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Designing and running pragmatic trials to deliver benefits for clinical practice: A UK investigators perspective

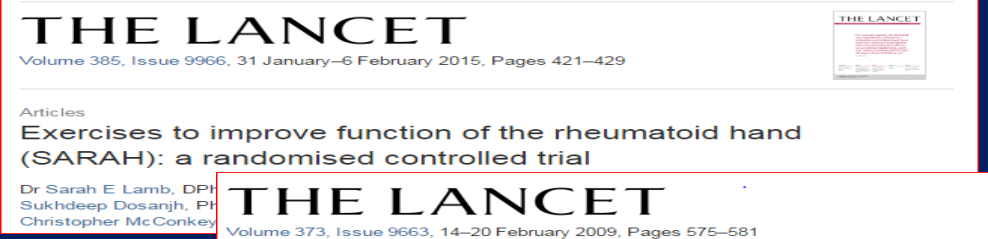
Professor Sallie Lamb
University of Oxford

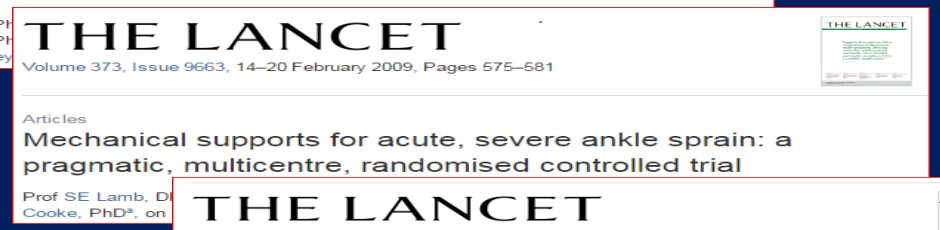
Conflicts

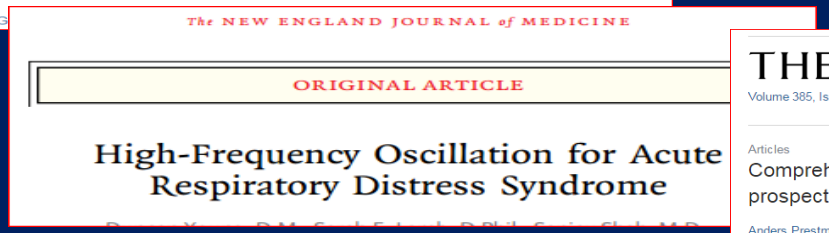
- None of relevance to this presentation
- Plueristem Inc, Stem Cell Company in Israel
- Eli Lily, specialist expertise in trauma trials for older people
- Trustee of Arthritis Research UK

Introduction

- Clinical trialist
- Chief investigator and supporting (senior investigator)
- As CI/active collaborator > 25,000 randomisations
- Foundation Director for 2 UK Clinical Trials Units (Warwick and Oxford)
- As Director of Trials Unit > 35,000 randomisations
- Early phase through to pragmatic phase III
- NIHR to commission and monitor pragmatic trials/evaluations
- Chair of HTA responsive mode board (2010 to 2015)
- Perspective “British Tax Payer” – value for money in our health system







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What is a pragmatic trial ?

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- Large experiment
- Benefits, harms, costs and value
- Multi-disciplinary team working
- Commitment, sacrifice and degree of risk taking
- Going to be a long and complex journey with multiple interfaces
- Conducted with precision, integrity and without bias
- Low volume, high quality yield activity
- Not necessarily valued by HE institutions or clinical colleagues (or public)
- It is going to be a practice, commissioning and policy changer (important)
- Enrich the subject base
- Both rewarding and daunting

