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– progress and hurdles!

Peter Hutchinson



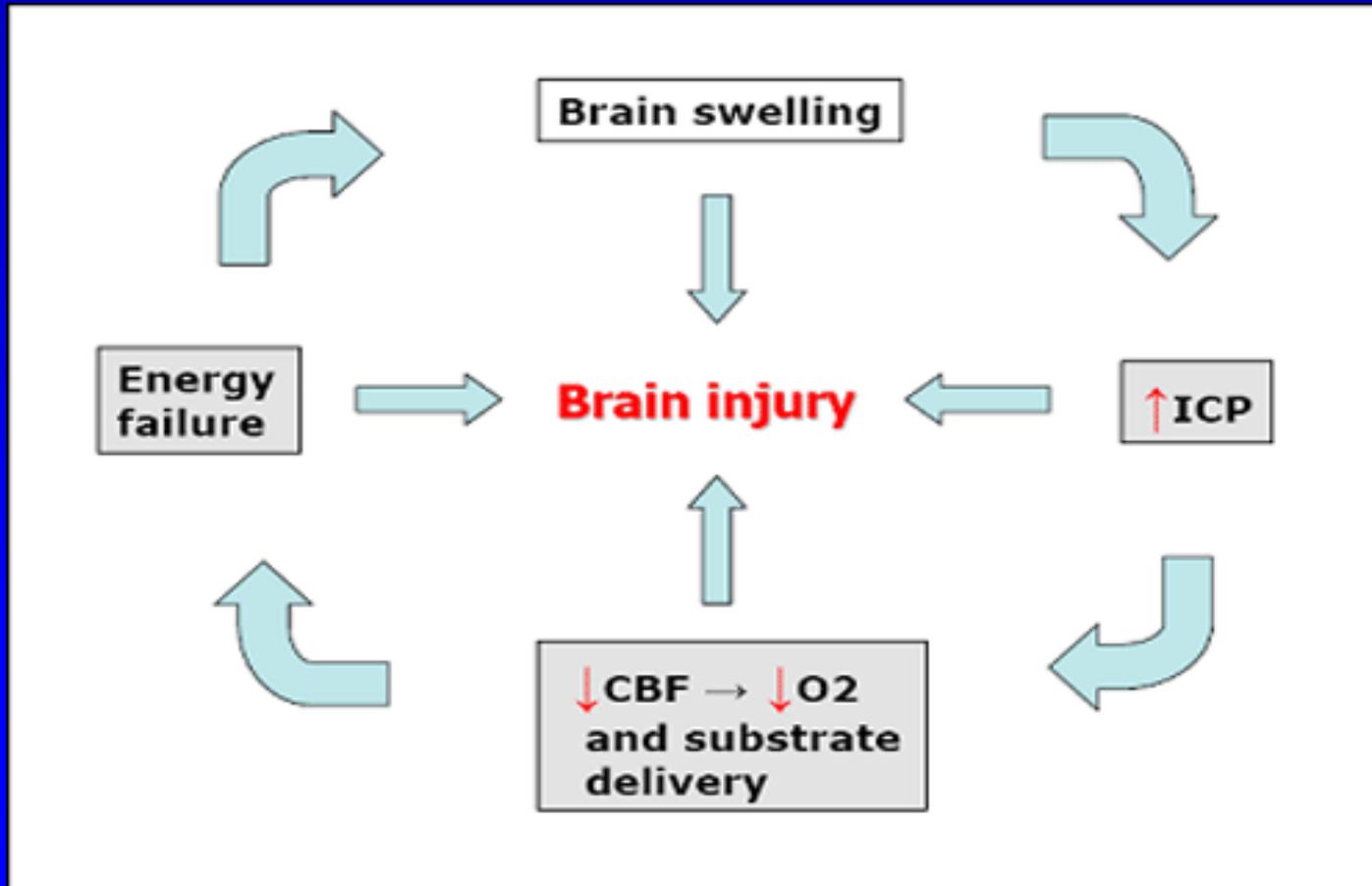
Academic Neurosurgery
University of Cambridge



Head Injury

- 1 000 000 A&E attendances per annum
- Majority minor
- Severe head injury is the commonest cause of death under the age of 40
- Survivors often severe disability
- Approx 10-15% of patients with severe head injury develop major brain swelling and uncontrollable elevation of intra-cranial pressure

