Clinical trials (FS-05)

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Frontiers in clinical trials

Prof Chris Maher
Prof Sallie Lamb
Prof Rob Herbert
Prof Rebecca Craik
Overview

› Introduction 10mins
› 3 x15min modules
  - Developments in design and conduct of clinical trials
  - Developments in analysis of clinical trials
  - Developments in publication and dissemination of clinical trials
› Discussion 30mins
› Summary 5mins
"For the purposes of registration, any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."
What clinical trials are we most interested in?

› Randomised
  - random allocation or intended-to-be-random allocation of subjects to intervention

› Controlled
  - comparison of at least two interventions

› Representative
  - at least one of the interventions being evaluated must be currently part of physiotherapy practice or could become part of physiotherapy practice
  - interventions should be applied to subjects who are representative (or who are intended to be representative) of those to whom the intervention might be applied in the course of physiotherapy practice.
Growth of clinical trials

Number of reports

- guidelines
- reviews
- trials

Year:
- 1930
- 1940
- 1950
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
Disciplines represented

- musculoskeletal
- cardiothoracics
- gerontology
- neurology
- continence & women's health
- paediatrics
- orthopaedics
- sports
- oncology
- ergonomics
- other

Number of reports

- guidelines
- reviews
- trials
12 RCTS n= 442 receiving MCE

9 RCTS ≤36 per arm: unable to detect a large effect size

(d=0.8, 80% power, alpha = 0.05, 15% loss & 15% non-compliance, n=40 per arm)
How was treatment conducted?

- **General exercise**: This exercise activates paravertebral and abdominal muscles. Because this exercise imposes extra loading on the spinal tissues, the general exercise was selected on the basis of maximising the contraction benefit/spinal loading ratio, according to the recommendations provided from recent experimental studies.
Research: increasing value, reducing waste 5

Reducing waste from incomplete or unusable reports of biomedical research

Paul Glasziou, Douglas G Altman, Patrick Bossuyt, Isabelle Boutron, Mike Clarke, Steven Julious, Susan Michie, David Moher, Elizabeth Wager

Research publication can both communicate and miscommunicate. Unless research is adequately reported, the time and resources invested in the conduct of research is wasted. Reporting guidelines such as CONSORT, STARD, PRISMA, and ARRIVE aim to improve the quality of research reports, but all are much less adopted and adhered to than they should be. Adequate reports of research should clearly describe which questions were addressed and why, what was done, what was shown, and what the findings mean. However, substantial failures occur in each of these elements. For example, studies of published trial reports showed that the poor description of interventions meant that 40–89% were non-replicable; comparisons of protocols with publications showed that most studies had at least one primary outcome changed, introduced, or omitted; and investigators of new trials rarely set their findings in the context of a systematic review, and cited a very small and biased selection of previous relevant trials. Although best documented in reports of controlled trials, inadequate reporting occurs in all types of studies—animal and other preclinical studies, diagnostic studies, epidemiological studies, clinical prediction research, surveys, and qualitative studies. In this report, and in the Series more generally, we point to a waste at all stages in medical research. Although a more nuanced understanding of the complex systems involved in the conduct, writing, and publication of research is desirable, some immediate action can be taken to improve the reporting of research. Evidence for some recommendations is clear: change the current system of research rewards and regulations to encourage better and more complete reporting, and fund the development and maintenance of infrastructure to support better reporting, linkage, and archiving of all elements of research. However, the high amount of waste also warrants future investment in the monitoring of and research into reporting of research, and active implementation of the findings to ensure that research reports better address the needs of the range of research users.
# Waste in medical research

Some examples

<table>
<thead>
<tr>
<th>Ideal</th>
<th>Reality</th>
</tr>
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<tbody>
<tr>
<td>Are research decisions based on questions relevant to users of research?</td>
<td>More than 50% of studies designed without reference to systematic reviews of existing evidence</td>
</tr>
<tr>
<td>Appropriate research design, methods and analysis?</td>
<td>Adequate steps to reduce bias not taken in more than 50% of studies</td>
</tr>
<tr>
<td>Fully accessible research information?</td>
<td>More than 50% of studies never fully reported</td>
</tr>
<tr>
<td>Unbiased and usable research reports?</td>
<td>More than 50% of planned study outcomes not reported</td>
</tr>
</tbody>
</table>

