International Trends in Clinical Research of Chinese Medicines

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Purpose of clinical trials

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Purpose of clinical trials

- Trials build evidence which guide policy (eg 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

Treatment Studies	Observational Studies
Randomised Controlled Trial -Double blind -Single-blind -Non-blind	Cohort Study -Prospective cohort -Retrospective cohort -Time-series study
Adaptive Clinical Trial	Case-control study - Nested case-control study
Non-randomized trial (quasi-experiment)	Cross-sectional study - Community survey
Superiority trials Non-inferiority trials Equivalence trials	Ecological study

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Matching research question and methodology

Research question	Methodology
What is the relative efficacy of CHM for a specific disease?	Blinded RCT - Placebo or active controlled
What is the effectiveness of CHM in clinical practice?	Pragmatic (open label) randomised trial
Are there side effects from CHM?	Observational study; longitudinal survey; case controlled study
What is the patient experience of taking CHM?	Qualitative research

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Phases of Clinical Trials

Phase of Trial	Purpose	Sample Size
Preclinical Studies	feasibility, iterative testing and drug safety data is collected	
Phase 0	Pharmacodynamics and Pharmacokinetics	10-15
Phase 1	Screening for safety	20-80
Phase 2	Establishing the efficacy of the drug, usually against a placebo	100-300
Phase 3	Final confirmation of safety and efficacy	1000-3000
Phase 4	Sentry studies during sales	

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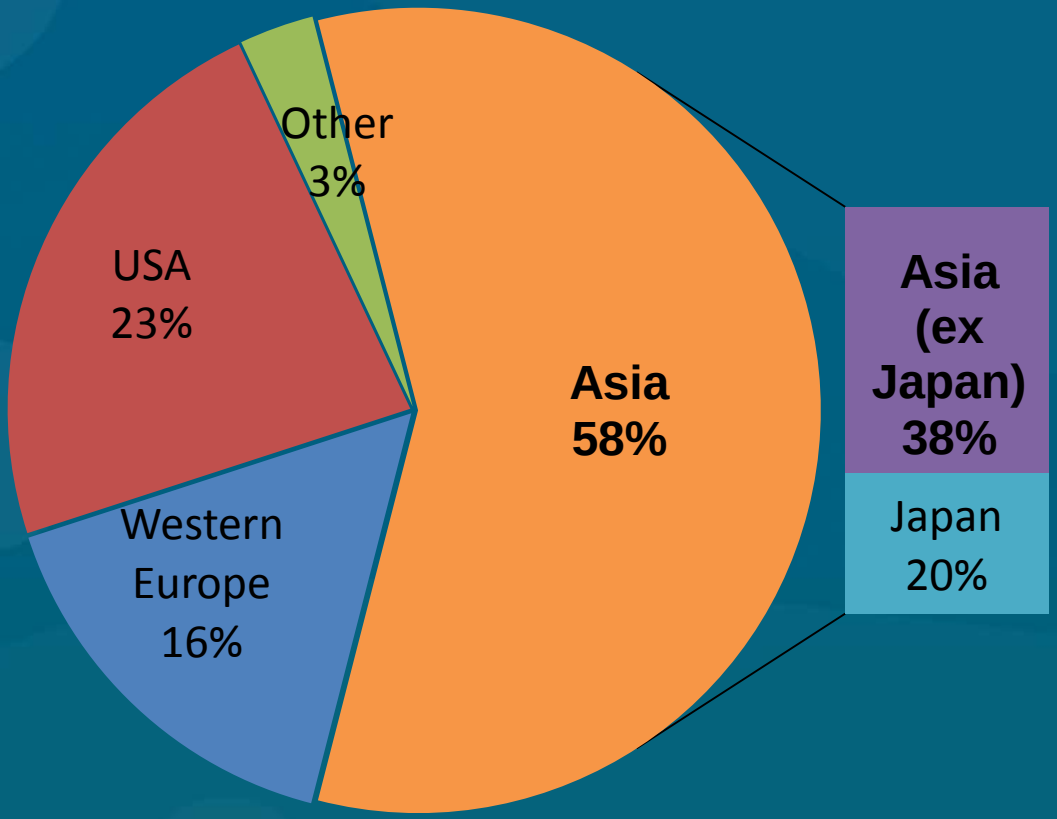
Worldwide TCM Market 2014



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

Helmut Kaiser Consultancy Report, 2012. *forecasted values

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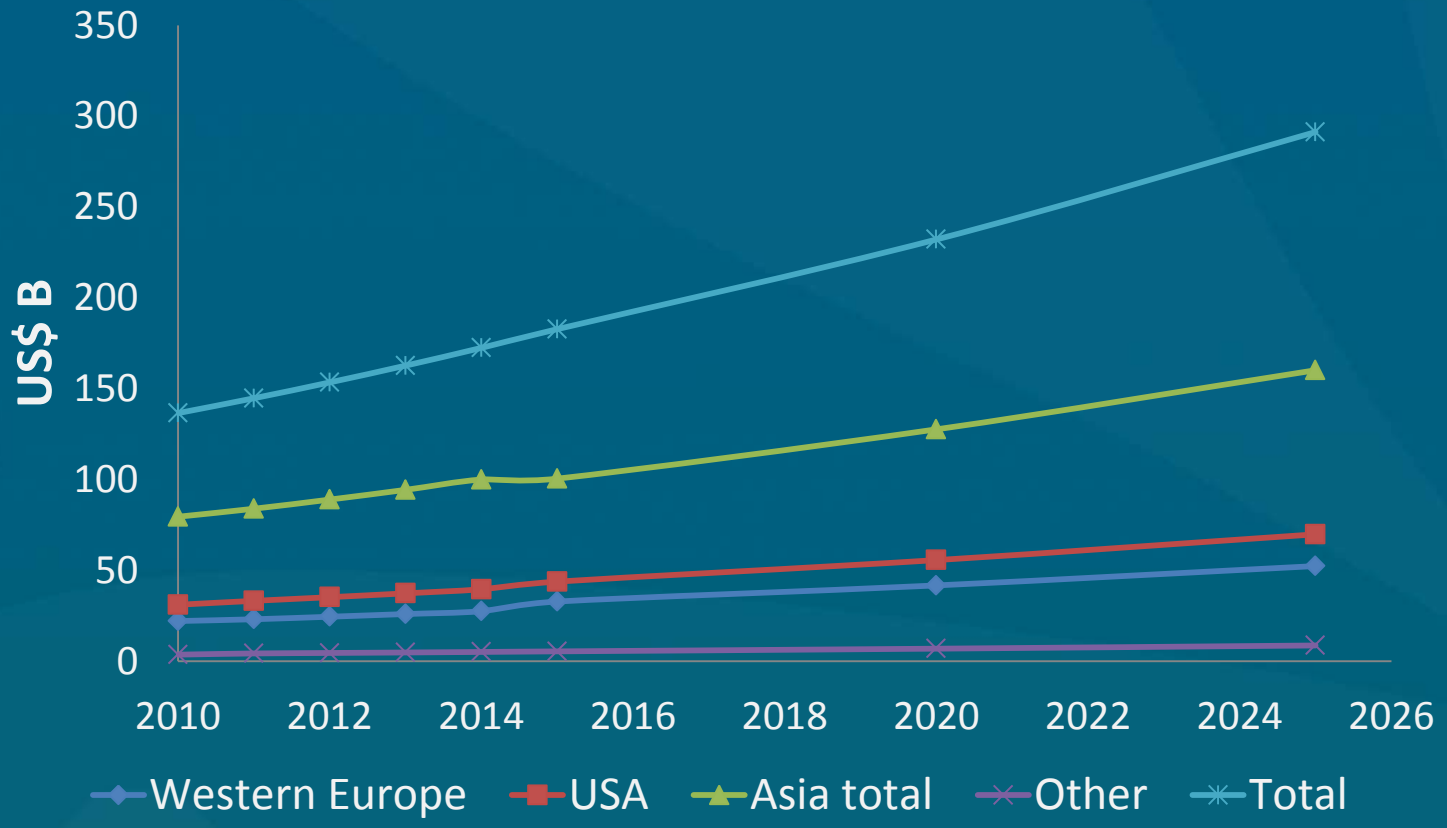
Growth of TCM Market