Variability the key to understanding pragmatism

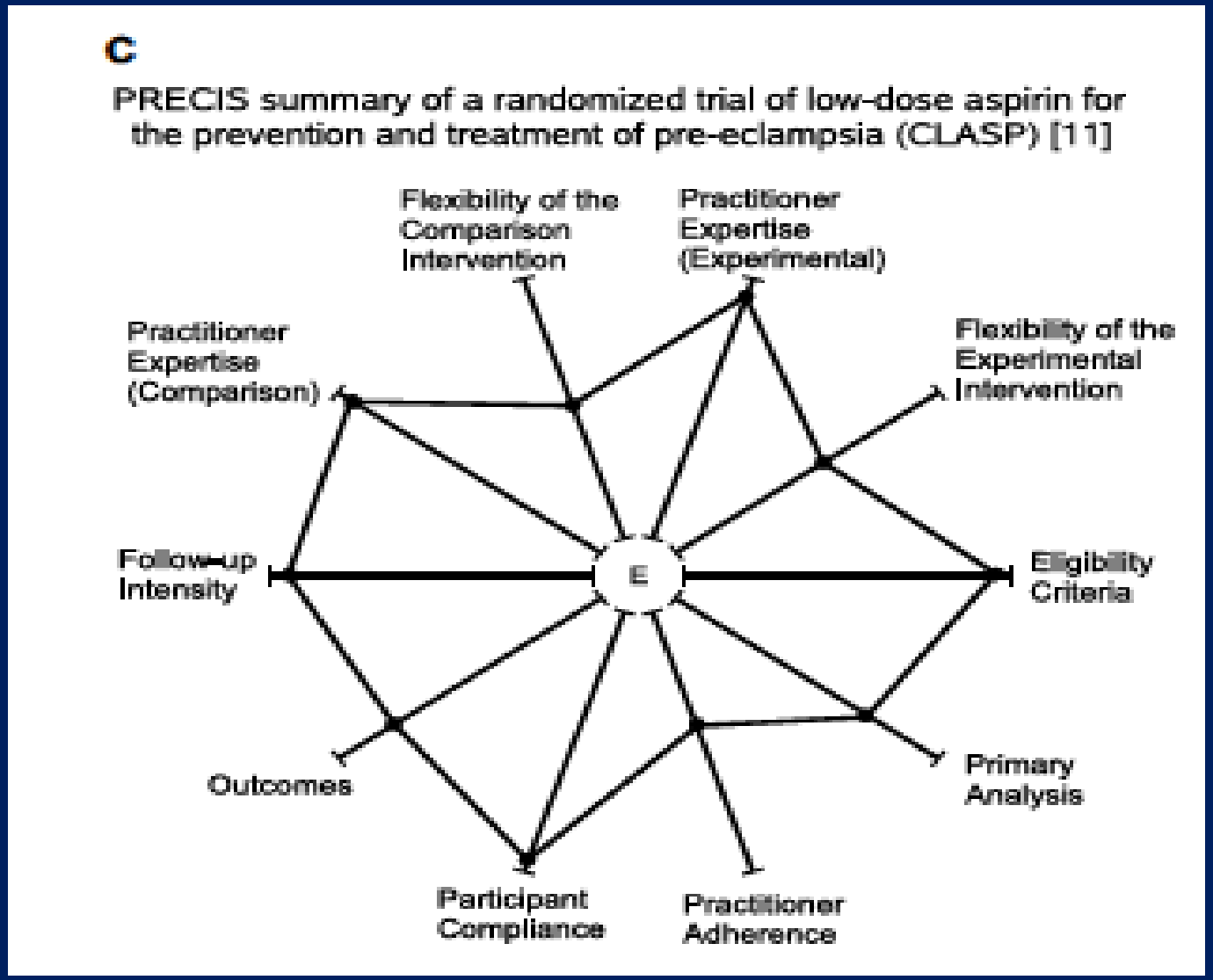
- Phase 1 and 2 trials design out variability
- Phase 3 trials incorporate variability and estimate the influence of variability
- Standardised effect

$$\frac{\text{Proposed treatment difference at primary time point}}{\text{Pooled baseline standard deviation (variability of the sample)}}$$

