Investigator-led trials: challenges and opportunities

Peter Sandercock

University of Edinburgh

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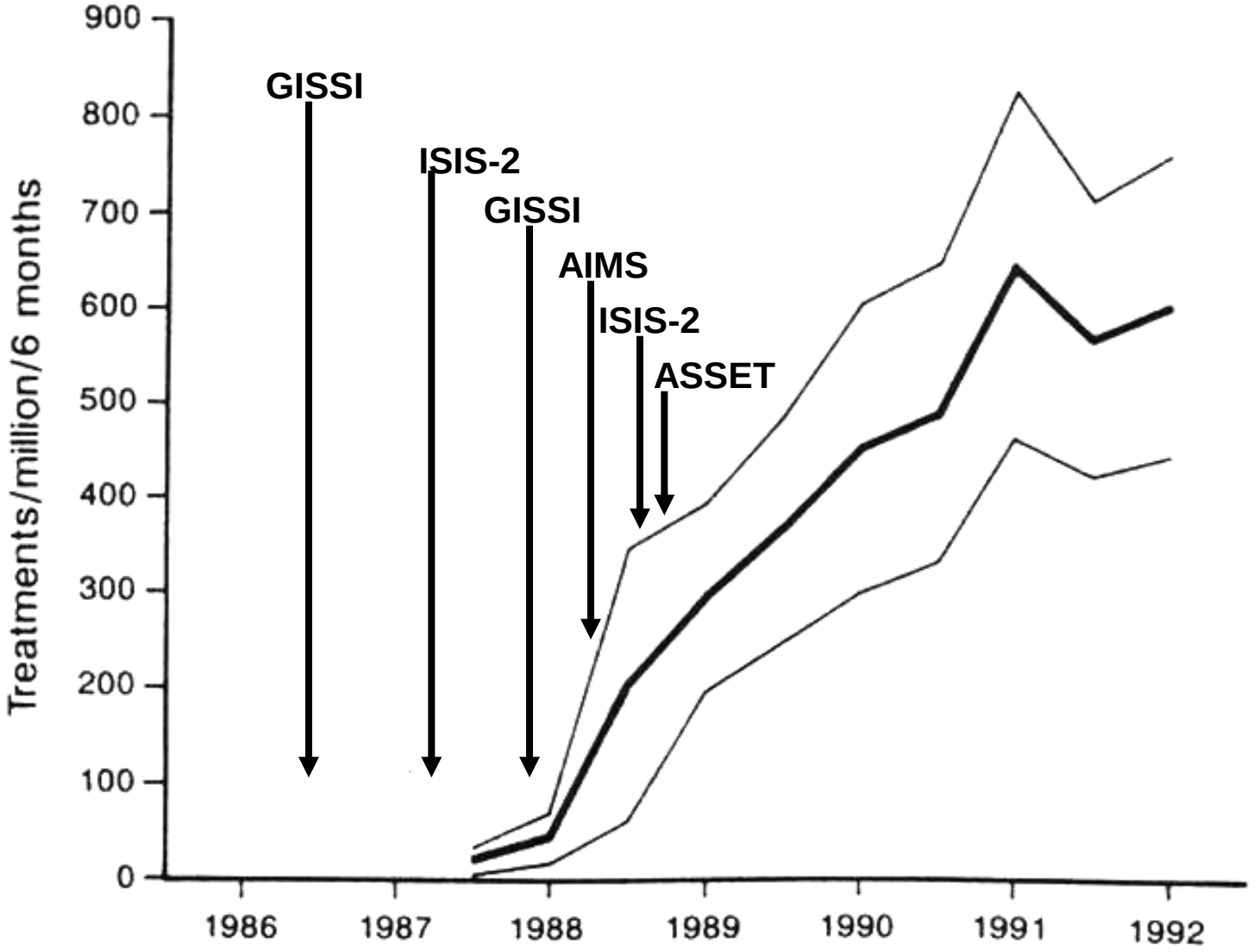
Outline