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Helmut Kaiser Consultancy Report, 2012. *forecasted values

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

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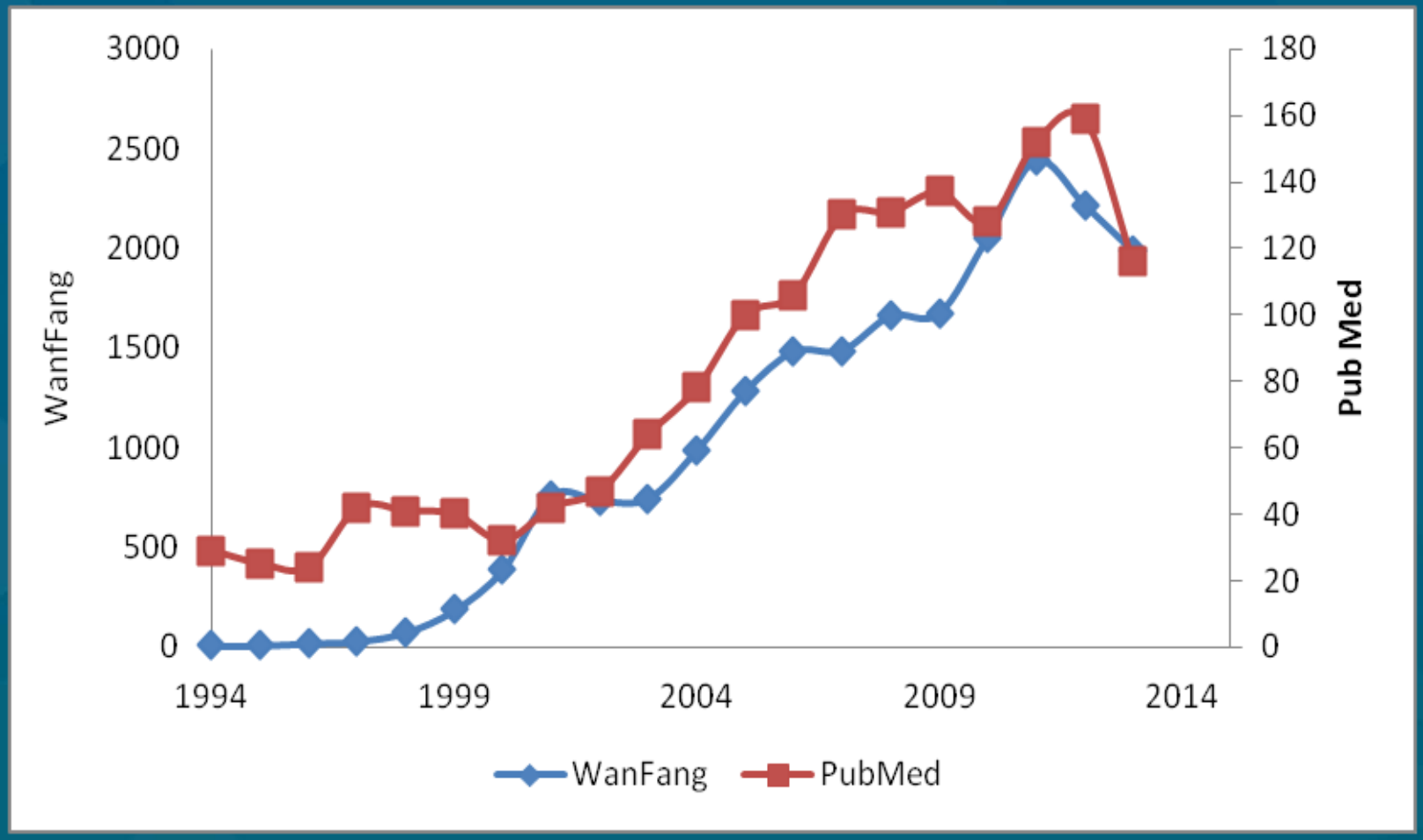
Chinese Medicine trials to date



PubMed – "chinese medicines" OR "chinese herbal medicine" OR "traditional chinese medicines"
Wan Fang - "Zhong Yao" or " Zhong Cao Yao"

