Finding solutions to challenging and complex Cochrane reviews:

the National Institute for Health Research Complex Reviews Support Unit (NIHR CRSU)

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Outline

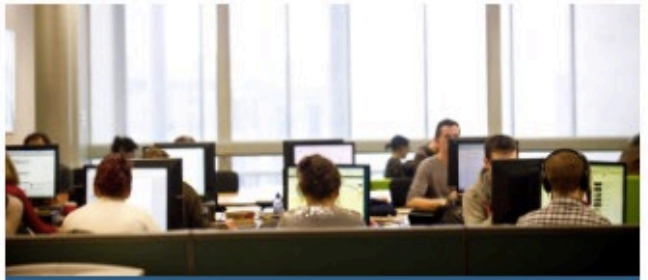
- NIHR CRSU
- Supporting complex reviews
- A Cochrane network meta-analysis: early mobilisation after stroke
- An app for network meta-analysis - MetaInsight
- Network meta-analysis of complex interventions - Component Analysis
- Further complex reviews issues

NIHR CRSU - Complex Reviews Support Unit

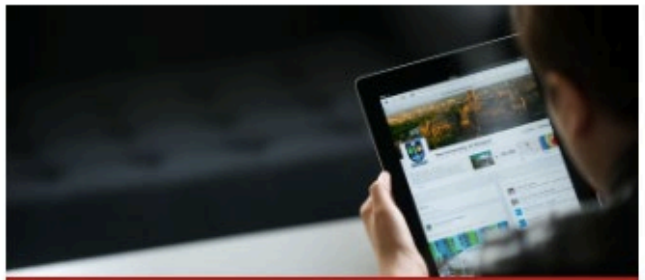
- About us
- The Team
- Apply for CRSU Support
- Materials and Guidance
- Courses and Conferences
- FAQs
- Contact us

About us

NIHR CRSU: Supporting Successful Delivery of Complex Reviews



The Team



Apply for CRSU Support

Submit an application for support to CRSU

Materials and Guidance

Materials and links to current guidance

website: www.nihrcrsu.org

twitter: @NIHRCRSU

Our Expertise

- Network meta-analysis
- Diagnostic test accuracy reviews
- Individual participant data meta-analysis
- Narrative synthesis
- Realist synthesis
- Economic evidence
- Use of routine data
- Non-randomised studies
- Prognostic reviews
- Prevalence reviews

Supporting Cochrane Reviews – Advice and Training

- Reviewers
- Review Groups
- Incentive Awards
- Programme Grants
- Editorial Teams

- Refining review questions
- Consideration of types of data and data structure
- Methodological approaches
- Applications, protocols and reporting

Complex Reviews in Hepato-Biliary Disorders

Priority topics in the diagnosis and management of liver, gallbladder, and biliary tract disorders

Kurinchi Gurusamy and colleagues

- Series of reviews of treatment for different indications
- Complex interventions – life-style modification
- Multiple treatment comparisons (network meta-analysis)

Complex Reviews in Oral Health

Detection and diagnosis of dental caries

Richard Macey and colleagues

- Variation in thresholds
- Imperfect reference standards
- Multiple examiners
- Multiple measurements per person

Cochrane Oral Health

Complex Reviews in COPD

Priority topics:

- Prognostic factors at EoL
- Use of weather forecasting/pollution monitoring
- Care pathways for multi-morbidity
- Prophylactic antibiotics

Rebecca Normansell and colleagues

- Complex questions
- Utility of the review
- Feasibility of quantitative synthesis
- Multiple treatment comparisons (network meta-analysis)

Cochrane Airways

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Contact us

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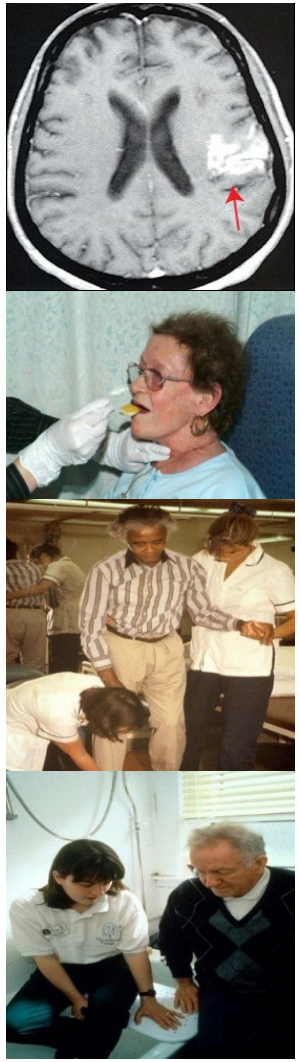
Early mobilisation after stroke:
Meta-analysis approaches

Peter Langhorne,
Professor of stroke care,
Glasgow University

Limited evidence for individual components of stroke unit care



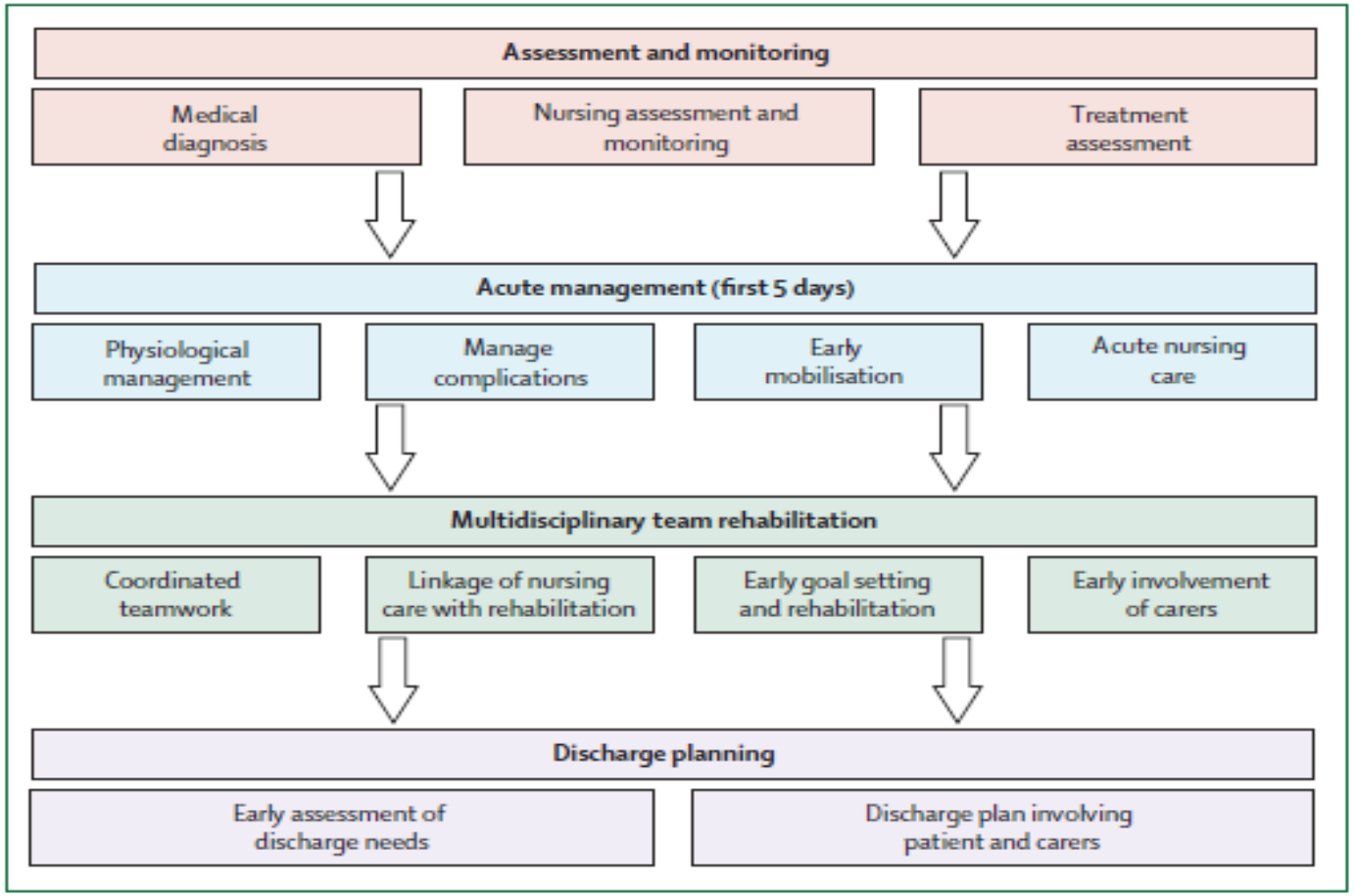
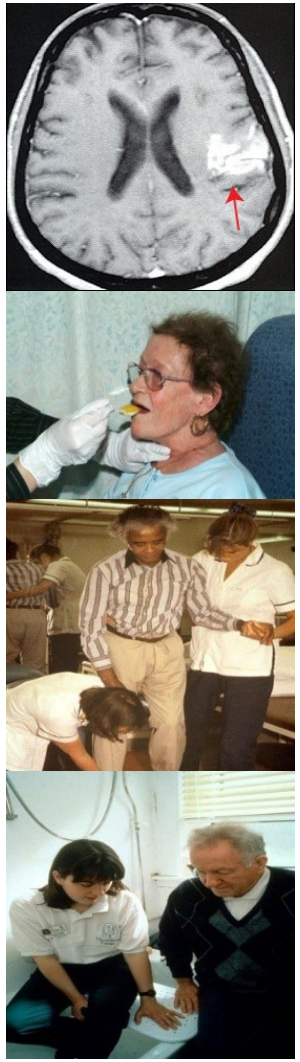


Figure 3: Key components of stroke-unit care

Langhorne et al Lancet Neurol (2012)