The escalating cycle of brain swelling



NCCU – Head injury management

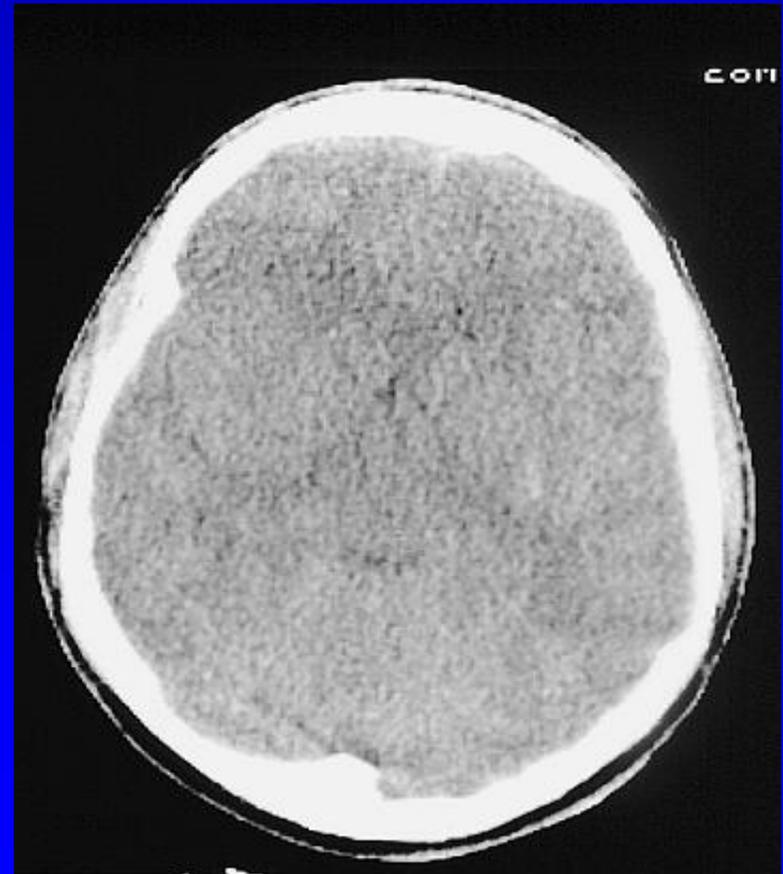
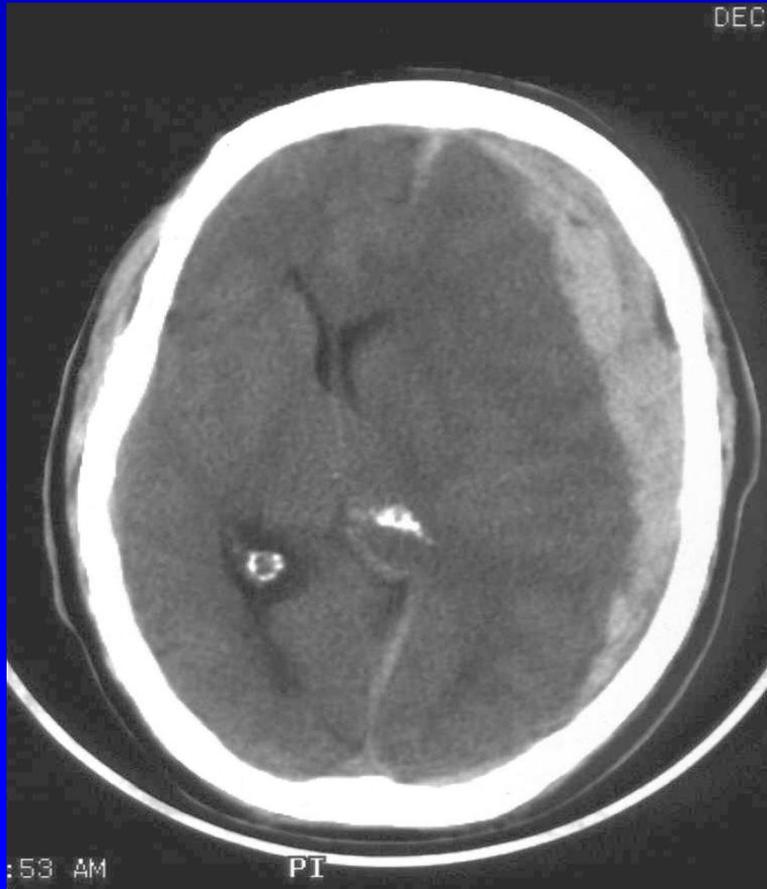
ICP < 25 mmHg

- **Stage I**
 - Sedation and ventilation
 - Nurse, head up
 - Control arterial CO₂ 4.5 kPa
- **Stage II**
 - External ventricular drain
- **Stage III**
 - Inotropes / hypertonic saline / mannitol
- **Stage IV**
 - Hypothermia
- **Stage V**
 - Barbiturates -Thiopentone
 - Decompressive craniectomy

Indications for surgery

Established

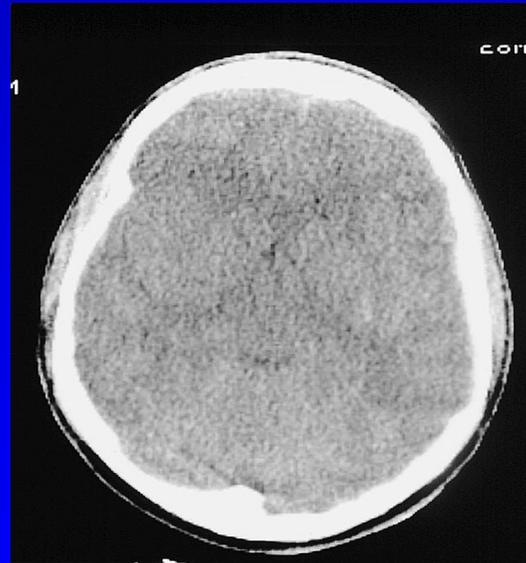
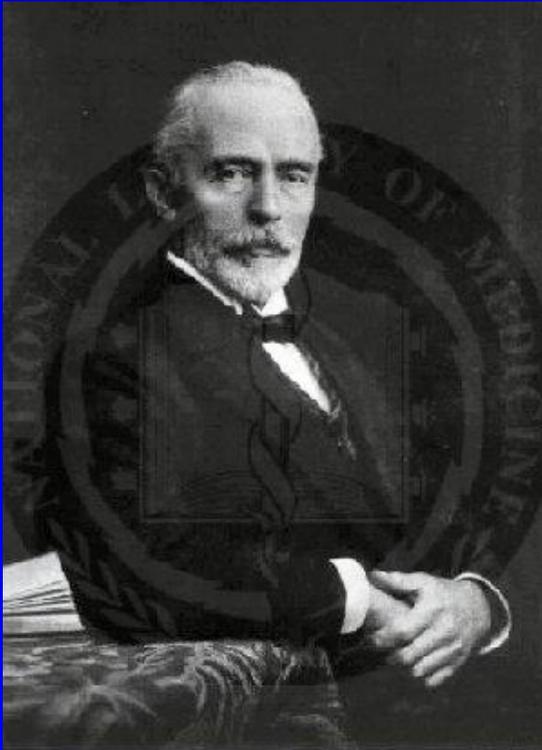
Unknown



Decompressive Craniectomy

‘If there is no CSF pressure, but brain pressure exists, then pressure relief must be achieved by opening the skull’

Kocher 1901



Does decompressive craniectomy work?



Brain Trauma Foundation

www.braintrauma.org

- DC may be a useful **option** when maximal medical treatment has failed to control ICP
- Bifrontal decompressive craniectomy within 48 hours of injury is a treatment **option** for patients with diffuse, medically refractory posttraumatic cerebral edema and resultant intracranial hypertension

Proposal for a Clinical Trial of Decompressive Craniectomy in TBI

The RESCUE_{icp} study

Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of ICP

Academic Neurosurgery University of Cambridge

European Brain Injury Consortium


National Institute for
Health Research

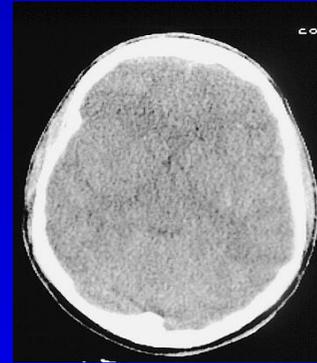

MRC | Medical
Research
Council


The
Health
Foundation


The Academy of
Medical Sciences

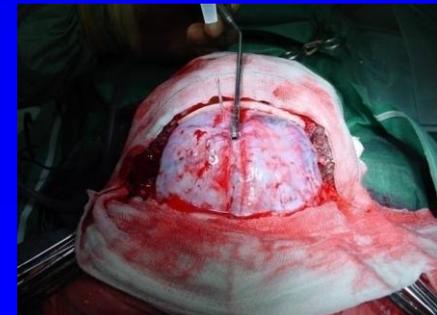
Principal hypothesis

- The application of decompressive craniectomy to head-injured patients with raised and refractory ICP results in improvement in outcome compared to optimal medical management



+ ICP > 25
↓
mmHg

?