- Ensuring we anticipate/capture either all or the important causes of variability
- Maximise the chance to learn from the variability

Variability and where it comes from: listening for noise

- Centres or units of health service provision
- Clinician learning effects, method of training, compliance or skill
- Natural variation in condition and response (external validity)
- Patient compliance
- Experimental variability - between and within raters (minimise)
- Experimental variability – confounding (randomisation)
- Experimental variability – measurement error
- Minimise experimental variability
- Utilise other variability to measure effect and learn about the technology



PRECIS summary of a randomized trial of low-dose aspirin for the prevention and treatment of pre-eclampsia (Collaborative Low dose Aspirin Study in Pregnancy [CLASP])

Example: Prevention of Fall Injury Trial

- Millions of pounds spent on fall prevention
- Much clinical enthusiasm
- Encouraging early (unregulated) small scale trials
- But mixed ability to replicate these
- No robust information on costs, fracture outcomes and quality of life
- Systematic reviews and clinical guidance supporting practice,
- Based on poor evidence
- Major plank of UK clinical practice and likewise around the world
- Sceptical

BMJ

336:105–164 No 7636 Clinical research ISSN 0959-8138
19 January 2008 | bmj.com

PREVENTING FALLS
WHAT WORKS?

PLUS Rational imaging after trauma to the neck
Teaching rounds: the "problem" junior doctor
Tooke's take on what went wrong with MMC

INCLUDING BMJ CAREERS

Design and framing

- Individually randomised
- Cluster randomised
- Step wedged randomisation
- Observational, non-randomised design
- Equivalence
- Two stepped, sequential, adaptive……..
- Understand where the technology is in its evolution
- Understand the key questions that inform effectiveness in everyday settings and experimental constraints

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Design

NHS National Institute for Health Research

N = 63

General Practices

OR OR

Advice

Exercise

MFFP

AgeUK

Otago exercise programme to prevent falls in older adults

Campbell *et al.* (1997; 1999; 2001 etc.)

Tinetti *et al.* (1994)