Limited evidence for individual components of stroke unit care



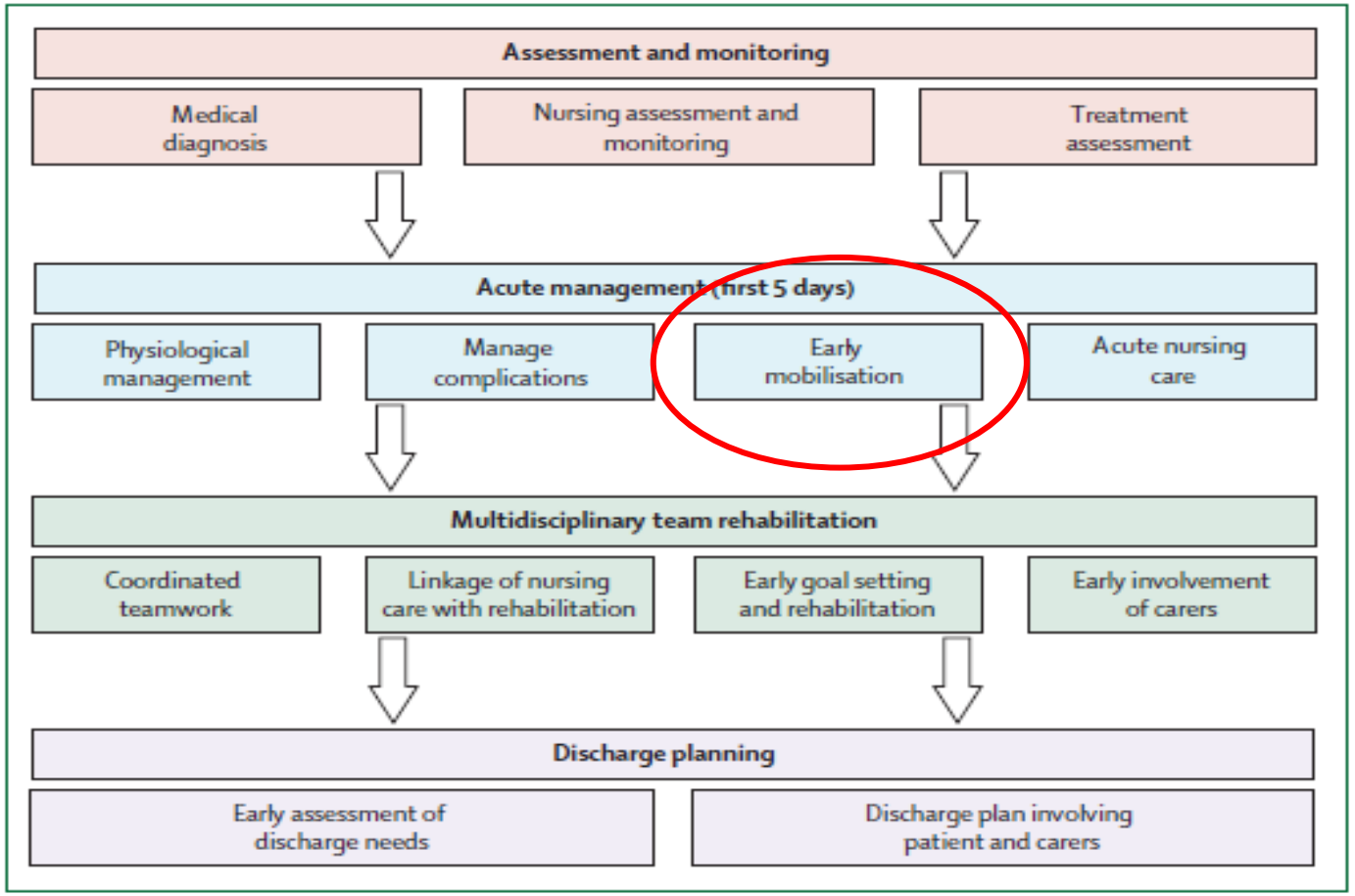
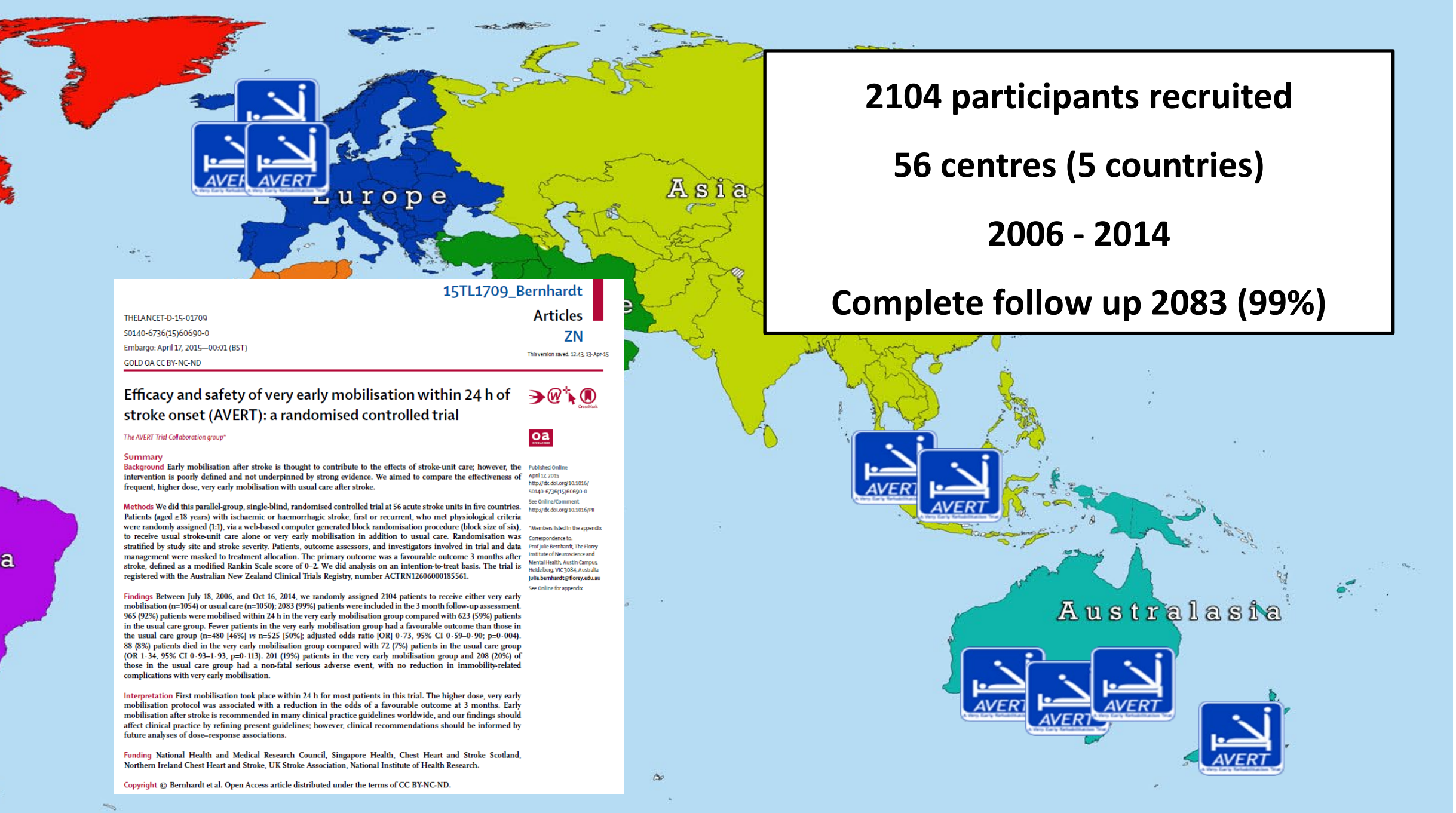


Figure 3: Key components of stroke-unit care

Langhorne et al Lancet Neurol (2012)



2104 participants recruited

56 centres (5 countries)

2006 - 2014

Complete follow up 2083 (99%)

15TL1709_Bernhardt

Articles

ZN

THELANCET-D-15-01709
S0140-6736(15)60690-0
Embargo: April 17, 2015—00:01 (BST)

This version saved: 12:43, 13-Apr-15

Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial

*The AVERT Trial Collaboration group**

Summary

Background Early mobilisation after stroke is thought to contribute to the effects of stroke-unit care; however, the intervention is poorly defined and not underpinned by strong evidence. We aimed to compare the effectiveness of frequent, higher dose, very early mobilisation with usual care after stroke.

Methods We did this parallel-group, single-blind, randomised controlled trial at 56 acute stroke units in five countries. Patients (aged ≥18 years) with ischaemic or haemorrhagic stroke, first or recurrent, who met physiological criteria were randomly assigned (1:1), via a web-based computer generated block randomisation procedure (block size of six), to receive usual stroke-unit care alone or very early mobilisation in addition to usual care. Randomisation was stratified by study site and stroke severity. Patients, outcome assessors, and investigators involved in trial and data management were masked to treatment allocation. The primary outcome was a favourable outcome 3 months after stroke, defined as a modified Rankin Scale score of 0–2. We did analysis on an intention-to-treat basis. The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12606000185561.

Findings Between July 18, 2006, and Oct 16, 2014, we randomly assigned 2104 patients to receive either very early mobilisation (n=1054) or usual care (n=1050); 2083 (99%) patients were included in the 3 month follow-up assessment. 965 (92%) patients were mobilised within 24 h in the very early mobilisation group compared with 623 (59%) patients in the usual care group. Fewer patients in the very early mobilisation group had a favourable outcome than those in the usual care group (n=480 [46%] *vs* n=525 [50%]; adjusted odds ratio [OR] 0·73, 95% CI 0·59–0·90; p=0·004). 88 (8%) patients died in the very early mobilisation group compared with 72 (7%) patients in the usual care group (OR 1·34, 95% CI 0·93–1·93, p=0·113). 201 (19%) patients in the very early mobilisation group and 208 (20%) of those in the usual care group had a non-fatal serious adverse event, with no reduction in immobility-related complications with very early mobilisation.

Interpretation First mobilisation took place within 24 h for most patients in this trial. The higher dose, very early mobilisation protocol was associated with a reduction in the odds of a favourable outcome at 3 months. Early mobilisation after stroke is recommended in many clinical practice guidelines worldwide, and our findings should affect clinical practice by refining present guidelines; however, clinical recommendations should be informed by future analyses of dose–response associations.

Funding National Health and Medical Research Council, Singapore Health, Chest Heart and Stroke Scotland, Northern Ireland Chest Heart and Stroke, UK Stroke Association, National Institute of Health Research.