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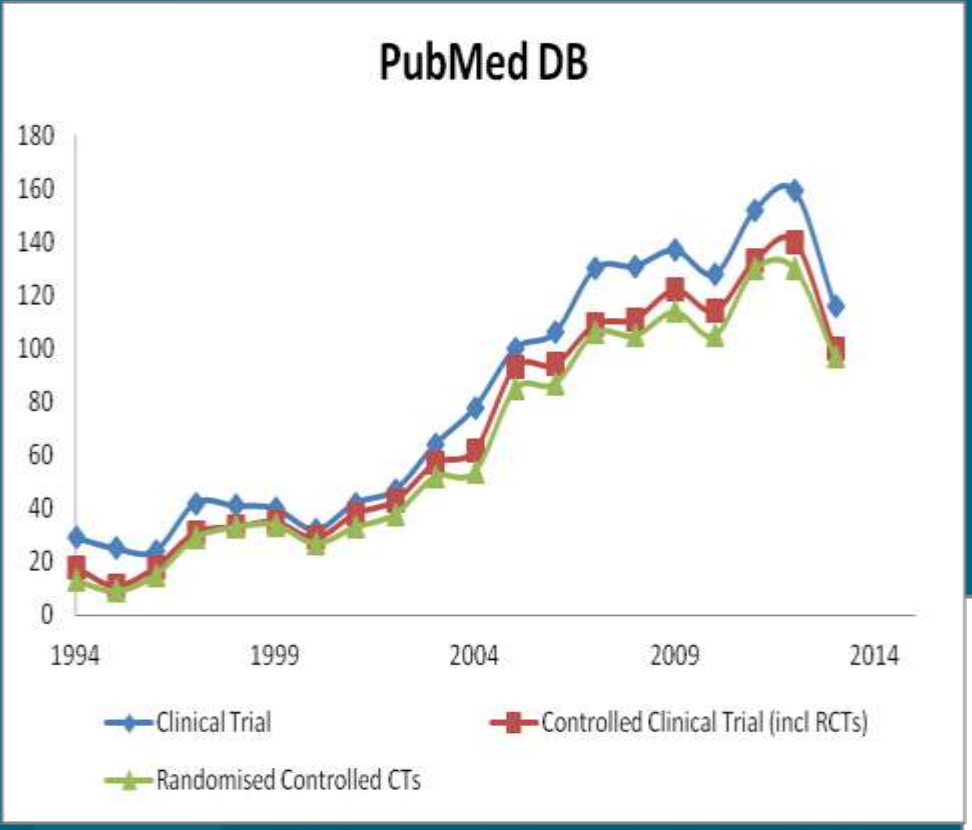
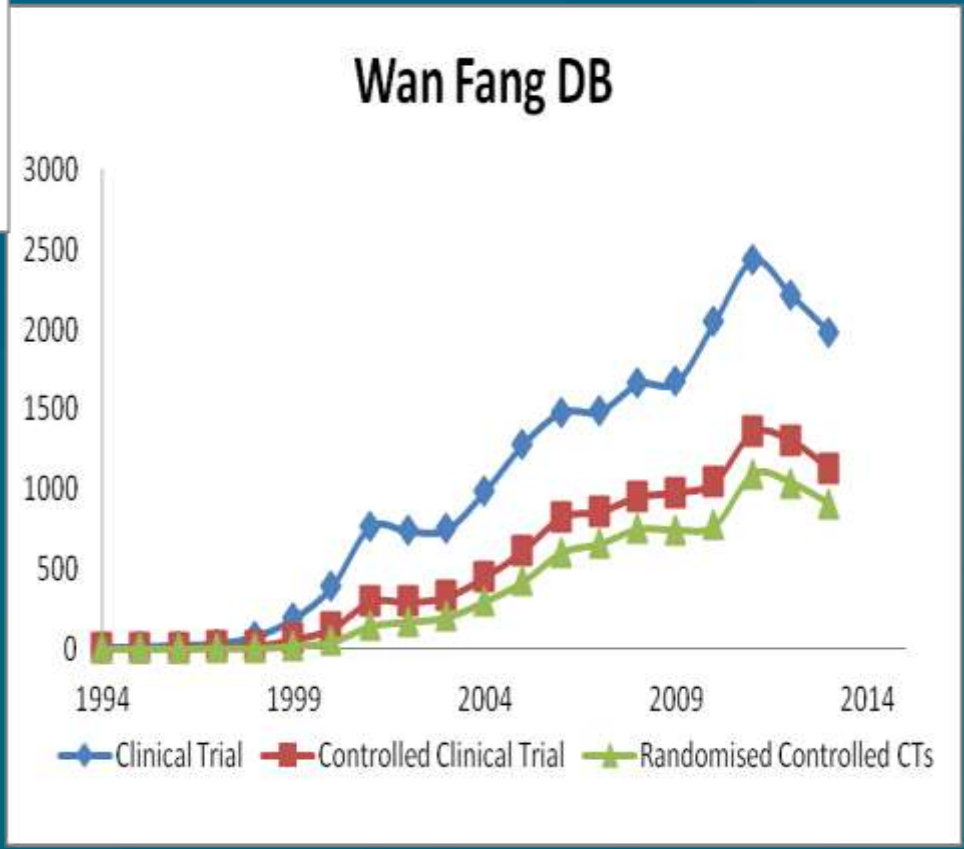


Clinical trials =
lin chuang yan jiu or lin chuang shi yan
CCTs = lin chuang dui zhao shi yan or lin chuang dui zhao yan jiu
RCTs = sui ji dui zhao lin chuang shi yan or sui ji dui zhao lin chuang yan jiu



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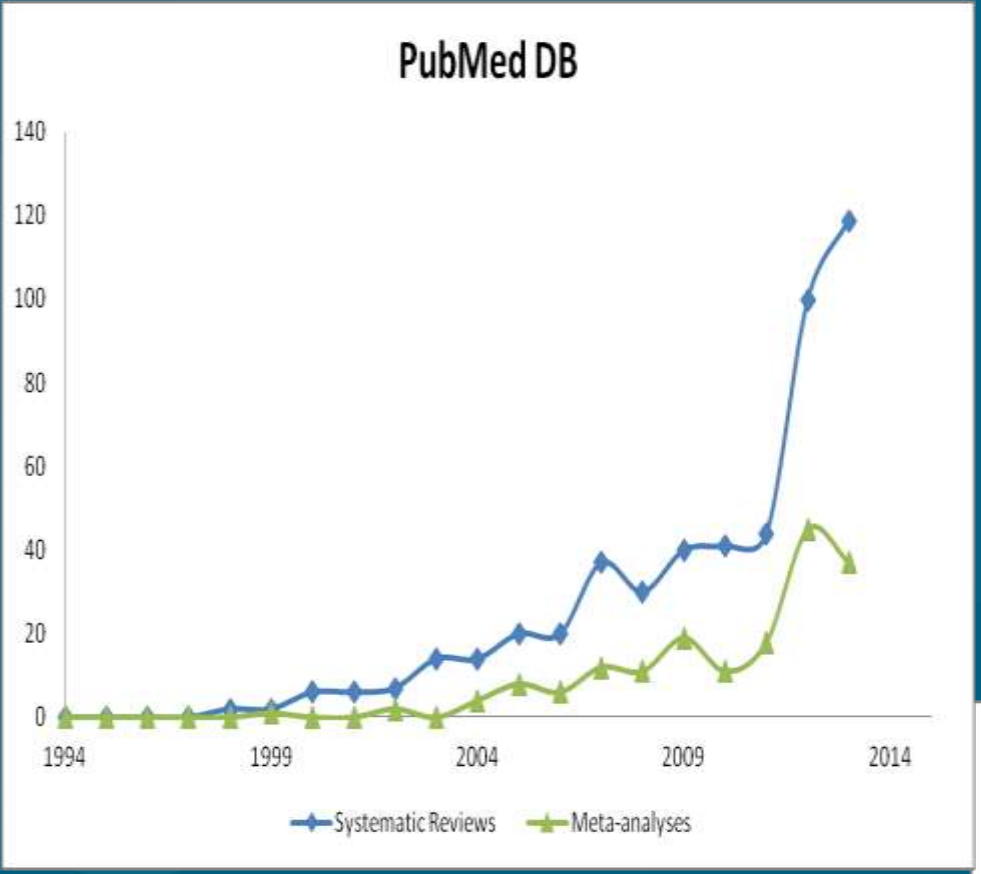
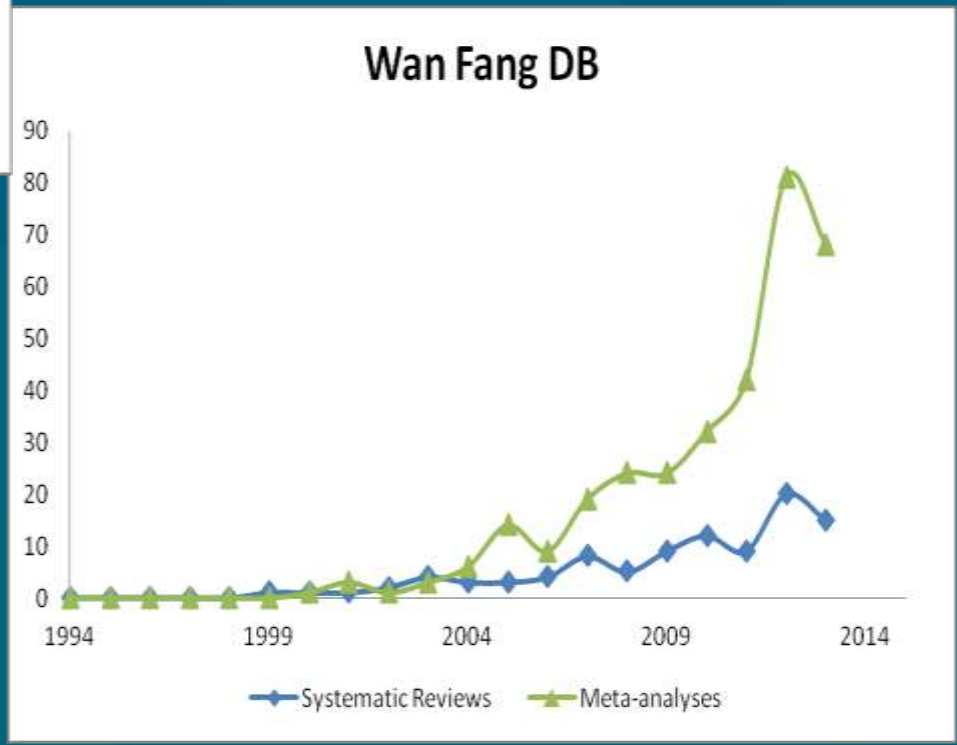