Prospective randomised study

Target study group n=400

Ventilated patients with refractory intracranial hypertension

Advanced medical management (inc barbiturates)

∨

Surgical management (decompressive craniectomy)

Outcome assessed at 6 months, 1 year and 2 years using extended Glasgow Outcome Score and SF-36

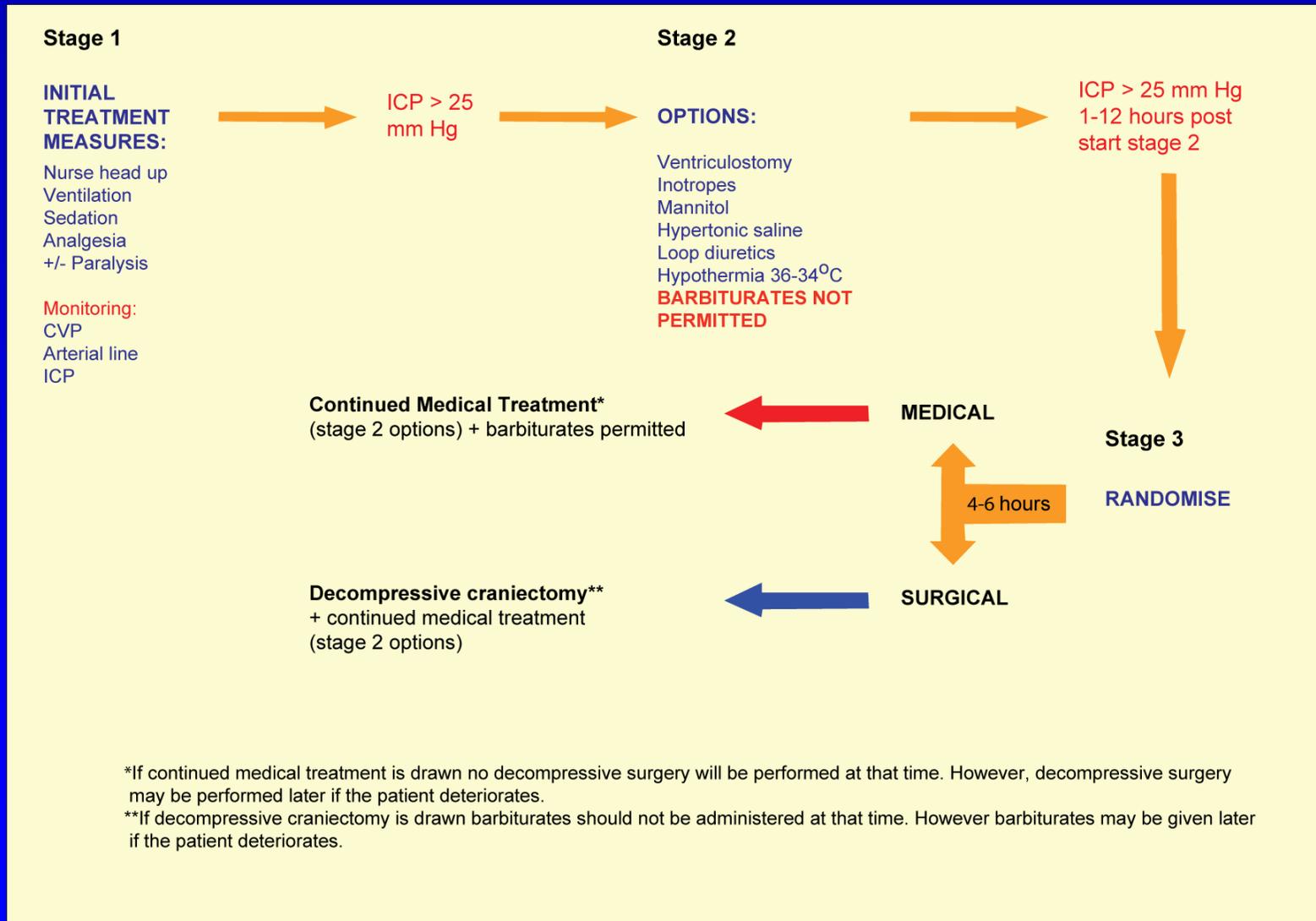
Progress

- Research Team
- Protocol
- Ethics
- R&D
- Randomisation
- Flow chart
- Case report form
- Data monitoring
- Funding - £1.15m

The Team

- Research Fellow
 - Ivan Timofeev
 - Angelos Kolias
- Research Nurse
 - Liz Corteen
- Academic FY2
 - Lucia Li
- University of Cambridge
- Research Services
- Addenbrooke's Hospital
- NHS R&D

The Protocol



Approval, consent and randomisation

- Approval
 - Ethics – information sheet
 - National ethical approval in the UK
 - R and D approval
 - Contracts
- Consent / Assent
 - next of kin *on* admission avoid delays in randomisation or independent consultant
- Randomisation
 - 24 hour international telephone number - switchboard
 - stratified by centre



RESCUE_{icp} - how to recruit a patient

Check inclusion and exclusion criteria

When patient reaches treatment stage 3, complete randomisation sheet

Obtain assent from next of kin if not already available

Telephone +44 (0) 1223 274534 to give details from randomisation sheet

Fax randomisation sheet to +44(0)1223414396 or email: liz@rescueicp.com

Complete data collection sheets including daily physiological data

When the patient is discharged from ITU, please post the data collection sheet to Liz Corteen. For the UK centres follow up will be arranged centrally. International centres should send questionnaires to their patients at 6 months and forward completed forms to Liz Corteen.