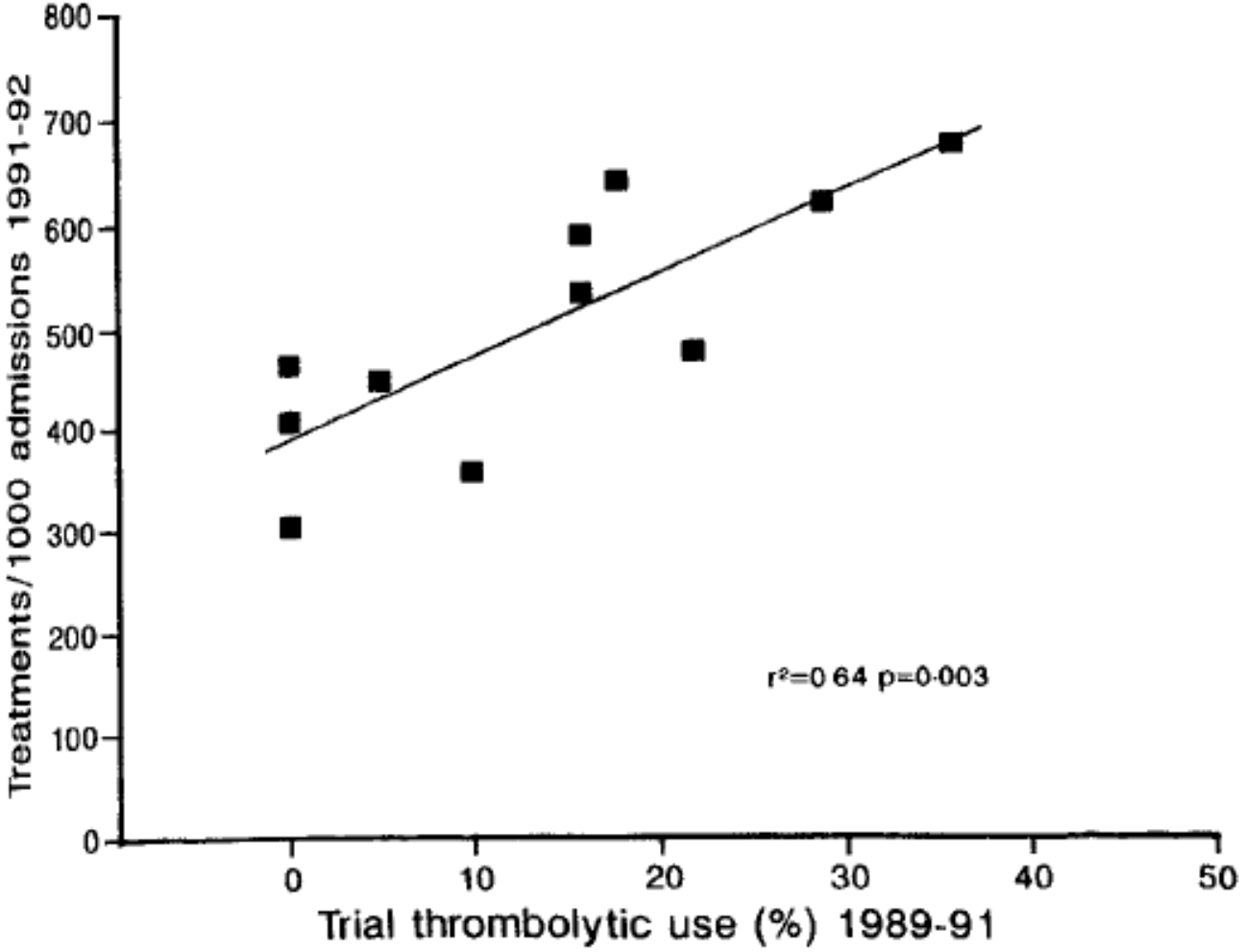
- Importance of investigator led trials
  - Impact on clinical practice
  - Training and education
  - Innovation
- What was feasible: life was easier!
- Challenges now
- Opportunities

Thrombolysis for the treatment of acute myocardial infarction (MI): huge increase after megatrials