Systematic reviews =
xi tong zong shu
Meta-analysis = meta fen xi



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Clinical disciplines

Condition	Trial #	SR #
Insomnia & Fatigue	19	3
GIT Disorders	256	28
(lower GIT disorders)	17	0
Common Cold & Influenza	49	12
Headache disorders	10	2
Anxiety, Depression & Stress	46	5
Allergies	99	19
Arthritis	117	8
Menstruation disturbances and menopause	79	9
Infertility	71	6

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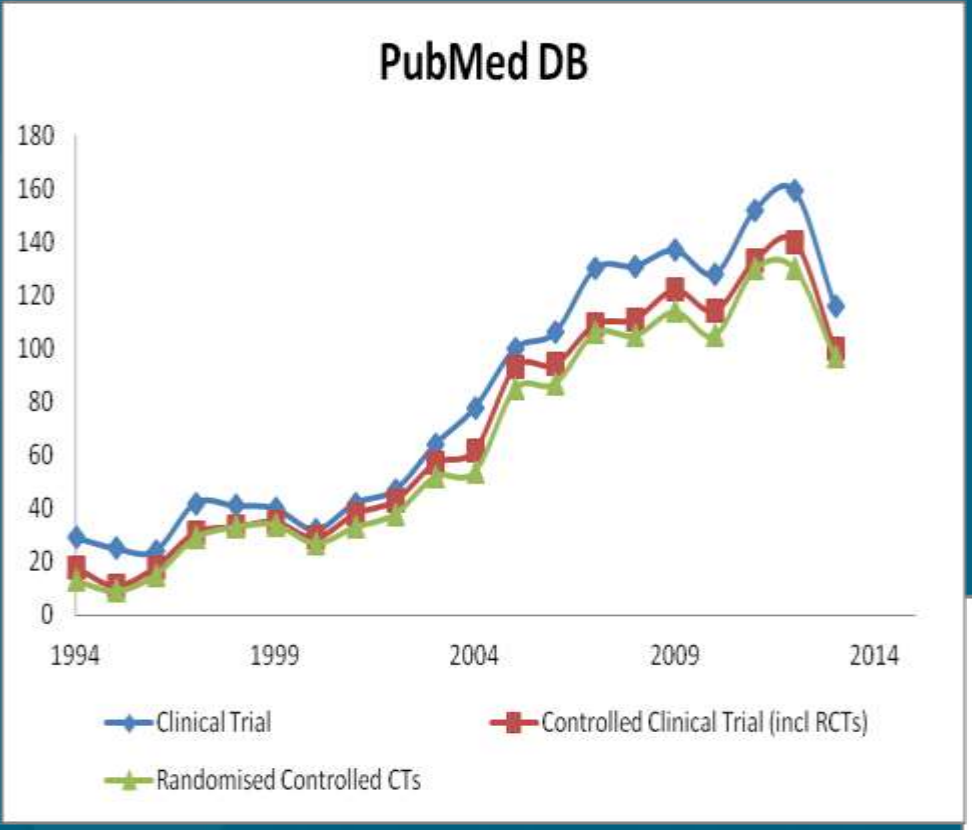

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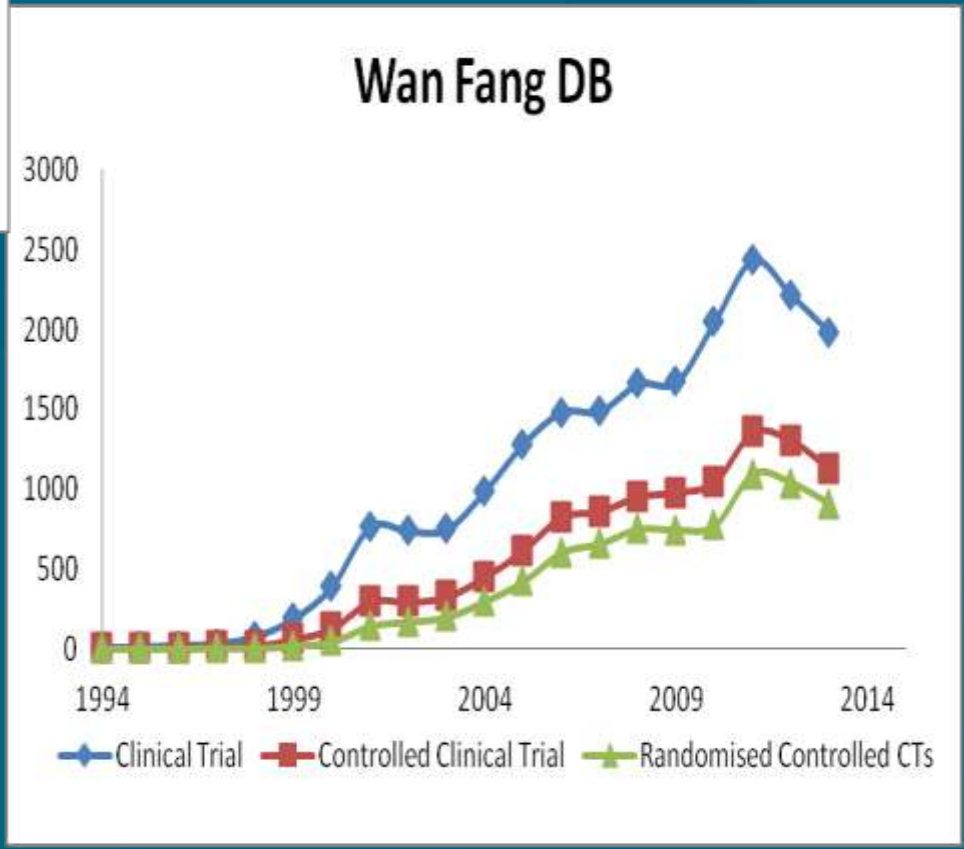

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What is convincing evidence in order to adopt a new treatment?

