, handicap and quality of life are reliably assessed.

Topic (Topic Tree)
Discharge planning and support *(Discharge from hospital)*
Intervention 1
Early discharge services not provided by a coordinated multidisciplinary team (MDT)
Further Research Required?
Trials
Further trials should:
•Be designed to define the important characteristics of effective ESD services and to define the balance of cost and benefit for different patient and service groups. •Aim to establish if more generic ESD teams (eg. services for a mixed elderly population) will obtain the same results as the stroke specific services reported here. •Address the role of ESD services in more dispersed rural communities.
Intervention 2
Early supported discharge (ESD) services coordinated by a multidisciplinary team (MDT)
Further Research Required?
Trials
Further trials should:
•As for Early discharge services not provided by a coordinated multidisciplinary team (MDT), see above.

Heading	Number of systematic review	Number of trials
Acute stroke management	35	1506
Common problems	54	1915
Life after stroke	8	182
Preventing stroke	18	607

Role of systematic reviews at each stage of a trial

- Planning
  - Initial thoughts
  - Design: selection of primary outcome
  - Sample size
  - Methods of improving follow-up response
- During the trial
- At the end of the trial & publishing the results
- Planning the next trial

SR's & planning stage of the trial

- Are pre-clinical data convincing enough to justify a clinical trial?->SR of experiments (relevant to rehab too!)
- Have existing trials already answered the question?
- If not, what are the key questions?

- Identify methodological problems in prior trials (to be avoided in planned trial)
- Guide choice of primary measure of outcome
- Estimate treatment effect -> sample size calculation
- Identify most efficient follow-up method

:

- MRC, NIHR now require SR of available evidence in the justification section

Example: planning CLOTS trial

Patients: 'in the first few days after stroke,

Intervention: do graded compression stockings,

Comparison: compared with 'no stockings',

Outcome: prevent deep vein thrombosis and pulmonary embolism?'

:

Mazzone C, Physical methods for preventing deep vein thrombosis in stroke. The Cochrane Database of Systematic Reviews 2004

CLOTS (trial 1) sample size

- To achieve at least 90% power we need to identify about 175 patients with a primary outcome event (DVT).
- If thrombus is detected in the popliteal or femoral veins within 30 days of randomisation in 15% of control patients & 9% of those wearing full length GCS & if the current event rate in our pilot phase applies, we may require about 2000 patients.
- These estimates are based on:
  - the Cochrane systematic review (and an HTA review)
  - the prevalence of DVT detected on Doppler ultrasound in stroke patients estimated from a previous RCT (Muir et al 2000),
  - an observational study (Oczkowski et al 1992)
  - the frequency of events in the CLOTS start up phase.

Atrial Fibrillation *(Preventing stroke / Primary prevention in high risk individuals)*

Further Research Required?

Trials

Further trials should:

•Provide more randomized data about the efficacy of non-aspirin antiplatelet regimens (including dipyridamole, clopidogrel and indobufen, alone and combined with aspirin)

CRASH trial: evidence-based design of follow-up method

- Outcome questionnaires shortened to:
  - Single-sided (A4) outcome form completed at 2 weeks
  - Final follow-up: single-sided (A4) postal questionnaire mailed to patients at 6 months (with evidence –based features)
- Response rate in the 10,000 randomised patients 99.6% (vs 80% in previous trials)

Discharge planning and support *(Discharge from hospital)*

Early discharge services not provided by a coordinated multidisciplinary team (MDT)

Further Research Required?

Trials

Further trials should:

- Be designed to define the important characteristics of effective ESD services and to define the balance of cost and benefit for different patient and service groups.
- Aim to establish if more generic ESD teams (eg. services for a mixed elderly population) will obtain the same results as the stroke specific services reported here.
- Address the role of ESD services in more dispersed rural communities.

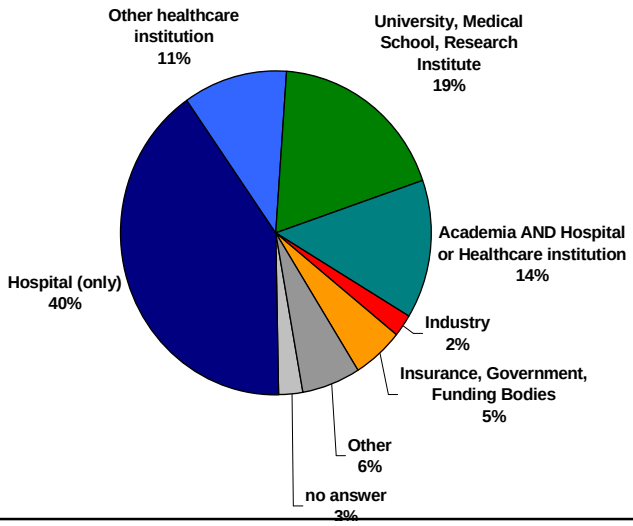
Stockings for DVT prevention after stroke

Implications for practice: The two small randomised controlled trials of physical methods for preventing DVT in acute stroke do not provide conclusive evidence on the balance of risk and benefit. There is thus insufficient evidence to support their use in routine clinical practice.

Implications for research: Although graded compression stockings and physical methods for the prevention of DVT and PE may be effective in some categories of high risk patients, there is clearly a need for large scale trials in stroke patients.

- CSO funded CLOTS randomised pilot study
- Cochrane review underpinned application to MRC
- CLOTS main trial awarded £1M funding by MRC

The Cochrane Library Evidence for healthcare decision-making



Recommendations for further primary research (systematic reviews suggest potential benefit)

- acute stroke unit care
- mixed rehabilitation ward care
- early supported discharge
- information provision with education
- occupational therapy for ADL
- therapy-based rehabilitation services at home
- repetitive task training
- physical fitness training
- oral protein and energy nutritional supplementation
- staff led interventions for oral hygiene
- psychotherapy for depression
- anti-depressants for emotionalism
- piracetam for aphasia

Results: questionnaire response rates were substantially higher with:-

- incentives, especially if unconditional
- shorter 'user-friendly' questionnaires
- providing a second copy of the questionnaire
- university sponsorship
- pre-notification
- 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

Thrombolysis in acute ischaemic stroke - An update of the Cochrane Thrombolysis metaanalysis

JM Wardlaw, V Murray, PAG Sandercock

University of Edinburgh and Karolinska Institutet, Stockholm