INTERNATIONAL TRENDS IN CLINICAL RESEARCH OF CHINESE MEDICINES

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Purpose of clinical trials

... before we think about surgical removal, we'll try putting you on camomile tea for a few weeks and see what happens.
Purpose of clinical trials

- Trials build evidence which guide policy (e.g., PBS)
- $Billions spent each year on trials to prove the commercial/public health value of an intervention.
- Match the trial type to address the clinical question (and suit the intervention)
# Types of Clinical Trial

<table>
<thead>
<tr>
<th>Treatment Studies</th>
<th>Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised Controlled Trial</td>
<td>Cohort Study</td>
</tr>
<tr>
<td>- Double blind</td>
<td>- Prospective cohort</td>
</tr>
<tr>
<td>- Single-blind</td>
<td>- Retrospective cohort</td>
</tr>
<tr>
<td>- Non-blind</td>
<td>- Time-series study</td>
</tr>
<tr>
<td>Adaptive Clinical Trial</td>
<td>Case-control study</td>
</tr>
<tr>
<td></td>
<td>- Nested case-control study</td>
</tr>
<tr>
<td>Non-randomized trial (quasi-experiment)</td>
<td>Cross-sectional study</td>
</tr>
<tr>
<td></td>
<td>- Community survey</td>
</tr>
<tr>
<td>Superiority trials</td>
<td>Ecological study</td>
</tr>
<tr>
<td>Non-inferiority trials</td>
<td></td>
</tr>
<tr>
<td>Equivalence trials</td>
<td></td>
</tr>
</tbody>
</table>
## Matching research question and methodology

<table>
<thead>
<tr>
<th>Research question</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the relative efficacy of CHM for a specific disease?</td>
<td>Blinded RCT - Placebo or active controlled</td>
</tr>
<tr>
<td>What is the effectiveness of CHM in clinical practice?</td>
<td>Pragmatic (open label) randomised trial</td>
</tr>
<tr>
<td>Are there side effects from CHM?</td>
<td>Observational study; longitudinal survey; case controlled study</td>
</tr>
<tr>
<td>What is the patient experience of taking CHM?</td>
<td>Qualitative research</td>
</tr>
</tbody>
</table>
## Phases of Clinical Trials

<table>
<thead>
<tr>
<th>Phase of Trial</th>
<th>Purpose</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical Studies</td>
<td>feasibility, iterative testing and drug safety data is collected</td>
<td></td>
</tr>
<tr>
<td>Phase 0</td>
<td>Pharmacodynamics and Pharmacokinetics</td>
<td>10-15</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Screening for safety</td>
<td>20-80</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Establishing the efficacy of the drug, usually against a placebo</td>
<td>100-300</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Final confirmation of safety and efficacy</td>
<td>1000-3000</td>
</tr>
<tr>
<td>Phase 4</td>
<td>Sentry studies during sales</td>
<td></td>
</tr>
</tbody>
</table>
Worldwide TCM Market 2014

2014 world market for TCM products and services > US$172 B

Growth of TCM Market

Forecasts for TCM use

• 75% of westerners use complementary medicine each year - Chinese medicine is the fastest growing

• Growth will continue steadily with:
  – an ageing population and increasing prevalence of chronic disease
  – need to manage healthcare costs away from hospital care
  – need to minimise risk in managing chronic disease - diet, exercise, non-pharmaceutical, non-surgical options
Chinese Medicine trials to date

PubMed - "chinese medicines" OR "chinese herbal medicine" OR "traditional chinese medicines"
Wan Fang - "Zhong Yao" or "Zhong Cao Yao"
Clinical trials = lin chuang yan jiu or lin chuang shi yan
CCTs = lin chuang dui zhao shi yan or lin chuang dui zhao yan jiu
RCTs = sui ji dui zhao lin chuang shi yan or sui ji dui zhao lin chuang yan jiu
Systematic reviews = xi tong zong shu
Meta-analysis = meta fen xi
<table>
<thead>
<tr>
<th>Condition</th>
<th>Trial #</th>
<th>SR #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia &amp; Fatigue</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>GIT Disorders (lower GIT disorders)</td>
<td>256</td>
<td>28</td>
</tr>
<tr>
<td>Common Cold &amp; Influenza</td>
<td>49</td>
<td>12</td>
</tr>
<tr>
<td>Headache disorders</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Anxiety, Depression &amp; Stress</td>
<td>46</td>
<td>5</td>
</tr>
<tr>
<td>Allergies</td>
<td>99</td>
<td>19</td>
</tr>
<tr>
<td>Arthritis</td>
<td>117</td>
<td>8</td>
</tr>
<tr>
<td>Menstruation disturbances and menopause</td>
<td>79</td>
<td>9</td>
</tr>
<tr>
<td>Infertility</td>
<td>71</td>
<td>6</td>
</tr>
</tbody>
</table>
Clinical trials = lin chuang yan jiu or lin chuang shi yan
CCTs = lin chuang dui zhao shi yan or lin chuang dui zhao yan jiu
RCTs = sui ji dui zhao lin chuang shi yan or sui ji dui zhao lin chuang yan jiu
What is convincing evidence in order to adopt a new treatment?