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"

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Reviews of CHM Trials

- Randomization unclear
- Blinding inadequate
- Outcome measures poorly defined
- Statistics need strengthening
- Potential for publication bias

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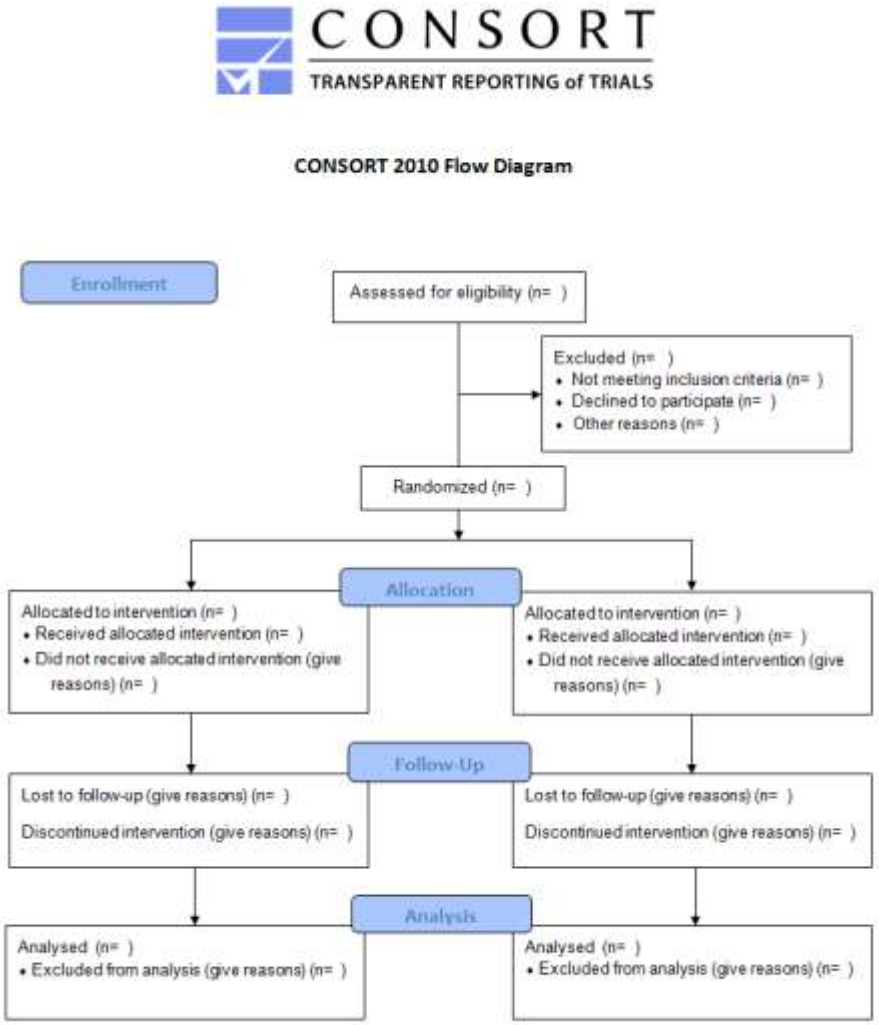
CONSORT criteria for reporting clinical trials



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*

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CONSORT for reporting of **herbal medicine** trials

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

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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

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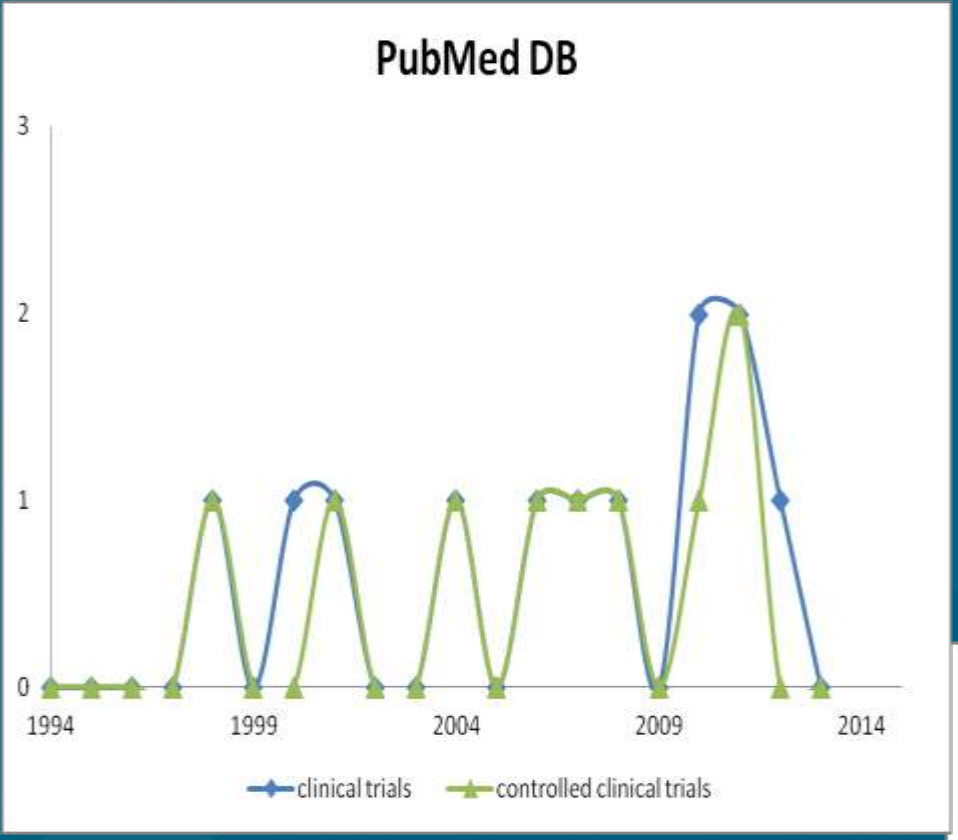
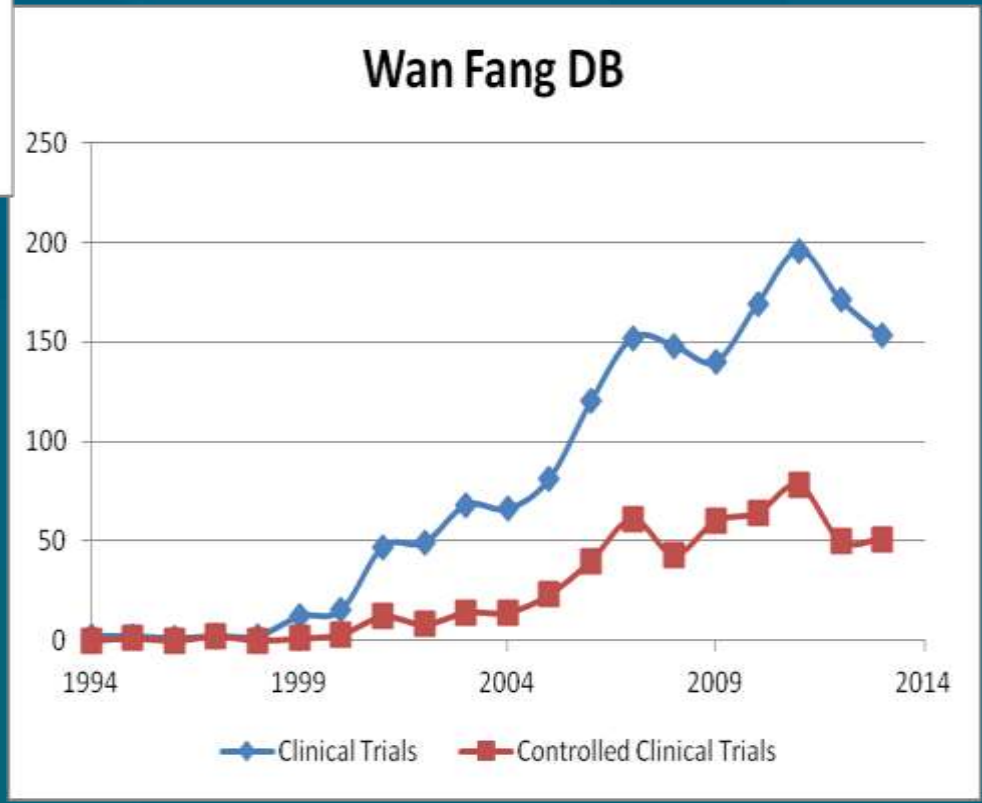