Ketley and Woods Lancet 1993: 342: 891-4

Why impact?: Extent of participation in trials and implementation of new Rx



Innovation: key stroke trials all investigator led

Stroke prevention

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

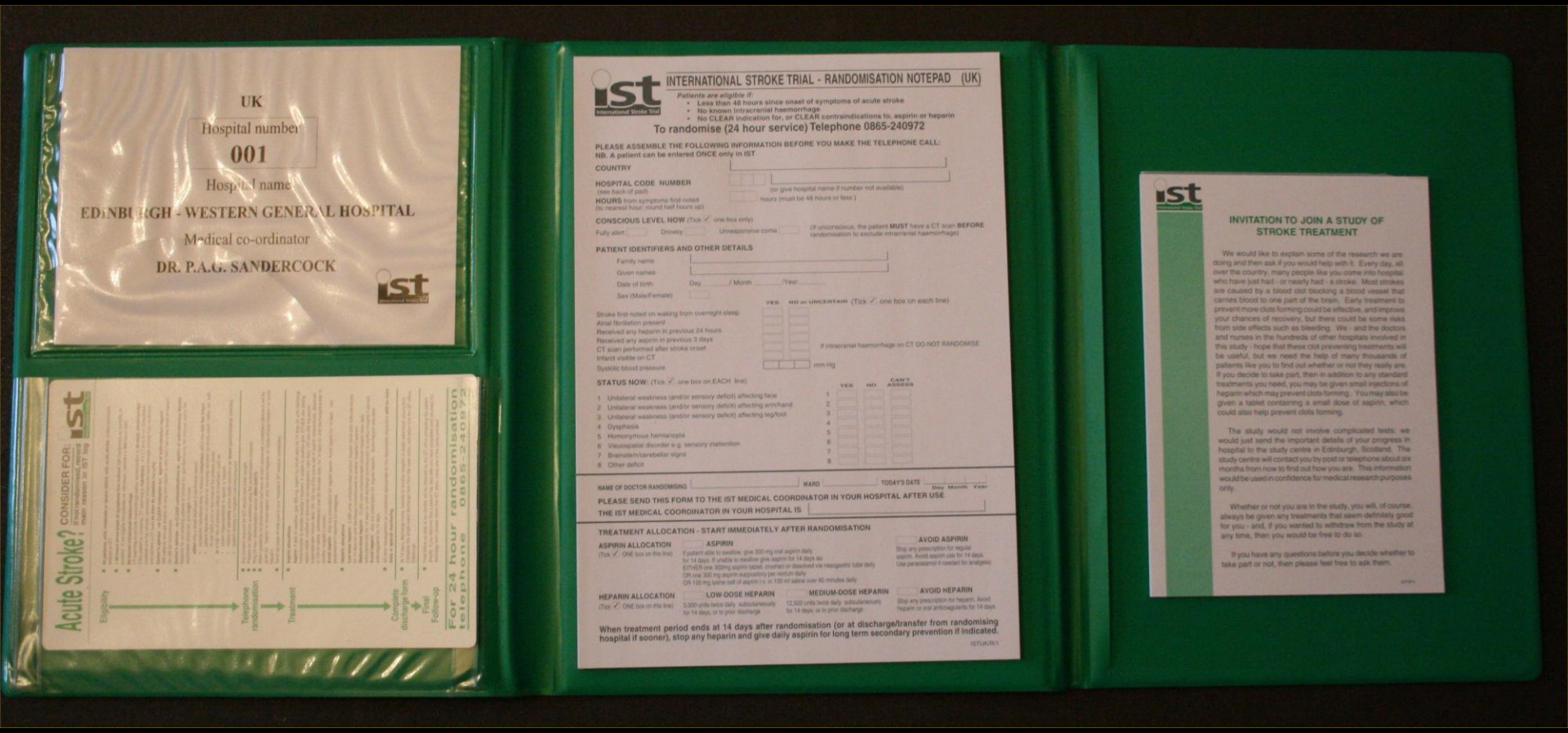
Stroke treatment

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

What was feasible in 1993. CAST & IST-1

- Broad entry criteria, stroke <48 hours
- IST: Aspirin vs open control. Telephone randomisation
- CAST: Aspirin vs placebo. Pack randomisation
- Only local ethical approval required
- Consent: give patient information leaflet, record consent in medical notes – no need for signed consent form
- Training: none needed!

The IST-1 materials



That really was everything!

Patients and centres

	CAST	IST-1
No. randomised	20,655	19,435
No Countries	1	37
No centres	413	467
Follow-up	99%	99%

Fast forward to 2000

Main features of IST - 3

- Randomised, open, blinded outcomes study of i.v. rt-PA vs control,
- Target 6000 patients, 200 centres
- Patients < 6 h of acute ischaemic stroke
- Primary outcome: the proportion of patients alive and independent at six months
- Randomisation by telephone or internet
- Training: NIHSS, CT, thrombolysis, GCP