Region Recruitment

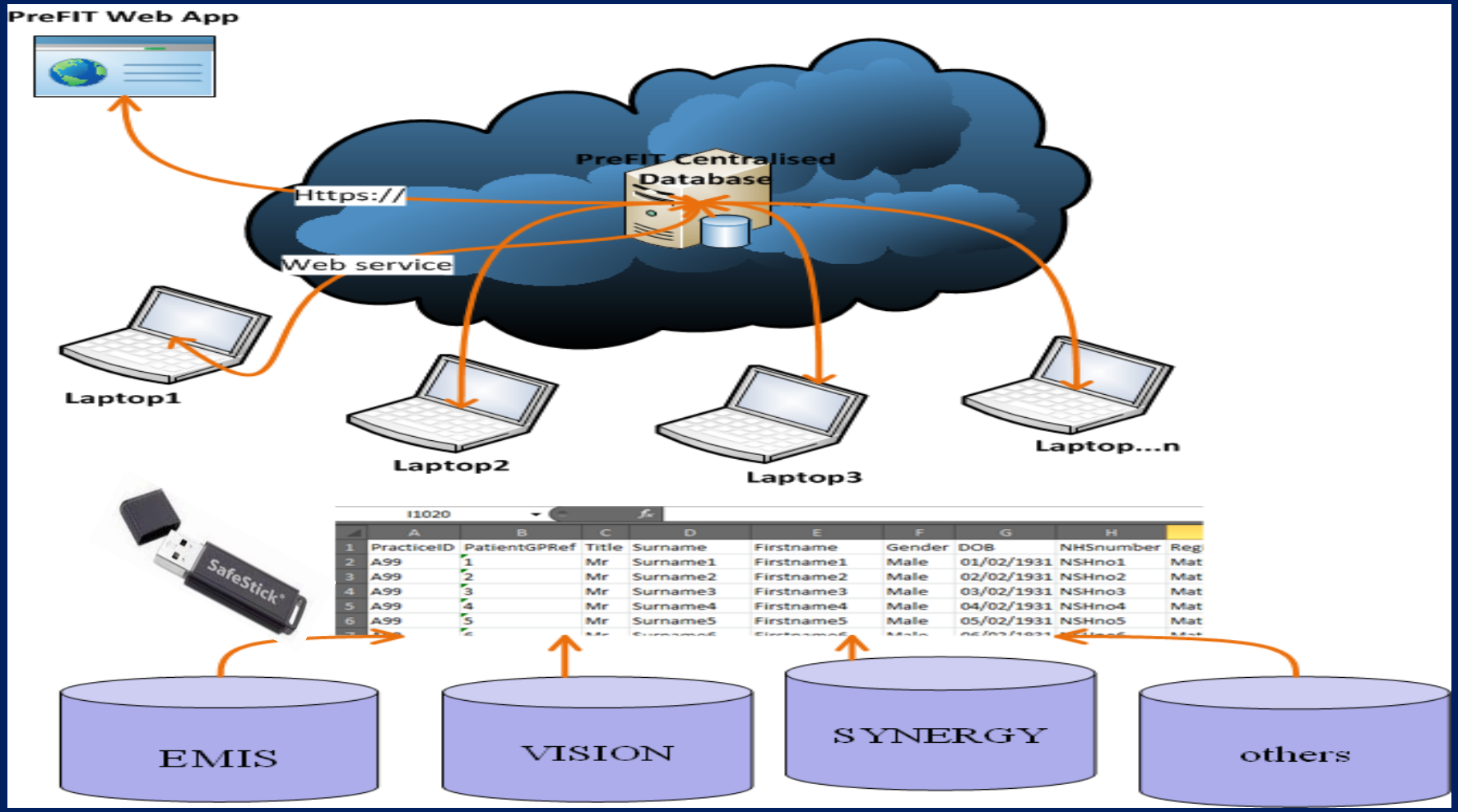
- Devon pilot region
- Main study across 4 regions
- 61 / 63 practices contracts signed
- Staggered recruitment
  ~ 3 practices [cluster] per month
  ~ not to overburden services
  ~ PreFIT team capacity
- All sites “active” in various stages

Newcastle City
- 12 practices

West Midlands
- Warwickshire: 9
- Herefordshire: 3
- Worcestershire: 15

Cambridgeshire
- 6 practices

Devon
- 12 pilot study
- 6 main study


PreFIT Web App
PreFIT Centralised Database
Https://
Web service
Laptop1
Laptop2
Laptop3
Laptop...n
SafeStick
I1020
A B C D E F G H
PracticeID PatientGPRef Title Surname Firstname Gender DOB NHSnumber Reg
A99 1 Mr Surname1 Firstname1 Male 01/02/1931 NSHno1 Mat
A99 2 Mr Surname2 Firstname2 Male 02/02/1931 NSHno2 Mat
A99 3 Mr Surname3 Firstname3 Male 03/02/1931 NSHno3 Mat
A99 4 Mr Surname4 Firstname4 Male 04/02/1931 NSHno4 Mat
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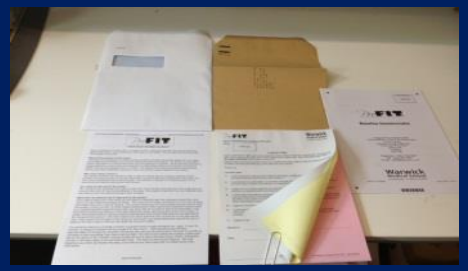
EMIS
VISION
SYNERGY
others

