

## Problems and Pitfalls in Engaging in Multi-National Trials

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## Trials: why bother?

- Review the rationale
- Discuss the current challenges
- Illustrate some problems and pitfalls
- Suggest some solutions



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## Rationale for multi-national RCTs

- We still require randomisation to balance known and unknown prognostic factors (bias)
- Large sample sizes still required to detect moderate treatment effects (random error)
- Thus the requirement for multi-site, international trials



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## Challenges - interconnected issues

1. Whose priority?
2. Money
3. Complexity of medicine and busy clinicians
4. Patients and recruitment
5. Academic rewards for researchers



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## Challenge - 1: whose agenda?

1. World-wide public health?
2. National public health?
3. Clinician led?
4. Shareholders via pharmaceutical companies?
5. Those who shout loudest?



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## Stroke treatments with important public health benefits

### Academic led and funded

- Stroke unit care
- All rehabilitation
- Antiplatelet therapy
- Cholesterol lowering\*
- Blood pressure lowering\*
- Thrombolysis for acute ischaemic stroke

\* Some industry support

### Commercially led and funded

- Marginal benefit of clopidogrel over aspirin
- "Non-inferiority"



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**As medical academics we need to seriously address the question: what sort of clinical trial do we need for our future generations?**

## **Challenge - 2: Money**



## **Why the costs?**

- Large complex trials versus large simple trials
- Non evidence based monitoring
- Commercial models of operation
- Privacy laws versus primary data

## **Large simple (streamlined) trials**

- Reduces the work for busy clinicians
- Easier to monitor
- “Less is more”

YUSUF, S., COLLINS, R. & PETO, R. (1984) Why do we need some large, simple randomised trials? *Stat Med*, 3, 409-420.

## **Evidence-based trial monitoring**

- Your streamlined design will help
- IT systems can monitor many variables
- Build in primary source data collection e.g. national mortality registers, national follow-up centres, direct questionnaire follow-up, engage in dialogue with those who create privacy laws
- Random audits of source data

Buyse et al. The role of Biostatistics in the Prevention, Detection and Treatment of Fraud in Clinical Trials. *Statistics in Medicine* 1999; 18: 3435-3451

## **The regulation of future international trials: is “one size fits all” appropriate?**

- New drugs and devices with commercial value: continue with current regulation
- But, what about new uses for: old drugs, comparison of established techniques?
- Non-negligent insurance issues

## Avoid commercial models

- National meeting of IST-3 < \$10,000 (equivalent to one business class airfare to the USA)
- Attend steering committee by videoconference (save \$6,000)

## Some solutions: money

- Identify key primary funding body for your trial
  1. UK MRC
  2. NHMRC
  3. NIH
  4. Bill Gates
- Top up with national funding

## Example: The Third International Stroke Trial (IST-3)

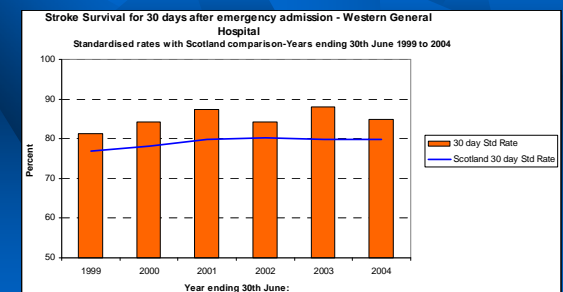
Source	Year awarded	Amount
Stroke Association	1999	£140,000
PPP Foundation	2002	£656,977
MRC	2004	£2,800,000
Heart Foundation	2004	AUD\$92,000
NHMRC	2006	AUD\$210,000

## International Support



## Challenge - 3: Complexity of medicine and busy clinicians

- Trials are time consuming: who will pay? (US versus Australian versus UK NHS)
- Time for training
- Why bother?



## Ingredients for a successful academic international trial

- Invest in appropriate methodology research and consumer involvement
- Streamline and simplify
- Identify a National Coordinator
- Check the trial is a burning issue in each country



## Joint academic meetings for specialties

- Emergency medicine
- Cancer
- Stroke



## Challenge - 4: Patients and recruitment

- Engage consumer advocate (e.g. breast cancer)
- Simplify ethics materials

Ross et al Barriers to Participation ... J Clin Epidemiol 1999; 52: 1143-1156



## The Readability of Sample Texts Published by Human Research Ethics Committees in the USA

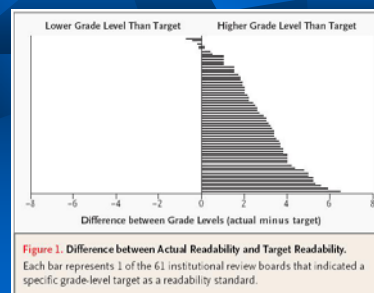


Figure 1. Difference between Actual Readability and Target Readability. Each bar represents 1 of the 61 institutional review boards that indicated a specific grade-level target as a readability standard.

Paasche-Orlow et al NEJM 2003; 348: 721

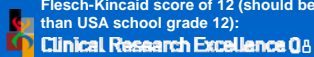


## Readability of a information leaflet for a treatment of mild dementia

"During the first visit (screening visit) to the clinic, a complete medical history, including all medication taken during the last 3 months, will be obtained. A complete physical examination, including a cardiovascular and neurological/psychiatric examination will be performed. Measurements of your heart rate and blood pressure and a recording of your heart rhythm (an ECG) will also be taken. Your doctor may ask for a computed tomography (CT) scan or a Magnetic Resonance Imaging (MRI) of your brain to help make the diagnosis. Blood samples (approximately 3-4 tablespoonfuls) will be taken for laboratory safety tests. You will also have special tests and answer questionnaires to classify the extent of your Alzheimer's disease symptoms. None of these tests are invasive except venipuncture (blood drawing)."

Flesch Reading Ease of 28 (should be 60-70, 100 represents the easiest text)

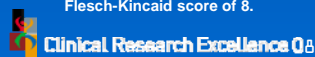
Flesch-Kincaid score of 12 (should be at Tabloid level of grade 8, rather than USA school grade 12):



## Alternative text

"During your first clinic visit you will have a full medical. We will check all the tablets and medicines you have taken in the past three months. During this medical, we will check your heart, nerves, brain and test your memory. You will have your pulse and blood pressure taken, and a trace recording of your heart (an ECG). Your doctor may order a brain scan to complete your check-up. This is usually a CAT scan (computed tomography scan) or a MRI (Magnetic Resonance Imaging scan). You will have some blood tests (approximately 3-4 tablespoons of blood) to check the study tablets will be safe for you. We will then check your memory with some more detailed tests, including some questionnaires. None of these other tests involve needles or injections."

Flesch Reading Ease of 65  
Flesch-Kincaid score of 8.



## Jetstar terms and conditions



## Non-medical life and information

- Jetstar terms and conditions
- 6889 words
- 34,000 characters
- 330 paragraphs
- Flesch ReadingEase 59
- Flesch-Kincaid Grade level 9.8

## Improve rewards for participating in RCTs

- UK Research networks
  - Academic recognition
  - Clinician training from students onwards
  - Politicians
- “Evidence based medicine versus anecdote based politics”

## Challenge -5: Academic rewards for researchers

- Research assessment often underemphasises international RCT involvement
- Yet, such RCTs often are the cause of the greatest advances in clinical medicine

## Summary

- Academic led international trials are under threat
- Public health imperative to retain such work
- RCTs must be supported by epidemiology, modelling, methodology research and audit to provide data to support the next generation of trials
- Academics must engage with politicians and funders