Individualized/tailored = Bian Zheng Lun/Shi Zhi



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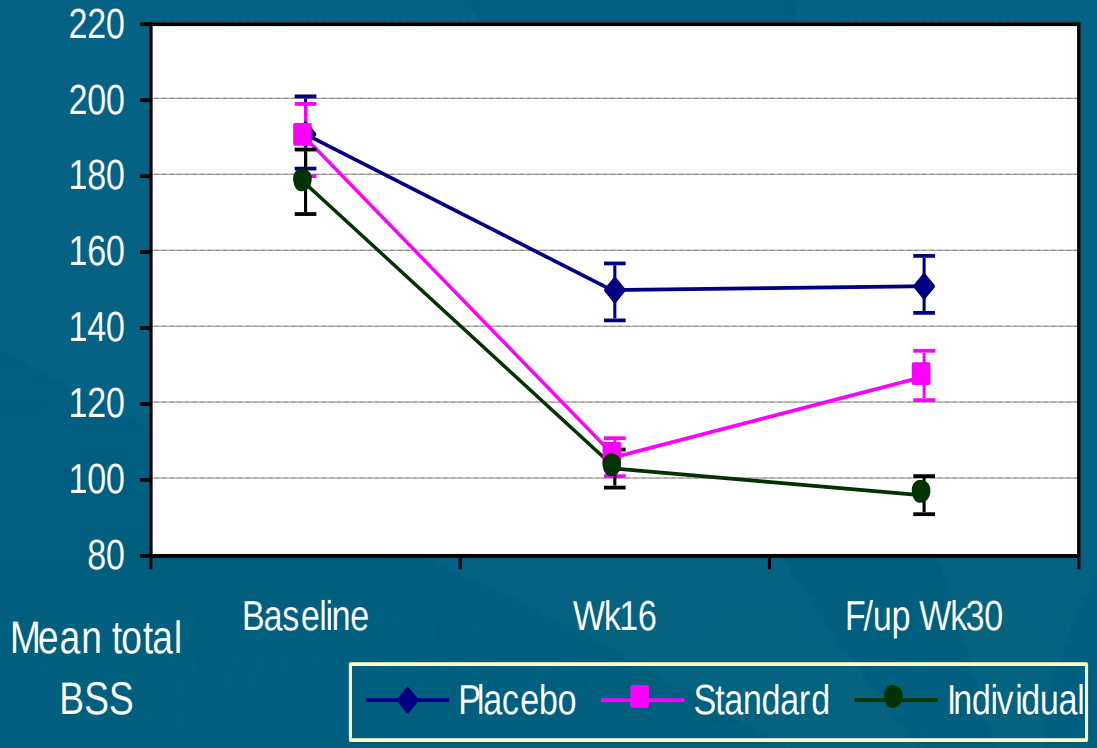
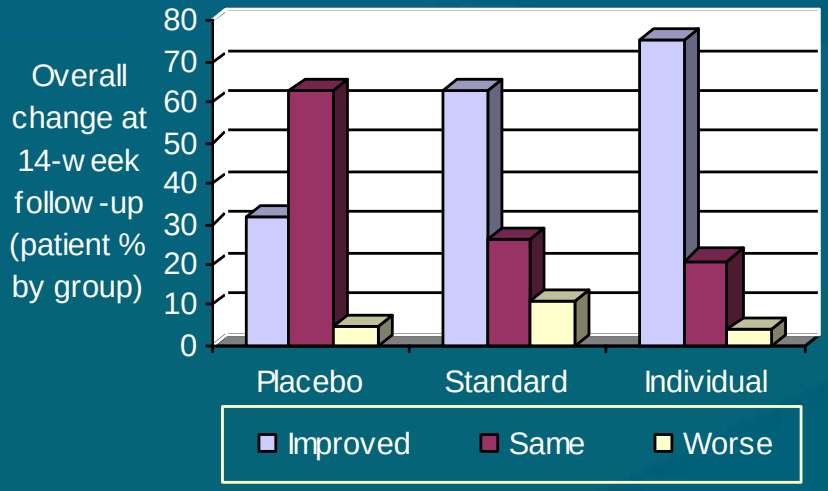
Individualised treatment - Irritable Bowel Syndrome

JAMA 1998;280:1585-1589

- 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 14wk follow-up





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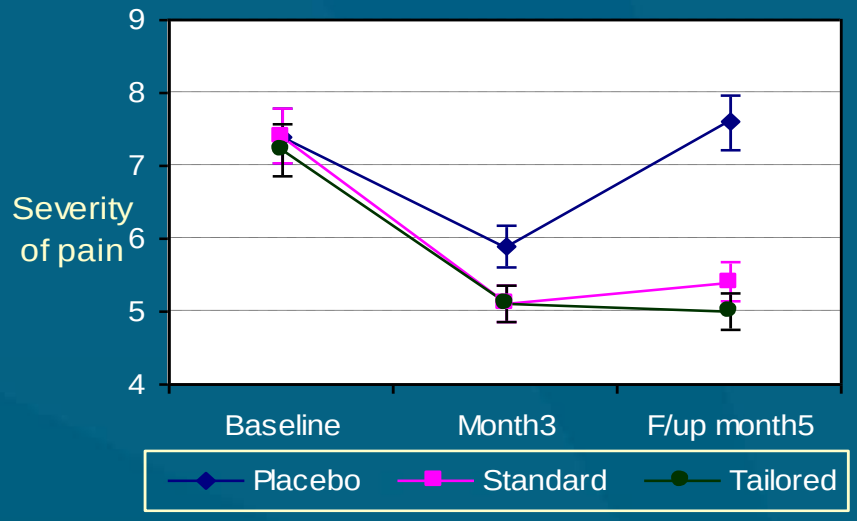
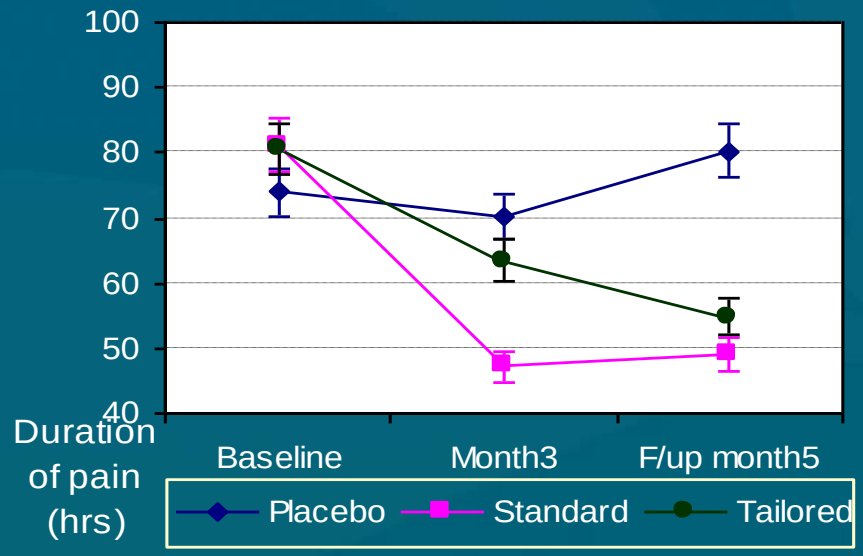
Diagnostic subgroups - Primary Dysmenorrhoea