ist-3 Thrombolysis

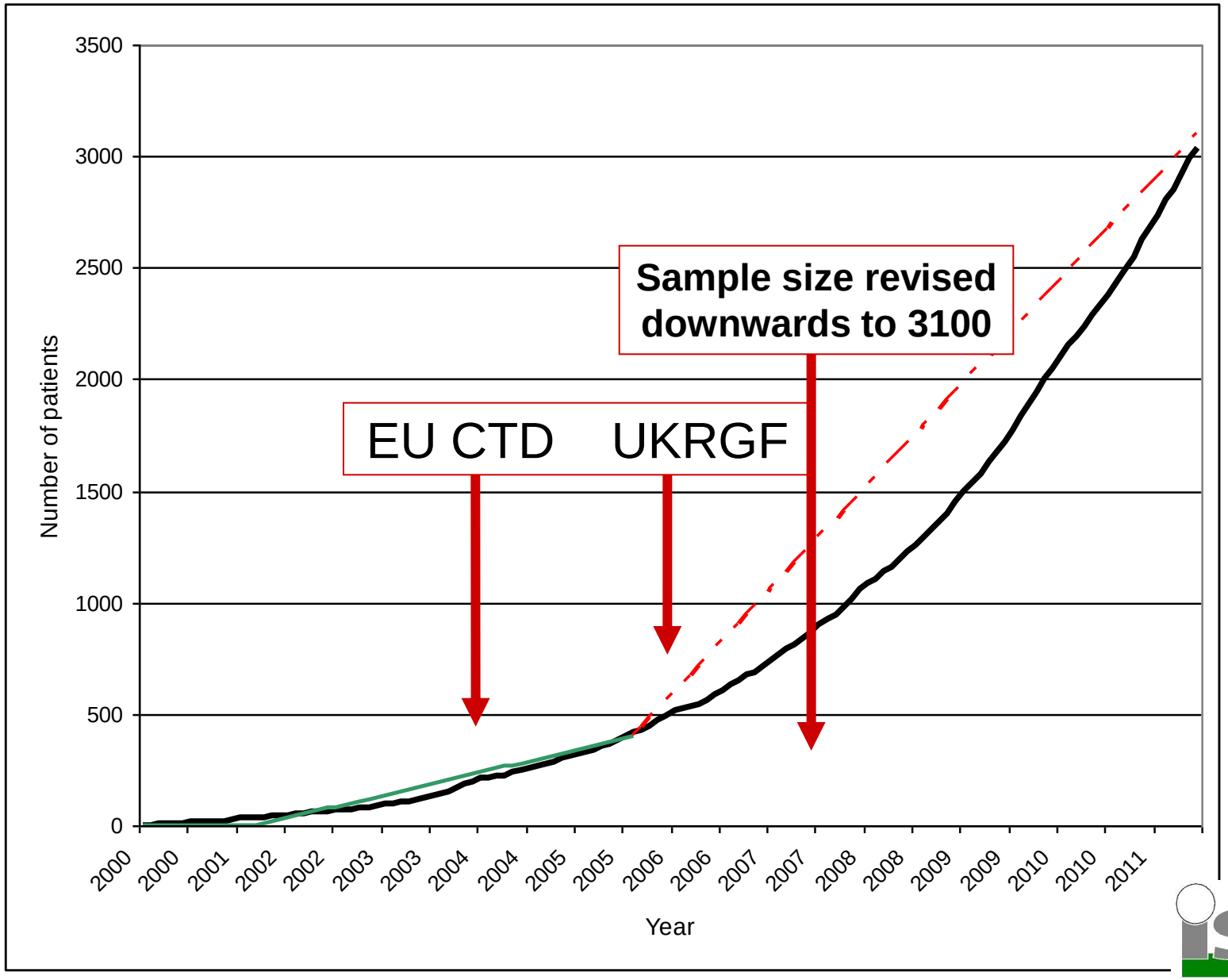
Challenges in 2000-2011 for IST3

- Approvals required:
  - DDX -> CTA, MREC, LREC, R&D, Insurance
- Approval process delays
  - University /NHS new to ‘sponsorship’ role
  - Regulations changed & increased year-on-year
  - R&D staff on steep learning curve
  - Non UK regulators unused to investigator led trials
- CTA/Insurance problems
  - DDX to CTA roll-over
  - Unable to insure (Germany, Hungary, Czech)
- Despite a full time ‘centre manager’…

Days from a centre 'registering interest' to recruiting 1st patient

Year	Days from 'interest' to ready to recruit	Days from 'ready' to patient 1	total days
2005	327	145	472
2006	292	171	463
2007	288	204	492
2008	361	202	563
2009	243	130	373
2010	145	49	194

Impact: recruitment 2000-2011



ist-3 Thrombolysis

Other challenges for trial managers (discussions with ECTMC participants)

Chief investigators

- Inexperience: clinical academic training does not favour training in clinical trials
- Grant applications over-optimistic
- Designs not ‘marketable’ & feasible