Miss E Corteen, University department of neurosurgery (box 167), Addenbrookes' hospital,
Level 4, Hills road, Cambridge, CB2 2QQ, England

Data collection and follow-up

CRF paper based

Postal questionnaire and telephone follow up

Nomadic, cognitive issues

>94% 6 months follow up

 RESOLVE_{ICP} data collection sheet		Date of completion: Person completing the form: Signature:																									
Index data		Page 1																									
1. Centre name: 2. Consultant: 3. Patient's name: 4. Age: 5. Date of birth: 6. Male <input type="checkbox"/> Female <input type="checkbox"/> 7. Contact telephone number: 2 nd contact telephone number: 8. Hospital number: 9. Patient's address: 9a. Name and contact details of the next of kin: 9b. Name, address and telephone number of patient's GP:	10. Does the patient have a history of drug or alcohol abuse? Yes <input type="checkbox"/> No <input type="checkbox"/> immunosuppression? Yes <input type="checkbox"/> No <input type="checkbox"/> 11. Mechanism of injury: Motor vehicle occupant <input type="checkbox"/> Domestic <input type="checkbox"/> Pedestrian <input type="checkbox"/> Sport <input type="checkbox"/> RTA other <input type="checkbox"/> Fall <input type="checkbox"/> Work <input type="checkbox"/> Assault <input type="checkbox"/> Other: 12. Hypoxic episode within 1 st 24 hrs? No <input type="checkbox"/> Suspected <input type="checkbox"/> Definite (PO ₂ a <8kpa) <input type="checkbox"/> 13. Hypotensive episode within 1 st 24 hrs? No <input type="checkbox"/> Suspected <input type="checkbox"/> Definite (syst. BP <90mmHg) <input type="checkbox"/>	14a. <table border="0" style="width: 100%;"> <tr> <td>Date (dd mm yy)</td> <td>Time (24h)</td> <td>GCS</td> </tr> <tr> <td><input type="text"/></td> <td><input type="text"/></td> <td>E M V</td> </tr> <tr> <td colspan="2">Injury: <input type="text"/></td> <td><input type="text"/></td> </tr> <tr> <td colspan="2">1st hospital: <input type="text"/></td> <td><input type="text"/></td> </tr> <tr> <td colspan="2">Neuro Unit: <input type="text"/></td> <td><input type="text"/></td> </tr> <tr> <td>Pupils on arrival to neuro unit:</td> <td>Size mm</td> <td>Reaction to light</td> </tr> <tr> <td>Left</td> <td><input type="text"/></td> <td>Yes <input type="checkbox"/> No <input type="checkbox"/></td> </tr> <tr> <td>Right</td> <td><input type="text"/></td> <td>Yes <input type="checkbox"/> No <input type="checkbox"/></td> </tr> </table> 14b. Reason for any delay in transfer: 14c. Sedated and ventilated on arrival to Neuro Unit? Yes <input type="checkbox"/> No <input type="checkbox"/> 15. Extra-cranial injuries <input type="checkbox"/> Chest: rib #s (>2 adjacent); haemothorax, pneumothorax, pulm contusion <input type="checkbox"/> CVS: myocard contusion, pericard effusion; major vasc injury <input type="checkbox"/> Pelvis: haemodynamically significant or unstable # <input type="checkbox"/> Spine: # dislocation, unstable injury, neurological deficit <input type="checkbox"/> Long bone: multiple (>2) or compound proximal long bone #, amputation at/above wrist/ankle <input type="checkbox"/> Abdomen/pelvis: Organ laceration, contusion or perforation <input type="checkbox"/> Neck: Penetrating injury, airway compromise		Date (dd mm yy)	Time (24h)	GCS	<input type="text"/>	<input type="text"/>	E M V	Injury: <input type="text"/>		<input type="text"/>	1 st hospital: <input type="text"/>		<input type="text"/>	Neuro Unit: <input type="text"/>		<input type="text"/>	Pupils on arrival to neuro unit:	Size mm	Reaction to light	Left	<input type="text"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>	Right	<input type="text"/>	Yes <input type="checkbox"/> No <input type="checkbox"/>
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Hurdles

- Administration
- Ethics
- R&D
- Contracts
- The Budget
- NHS support costs
- Protocol insurance
- Clinical
- Recruitment rate
- Trial fatigue
- Lack of equipoise
- Crossover
- Results from other studies

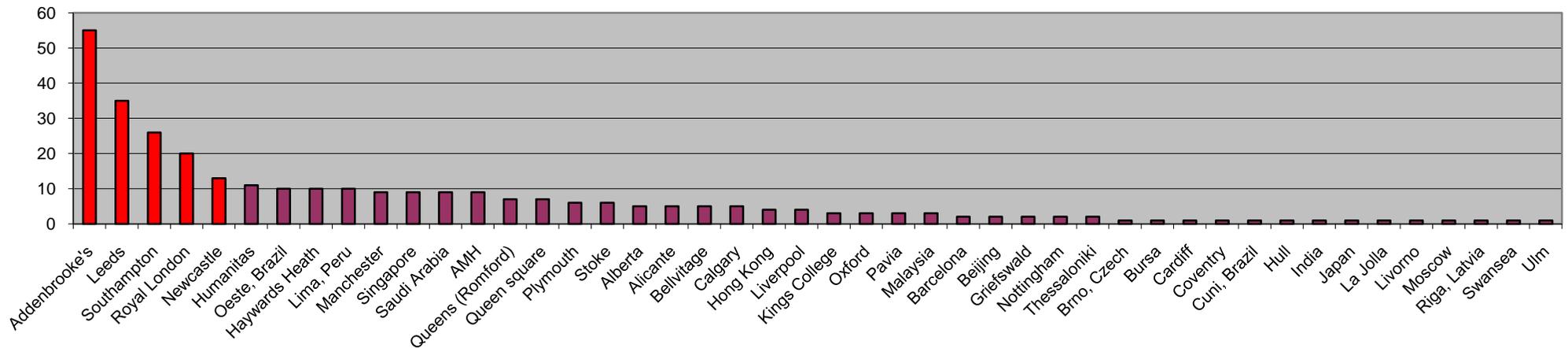
Protocol insurance

- Became an issue in 2009
- No new contracts / new centres without insurance
- Cost worldwide insurance £250 000
- Solution
 - Blanket country policy £42000
 - UK
 - Canada
 - Australia
 - Singapore
 - Malaysia
 - USA