Macleod et al Lancet 2014
Waste in physiotherapy research

Clinical trial examples

› Unregistered, unreported trials

› Wrong question
  - Unimportant
  - Already answered

› Great question
  - Pilot trials that never proceed to definitive trials
  - Trials poorly conducted or abandoned
  - Design problems
  - Analysis problems
  - Reporting problems

› Post trial
  - No dissemination or implementation plan
<table>
<thead>
<tr>
<th>Speaker</th>
<th>Developments in..</th>
</tr>
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<tbody>
<tr>
<td><strong>Prof Sallie Lamb</strong></td>
<td>design &amp; conduct of clinical trials</td>
</tr>
<tr>
<td>• Professor of Rehabilitation at Warwick Clinical Trials Unit at the University of Warwick</td>
<td></td>
</tr>
<tr>
<td>• Kadoorie Professor of Trauma Rehabilitation at the University of Oxford.</td>
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<tr>
<td>• Published major trials in NEJM, Lancet etc</td>
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<tr>
<td><strong>Prof Rob Herbert</strong></td>
<td>analysis of clinical trials</td>
</tr>
<tr>
<td>• Senior Principal Research Fellow at Neuroscience Research Australia (NeuRA)</td>
<td></td>
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<tr>
<td>• One of the developers of PEDro</td>
<td></td>
</tr>
<tr>
<td>• Published basic and clinical research in JAMA, Annals etc</td>
<td></td>
</tr>
<tr>
<td><strong>Prof Rebecca Craik</strong></td>
<td>publication &amp; dissemination of clinical trials</td>
</tr>
<tr>
<td>• Chair, Department of Physical Therapy, Arcadia University</td>
<td></td>
</tr>
<tr>
<td>• Editor in Chief, Physical Therapy.</td>
<td></td>
</tr>
<tr>
<td>• Major NIH funding to examine motor control, ageing and recovery following nervous system injury.</td>
<td></td>
</tr>
</tbody>
</table>
Designing and doing Trials

PROFESSOR SARAH (SALLIE) LAMB
UNIVERSITY OF OXFORD
UNIVERSITY OF WARWICK

World Confederation for Physical Therapy
CONGRESS 2015
Singapore
processes for evaluation of established and novel physiotherapy interventions and for development of novel interventions, particularly complex interventions,
the continuum from early-phase explanatory trials to late-phase pragmatic trials, when to choose which, and how to design them,
common pitfalls in the design and conduct of pragmatic trials to inform health policy, commissioning and clinical practice, and
infrastructure requirements and teams needed to deliver high quality randomised evidence, and insights into project management for large-scale trials.
Very important to understand who the trial is for and what you are doing it for

- To prove a scientific point “mechanistic trial”
- To determine whether large research investment is likely to be worthwhile “proof of concept trial” “efficacy trial” “early phase trial” “safety” “toxicity”
- To demonstrate improved clinical outcomes in comparison to some other treatment strategy “effectiveness trial”
- To demonstrate improved cost effectiveness in comparison to some other treatment strategy “within trial cost effectiveness”
- To initiate disinvestment or changed investment “equivalence trials”
- (To demonstrate implementation effectiveness)”stepped wedge” “regression discontinuity” “post marketing surveillance
Box 1 What makes an intervention complex?

- Number of interacting components within the experimental and control interventions
- Number and difficulty of behaviours required by those delivering or receiving the intervention
- Number of groups or organisational levels targeted by the intervention
- Number and variability of outcomes
- Degree of flexibility or tailoring of the intervention permitted

Sequential phases of developing randomised controlled trials of complex interventions:

- **Preclinical**
  - Explore relevant theory to ensure best choice of intervention and hypothesis and to predict major confounders and strategic design issues.

- **Modelling**
  - Identify the components of the intervention and the underlying mechanisms by which they will influence outcomes to provide evidence that you can predict how they relate to and interact with each other.