- 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





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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

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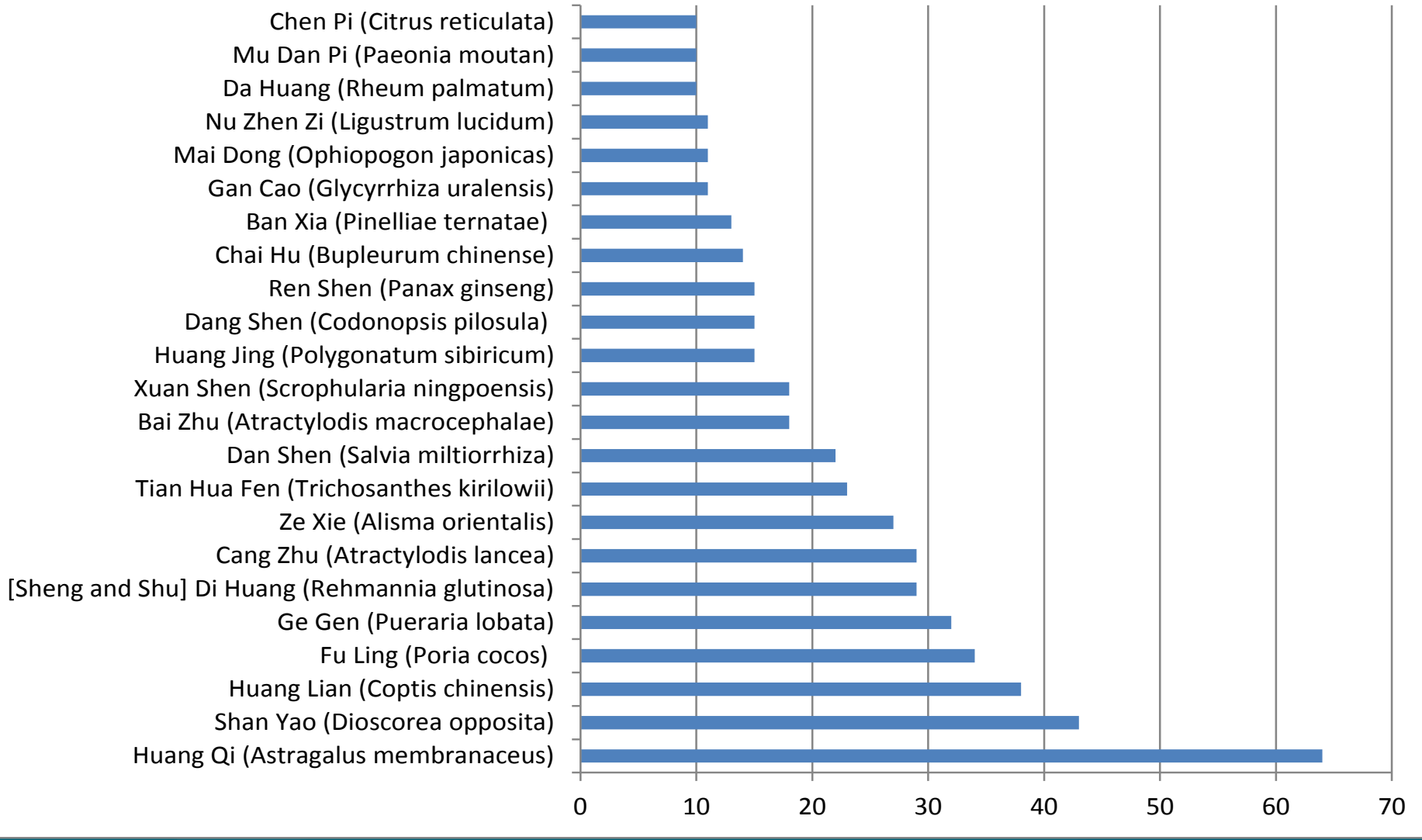
Review of CHMs for pre-diabetes: Herbs appearing in at least 10% of the trials. Of the 100 formulas trialled, only 13 were trialled more than once.



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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!

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Meta-analysis of 17 trials comparing two different forms of heparin for prevention of postoperative thrombosis, applying 25 different clinical trial rating scales

Juni P et al. Hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999: 282(11): 1054-60.

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		Key methodological domains (weight %)			Heparin use
Scale	# items	Randomisation	Blinding	Withdrawal	Score (%)
Poynard, 1988	14	7.7	23.1	15.4	39
Chalmers et al, 1981	30	13.0	26.0	7.0	40
Spitzer et al, 1990	32	3.1	3.1	9.4	48
Linde et al, 1997	7	28.6	28.6	28.6	50
Chalmers et al, 1990	3	33.3	33.3	33.3	56
Cho and Bero, 1994	24	14.3	8.2	8.2	56
Colditz et al, 1989	7	28.6	0	14.3	57
Gotzsche, 1989	16	6.3	12.5	12.5	57
Smith et al, 1992	8	0	25.0	12.5	57
Imperiale & McCullough 1990	5	0	0	0	60
Jadad et al, 1996	3	40.0	40.0	20.0	60
Koes et al, 1991	17	4.0	20.0	12.0	60
Reisch et al, 1989	34	5.9	5.9	2.9	63
Evans and Pollock, 1985	33	3.0	4.0	11.0	64
Levine, 1991	29	2.5	2.5	3.1	64
Goodman et al, 1994	34	2.9	2.9	5.9	68
Kleijnen et al, 1991	7	20.0	20.0	0	70
Nurmohamed et al, 1992	8	12.5	12.5	12.5	75
Brown, 1991	6	14.3	4.8	0	81
ter Riet et al, 1990	18	12.0	15.0	5.0	83

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.

Juni P et al. Hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999: 282(11): 1054-60.

