

# Additional data on Shang 2005

We here present data for the comparison of meta-analyses (MAs) of placebo-controlled trials of homoeopathic and conventional treatment, respectively, in Shang 2005.<sup>1</sup>

## 1. Methods

### 1.1 Research hypothesis

The authors (Shang 2005, Discussion, p.730) “assumed that the effects observed in placebo-controlled trials of homoeopathy could be explained by a combination of methodological deficiencies and biased reporting” and “that the same biases could not explain the effects observed in comparable placebo-controlled trials of conventional medicine”.

### 1.2 Design, literature search and inclusion

Shang 2005 was designed as a prospective comparison of two MAs of placebo-controlled trials: one MA of any type of homoeopathic treatment for any disorder and one MA on conventional treatment, whereby each homoeopathy trial (HOM trial) was matched with a trial on conventional treatment (CON trial) “that enrolled patients with similar disorders and assessed similar outcomes” (Shang 2005, Methods, p.727).

Potentially eligible HOM trials were searched for in 19 electronic databases and by hand search of the Linde 1997 MA.<sup>2</sup> Matching CON trials were searched for in 1 database (Cochrane Controlled Trials Register, 2003, Issue 1). The authors “used computer-generated random numbers to select one from several eligible trials of conventional medicine. Outcomes were selected and trials matched without knowledge of trial results” (Shang 2005, Methods, p.727).

## 2. Results

### 2.1 All trials

#### 2.1.1 Descriptive data, trial results

Among all trials, (n = 110 patients in each group) sample size was very similar (median 65.5 and 65.0 patients in HOM and CON trials, respectively, p = 0.875) (Table 1).

Regarding publication format, a significantly smaller proportion of HOM trials than CON trials were published as journal articles (85.5%, n = 94/110 vs. 100.0%, n = 110/110, p < 0.001), published in Medline-indexed journals (40.0% vs. 86.4%, p < 0.001) and published in the English language (52.7% vs. 85.5%, p < 0.001), respectively (Table 1).

Median publication year was 1992 and 1994 for HOM and CON trials, respectively. Outcome types and outcome assessments were very similar among HOM and CON trials, without any significant differences (Table 1).

In accordance with the matching, the distribution of indication groups was identical in the two trial sets (Table 2).

The proportion of trials with a significant effect of the intervention, compared to placebo was 36.4% (n = 40/110) for HOM trials and 50.0% (n = 55/110) for CON trials (p = 0.056) (Table 1).

Table 1 Characteristics of trials of homoeopathy and conventional medicine, respectively