Recruitment by centre

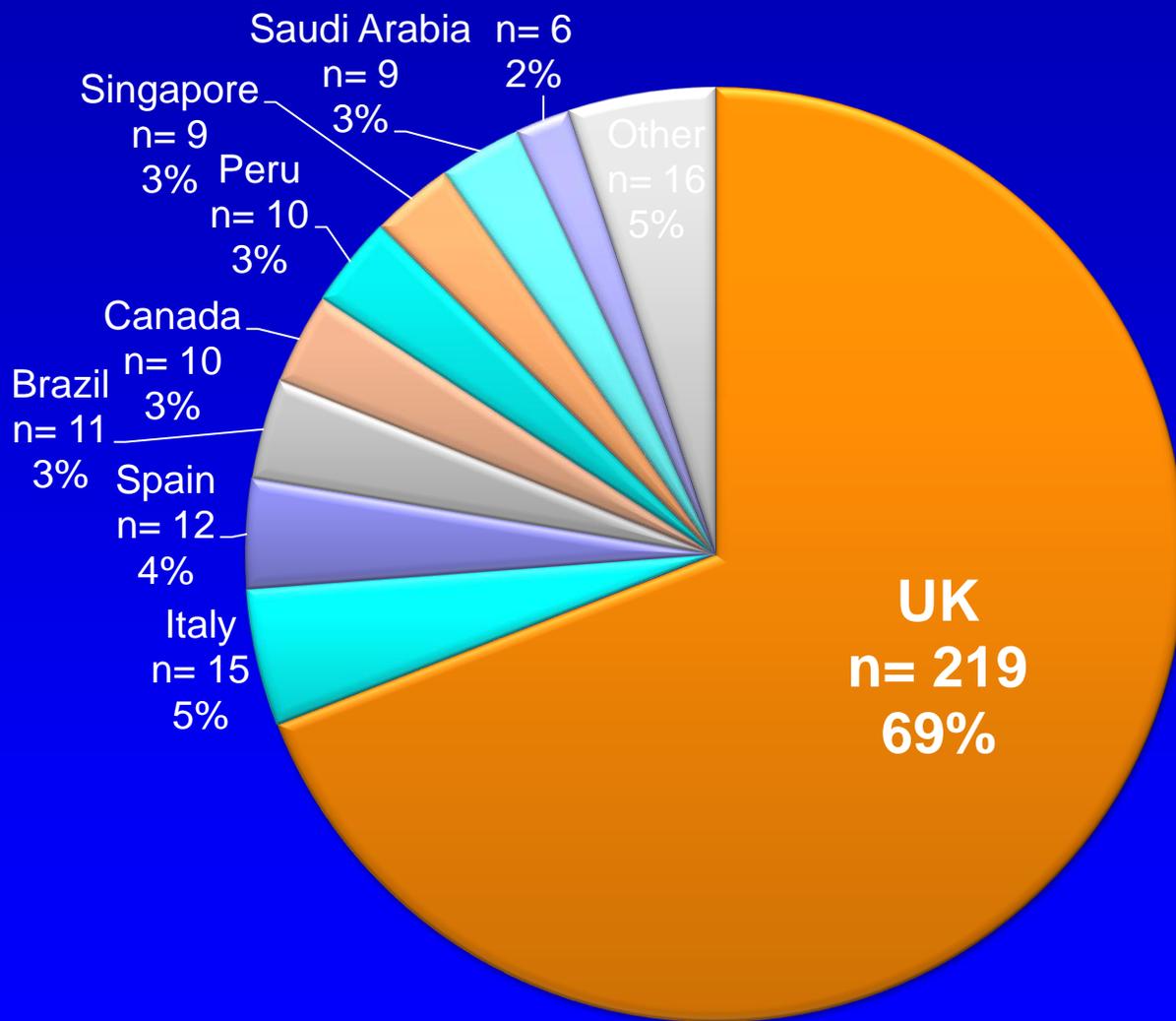
n=317 / 400

47 centres

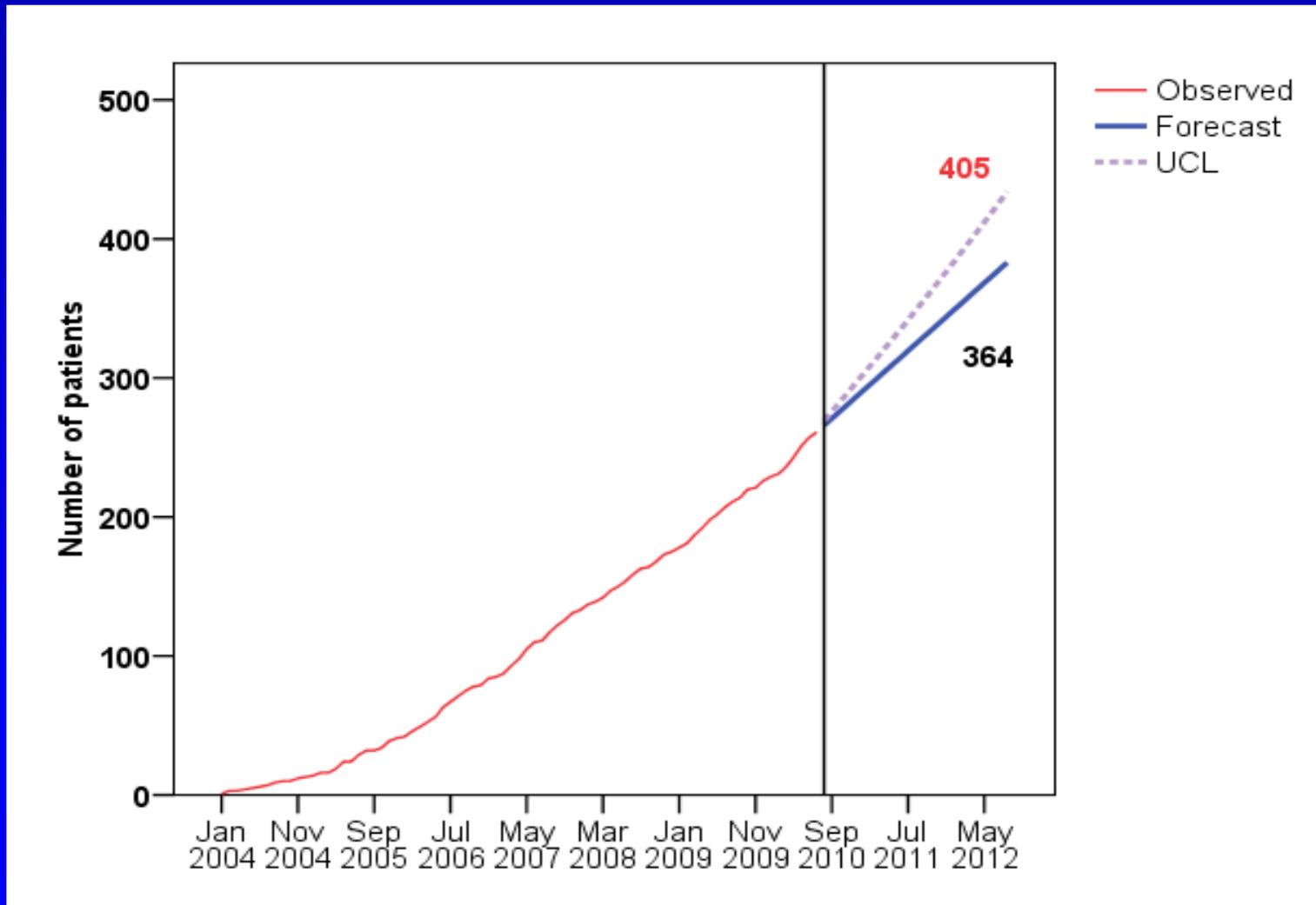