Preparation for each General Practice



Prepare 400 packs

Packs posted from GP surgery

Reminder packs sent from Warwick

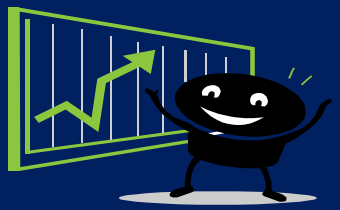
Preparation	400 packs delivered to surgery	Week 0	Reminder packs prepared	Week 2	Reach target 150

Pack contains:

Pt Info Sheet
Consent forms
Questionnaire
Return SAE

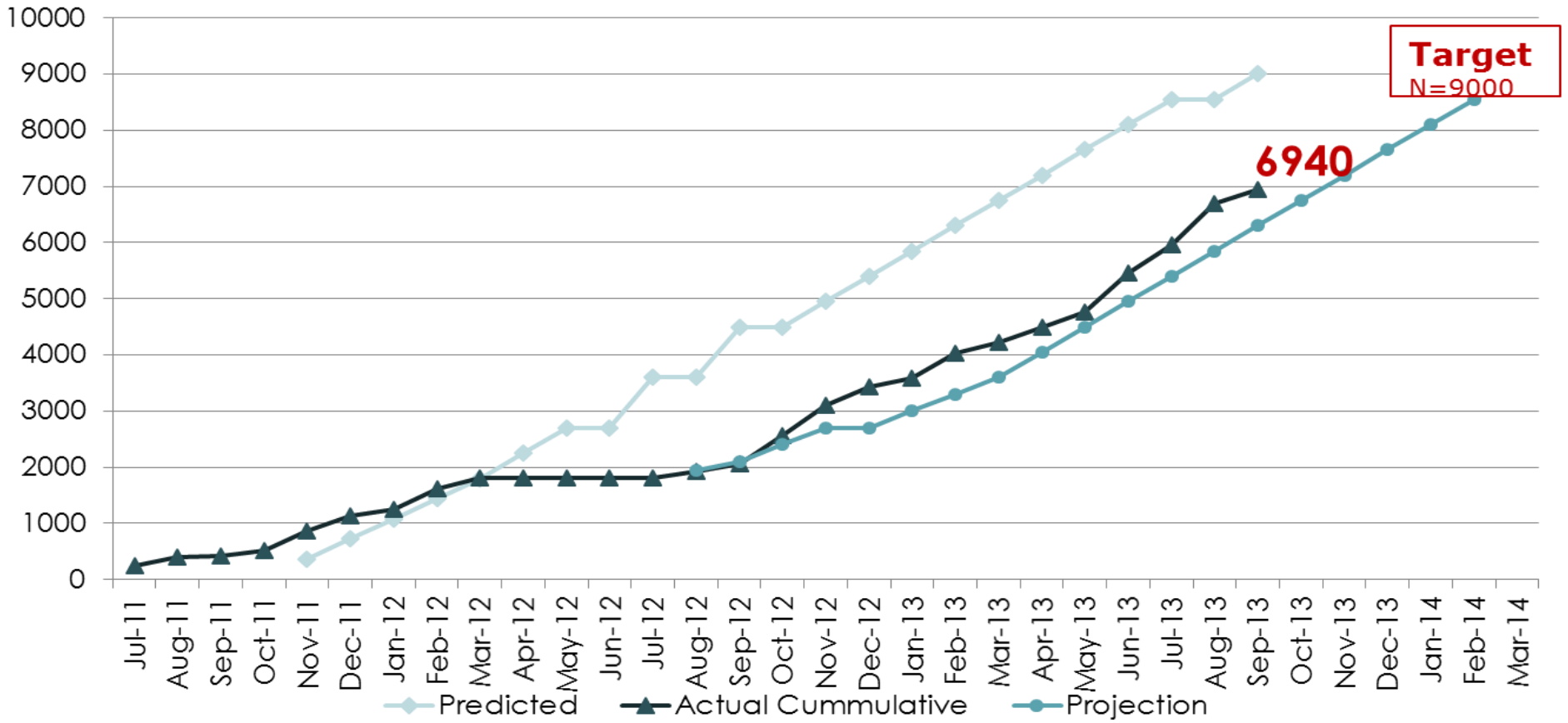
We only need 150!