|                                               | Homoeopathy<br>(n = 110) |         | Conventional<br>medicine (n = 110) |         | Comparison*                                                                 |
|-----------------------------------------------|--------------------------|---------|------------------------------------|---------|-----------------------------------------------------------------------------|
| Sample size                                   |                          |         |                                    |         | Mann-Whitney U-test                                                         |
| Median                                        | 65.5                     |         | 65.0                               |         | p = 0.875,<br>median difference<br>(HOM-CON) -1.0,<br>95% CI -14.0 to +10.0 |
| Interquartile range                           | 37.0-104.0               |         | 35-131.5                           |         |                                                                             |
| Total range                                   | 10-1573                  |         | 12-1367                            |         |                                                                             |
| Mean (SD)                                     | 117.1 (211.2)            |         | 132.7 (225.9)                      |         |                                                                             |
| Publication year                              |                          |         |                                    |         |                                                                             |
| Median year (range)                           | 1992 (1966-2003)         |         | 1994 (1974-2002)                   |         |                                                                             |
| Publication format                            | N                        | Percent | N                                  | Percent | Fisher's exact test                                                         |
| Journal article                               | 94                       | 85.5%   | 110                                | 100.0%  | p < 0.001                                                                   |
| Medline-indexed journal                       | 45                       | 40.9%   | 95                                 | 86.4%   | p < 0.001                                                                   |
| English language                              | 58                       | 52.7%   | 94                                 | 85.5%   | p < 0.001                                                                   |
| Type and assessment of outcome                |                          |         |                                    |         |                                                                             |
| Overall assessment of response                | 54                       | 49.1%   | 49                                 | 44.5%   | p = 0.5890                                                                  |
| Occurrence or duration of disorder            | 26                       | 23.6%   | 26                                 | 23.6%   | No difference                                                               |
| Assessment of symptoms                        | 21                       | 19.1%   | 26                                 | 23.6%   | p = 0.5109                                                                  |
| Measurement of function or state              | 6                        | 5.5%    | 6                                  | 5.5%    | No difference                                                               |
| Assessment of clinical signs                  | 3                        | 2.7%    | 3                                  | 2.7%    | No difference                                                               |
| Trial results                                 |                          |         |                                    |         |                                                                             |
| Intervention > Placebo significant (p < 0.05) | 40                       | 36.4%   | 55                                 | 50.0%   | p = 0.056                                                                   |
| Intervention > Placebo not significant        | 51                       | 46.4%   | 38                                 | 34.5%   |                                                                             |
| Placebo > Intervention not significant        | 18                       | 16.4%   | 16                                 | 14.5%   |                                                                             |
| Placebo > Intervention significant (p < 0.05) | 1                        | 0.9%    | 1                                  | 0.9%    |                                                                             |
| Methodological quality                        |                          |         |                                    |         |                                                                             |
| Described as double-blind                     | 101                      | 91.8%   | 96                                 | 87.3%   | p = 0.3785                                                                  |
| Adequate generation of allocation sequence    | 27                       | 24.5%   | 30                                 | 27.3%   | p = 0.7585                                                                  |
| Adequate concealment of allocation            | 49                       | 44.5%   | 21                                 | 19.1%   | p < 0.0001                                                                  |
| Intention-to-treat analysis                   | 33                       | 30.0%   | 40                                 | 36.4%   | p = 0.3904                                                                  |
| High-Quality trials                           | 21                       | 19.1%   | 9                                  | 8.2%    | p = 0.0294                                                                  |

\*Statistical tests analysed by authors of this systematic review.

Table 2 Indication groups of all trials of homoeopathy and conventional medicine, respectively

| Indication groups            | Homoeopathy |         | Conventional medicine |         | Total |         |
|------------------------------|-------------|---------|-----------------------|---------|-------|---------|
|                              | N           | Percent | N                     | Percent | N     | Percent |
| Gastroenterology             | 12          | 10.9%   | 12                    | 10.9%   | 24    | 10.9%   |
| Gynaecology and obstetrics   | 14          | 12.7%   | 14                    | 12.7%   | 28    | 12.7%   |
| Musculoskeletal disorders    | 11          | 10.0%   | 11                    | 10.0%   | 22    | 10.0%   |
| Neurology                    | 10          | 9.1%    | 10                    | 9.1%    | 20    | 9.1%    |
| Pollinosis and asthma        | 16          | 14.5%   | 16                    | 14.5%   | 32    | 14.5%   |
| Respiratory-tract infections | 21          | 19.1%   | 21                    | 19.1%   | 42    | 19.1%   |
| Surgery and anaesthetics     | 12          | 10.9%   | 12                    | 10.9%   | 24    | 10.9%   |
| Miscellaneous                | 14          | 12.7%   | 14                    | 12.7%   | 28    | 12.7%   |
| TOTAL                        | 110         | 100.0%  | 110                   | 100.0%  | 220   | 100.0%  |

Indications and outcomes were listed in separate supplementary tables for HOM and CON trials, respectively, without apparent matching of individual trials. In Table 3 we have matched trials within each indication group for similar indications and similar outcomes.