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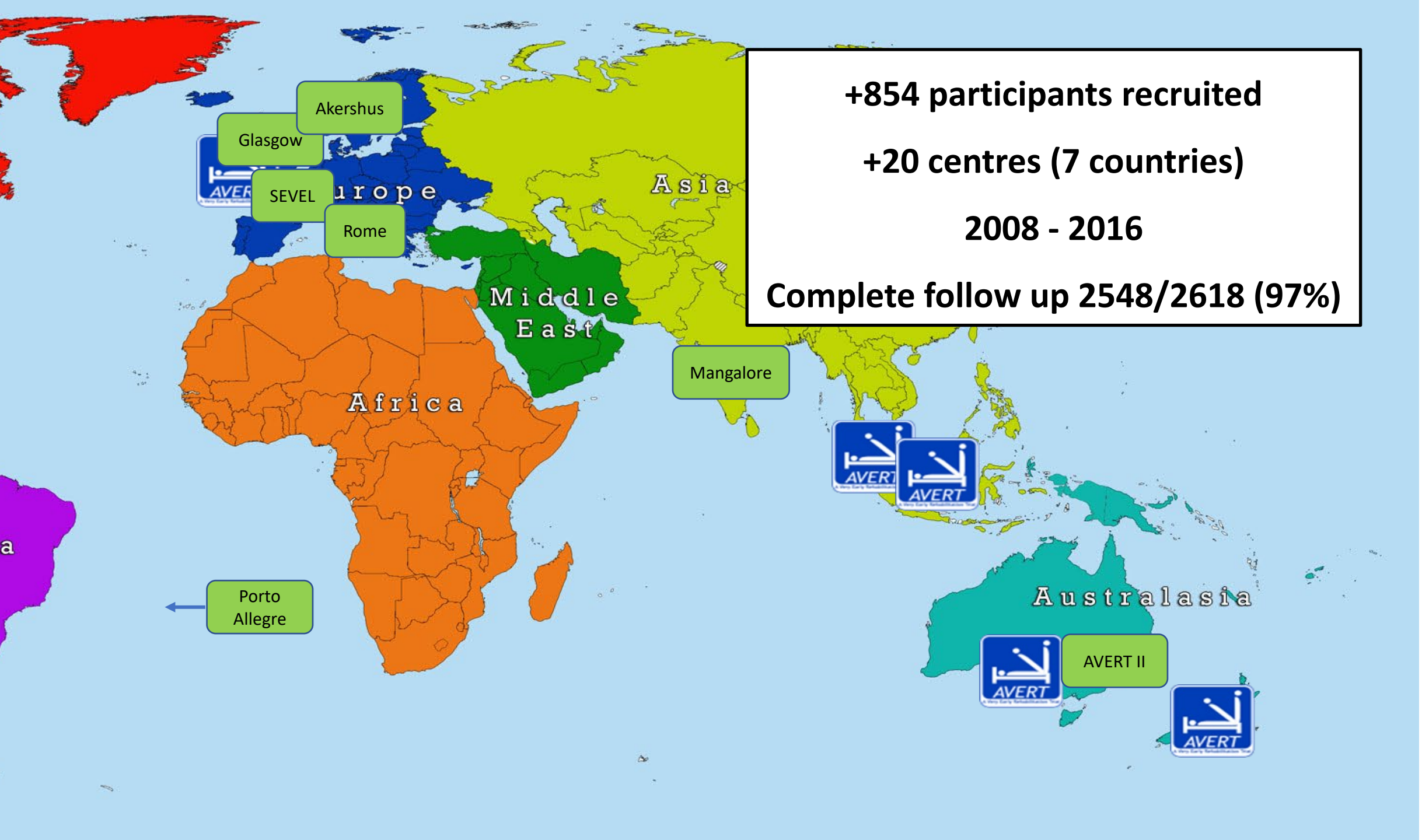
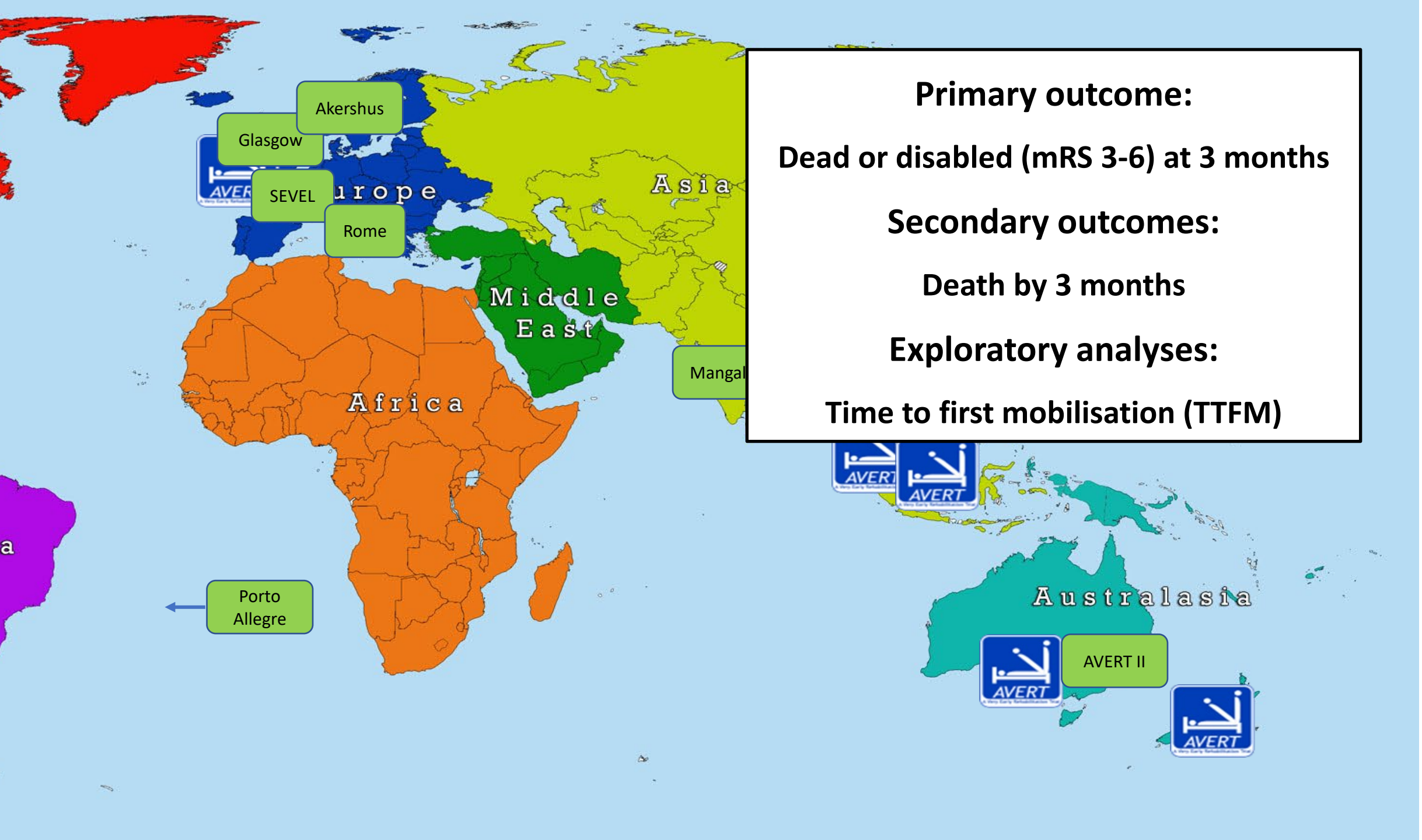
See Online for appendix


+854 participants recruited
+20 centres (7 countries)
2008 - 2016
Complete follow up 2548/2618 (97%)
Akershus
Glasgow
SEVEL
Rome
Europe
Asia
Middle East
Africa
Mangalore
Porto Allegre
Australasia
AVERT II
AVERT



Primary outcome:

Dead or disabled (mRS 3-6) at 3 months

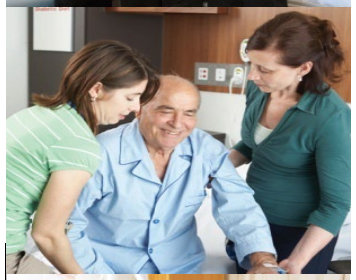
Secondary outcomes:

Death by 3 months

Exploratory analyses:

Time to first mobilisation (TTFM)

What is Very Early Mobilisation (VEM)?



- Out of bed mobilisation within 48 hours of stroke
- Aimed to reduce time to first mobilisation (TTFM)
  - with or without an increase in the amount or frequency of mobilisation activities
- Compared with usual care
  - time to first mobilisation commenced later
- Interventions provided by a physiotherapist ± nurse team
- Protocol/training provided to staff

Mobilisation trials
Time to first mobilisation)

Across all the trials in the Cochrane review:

Group	Median (range) TTFM
Very early mobilisation (VEM)	18 (13 - 43) hours
Usual care (UC)	33 (23 - 72) hours
Within trial difference (UC – VEM)	13 (4 - 46) hours

Cochrane review (update in progress)

Trials of very early mobilisation

Trial	Aim	Early mobilisation TTFM (hours)	Usual Care TTFM (hours)	Frequency of mobilisation events per day	Average amount of mobilisation activity
AKEMIS 2012	Earlier	13.1 (8.5-25.6)	33.3 (26.0-39.0)	Not stated	Not stated
AVERT II 2008	Earlier & more	18.1 (12.8-21.5)	30.8 (23.0-39.9)	2 vs 0	167 vs 69 mins mobilisation activity
AVERT III 2015	Earlier & more	18.5 (12.8-22.3)	22.4 (16.5-29.3)	6.5 vs 3	31 vs 10 mins per day of mobilisation activity
Glasgow 2010	Earlier & more	27.3 (26.0-29.0)	32.0 (22.5-47.3)	Not stated	More EM patients (P=0.02) achieved standing or walking
Mangalore 2015a	Earlier & more	18 (16.6-19.8)	30.5 (29.0-35.0)	Not stated	Extra 5-30 mins per day of out of bed activity
Mangalore 2015b	Earlier & more	Same as 2015a	Same as 2015a	Same as 2015a	Same as 2015a
Porto Allegre 2015	Earlier & more	43	72	0.54 vs 0.03	Extra 30 mins per day of out of bed activity
Rome 2016	Earlier	<24	96	Not stated	60 mins per day for first 4 days
SEVEL 2016	Earlier	25.9 (22.5-29.3)	71.5 (68.1-74.9)	Not stated	83.7 vs 56.6 mins per day

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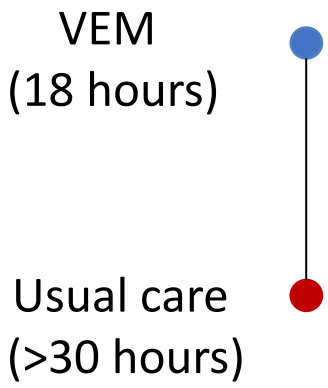
Early Mobilisation trials – Network meta-analysis

TTFM (time to first mobilisation) groups



Cochrane review (update in progress)

Early Mobilisation trials – Network meta-analysis

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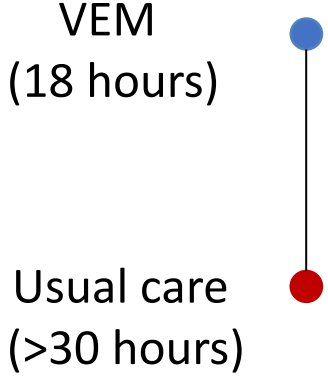
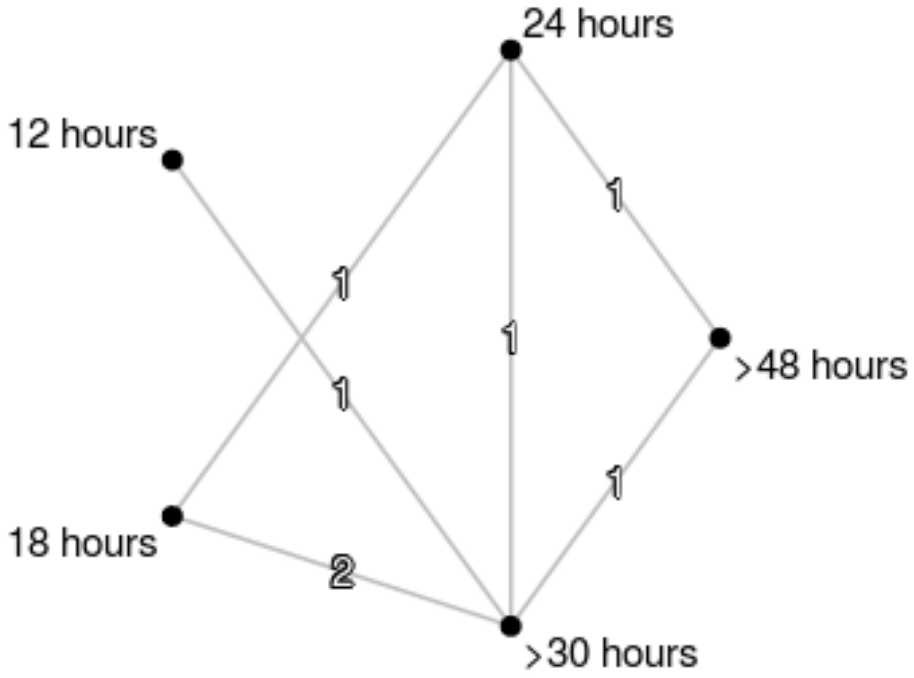