RANDOMISE



Checking all incoming data

Recruitment graph



The trial team: 7 years, 42 close collaborators, list will extend to 100+ by close

	CI	HCPs	Stats	£	Ethicist	PPI	QA	PMs	Progr	CRN
Getting the framing right	Y	Y	Y	Y	Y	Y				
Designing the experiment	Y		Y	Y	Y	Y	Y	Y	Y	(Y)
Designing the intervention	Y	Y				Y				
Making a high quality experiment that works efficiently	Y	Y	Y	Y		Y	Y	Y	Y	Y
Doing the experiment	Y	Y	(Y)	(Y)			Y	Y		Y
Analysing and interpreting	Y	Y	Y	Y	Y	Y	Y	Y		
Dissemination and implementation	Y	Y				Y				

How can patients and public get involved?

- Equal team members
- Locating willing and suitable PPI representatives
- Training and supporting them
- Defining roles
- Intervention days, intervention development, outcome measures, ethical issues
- PPI officers – research design service and other local infrastructure
- Management groups, trial steering committees, DMECs
- Citizens can surprise you with their abilities!

the PreFIT office….

Why are pragmatic trials of relevance to decision makers, clinicians and patients

- Regardless of the health system resources are finite (and hence limited)
- Patient, insurance company, government, clinician
- Adds in the lottery of the everyday
- We might not have the best clinician, the best hospital
- Set within context about a service
- Helps us to understand and improve health services
- Maximise value – value for all

Why should clinicians get involved

- If they want to be part of a profession that knows what works best and minimises harm to patients
- As responsible members of society - they pay tax just like anyone else (in fact a bit more tax than most)
- As members of responsible professional groups
- Dis-invest, move on, innovate
- Encourage not just to participate but to lead
- Higher profile value science

THE TIMES FRIDAY SEPTEMBER 24 2004

It's not worth breaking your back for a trip to the physio

By Sam Lister
Health Correspondent

ers of chronic back pain generally recommend remaining active.

Why going to a physio won't fix that bad back

BEING treated by a physiotherapist for back pain is a waste of time and money,

By **Jenny Hope**
Medical Correspondent

University of Warwick, said: 'People think there's going to be a magic wand – there isn't with back pain. Our study shows

Therapy Weekly
www.therapyweekly.co.uk
The UK's favourite therapy magazine

Physios furious at reports on futility of back pain therapy

Charlotte Dennis-Jones
charlotte.dennis-jones@emap.com

Therapists attacked the national media this week for claiming that physiotherapy does not help relieve back pain.

Graham Pope, Chartered Society of Physiotherapy chair of council, accused national newspapers of wrongly implying that physiotherapy for back pain is pointless.

Last week researchers from Warwick University released a study that compared different treatments given to 286 patients with mild lower back pain. Of the patients, 142 received one hour of physio assessment and advice, whereas 144 were given routine NHS physio sessions.

OSCAR BURRIEL/ SCIENCE PHOTO LIBRARY

There are fears that some people with back pain will not now see a physio.

presented in the press is not what the study is saying. It is certainly not

improved under the specialist guidance of a physio."

PHYSIOS' VIEWS

Has your image been tarnished by the national media this week?

- "The press finds it difficult to report on research and tends to use a sensational headline, which is a poor reflection of the findings."
- "Yes, especially as this has come from the findings of just one solitary study. The media should not jump to conclusions until they are privy to more information."

Physiotherapy doesn't work for back pain, study says

Sarah Boseley
Health Editor

You are wasting your time. It isn't going to help you."

The study followed two

those in the advice group to say they felt better, but when they filled in a questionnaire

expectations of medical intervention."

Physiotherapy has always