Recruitment by country

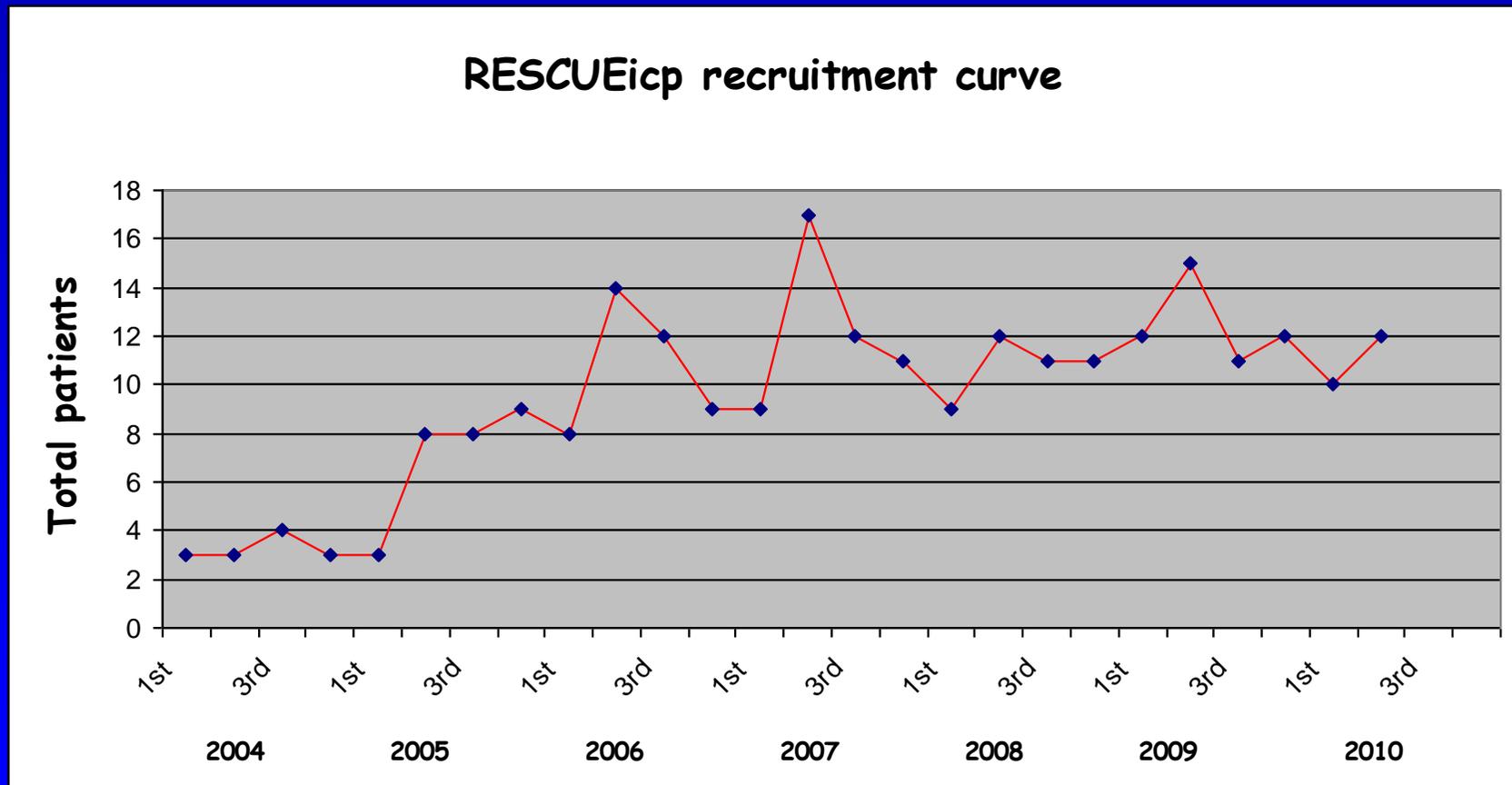
UK Italy Spain Brazil Canada China Peru Singapore Saudi Arabia Other