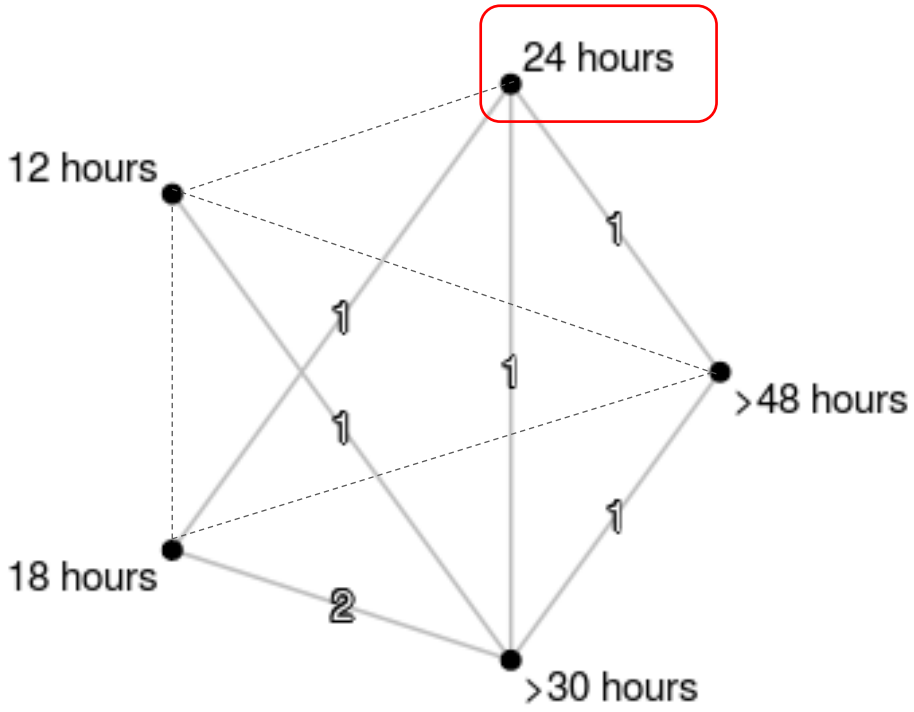
Cochrane review (update in progress)

Early Mobilisation trials – Network meta-analysis

TTFM (time to first mobilisation) groups

VEM
(18 hours)

Usual care
(>30 hours)



Cochrane review (update in progress)

Early Mobilisation trials – Network meta-analysis

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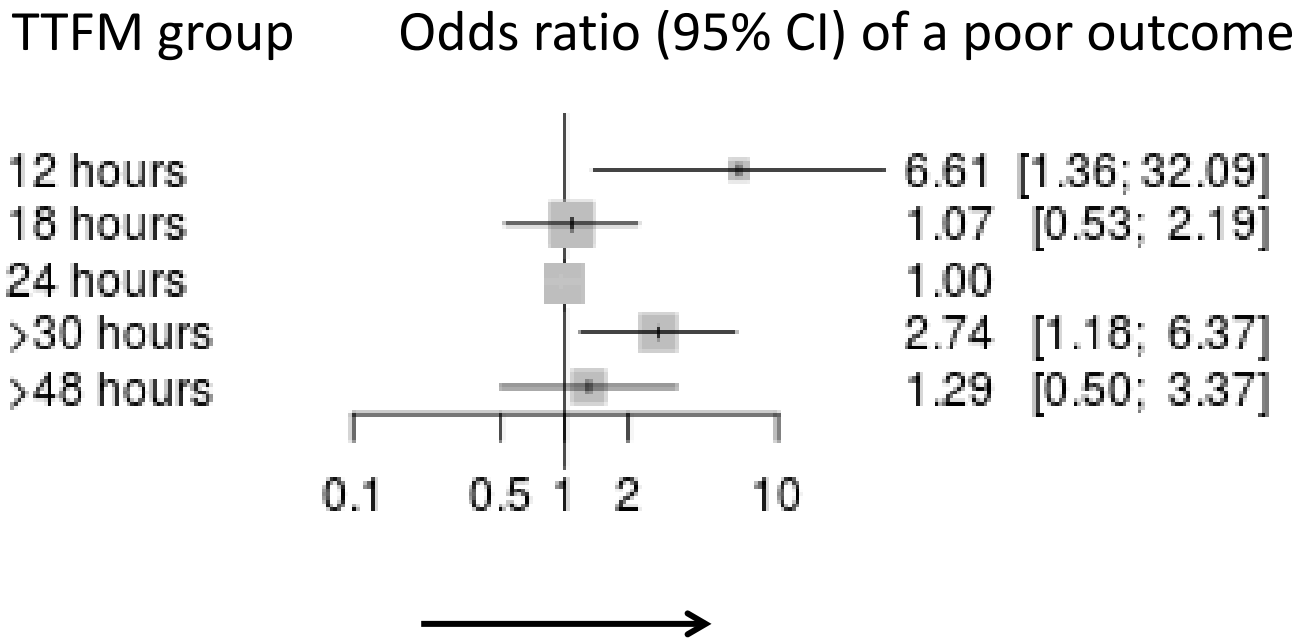

Cochrane review (update in progress)

Early Mobilisation trials – Network meta-analysis

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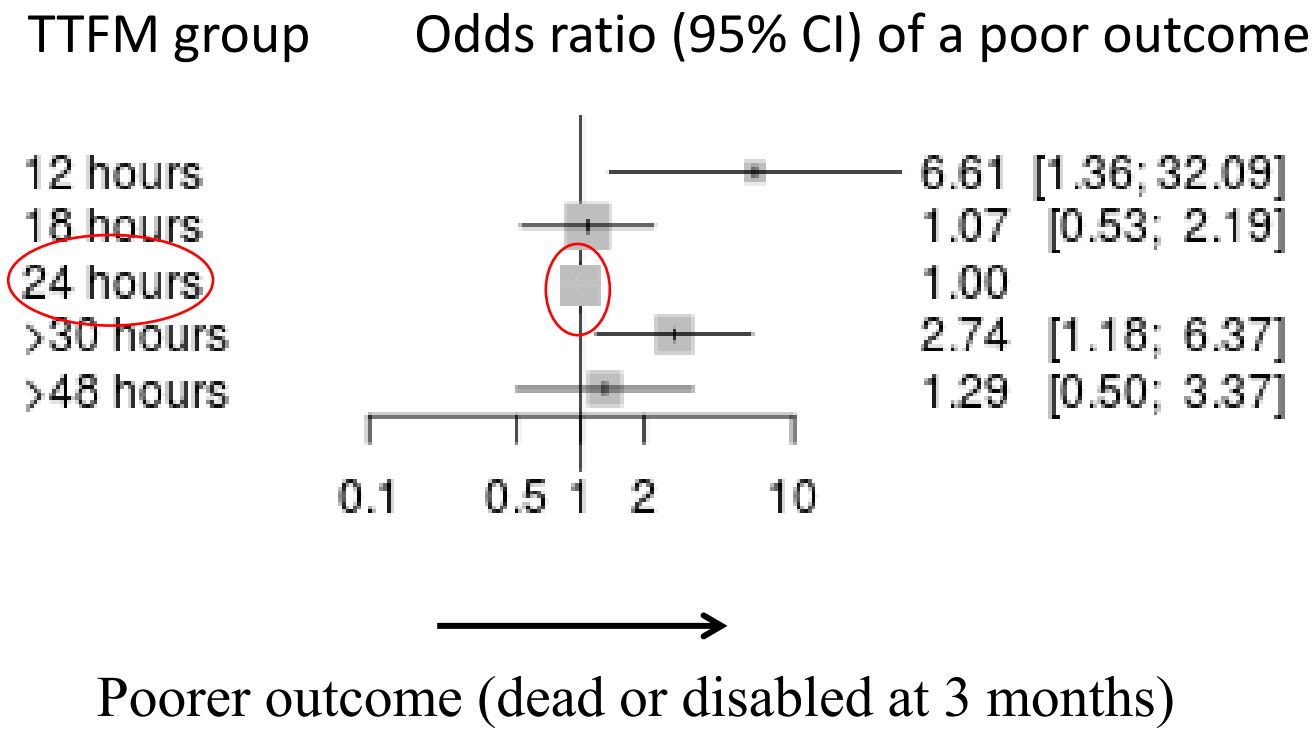
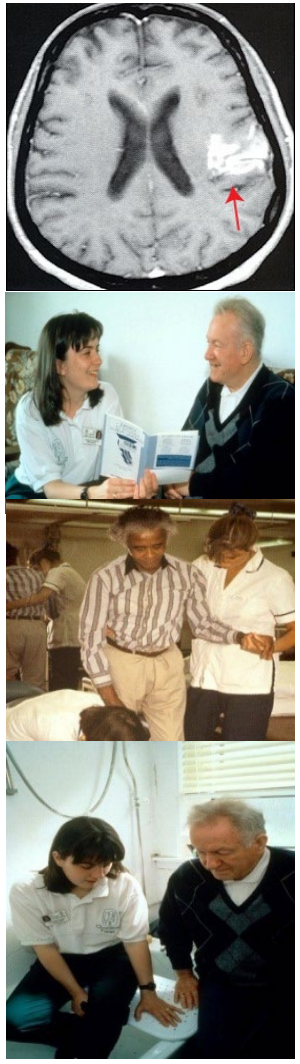


Cochrane review (update in progress)

Early mobilisation after stroke



1. Very early (<24 hours) higher dose out of bed activity protocol reduced the odds of favourable outcome
2. Exploratory analysis suggests no TTFM was better than 24 hours
3. Guideline advice seems appropriate at present:

"Patients with difficulty moving early after stroke who are medically stable should be offered frequent, short daily mobilisations typically beginning between 24 and 48 hours of stroke onset"