1a: Systematic reviews (with homogeneity) of randomized controlled trials
1b: Individual randomized controlled trials (with narrow confidence interval)
1c: All or none randomized controlled trials

2a: Systematic reviews (with homogeneity) of cohort studies
2b: Individual cohort study or low quality randomized controlled trials (e.g. <80% follow-up)
2c: "Outcomes" Research; ecological studies

3a: Systematic review (with homogeneity) of case-control studies
3b: Individual case-control study

4: Case-series (and poor quality cohort and case-control studies)

5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
Reviews of CHM Trials

- Randomization unclear
- Blinding inadequate
- Outcome measures poorly defined
- Statistics need strengthening
- Potential for publication bias
CONSORT criteria for reporting clinical trials

1 & 2 - Title and Abstract

3 - Introduction  
Background and objectives

4 - Methods  
Trial design; Participants; Interventions; Outcomes; Sample size; Randomisation; Blinding; Statistical methods

5 - Results  
Participant flow; Recruitment; Baseline data; Numbers analysed; Outcomes and estimation; Ancillary analyses; Harms

6 - Discussion  
Limitations; Generalisability; Interpretation

7 - Other Information  
Registration; Protocol; Funding
Additional checklist points in *Methods*
- 4A: Herbal medicinal product name
- 4B: Characteristics of the herbal product
- 4C: Dosage regimen and quantitative description
- 4D: Qualitative testing
- 4E: Placebo/control group
- 4F: Practitioner
Additional challenges of Chinese medicine trials

• Personalised medicine approach
  – Formulae for different classification of disease
  – Tailoring of formulae for different phases of treatment
  – (N of 1 studies; pharmacogenomics)

• Difficulties in designing controls for tailored treatment process

• Chemical definition of complex medicines and stability through trial
Individualized/tailored = Bian Zheng Lun/Shi Zhi
Individualised treatment - Irritable Bowel Syndrome

- Active treatment significantly more effective than placebo (p<0.05)
- Individualization proved no better than standard at end of treatment
- Individually treated patients maintained significant improvement at 14 wk follow-up
Diagnostic subgroups - Primary Dysmenorrhoea

- **Active treatment significantly more effective than placebo in terms of menstrual pain intensity on worst day of menstruation** (p=0.001) and duration of menstrual pain (p<0.005).

- **Efficacy sustained at follow-up - two menstrual cycles after cessation of intervention**.

- **No significant difference between the tailored and standard treatment**.
How might we best test Chinese Medicine?

RCT of one fixed intervention  Vs  RCT where intervention is modified according to patient presentation AND varied as patient condition changes
Review of CHMs for pre-diabetes: Herbs appearing in at least 10% of the trials. Of the 100 formulas trialled, only 13 were trialled more than once.
Is the CONSORT sufficient to guide CM trials?

- CONSORT: CONsolidated Standards of Reporting Trials
- Reporting not Doing
- Does a good reporting score provide us with an adequate assessment of the quality of a trial?

NO!
Meta-analysis of 17 trials comparing two different forms of heparin for prevention of postoperative thrombosis, applying 25 different clinical trial rating scales