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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

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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

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All we need is a peer reviewed,
internationally agreed
clinical trial rating scale
for the evaluation of Chinese herbal trials.

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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

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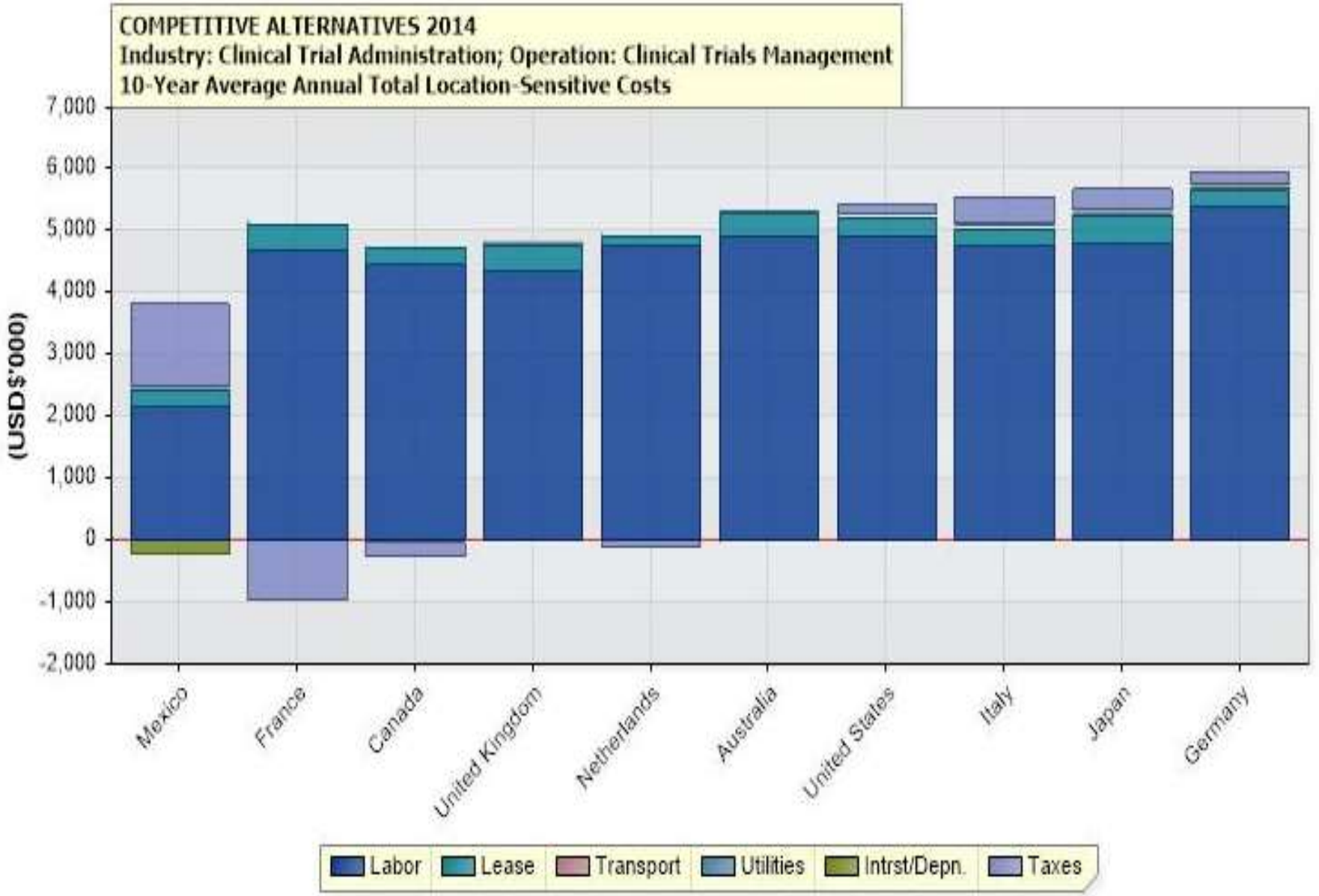
Clinical trial costs



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

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Standard Operating Procedures for Clinical Trials

ICH Guidelines / Work Products /

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

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.

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.

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.

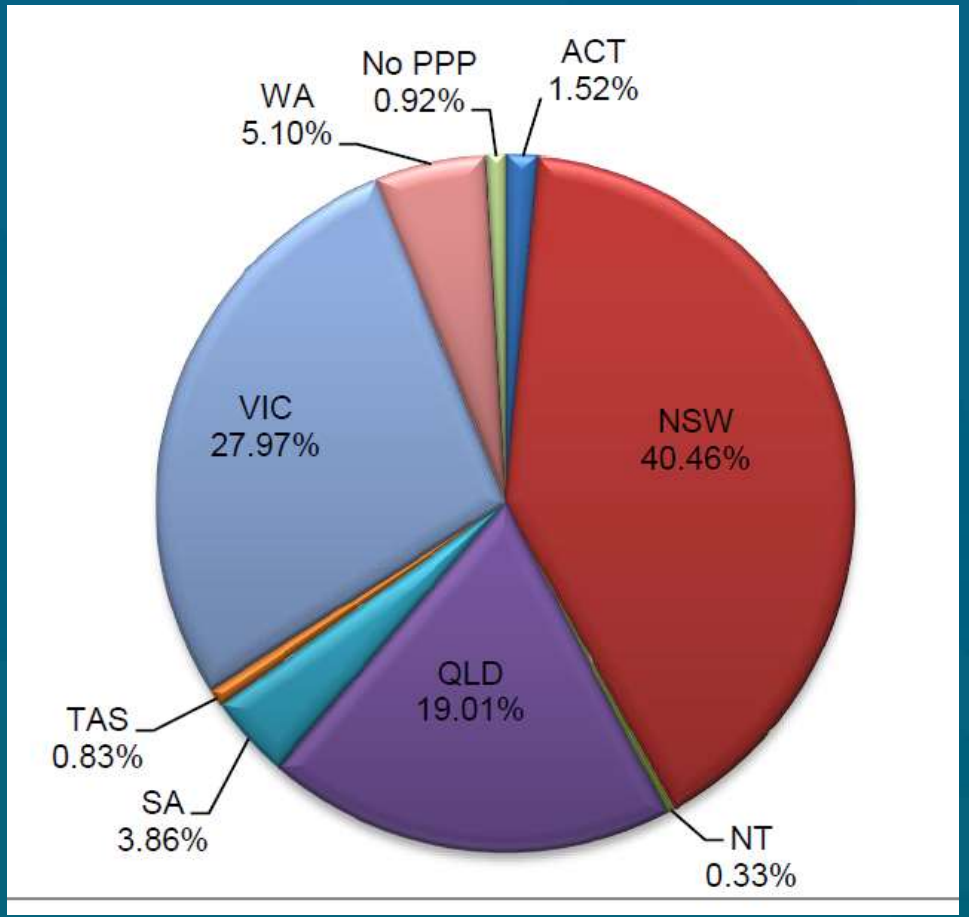
Multidisciplinary Guidelines

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 (ESTRI).

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

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Opportunities – Next Steps

- New Vice Chancellor - $30M building
- TCM $100M R & D Institute

- Integrative Medicine Hospital initiatives
- Electronic patient records; medicinal herb farming

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Thank you