- **Exploratory trial**
  - Describe the constant and variable components of a replicable intervention and a feasible protocol for comparing the intervention with an appropriate alternative.

- **Definitive randomised controlled trial**
  - Compare a fully defined intervention with an appropriate alternative using a protocol that is theoretically defensible, reproducible, and adequately controlled in a study with appropriate statistical power.

- **Long term implementation**
  - Determine whether others can reliably replicate your intervention and results in uncontrolled settings over the long term.

Continuum of increasing evidence.
Fig 1 Key elements of the development and evaluation process.

- **Feasibility and piloting**
  - Testing procedures
  - Estimating recruitment and retention
  - Determining sample size

- **Development**
  - Identifying the evidence base
  - Identifying or developing theory
  - Modelling process and outcomes

- **Evaluation**
  - Assessing effectiveness
  - Understanding change process
  - Assessing cost effectiveness

- **Implementation**
  - Dissemination
  - Surveillance and monitoring
  - Long term follow-up

Peter Craig et al. BMJ 2008;337:bmj.a1655
Novel Intervention: Translational pathway

Proof of Concept

Prototype discovery and design
Preclinical development

Efficacy and safety
Early phase trials

Effectiveness
Late phase trials

Implementation, Impact
Surveillance
Early phase designs

- Safety and toxicity
- Dose
- Efficacy
- Feasibility
- Pilot (internal and external)
- 200 participants, larger effect size, well controlled noise
Later phase - pragmatic trials

- Reflect everyday life
- Provide the most robust evidence of generalisable effect (harm or benefit)
- Provide good evidence of cost effectiveness
- Evidence that is credible to patients, practitioners, commissioners and policy/commisioning advisors (NICE)
Figure 1 Pragmatic Explanatory Continuum Indicator Summary (PRECIS) [10].
Understand bias and where it comes from

- Sampling bias
- Channelling bias (confounding by indication)
- Manipulation of randomisation
- Contamination of treatments
- Blinding (outcome assessors, participants, investigators)
- Sample size
- Differential loss to follow up (DNMR)
How to design them?

- Randomised – lots of different designs!
- Consider the degree of contamination
- Consider need for placebo
- Blind (mask) as well as possible
- Sample size specified a priori and correct
- Follow up designed to enable completeness
- Pre-specified data analysis plans
- Pre-publication of protocol
- Blinded data analysis, no sneak previews
- Think!!!!
Infrastructure, teams and project management

- Effective project management and project managers
- Efficient use of IT to maximise efficiency and minimise error
- Highly skilled and reliable team
- Motivated, managed and focused
- Effective leadership
Recruitment graph

Target
N=9000

6940
Design

General Practices

OR

Advice

OR

Exercise

OR

MFFP

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

Total 63 practices

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

Newcastle City
- 12 practices

Cambridgeshire
- 6 practices

Devon
- 12 pilot study
- 6 main study
Preparation for each General Practice

Prepare 400 packs

400 packs delivered to surgery

Week 0

Reminder packs prepared

Week 2

Reach target 150

We only need 150!

Pack contains:
- Pt Info Sheet
- Consent forms
- Questionnaire
- Return SAE

Repeat x 63
Checking all incoming data
the PreFIT office....
How to run and deliver a good trial

- Minimum of a monthly team meeting
- Learn to communicate within the team
- Spot problems early
- Institute diagnostics
- Implement solutions
- ...... or risk closure
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<th>A</th>
<th>B</th>
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<th>D</th>
<th>E</th>
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<td>32</td>
<td>77</td>
<td>190</td>
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Participants - Recruited

- Actual
- Initial Target

Timeline:
- April-13
- June-13
- August-13
- October-13
- December-13
- February-13
- April-14
- June-14
- August-14
- October-14
- December-14
- February-15
- April-15
- June-15
- August-15