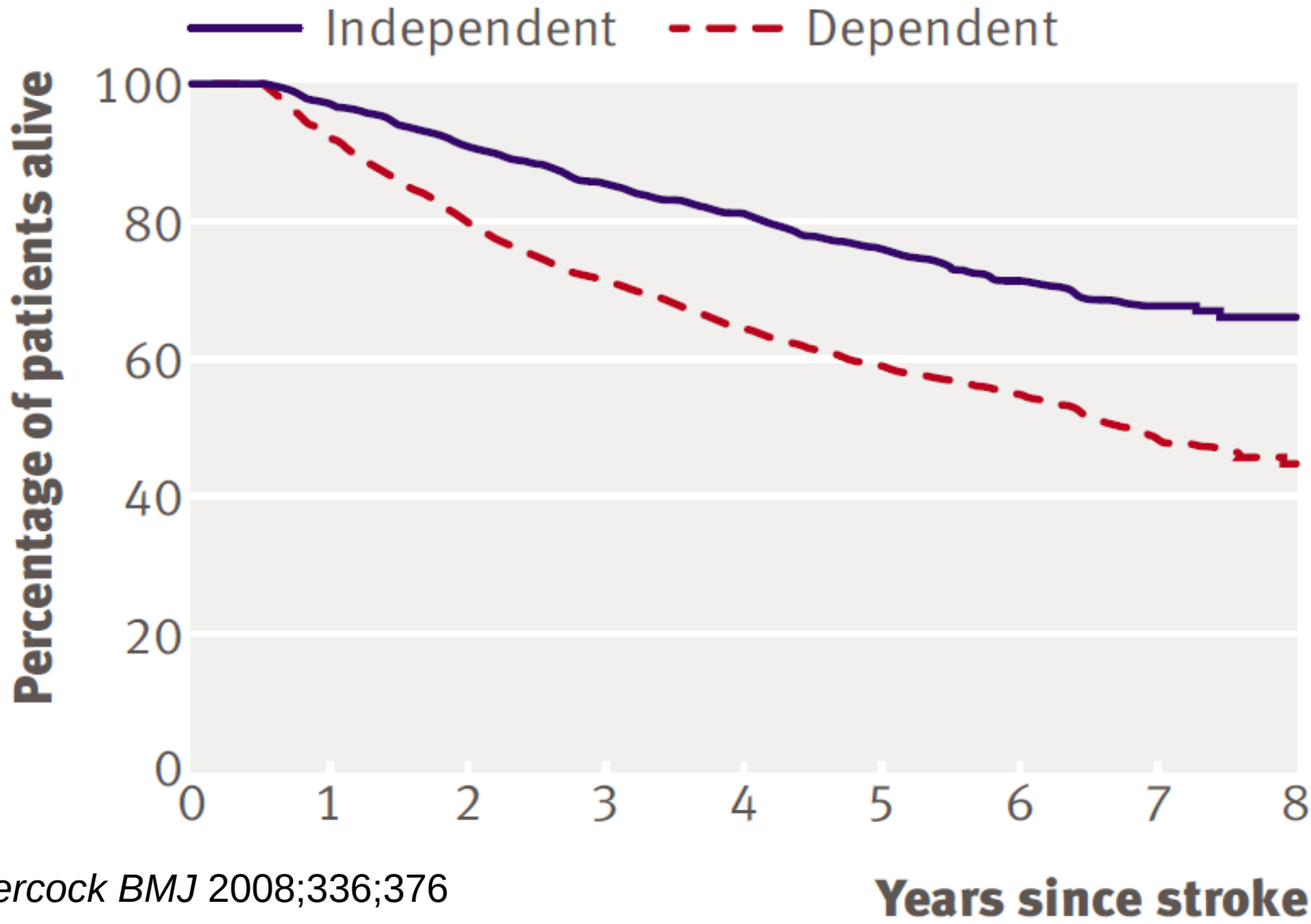
Lack of career security in CTU’s

- Short contracts - retaining key expertise
- Career progression

Some UK good news

- Support for start-up / feasibility phases
  - Charities (CHSA, Stroke Assoc, BHF etc)
  - NIHR/HTA
- Better project oversight by some funders
- More streamlined ethics
  - CORRECT RCT of simplified assessment
- UK NHS record linkage as
  - Trial planning tool
  - Trial F/U tool

ONS follow-up. Effect of dependency at 6 months on long term survival in 6257 UK IST-1 patients



Sandercock BMJ 2008;336;376

Positive international developments

- ‘Sensible Guidelines’ group
- FDA/MHRA - risk based monitoring
- Support for trials in resource-poor settings

GlobalHealthTrials http://ght.globalhealthehub.org/

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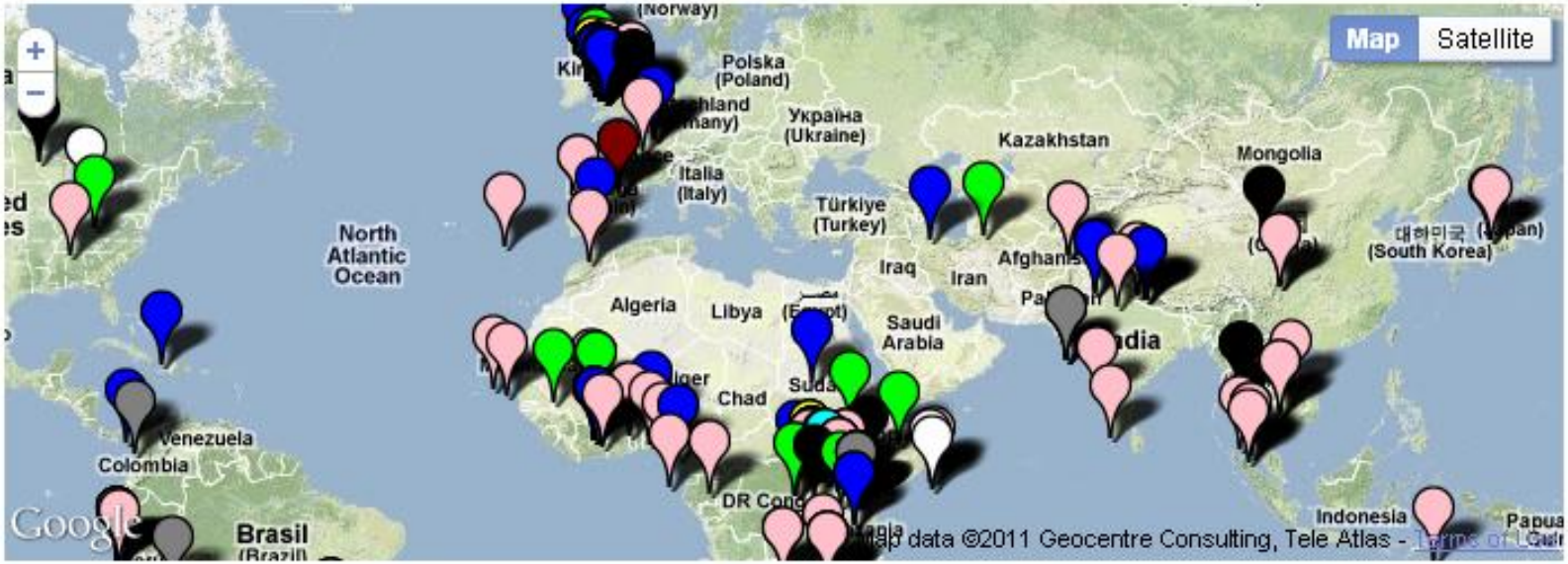


PARTICIPATORY ACTION RESEARCH

Take part in studies to improve how we run trials

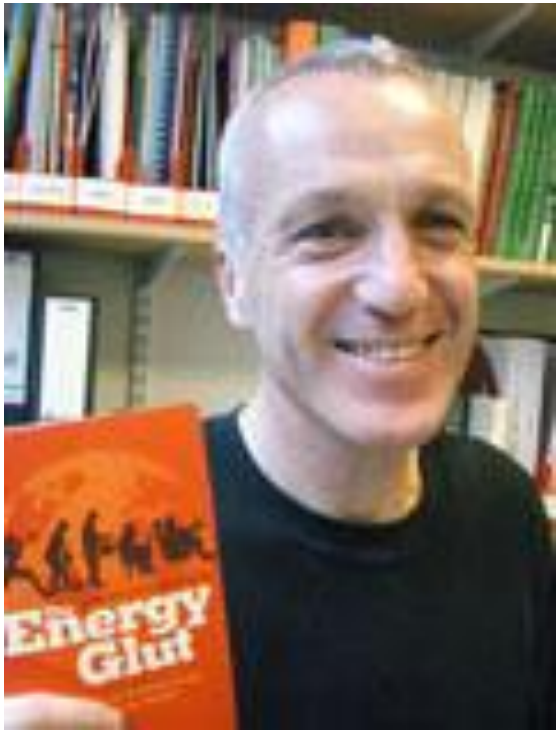
EDUCATION & TRAINING

eLearning Modules

CONTRIBUTE

Submit a guidance article
Start a discussion
Write a blog

Investigators learn the importance of marketing



http://www.trialsjournal.com/content/8/1/37

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]