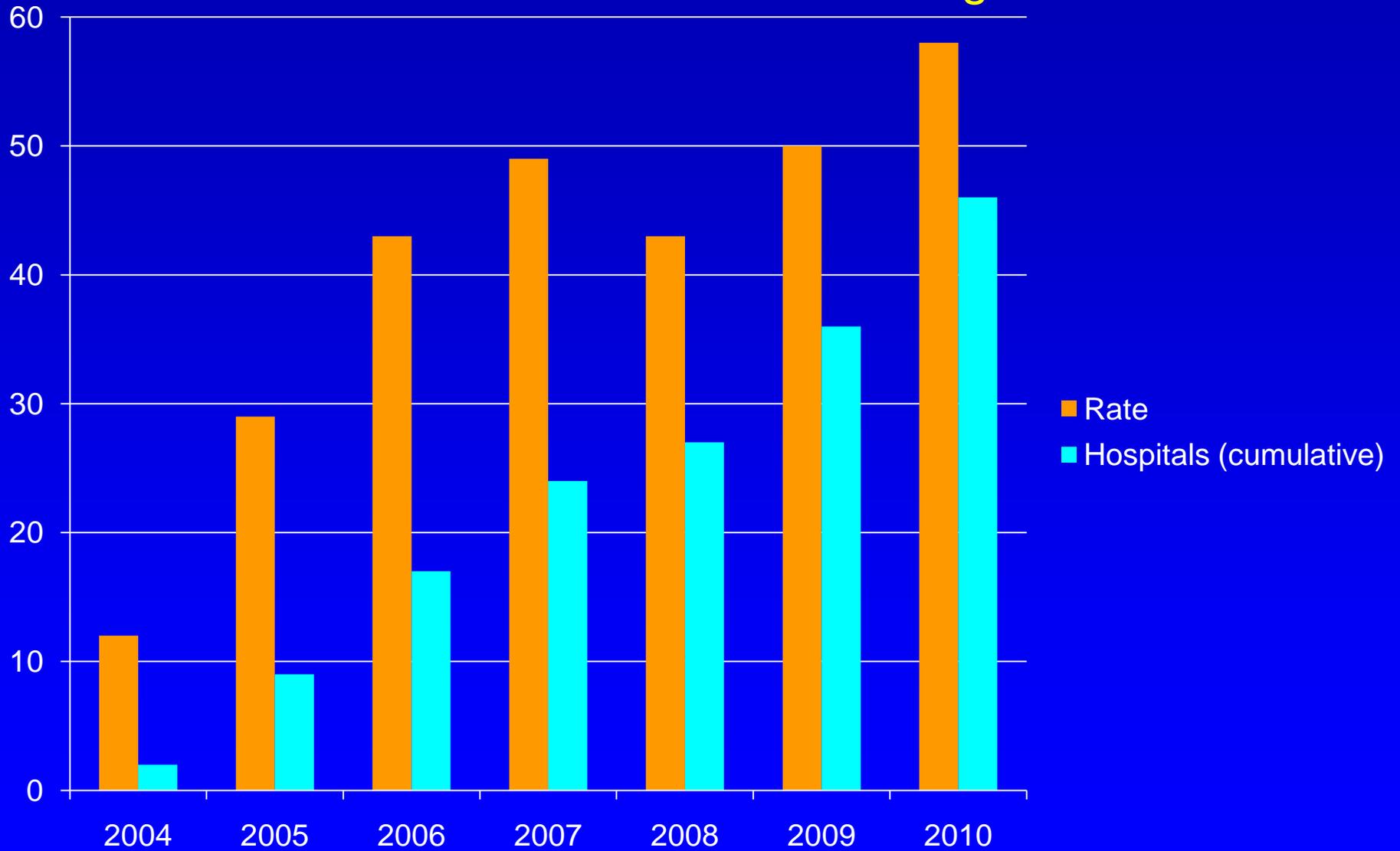
Current recruitment forecast for April 2012