Graph shows the increase in participants recruited over time, comparing actual recruitment against an initial target.
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<th>Months open</th>
<th>Randomisations</th>
<th>Randomisations a month</th>
<th>Number screened</th>
<th>Number SBT</th>
<th>% SBT</th>
<th>% fail SBT</th>
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<td>12</td>
<td>1.09</td>
<td>204</td>
<td>58</td>
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<td>QEHB</td>
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<td>0.00</td>
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<td>John Radcliffe</td>
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<td><strong>366</strong></td>
<td><strong>11%</strong></td>
<td><strong>16%</strong></td>
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</table>
Common pitfalls

- FAILURE to understand the funders perspective
- FAILURE to engage the right people
- EFFECT SIZE UNREALISTICALLY LARGE
- Recruitment poor
- Retention poor
- Underpowered (increases change of error)
- Biased (increase change of a false positive)
- Under resourced with poor infrastructure
Enjoy!
Any questions?
Developments in analysis of clinical trials

Rob Herbert
Context

- Until recently, most clinical trials have been analysed using simple statistical methods.
- In recent years the use of more sophisticated methods has become more widespread, because:
  - better methods have been developed
  - statistical software has made complex methods more accessible.
Four advances in analysis of clinical trials

Important advances have been made in methods for analysing randomised trials with:

1. repeated measurements of outcomes
2. missing data
3. non-compliance
4. mediation
Repeated measurement of outcomes

Repeated measurement of outcomes

Longitudinal approaches to analysis might be preferred to cross-sectional approaches. They:

- use data from all time points to estimate effects at each time.
- naturally accommodate outcomes that were measured at times other than the time specified in the protocol.
- are partially protected from bias caused by missing data.
Repeated measurement of outcomes

Longitudinal approaches include:

- Repeated measures ANOVA
- Longitudinal regression models
  - Generalized estimating equations
  - Mixed models (e.g., random intercept models, …)

Contemporary regression-based methods make fewer assumptions, are generally more robust, and naturally generate useful estimates of effects. So they are preferred to ANOVA.
Treatment effects were estimated using linear mixed models (random intercepts and fixed coefficients) which incorporated treatment, time, and the interaction between treatment and time (p5).
Missing data

- Loss to follow-up is inevitable in most clinical trials. It causes outcome data to be missing.
- Conventional methods for dealing with missing outcome data are problematic when data are not missing completely at random:
  - Analysis of only the available (non-missing) data generates biased estimates of effect.
  - Single imputation methods (such as imputation of means, last value carried forward and simple regression methods) generate biased estimates of effect and have spurious precision.
Missing data

Multiple imputation:

- predicts multiple values for each missing outcome and then combines the multiple observations in a way that properly accounts for the uncertainty of the predictions.
- is unbiased if outcomes are missing at random conditional on the data used to predict missing outcomes.
- generates estimates of effects that do not have spurious precision.
Is Behavioral Graded Activity Cost-Effective in Comparison With Manual Therapy for Patients With Subacute Neck Pain?

An Economic Evaluation Alongside a Randomized Clinical Trial

Judith E. Bosmans, PhD,∗ Jan J. M. Pool, PhD,†† Henriëtta C. W. de Vet, PhD,† Maurits W. van Tulder, PhD,** and Raymond W. J. G. Ostelo, PhD††

Complete clinical outcome data were available for 65 (92%) BGA patients and 67 (89%) MT patients ...

The statistical analyses were performed according to the intention-to-treat principle. Multiple imputation as implemented in SPSS-17 (SPSS Inc., Cary, NC) was used to impute missing cost and effect data. By multiple imputation, five imputed data sets were created, each of which was analyzed separately. The results of the five analyses were pooled using Rubin’s rules.²⁰
Non-compliance

- In many trials, participants don’t comply with the allocated intervention (e.g., participants in the exercise group don’t do their exercises).
- Analysis by intention to treat provides an unbiased estimate of the effect of the intention to treat, but not of the effect of treatment.
- Conventional approaches to estimating effects of treatment (per protocol and as treated analyses) will be biased if people who comply with intervention are not exchangeable with people who comply with control.
Non-compliance

Several contemporary methods provide unbiased estimates of complier average causal effects (CACE) if plausible assumptions are met:

- Principal stratification and instrumental variable regression assume “monotonicity” and “exclusion restriction”. In some circumstances these assumptions are reasonable and the methods are easy to use.
- Propensity score matching assumes “principal ignorability”.
We produced CACE estimates of the difference between the mean score for the compliers in the intervention group compared to the would-be compliers in the control group [16]. To obtain a CACE estimate we used a latent class model approach using the gllamm command in STATA [9,17,18].
Mediation

- Often we have hypotheses about mechanisms by which interventions work. For example:
  
  - We can ask: how much of the total effect is mediated by the effects of intervention on the mediating variable?
Mediation

- Methods for analysing mediation effects (e.g., Baron and Kenny’s “product of coefficients” method) have been used for decades but more rigorous methods have been developed.
- Contemporary methods:
  - make clearly defined assumptions.
  - can be applied to many types of data (e.g., binary, time-to-event and count data) and many designs including randomised trials with repeated measures.
- Mediation analysis makes strong assumptions, even when used in randomised trials.
Mediation

- In the WEBB trial, 340 older people recently discharged from hospital were randomised to home-based falls prevention exercise or usual care.
- Participants in the exercise group subsequently experienced more falls than controls (IRR = 1.43, 95% CI 1.07 to 1.93).
- Mediation analysis was used to explore if the increase in falls was mediated by an increase in physical activity in those who exercised.

Sherrington C. Older people and falls (PLR5-09), 4:00-5:30 pm, room 324-6.
Summary

1. Mixed linear models can provide precise, robust estimates of effects from trials with repeated measurements of outcome.

2. Multiple imputation can provide unbiased estimates of effects when data are missing, even if data are not missing completely at random.

3. Principal stratification, instrumental variable regression and propensity score matching can estimate effects of treatment in people who comply with the intervention.

4. Contemporary mediation analyses estimate indirect (mediated) causal effects which can provide insights into the mechanisms by which treatments work.
Further reading

Repeated outcome measurements:

Missing data:

Non-compliance:

Mediation:
Developments in Publication & Dissemination of Clinical Trials

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Objectives

- Identify and use the standardized checklists
  - CONSORT – for randomized controlled trials
  - TIDieR – to enhance intervention reporting
  - STROBE – for observational studies in epidemiology
  - STARD – for studies of diagnostic accuracy
  - QUALRES – for qualitative studies
  - COREQ – for qualitative studies
  - PRISMA – for systematic reviews and meta-analyses

- Describe clinical trials registration
- Discuss future of online clinical trial reporting
Purpose of Guidelines

- Assist in standardizing the reporting of research
- Educate future authors, reviewers, consumers about “good” research design
- Enhance research reporting
CONSORT Statement

- CONSOLIDATED STANDARDS OF REPORTING TRIALS
  - http://www.consort-statement.org

CONSORT encourages:
- transparent reporting of clinical trials

Authors are required to:
- follow the guidelines
- include a flow diagram within the manuscript
- submit the checklist for randomized trials of nonpharmacologic treatment
## CONSORT Extensions

<table>
<thead>
<tr>
<th>Designs</th>
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CONSORT Flow Diagram

No. Assessed for Eligibility

No. Excluded
  No. Not Meeting Inclusion Criteria
  No. Refused to Participate
  No. Other Reasons

No. Randomized

No. Assigned to Receive Intervention
  No. Received Intervention as Assigned
  No. Did Not Receive Assigned Intervention
    (Give Reasons)

No. Lost to Follow-up
  (Give Reasons)

No. Discontinued Intervention
  (Give Reasons)

No. Included in Analysis
  No. Excluded From Analysis
    (Give Reasons)

No. Assigned to Receive Intervention
  No. Received Intervention as Assigned
  No. Did Not Receive Assigned Intervention
    (Give Reasons)

No. Lost to Follow-up
  (Give Reasons)

No. Discontinued Intervention
  (Give Reasons)

No. Included in Analysis
  No. Excluded From Analysis
    (Give Reasons)
TIDieR Guide

- TIDieR
  - Template for intervention description and replication
- Enhancing quality & transparency of health research
- Providing sufficient description of intervention for replication
STROBE Statement