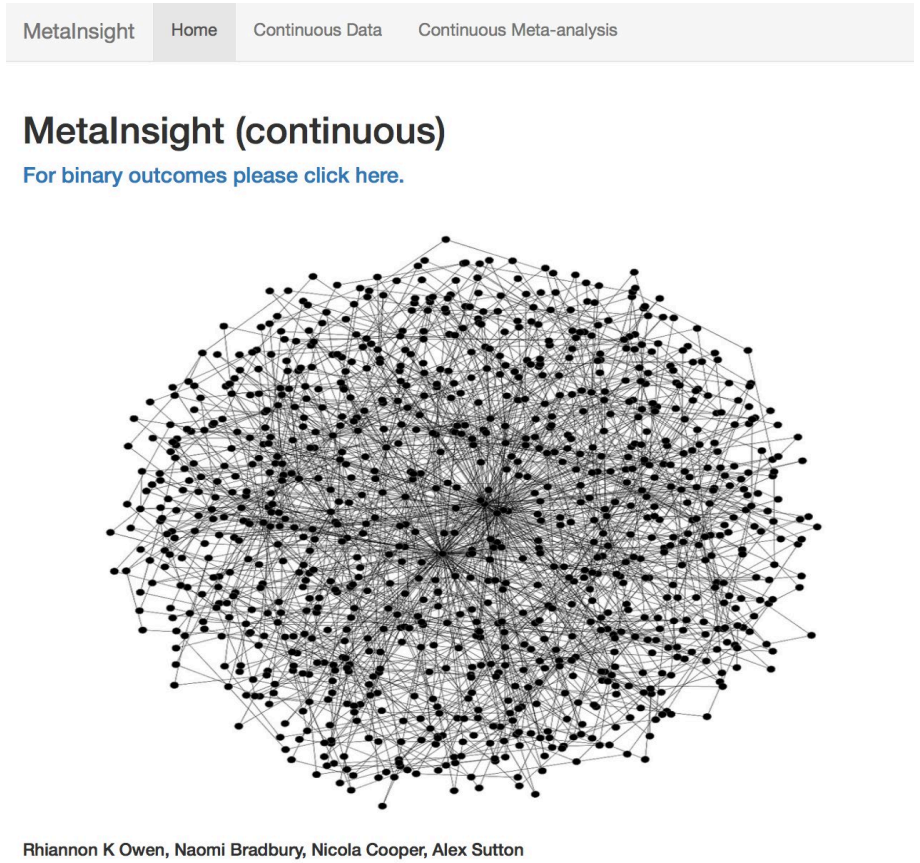
4. Work in progress!


Stroke Unit
Ward 74
AVERT
Thank you for your attention

UNIVERSITY OF LEICESTER

Biostatistics Research Group, Department of Health Sciences

MetaInsight: an interactive web-based tool for analyzing, interrogating and visualizing network meta-analyses



Rhiannon K Owen

@RhiannonKOwen

Acknowledgements: Naomi Bradbury, Nicola Cooper, Alex Sutton

UNIVERSITY OF LEICESTER

Biostatistics Research Group, Department of Health Sciences

MetaInsight demonstration

If you would like to follow the demo on your own device please scan the QR code or go to:

https://crsu.shinyapps.io/metainsightc/

University of Glasgow | University of Leicester | London School of Hygiene & Tropical Medicine | NHS National Institute for Health Research

NIHR CRSU

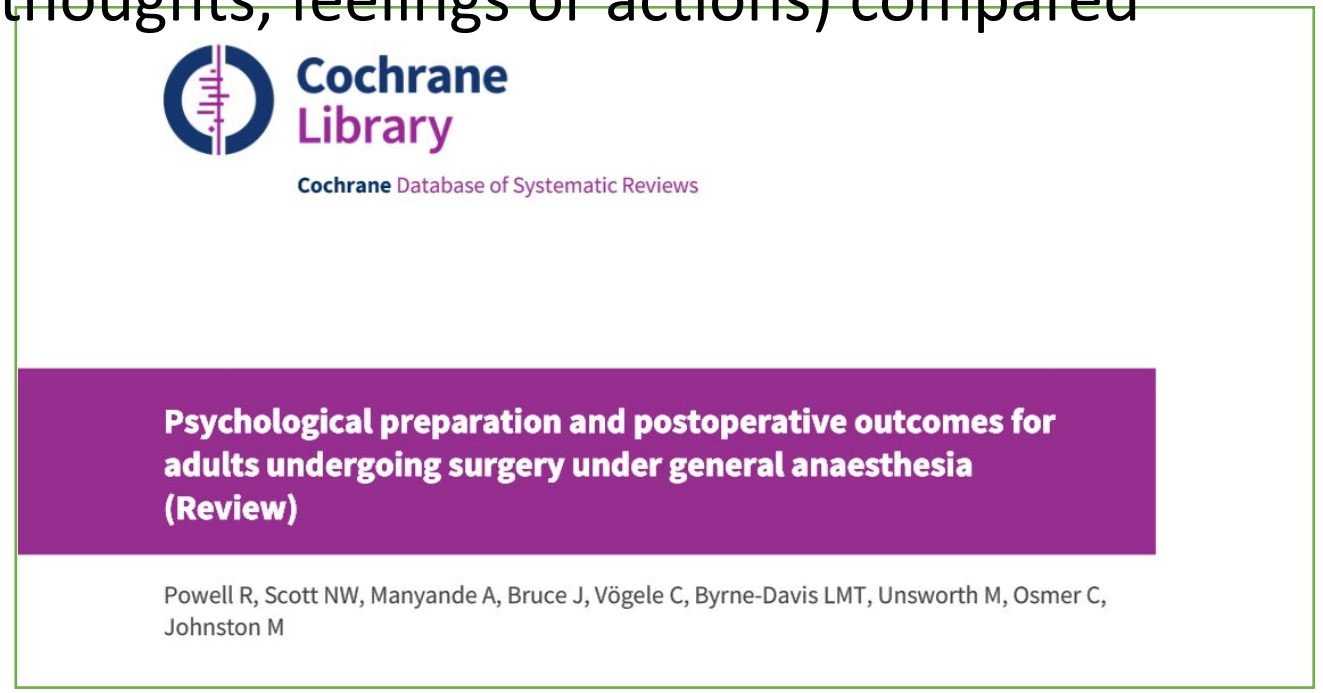
Complex Reviews Support Unit

Component Network Meta-Analysis

The Complex Reviews Support Unit (CRSU) is funded by the National Institute for Health Research (project number 14/178/29)

Background

- May 2016 - Meta-analysis published in the Cochrane Database of Systematic Reviews identifying better postoperative outcomes (e.g. reduced length of stay in hospital, lower pain, reducing negative emotion) for patients who received any psychological preparation (strategies designed to influence thoughts, feelings or actions) compared to usual care



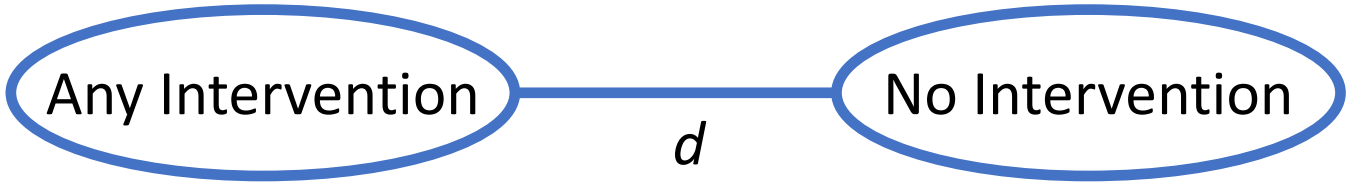
What is Psychological Preparation?

- Can be considered as the intervention received by patients prior to surgery to help prepare them for surgery and minimise length of stay, pain and negative affect
- Psychological preparation can consist of multiple components:
  - Procedural information (What, when and how events will occur)
  - Sensory information (What it will feel/smell like)
  - Behavioural instruction (Teaching patients actions to perform to enhance the experience)
  - Cognitive intervention (To change how an individual thinks)
  - Relaxation (including hypnosis)
  - Emotion-focused techniques (To help an individual manage their feelings)

What did they do in the Cochrane review?

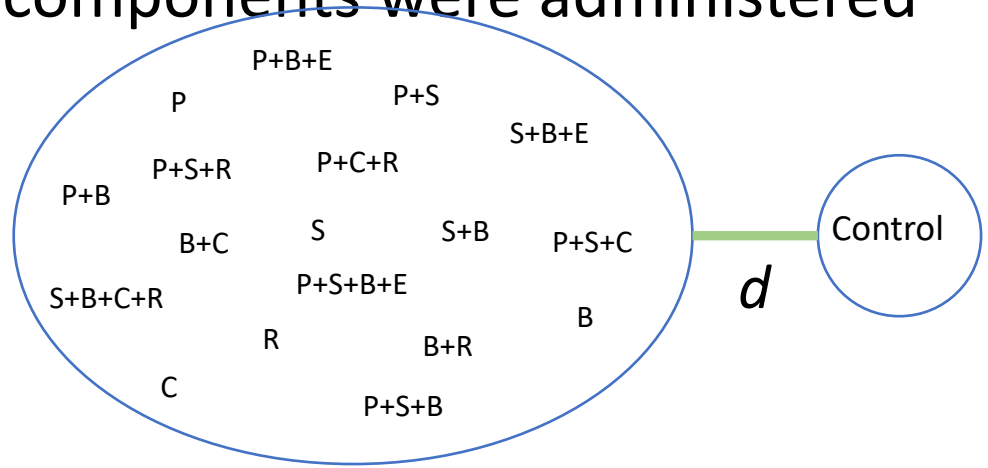
Wanted to answer the question:

> *"What is the effect of psychological preparation on postoperative outcomes in adults undergoing elective surgery under general anaesthetic?"*



Assumptions in the Cochrane review?

- All intervention arms were assumed to be equally effective irrespective of which treatment components were administered



Assumptions:

- The effect of each component of intervention is the same
- The effect of a single component is the same as a combination of components

Additional Questions for NMA

- Which individual components of psychological preparation before surgery are associated with better outcomes?
- Are components more effective when delivered on their own or in combination?
- Are component effects associated with control group risk? (i.e. Does length of stay in the control group affect length of stay in the intervention group?)
- Are component effects associated with type of surgery?