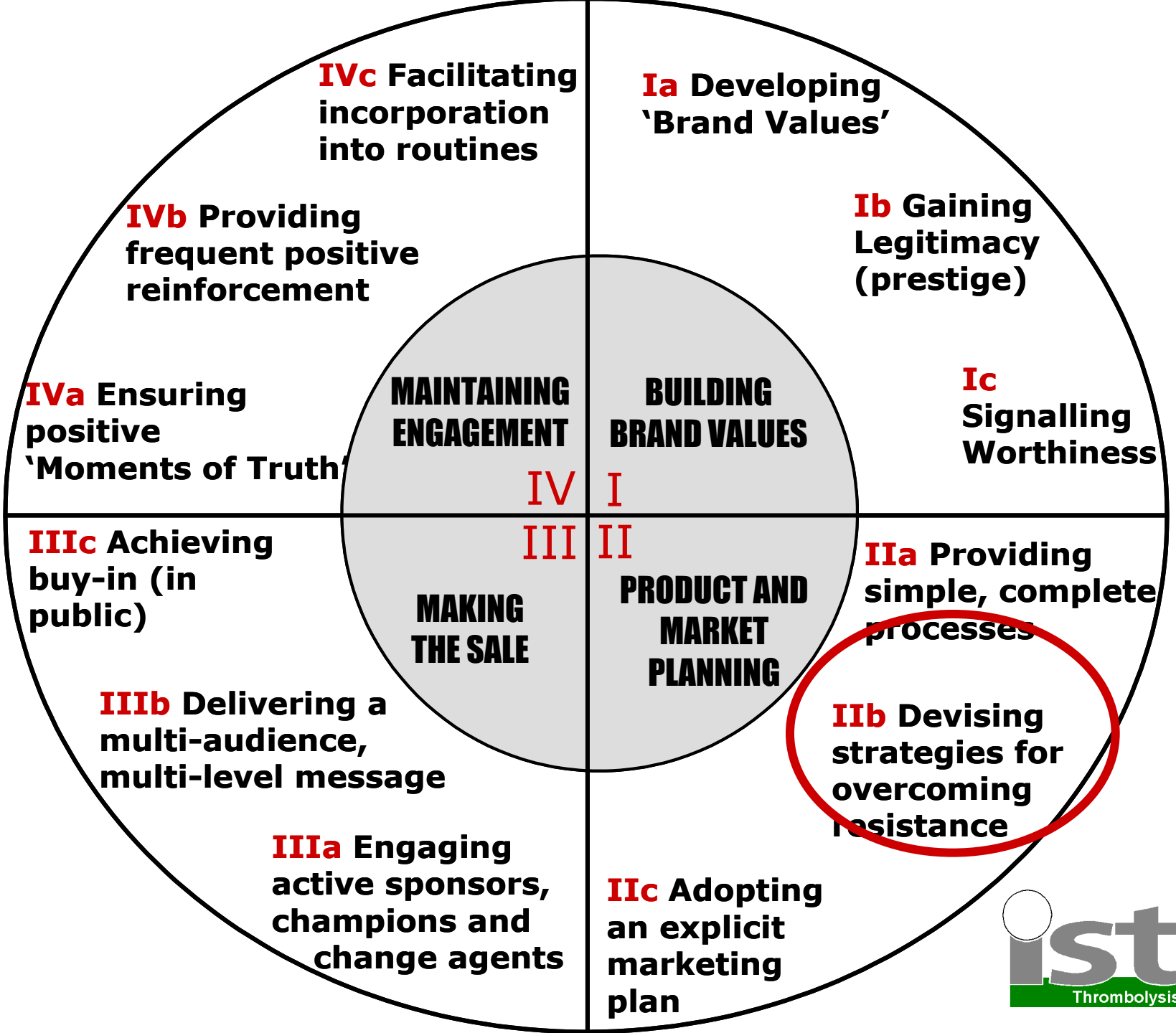
* Corresponding author: David Francis dlf@brighton.ac.uk

▾ Author Affiliations

1 Centre for Research and Innovation Management, Brighton, UK
2 Nutrition and Public Health Interventions Research Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK
3 Medical Statistics Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, UK
4 Centre for Family Research, University of Cambridge, Free School Lane, Cambridge, CB2 3RF, UK
5 Health Services Research Unit, University of Aberdeen, Health Sciences Building, Foresterhill, Aberdeen, UK