<table>
<thead>
<tr>
<th>Scale</th>
<th># items</th>
<th>Randomisation</th>
<th>Blinding</th>
<th>Withdrawal</th>
<th>Score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poynard, 1988</td>
<td>14</td>
<td>7.7</td>
<td>23.1</td>
<td>15.4</td>
<td>39</td>
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<tr>
<td>Chalmers et al, 1981</td>
<td>30</td>
<td>13.0</td>
<td>26.0</td>
<td>7.0</td>
<td>40</td>
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<tr>
<td>Spitzer et al, 1990</td>
<td>32</td>
<td>3.1</td>
<td>3.1</td>
<td>9.4</td>
<td>48</td>
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<tr>
<td>Linde et al, 1997</td>
<td>7</td>
<td>28.6</td>
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<td>Cho and Bero, 1994</td>
<td>24</td>
<td>14.3</td>
<td>8.2</td>
<td>8.2</td>
<td>56</td>
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<tr>
<td>Colditz et al, 1989</td>
<td>7</td>
<td>28.6</td>
<td>0</td>
<td>14.3</td>
<td>57</td>
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<tr>
<td>Gotzsche, 1989</td>
<td>16</td>
<td>6.3</td>
<td>12.5</td>
<td>12.5</td>
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<td>Smith et al, 1992</td>
<td>8</td>
<td>0</td>
<td>25.0</td>
<td>12.5</td>
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<tr>
<td>Imperiale &amp; McCullough 1990</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>60</td>
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<tr>
<td>Jadad et al, 1996</td>
<td>3</td>
<td>40.0</td>
<td>40.0</td>
<td>20.0</td>
<td>60</td>
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<tr>
<td>Koes et al, 1991</td>
<td>17</td>
<td>4.0</td>
<td>20.0</td>
<td>12.0</td>
<td>60</td>
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<tr>
<td>Reisch et al, 1989</td>
<td>34</td>
<td>5.9</td>
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<td>2.9</td>
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<tr>
<td>Evans and Pollock, 1985</td>
<td>33</td>
<td>3.0</td>
<td>4.0</td>
<td>11.0</td>
<td>64</td>
</tr>
<tr>
<td>Levine, 1991</td>
<td>29</td>
<td>2.5</td>
<td>2.5</td>
<td>3.1</td>
<td>64</td>
</tr>
<tr>
<td>Goodman et al, 1994</td>
<td>34</td>
<td>2.9</td>
<td>2.9</td>
<td>5.9</td>
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<tr>
<td>Kleijnen et al, 1991</td>
<td>7</td>
<td>20.0</td>
<td>20.0</td>
<td>0</td>
<td>70</td>
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<tr>
<td>Nurmohamed et al, 1992</td>
<td>8</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>75</td>
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<tr>
<td>Brown, 1991</td>
<td>6</td>
<td>14.3</td>
<td>4.8</td>
<td>0</td>
<td>81</td>
</tr>
<tr>
<td>ter Riet et al, 1990</td>
<td>18</td>
<td>12.0</td>
<td>15.0</td>
<td>5.0</td>
<td>83</td>
</tr>
</tbody>
</table>
MA of 17 trials comparing two different forms of heparin for prevention of postoperative thrombosis

For 6 scales high quality trials showed the old heparin was better than the new, and low quality trials showed the opposite.

For 7 scales high quality trials showed the new heparin was better than the old, which was not supported by low quality trials.

Conclusions of systematic reviews

- Consistent criticism of quality of trials
- Often ‘best’ trials reported as having negative outcomes

Who determines what is methodologically best?

- Systematic review conclusions depend on how we analyse trials, that is, what scales we use to assess trials
- Different rating scales for clinical trials => different outcomes in SRs
Jadad scale (1996)

1. Study described as randomized => 1 point
2. Adequate randomisation technique => 1 point (if method inappropriate, deduct 1 point)
3. Subject blinding (i.e. control indistinguishable from acupuncture) => 1 point
4. Evaluator blinded to treatment => 1 point
5. Description of withdrawals and dropouts => 1 point
All we need is a peer reviewed, internationally agreed clinical trial rating scale for the evaluation of Chinese herbal trials.
Acupuncture rating scale

Example items

• Study design is generally appropriate for the research question.
• TCM differential diagnosis (if undertaken) is stated.
• Acupuncture points selected according to diagnosis. Rationale given.
• Point location
• Needling: depth and manipulation
• Number of treatments
• Training of practitioner doing the diagnosis, administering the intervention
• Weighting of importance of factors
Clinical trial costs
NICM clinical trials

Herbal medicine
- Irritable Bowel Syndrome x 3
- Primary dysmenorrhoea
- Chronic hepatitis C
- Common cold
- Cold Sores
- Menopausal flushing
- Post-laparoscopic endometriosis
- Vascular dementia
- DOMS in sub-elite athletes
- Metabolic syndrome
- Pre-diabetes
- Polycystic ovary syndrome (PCOS)
- Post stroke sequelae

Acupuncture and others
- Acup to improve IVF birth rates
- Acupuncture for period pain
- Yoga for Mental Health
- CompleTE Birth Study
- Inter-rater reliability in CVD
- Post stroke sequelae
- Yoga for CVD recovery
Standard Operating Procedures for Clinical Trials

ICH Guidelines

The ICH topics are divided into four categories and ICH topic codes are assigned according to these categories.

Q: Quality Guidelines
Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

E: Efficacy Guidelines
The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

S: Safety Guidelines
ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

M: Multidisciplinary Guidelines
Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTR).
Chinese Medicine Practitioners - Australia

First western nation to nationally regulate Chinese Medicine practitioners

- 4219 registered TCM practitioners
- 62% practice CHM
- 97% practice acupuncture

Chinese Medicine Board of Australia, March 2014
Opportunities - Next Steps

• New Vice Chancellor - $30M building
• TCM $100M R & D Institute
• Integrative Medicine Hospital initiatives
• Electronic patient records; medicinal herb farming
Thank you