Modelling Component Effects (1)

Let *d* represent the treatment effect, *b* the baseline treatment and *k* the intervention

Component effects can be accounted for by varying the assumption for d_{bk}

Pairwise Meta-Analysis (any intervention vs no intervention)

$$d_{bk} = d$$

Network Meta-Analysis (each unique combination of interventions treated as a separate 'treatment')

$$d_{bk} = d_{bk}$$

Modelling Component Effects (2)

Component NMA models

- **Additive effects**: separates out the component effects

$$d_{bk} = d_P + d_S + d_B + d_C + d_R + d_E$$

where d_P is an indicator variable taking the value 1 if P is a component of treatment *k* and 0 otherwise

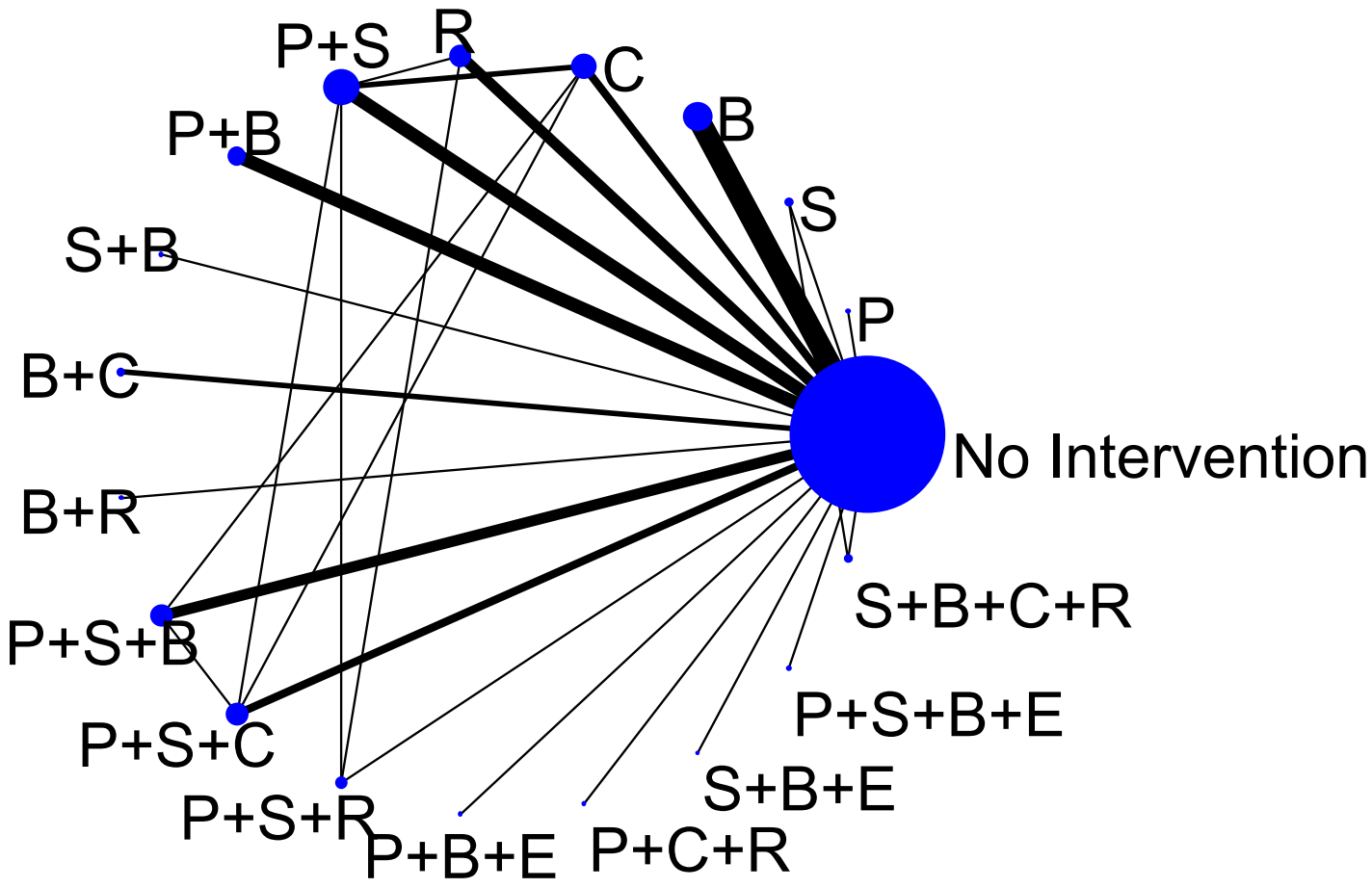
- **Pairwise interactions between components**: allows the effect of a combination to be greater/less than the sum of its individual components

$$d_{bk} = d_P + d_S + d_B + d_C + d_R + d_E + d_{PS} + d_{PB} + \cdots + d_{RE}$$

Modelling Component Effects (3)

- Study level covariates:
  - Control group risk
  - Type of surgery
- Software
  - All models fitted in WinBUGS
- Comparison of models
  - using the Deviance Information Criteria (DIC) but clinical expertise also sought to ensure appropriate model selected

Network Diagram for Length of Stay

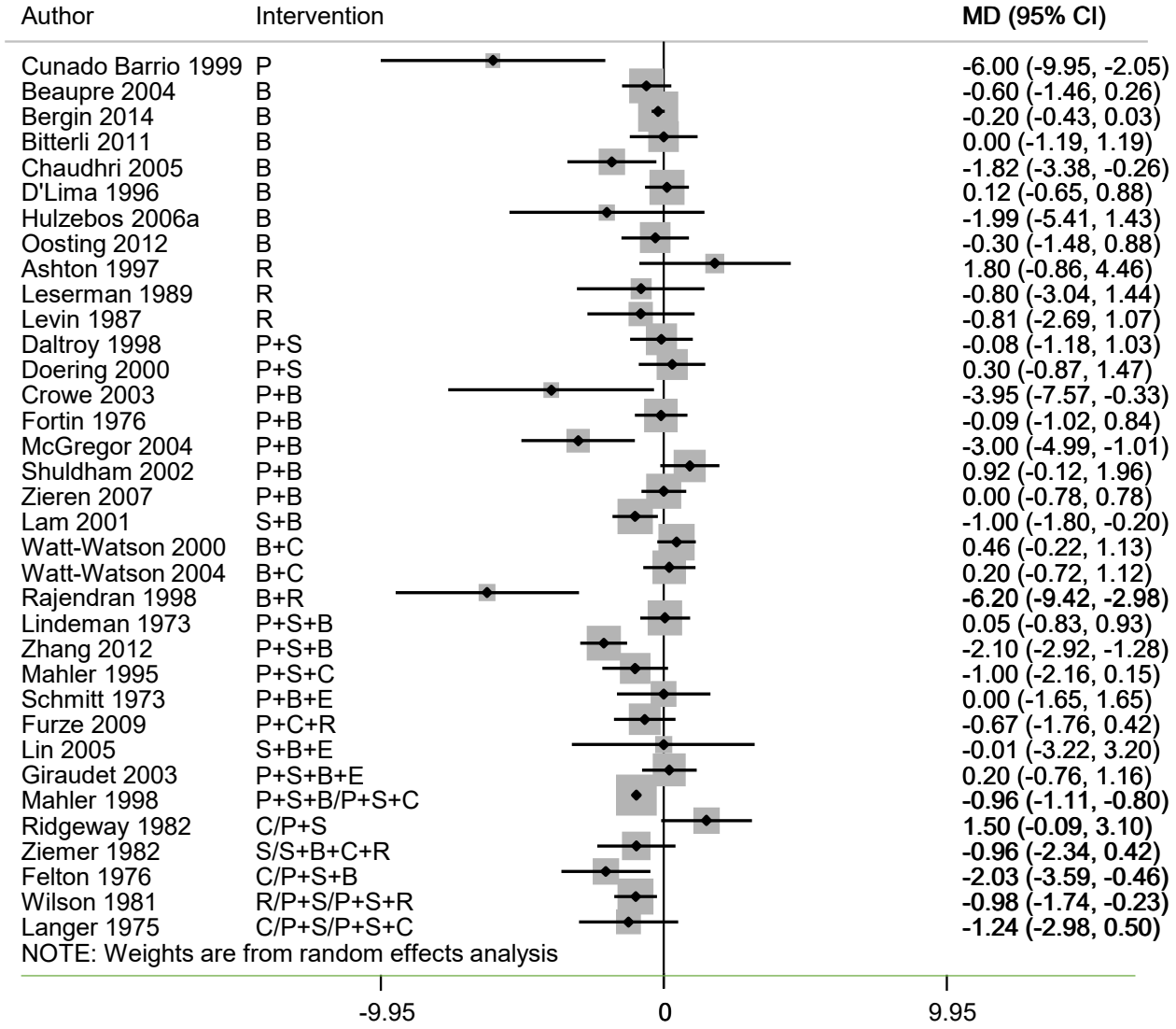


P = procedural information, S = sensory information, B = behavioural instruction, C = cognitive intervention, R = relaxation techniques, E = emotion-focused intervention

Length of Stay

- 35 trials including four three-arm trials and two four-arm trials
- 18 interventions
- Continuous outcome – number of days in hospital
- All trials had a ‘no intervention’ control arm
- Cochrane review identified any intervention reduces length of stay by 0.52 days (95% CrI: -0.82, -0.22)