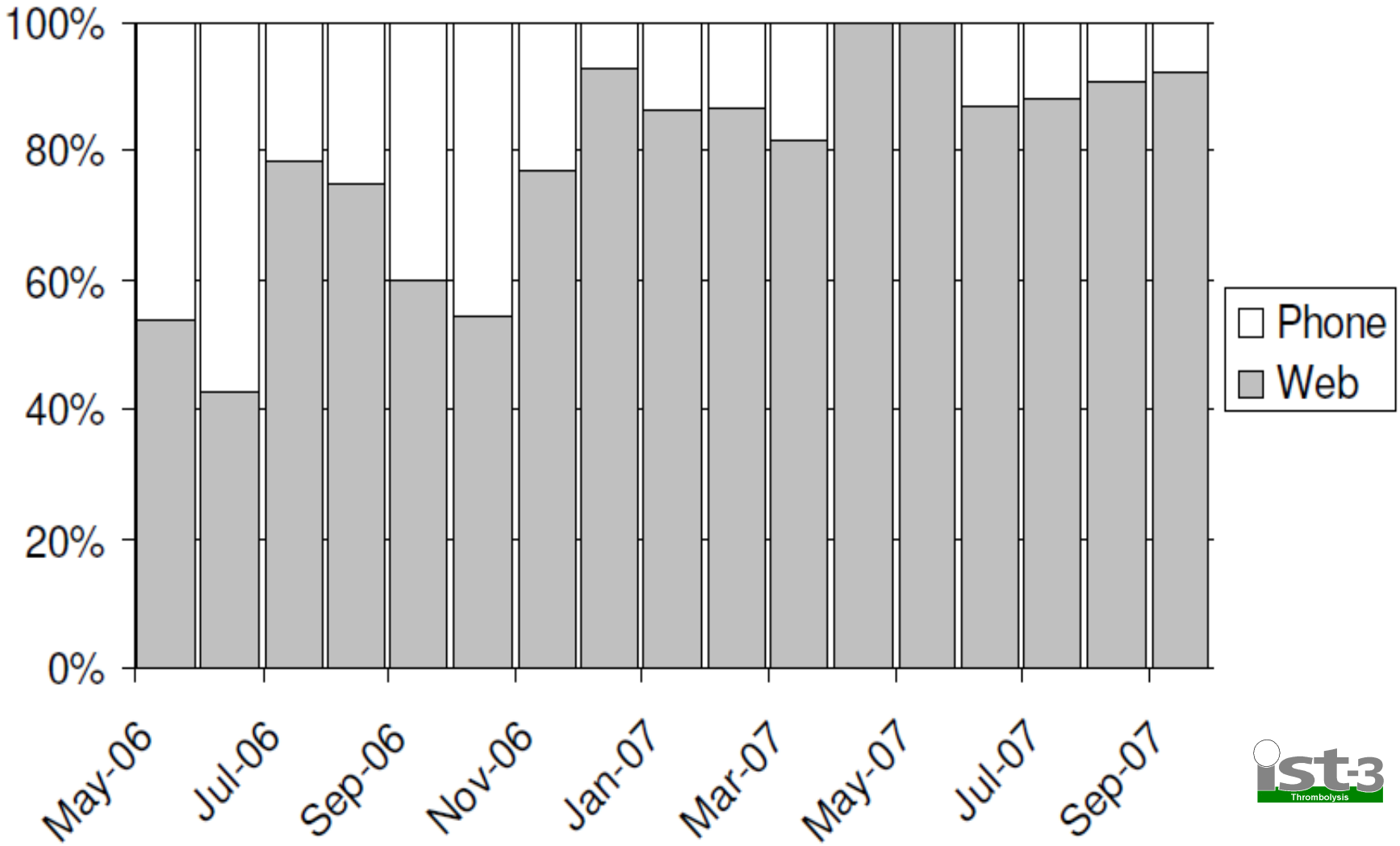
For all author emails, please log on.

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



ist-3 Thrombolysis

Overcome resistance: introduce web-based randomisation system



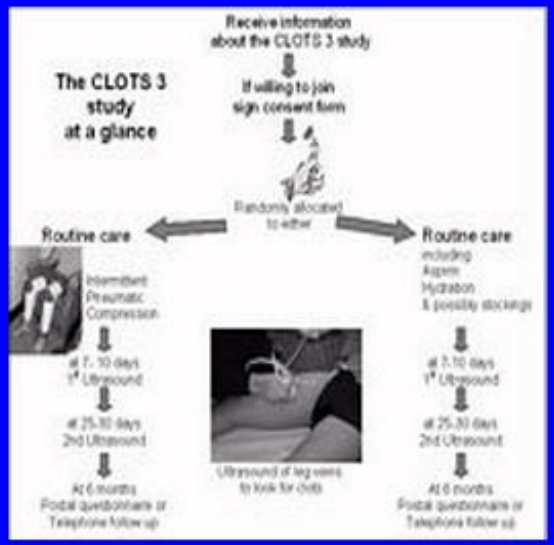
CLOTS-3 trial: a cause for optimism

- RCT of intermittent pneumatic compression vs control to prevent DVT after stroke
- UK only
- Stroke Research Network support
- Largely web based

The CLOTS Collaboration

Clots in Legs Or sTockings after Stroke

CLOTS Trial 3 - A Randomised Trial to Establish the Effectiveness of Intermittent Pneumatic Compression to Prevent Post Stroke Deep Vein Thrombosis (DVT).



