Clinical Trials in (liaison) Psychiatry

Michael Sharpe,
University of Edinburgh

Michael.Sharpe@ed.ac.uk
All who drink of this remedy recover in a short time, except those who it does not help, who all die.

Therefore it is obvious that it fails only in incurable cases.

Galen (AD 130-200)
How do we know what works?
Clinical trials (fair tests)

- Trial from Anglo-French *trier*, to try (put something to the test).

- Clinical from Greek *klinike*, bedside (caring at the bedside)
A Scottish physician described a ‘clinical trial’ of the treatment of scurvy in sailors in 1774.

12 cases of scurvy who ‘looked similar’. Allocated 2 to each of 6 diets – only those given oranges and lemons improved.

But findings were not implemented until 1800. Then limes were introduced into sailors’ diets (Limeys!)

http://www.jameslindlibrary.org/
History of trials - the MRC

BRITISH MEDICAL JOURNAL
LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS
A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heath, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tyler, Professor G. S. Wilson, and Dr. P. D’Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Michison.

Collindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bougour Hospital, Bougour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reeve; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. E. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Stfr Hospital, Stfr, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tyler.

[MRC, BMJ 1948, 4582-97]
Elements of the clinical trial
Impression of outcome with new treatment
Systematically measure outcome with new treatment
Compare the outcome with patients who have not received the treatment

Patients

New treatment

Other treatment
Use random allocation of treatments
What do we need?

- Patients
  - Enough and representative

- Treatments
  - Delivered as described

- Outcome
  - Relevant, unbiased and collected on all patients
Three (liaison) psychiatry trials
Edinburgh Psychological Medicine & Symptoms Research Group

Neurology
Charles Warlow (CSO; MRC)

Primary care
David Weller (CSO)

Oncology
John Smyth (CR-UK)

MUS & CFS

Stroke

MUS & children

Depression & symptoms
Major depression in cancer patients

- 10% of cancer outpatients have MDD
- On these only 10% treated
- Need a practical treatment integrated with cancer care

Sharpe, Strong et al. Br J Cancer 2004
A new approach (collaborative care)

- Multi-modal
- Specially trained cancer nurses in cancer centre
- Focus on depression
  - Coordinate drug treatment with GP
  - Provide psychological treatment (PST)
  - Monitor progress (PHQ-9)
- Supervised by a specialist
Getting patients
SMaRT about Cancer

Does supplementing the usual care of depressed cancer outpatients with a complex cancer-nurse delivered intervention (problem solving + antidepressants + coordination of care) improve the resolution of major depression at 3 months?

Funded by Cancer Research UK
The design (single centre)

Depressed cancer
Outpatients
(n=200)

- Usual care + nurse treatment
- Usual care only
The issue

How do we get adequate numbers of representative patients with the condition to enter into the trial?
The answer

- Systematic screening
- 5,000 patients per year
- 10% major depression
- Recruitment completed on target Dec 2005!

Funded by Cancer Research UK
Treatment for patients for CFS/ME

- CFS/ME is problematic to treat
- There is much controversy about treatment
- CBT or exercise or adaptation to illness
Defining and delivering treatments
The PACE trial

What is the relative effect of three different supplements to usual medical care (CBT, graded exercise and adaptive pacing) for outpatients with a diagnosis of CFS/ME compared with usual medical care alone on fatigue and function at 12 months?

Funded by Medical Research Council
The design (6 centres)

- 600 patients with CFS
  - Medical care
  - Medical Care + CBT
  - Medical Care + GET
  - Medical Care + pacing
The issue

- How do we specify and maintain quality control of complex non-drug therapies?
The answer  part one

- Complex interventions
- Systematic development

MRC guidelines on developing and evaluating complex interventions (2000)
www.mrc.ac.uk
The answer  part 2

- Manuals
- Record and monitor
- Supervise
Neurology out patients with medically unexplained symptoms

- 30% OPD
- Disabled
- Poor outcome
- No treatment

“`I’m stumped. We’ll have to wait for the autopsy.”`
To what extent can the patient’s symptoms be explained by disease? (n=3748)

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Somewhat</th>
<th>Largely</th>
<th>Completely</th>
</tr>
</thead>
<tbody>
<tr>
<td>12%</td>
<td>19%</td>
<td>24%</td>
<td>45%</td>
</tr>
</tbody>
</table>
Collecting outcomes

The SMaRT neurology trail (MRC)

Does supplementing the usual care of neurology patients with medically unexplained symptoms with a CBT based guided self-help programme produce a better outcome than usual care alone at 3 months?

Funded by Medical Research Council
The design (2 centres)

- Neurology outpatient with MUS (n=160)
  - Usual care + CBSH
  - Usual care only
The issue

- What outcome measure should we use and how is it collected?
The answer

- Self-rated
- Simple
- Collect by post/phone

- Primary
  - Global improvement
- Secondary
  - Symptoms, distress, beliefs, care
General lessons for psychiatry trials

- Exposure to medical thinking and trials

- Theirs are
  - Much more integrated with usual practice
  - Bigger – much bigger
  - Often (but not always) have simpler interventions
  - Have simple outcomes
Specific lessons from these trials

- Recruitment
  - Screen consecutive patients not just referrals.
  - Why do robbers rob banks?

- Interventions
  - Complex: need quality control

- Outcome
  - Keep it simple and easy
Where we are now?
Current state of Mental Health research

- Less than 5% of the trials on the Cochrane database indexed under mental disorder

- Literature dominated by
  - Small short term trials
  - Hospital based
  - Medication studies
Distribution of UK mental health research

- Brain sciences and epidemiology
- Domain specific research e.g. mental health law
- Aetiology
- Prevention
- Assessment and diagnosis
- Treatment
- Natural history
Where do we need to go?
We need

- RCTs to provide applicable findings.

This requires...
- Large representative samples
- Well designed and reproducible treatments
- Simple relevant outcomes
A UK Mental Health Research Network for trials
Background

- The UK Clinical Research Collaboration (UK CRC) established in April 2004

- Vision is to make the UK the best place in the world to do clinical research

- UK Clinical Research Network (CRFs)

- Selected disease specific networks
Why a Mental Health Network?

- ‘Until now mental health research has not led or supported practice development. Reliance on small studies has prevented researchers from drawing valid, general conclusions …
- Research has been unable to attract the support from major funding bodies that it deserves, and there has been little active involvement of people in the front line.
- ‘The UK MHRN provides an opportunity to widen participation in mental health research and to help reshape mental health practice through its findings’
Established to provide the NHS infrastructure for clinical trials in ‘mental health’

Coordinating centre(s) and hubs

- Centre IoP and University of Manchester
- Eight hubs

http://www.mhrn.info/dnn/
Scotland
In Scotland

- Subject-specific research networks
  - [Cancer]
  - Medicines for children
  - Diabetes
  - Stroke
  - Mental health

- Other developments
  - NHS infrastructure
  - Clinical research facilities (CRFs)
A Scottish Mental Health Research Network:
part of the &UK MHRN

To attract, develop and support multi-centre studies of international quality for Scotland
Benefits - for adopted studies include

- Assistance with planning and administration
- Facilitation of recruitment by linking centres and assisting
- Access to specific research expertise; Trial design and management, Financial, Statistics, Health economics
- Trial monitoring and support
Proper RCTs are only 50 years old
Psychiatry needs more RCTs
Compared to many (but not all) areas of medicine psychiatry is lagging behind
We need to collaborate to do bigger trials with carefully specified interventions and simple relevant outcomes
We now have an opportunity…