Length of Stay Forest Plot

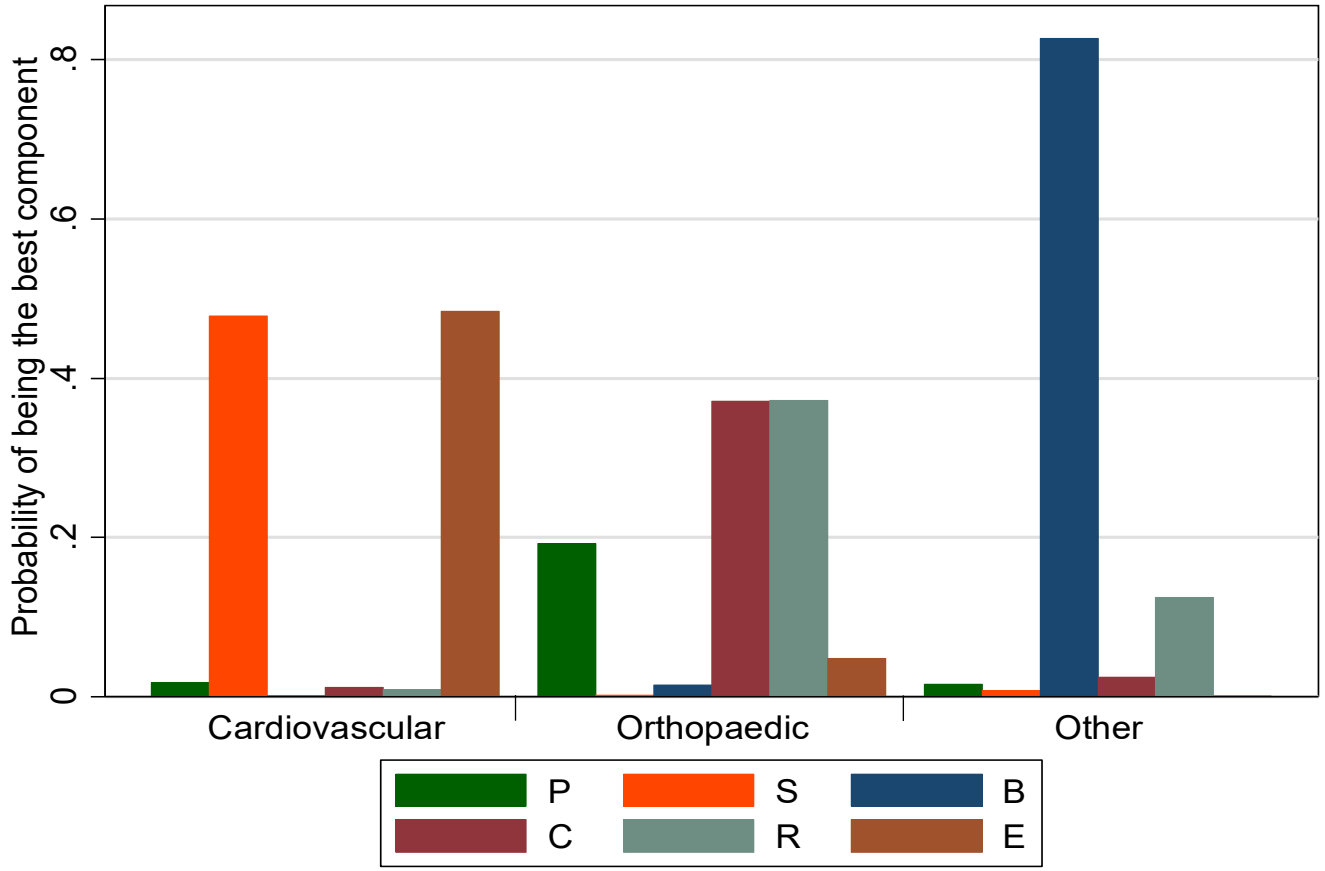


Length of Stay – Additive Effects

Intervention	Mean (95% Credible Interval)
Control group risk (centered on mean of 9 days)	-0.098 (-0.157, -0.043)
Procedural information (P)	-0.308 (-1.022, 0.360)
Sensory information (S)	-0.313 (-1.004, 0.439)
Behavioural instruction (B)	**-0.561 (-1.047, -0.111)**
Cognitive intervention (C)	-0.444 (-1.106, 0.214)
Relaxation techniques (R)	-0.368 (-1.154, 0.412)
Emotion-focused techniques (E)	1.296 (-0.028, 2.700)

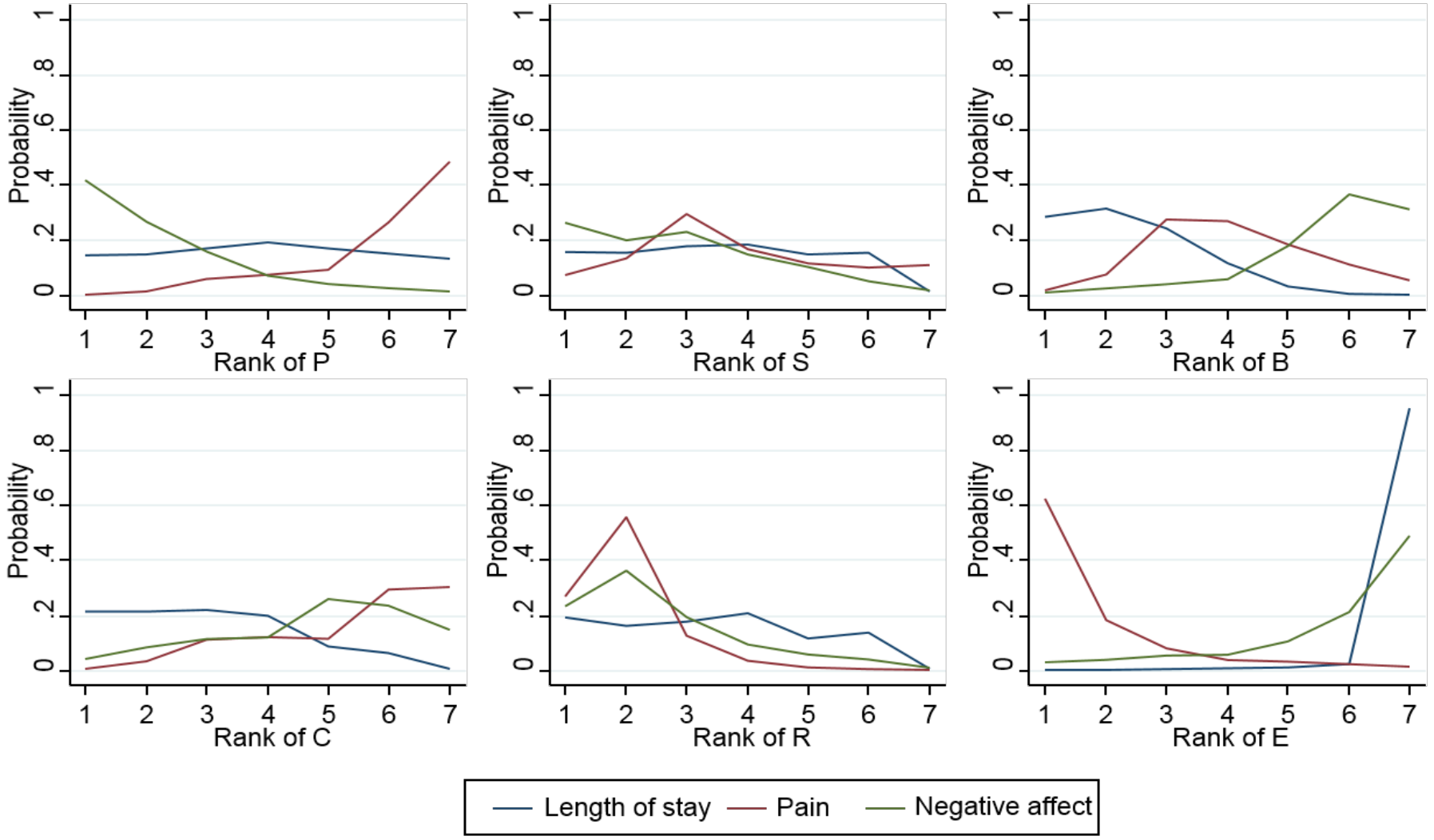
For every one day increase in control group length of stay, the length of stay in the intervention arm is reduced by 0.1 days

Effect of type of surgery on length of stay



Most effective component dependent on type of surgery

Simultaneous assessment across outcomes



Summary

- For all three outcomes the additive effects model was most appropriate
  - No important pairwise interactions between components were identified for any outcome
- Reduction in length of stay and negative emotion were associated with control group risk
- Procedural information, sensory information and behavioural instruction may reduce length of stay but this depends on type of surgery
- Relaxation effective at reducing pain
- No single component identified as most effective across all three outcomes

Limitations

- We only assessed pairwise interactions and the model may have been underpowered to identify pairwise interactions as there were few studies evaluating each component
  - There may be interactions between three or more components but too few studies to evaluate
- We assumed consistency between the direct and the indirect evidence but were unable to test this assumption
- Between-study heterogeneity only partly explained by inclusion of control group risk as a covariate
  - Is an additive scale inappropriate?
  - Could a ratio scale be better?

Conclusions

- Component network meta-analysis added value to an existing meta-analysis
  - Allowed us to answer more clinically relevant questions regarding effectiveness of individual components
- Component network meta-analysis could be more widely used in systematic reviews involving complex interventions
- This approach could be utilised when considering cost-effectiveness - more intensive interventions may be justified on cost-effectiveness grounds for certain types of surgery

Ongoing Projects in Component NMA

- Cochrane Tobacco Addiction
  - Behavioural interventions for smoking cessation

- Cochrane Dementia & Cognitive Improvement
  - Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients

References

Freeman SC, Scott NW, Powell R, Johnston M, Sutton AJ, Cooper NJ. Component network meta-analysis identifies the most effective components of psychological preparation for adults undergoing surgery under general anesthesia. *Journal of Clinical Epidemiology* 2018 https://doi.org/10.1016/j.jclinepi.2018.02.012

Powell R, Scott NW, Manyande A, et al. *Cochrane Database of Systematic Reviews* 26 MAY 2016 DOI: 10.1002/14651858.CD008646.pub2 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008646.pub2/full#CD008646

Welton NJ, Caldwell DM, Adamopoulos E, Vedhara K. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. *Am J Epidemiol* 2009:169 (9);1158-1165

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Further Topics

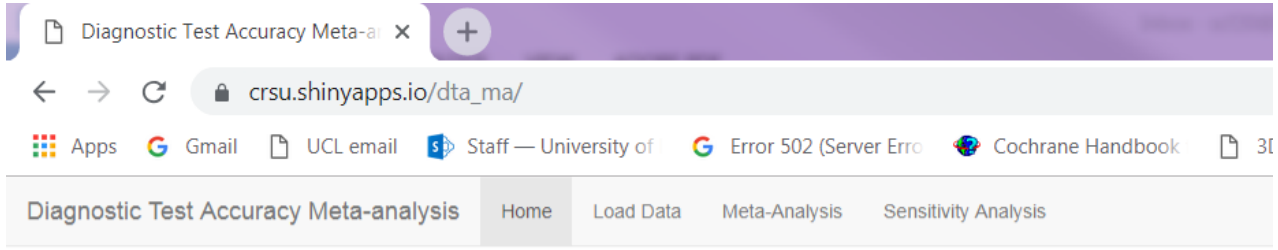
The Complex Reviews Support Unit (CRSU) is funded by the National Institute for Health Research (project number 14/178/29)

OUTLINE

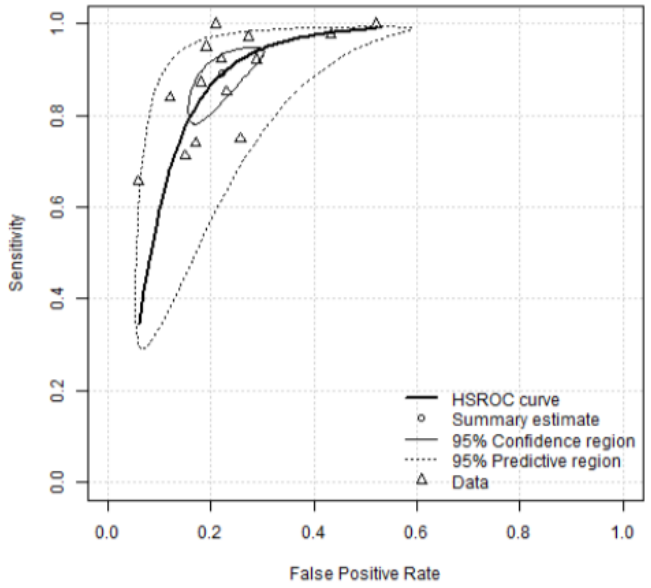
✓Network meta-analysis

- Diagnostic Test Accuracy Reviews
  - DTA-MA App https://crsu.shinyapps.io/dta_ma/
- Individual patient data
- Prognostic Reviews
- Sequential analysis
- Using evidence synthesis to help inform the next study
- Non-statistical synthesis of qualitative data
- How can the CRSU help your group