CLOTS 3 study at a glance

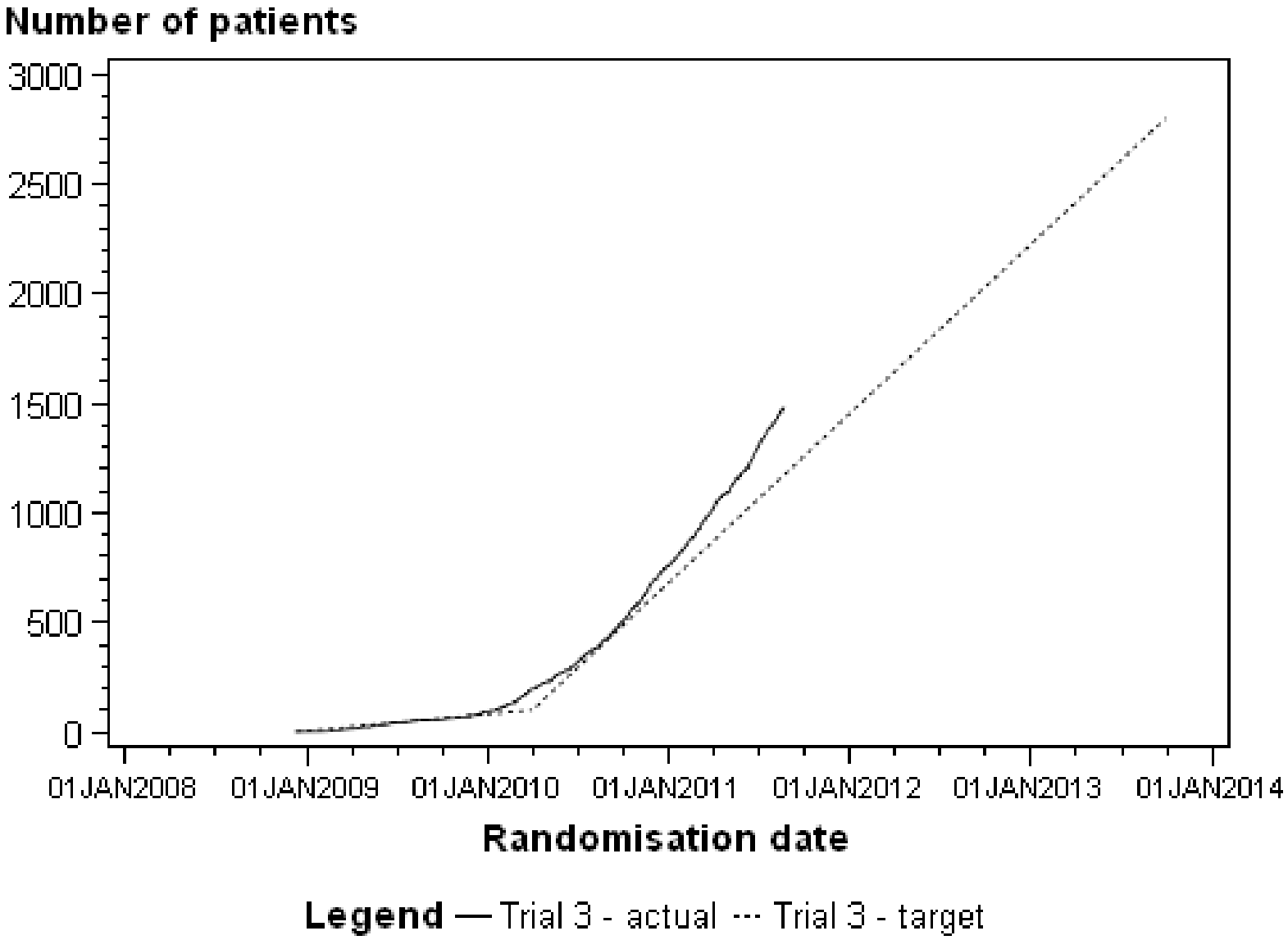
(click picture to enlarge)

Collaborators please use these buttons to enter your examination and followup data online

- RANDOMISE A PATIENT
- REPORT A LEG VEIN EXAMINATION
- DISCHARGE DATA ENTRY
- SERIOUS ADVERSE EVENT
- OTHER SERVICES

Use the 'Other Services' button to logon and access useful information about your centre

CLOTS3 recruitment: ahead of target



Summary

Challenges

- Trials are now more labour intensive /costly
- Investigator led trials are not getting easier
- Training (and retaining) the next generation of clinical trial leaders and managers

Opportunities

- UK NHS
- Increased CTU capacity
- Support for research:
  - Research networks
  - Methodology hubs
- New technology

Acknowledgements

IST-3 collaborative group
Staff at NTU/ECTU Edinburgh
David Perry & DCN IT Group
Barbara Farrell
Ian Roberts
Haleema Shakur
Faculty for ECTMC

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Large-scale investigator-led clinical trials

1980 Acute MI: ISIS 1-4

1990 Acute stroke: IST, CAST

2000 Subarachnoid haemorrhage: ISAT

2004 Head Injury: CRASH 1

2010 Bleeding from trauma: CRASH 2

IST-3 trial: eligibility and randomisation

If patient fits main eligibility/exclusion criteria clinician/patient/family discuss. If there is a:

- Clear **INDICATION FOR** rt-PA **→TREAT**
  (i.e. meets terms of current licence and patient agrees)
- Clear **CONTRAINDICATION TO** rt-PA → **DON'T TREAT**
- rt-PA **'PROMISING BUT UNPROVEN'** → **RANDOMISE**

ist-3 Thrombolysis

Moments of truth

Putting that all together…