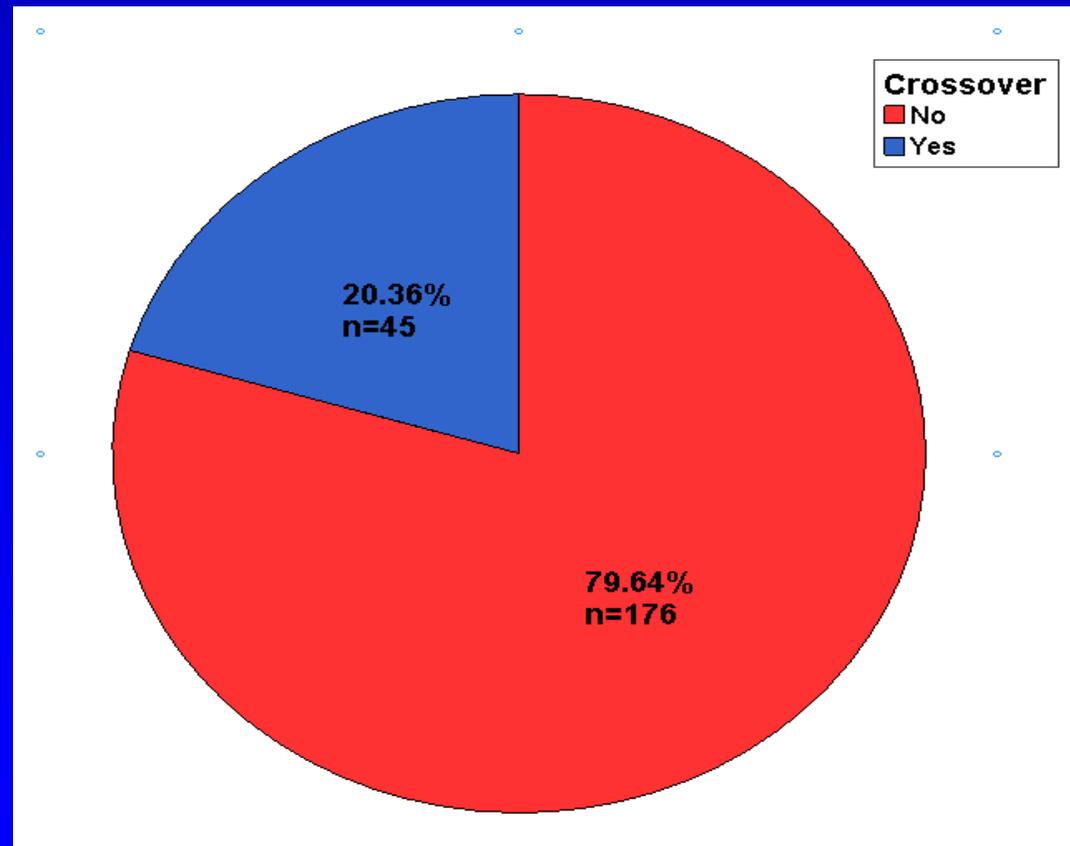
Recruitment curve



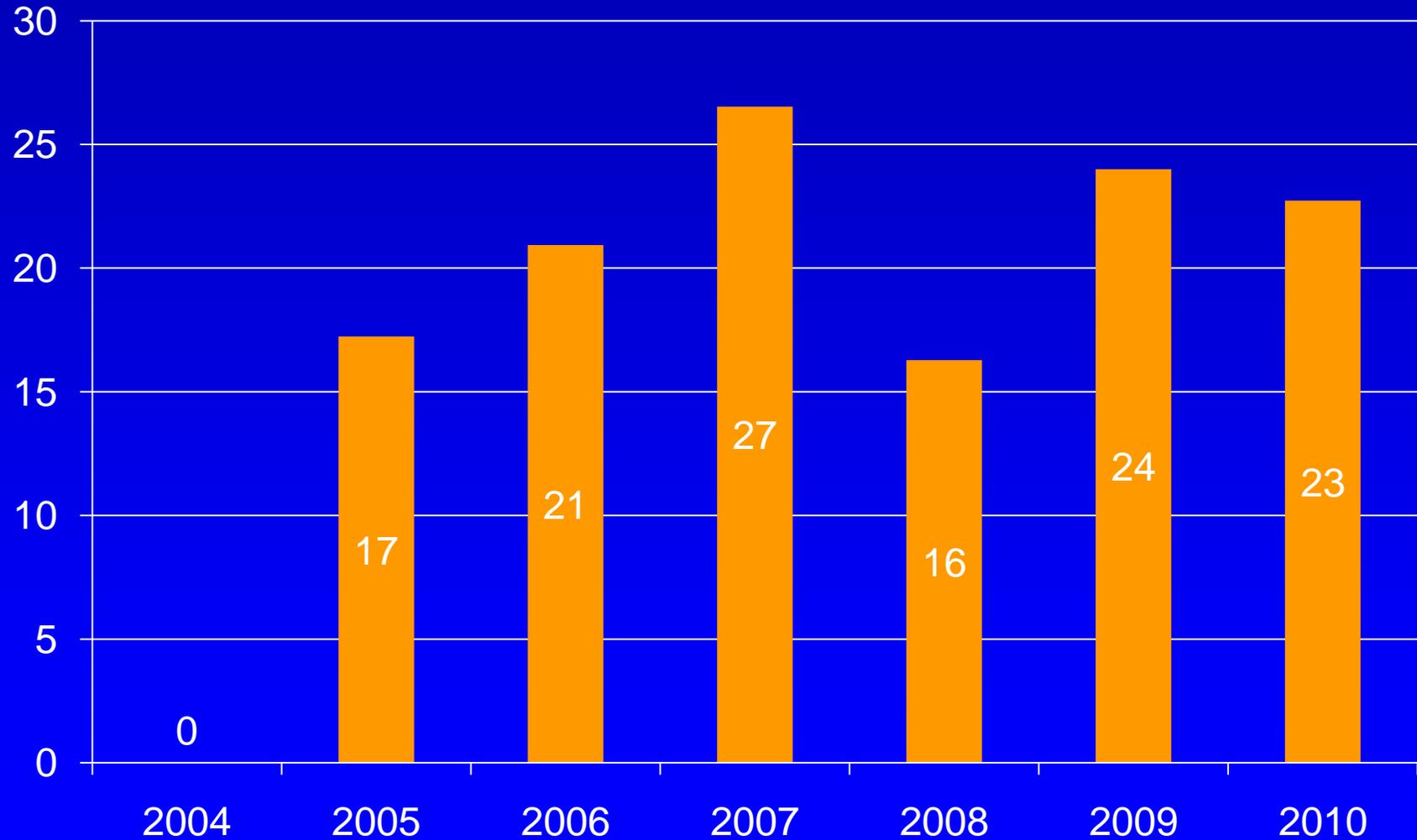
Recruitment v number of centres recruiting



Crossover – a problem for surgical trials total

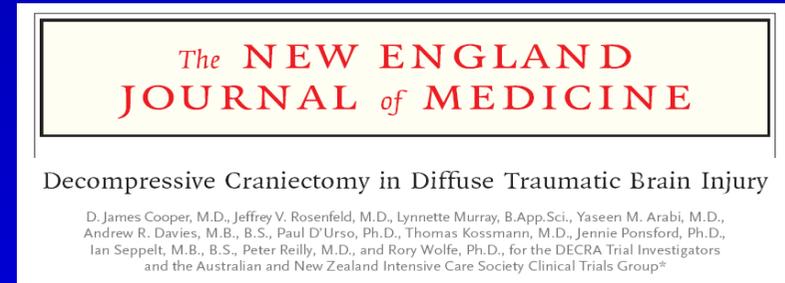


Crossover as % of annual recruitment



What happens to recruitment
when a similar study is
published!!!

Randomised trials of decompressive craniectomy for TBI



- RESCUEicp
- Cambridge UK
- 400 patients
- Recruitment on-going
- 10-65 years
- Raised ICP refractory to protocol-based medical management
- ICP threshold 25mmHg

- DECRA
- Melbourne Australia
- 155 patients randomised
- Completed
- 15-60 years
- Severe diffuse brain injury within 72 hours injury
- ICP threshold 20mmHg

DECRA – results – decompressive craniectomy resulted in worse outcome

Outcome	Decompressive Craniectomy (N = 73)	Standard Care (N = 82)	P Value†
Extended Glasgow Outcome Scale			
Score — no. (%)			
1 (dead)	14 (19)	15 (18)	
2 (vegetative state)	9 (12)	2 (2)	
3 (lower severe disability)	18 (25)	17 (21)	
4 (upper severe disability)	10 (14)	8 (10)	
5 (lower moderate disability)	13 (18)	20 (24)	
6 (upper moderate disability)	6 (8)	13 (16)	
7 (lower good recovery)	2 (3)	4 (5)	
8 (upper good recovery)	1 (1)	3 (4)	
Median score (IQR)	3 (2–5)	4 (3–5)	0.03
Unfavorable score of 1 to 4 — no. (%)	51 (70)	42 (51)	0.02

Summary - project timeline

- 2004: start of recruitment
- 2007: MRC/NIHR Clinical Trials Grant awarded (2nd attempt)
- 2011: applying for grant extension
- December 2012: end of recruitment
- June 2013: 6 months follow-up completed (primary endpoint)
- October 2013: trial results (6 month follow-up) published
- December 2013: 1 year follow-up completed
- April 2014: 1 year follow-up results published
- December 2014: 2 year follow-up completed (end of trial)
- April 2015: 2 year follow-up results published

RESCUEicp – study - conclusion

- Decompressive craniectomy is a treatment option for patients with refractory posttraumatic cerebral oedema and resultant intracranial hypertension
- But..
- Has a significant complication rate
- May be performed in patients who will do well with medical treatment alone
- Risks severe disability and vegetative state
- RESCUEicp on going 83 more out of 400 needed!
- A long journey 2004-2014
- Ups and downs
- Travelling
- Visiting different units
- Hurdles – some avoidable, some unavoidable
- Would we do it again?
- Son of RESCUEicp in preparation!

Acknowledgements- thank you!

- Peter Kirkpatrick
- John Pickard
- Ivan Timofeev
- Angelos Kalias
- Liz Corteen
- Lucia Li
- Marek Czosnyka
- David Menon
- Barbara Sahakian
- Medical / Nursing Staff on NCCU
- Martin Buxton
- David Mendelow
- Patrick Mitchell
- Graham Teasdale
- Franco Servadei
- Gordon Murray
- Juan Sahuquillo
- Andy Unterberg
- Local investigators

- Hugh Richards
- Donald Shaw
- Martin Smith
- Lennart Persson

- Anthony Bell
- Mark Dearden
- Nicola Latronico
- Eckhard Rickels



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