Diagnostic Test Accuracy Meta-analysis



Diagnostic Test Accuracy Meta-Analysis



Suzanne Freeman, Clareece Kerby, Nicola Cooper, Alex Sutton

For feedback/questions about this app please contact suzanne.freeman@leicester.ac.uk

App powered by Rshiny with statistical analyses performed using the package lme4:

https://CRAN.R-project.org/package=lme4

Tuesday 18th September 11:00 – 11:10 Carrick 3, OS43

'An interactive web application to aid diagnostic test accuracy meta-analysis'

https://crsu.shinyapps.io/dta_ma/

Individual Patient Data (IPD)

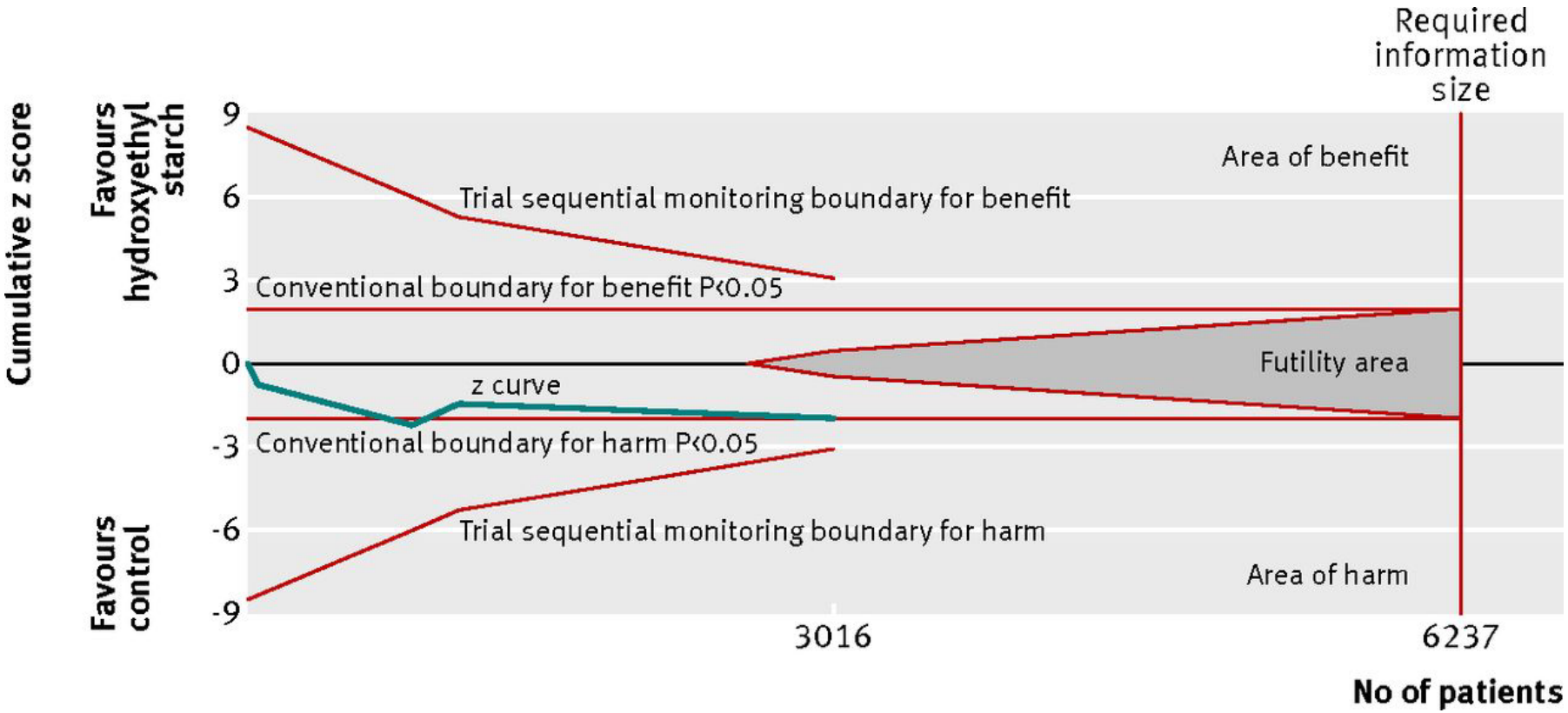
- Desirable
- Can greatly improve power and reliability of patient level covariate (e.g. subgroup) analyses
- IPD models for pairwise meta-analysis and NMA possible
- IPD diagnostic test models evolving
- Often not possible to obtain IPD from all relevant studies
  - Methods to use IPD where available and summary data otherwise exist

Prognostic Reviews

- First Cochrane pilots / exemplar reviews underway
- Under developed area
- Seek guidance from Cochrane Prognostic Review Methods Group in the first instance
- CRSU has some, but not extensive, experience

Trial Sequential Analysis (TSA)

- TSA used to adjust meta-analysis for multiple looks at the data when a M-A is updated
  - Similar to interim analysis in a single clinical trial
  - Crudely, the effect will be to make p-values less “significant”



Using evidence synthesis to help inform the next study

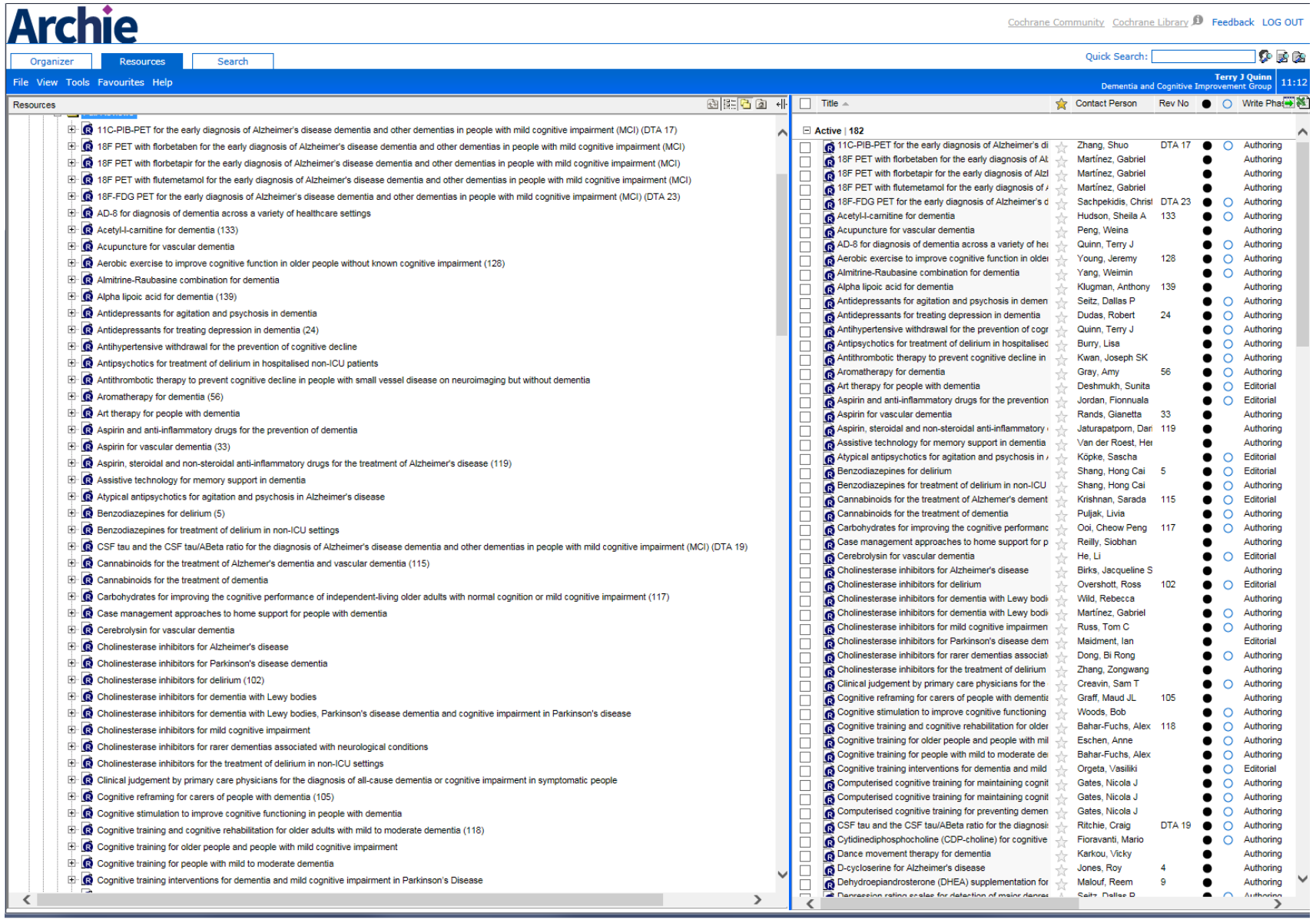
- Related to TSA is the issue of how a meta-analysis should inform the design of future studies
  - Including comparators & sample size
- Would you be comfortable with a £1 million trial going ahead that had 0 chance of changing the conclusion of an existing meta-analysis?
  - When there is some heterogeneity this is very possible(!)
- Should Cochrane reviews place more emphasis here and play an active role in Evidence Based Research?

  “Inform the future as well as summarise the past”

Narrative synthesis of qualitative data

- Textually describing the overall effect noting variations in study characteristics, implementation, etc.
- Synthesis involved bringing data together at some level – more than simply summarising one study at a time
- Used when high level of heterogeneity contra-indicate meta-analysis
  - Not just when statistical heterogeneity – other sources include study design, conceptual (intervention, outcome, context, population)
- Identifies patterns and explanations for variation in effects
  - E.g. what works for who, in what circumstances
- Workshops on this over the last couple of days by Hilary Thomson and others.

How can CRSU help your group



Cochrane
Dementia and
Cognitive Improvement

How can CRSU help your group

Cochrane
Dementia and
Cognitive Improvement

Studies needing updates
Donepezil for vascular dementia
Galantamine for vascular dementia
Rivastigmine for vascular dementia
Non-pharmacological (multi-component) interventions for managing delirium
IQCODE for detection of dementia
AD-8 for detection for dementia
Exercise interventions in dementia

How can CRSU help your group

Cochrane
Dementia and
Cognitive Improvement

Studies needing updates	Can CRSU help
Donepezil for vascular dementia	NMA of cholinesterase inhibitors in vascular dementia
Galantamine for vascular dementia	
Rivastigmine for vascular dementia	
Non-pharmacological (multi-component) interventions for managing delirium	Component NMA of non-pharm interventions
IQCODE for detection of dementia (x3)	Overview of informant tools for detection of dementia Comparative DTA
AD-8 for detection for dementia	
Exercise interventions in dementia	Implications for research – what size should the next study be…….

NIHR CRSU - Complex Reviews Support Unit

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