- STROBE
  - STrengthening the Reporting of OBservational Studies in Epidemiology
  - http://www.strobe-statement.org

- STROBE checklists are available for:
  - cohort studies
  - case-control studies
  - cross-sectional studies
STROBE Statement

- PTJ endorses:
  - the STROBE statement

- Authors are required to:
  - follow these guidelines
  - include a flow diagram within the manuscript
  - submit the most appropriate STROBE checklist for the paper (cohort, case-control, or cross-sectional design), including it as the last page of the manuscript
STARD Statement

- **STARD**
  - STA**ndards for the R**eporting of D**iagnostic accuracy studies
  - www.stard-statement.org

- Sensitivity and specificity alone are insufficient for diagnostic studies

- The likelihood ratio (LR) with CI must be reported

- An interpretation of the clinical relevance of the findings must be included
STARD Statement

PTJ endorses:
- the STARD statement

Authors are required to:
- follow these guidelines
- include a flow diagram within the manuscript
- submit the completed STARD checklist as the last page of the manuscript
PTJ endorses:
- the QUALRES guidelines (http://www.qualres.org)

Authors are required to:
- follow these guidelines
- 2 sets of acceptable guidelines:
  - Malterud's guidelines
  - Crabtree and Miller's guidelines
QUALRES Guidelines
Malterud K (2001)

CATEGORIES:
- AIM
- REFLEXIVITY
- METHODS and DESIGN
- THEORETICAL FRAMEWORK
- ANALYSIS
- FINDINGS
- DISCUSSION
- PRESENTATION
- REFERENCES
COREQ Guidelines

- COREQ
  - Consolidated criteria for reporting qualitative research
  - http://www.equator-network.org/reporting-guidelines/coreq/
- 32 item checklist for interviews and focus groups
MIXED METHODS RESEARCH

- Best Practices for Mixed Methods Research in Health Sciences
  - [http://obssr.od.nih.gov/mixed_methods_research/](http://obssr.od.nih.gov/mixed_methods_research/)

- Developed to assist NIH investigators and reviewers to create competitive grant applications

- Developed to enhance “best practice”
PRISMA Statement

- **PRISMA** - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
  - [www.prisma-statement.org](http://www.prisma-statement.org)
  - An evidence-based minimum set of items for reporting in systematic reviews and meta-analyses
Clinical Trials Registration – Why?

- Prospective protocol registration:
  - allows determination of duplication
  - allows people to enroll in clinical trials

- Transparency
  - Reviewers understand original intent
    - prevents selective reporting
    - prevents publication bias

- Ethical practice – Declaration of Helsinki
Requirements for Clinical Trials

- Trials Registration
  - Defined by the International Committee of Medical Journal Editors (ICMJE)
  - Definition: any research project that:
    - prospectively assigns human subjects to intervention or comparison groups to determine a cause-and-effect relationship between an intervention and an outcome
    - must have at least one prospectively assigned concurrent control or comparison group in order to trigger the requirement for registration
    - nonrandomized trials are not exempt from the registration requirement if they meet the above criteria
Clinical Trials Registration – ISPJE

- **PTJ** - Effective January 1, 2009
- Editorial by ISPJE in 2012-2013
- Authors should specify where the trial is registered and the trial's unique registration number in their cover letter
Clinical Trials Registration

- Free, available to public
- Takes about 30 minutes to complete
- No charge
Clinical Trials Registries

- strokecenter.org/trials
- www.ClinicalTrials.gov
- www.pactr.org
- www.anzctr.org.au
- www.umin.ac.jp/ctr/index/htm
- www.trialregister.nl
- https://eudract.ema.europa.eu/
Conflict of Interest

- **PTJ** has adopted the International Committee of Medical Journal Editors (ICMJE) initiative to standardize a format for disclosing competing interests

- This information is held in confidence by the Editor in Chief during the review process and, if the paper is accepted for publication, will be shared with readers as appropriate
Future

- Online access to raw data
- Opportunity for secondary analyses
- Pragmatic trials
- Health service research