Table 3 Indications and outcomes of all trials of homoeopathy and conventional medicine, respectively

| HOMOEOPATHY              |                                      |                               |         | CONVENTIONAL MEDICINE   |                           |        |                              |
|--------------------------|--------------------------------------|-------------------------------|---------|-------------------------|---------------------------|--------|------------------------------|
| Author (ref)             | Indications                          | Outcomes                      | ICD-10  | Author (ref)            | Indications               | ICD-10 | Outcomes                     |
| Gastroenterology         |                                      |                               |         | Gastroenterology        |                           |        |                              |
| Solanki (85)             | Intestinal amoebiasis and giardiasis | Global assessment, other      | A06-A07 | Rossignol (82)          | Intestinal infection      | A09    | Global assessment, other     |
| Mössinger (64)           | Cholecystopathia                     | Global assessment, physician  | A09     | Sand (86)               | Gallbladder stones        | K80    | Pain                         |
| Jacobs (46)              | Diarrhoea                            | Duration of diarrhoea         | A09     | Alam (2)                | Diarrhoea                 | A09    | Duration of diarrhoea        |
| Jacobs (48)              | Diarrhoea                            | Duration of diarrhoea         | A09     | Cezard (18)             | Diarrhoea                 | A09    | Duration of diarrhoea        |
| Jacobs (49)              | Diarrhoea                            | Duration of diarrhoea         | A09     | Kaplan (53)             | Diarrhoea                 | A09    | Duration of diarrhoea        |
| Ritter (79)              | Gastropathy                          | Global assessment, other      | K31     | Battaglia (7)           | Irritable bowel syndrome  | K58    | Global assessment, other     |
| Mössinger (65)           | Gastropathy                          | Global assessment, patient    | K31     | Skoubo-Kirstensen (93)  | Gastritis                 | K29    | Global assessment, patient   |
| Mössinger (65)           | Gastropathy                          | Global assessment, patient    | K31     | Nayak (69)              | Irritable bowel syndrome  | K58    | Pain                         |
| Mössinger (65)           | Irritable bowel syndrome             | Global assessment, patient    | K58     | Gade (38)               | Irritable bowel syndrome  | K58    | Global assessment, physician |
| Rahlfs (73)              | Irritable bowel syndrome             | Global assessment, patient    | K58     | Hovdenak (46)           | Irritable bowel syndrome  | K58    | Global assessment, patient   |
| Rahlfs (74)              | Irritable bowel syndrome             | Global assessment, patient    | K58     | Milo (64)               | Irritable bowel syndrome  | K58    | Global assessment, other     |
| Bignamini (12)           | Anal fissures                        | Global assessment, patient    | K60     | Maria (57)              | Anal fissure              | K60    | Global assessment, physician |
| Gynaecology & obstetrics |                                      |                               |         | Gynecology & obstetrics |                           |        |                              |
| Carey (18)               | Vaginal discharge                    | Global assessment, other      | N89     | Stein (95)              | Vaginal candidiasis       | B37    | Global assessment, physician |
| Ustianowski (92)         | Cystitis                             | Global assessment, physician  | N30     | Warren (107)            | Cystitis                  | N30    | Global assessment, patient   |
| Bergmann (10)            | Amenorrhea                           | Global assessment, physician  | N91     | Mendes (63)             | Amenorrhoea               | N91    | Global assessment, physician |
| Bergmann (10)            | Oligomenorrhea                       | Global assessment, physician  | N91     | Fleming (35)            | Oligomenorrhoea           | N91    | Global assessment, physician |
| Chapman (22)             | Premenstrual syndrome                | Global assessment, other      | N94     | Grio (41)               | Premenstrual syndrome     | N94    | Global assessment, other     |
| Lepaisant (58)           | Premenstrual syndrome                | Global assessment, other      | N94     | Di Carlo (28)           | Premenstrual syndrome     | N94    | Depression                   |
| Yakir (104)              | Premenstrual syndrome                | Global assessment, patient    | N94     | Eriksson (33)           | Premenstrual syndrome     | N94    | Global assessment, patient   |
| Gauthier (39)            | Menopausal complaints                | Global assessment, patient    | N95     | Von Holst (106)         | Postmenopausal complaints | N95    | Flushes                      |
| Beer (9)                 | Childbirth                           | Time to uterine contraction   | O80     | McCaul (58)             | Childbirth                | O80    | Time to delivery             |
| Coudert (25)             | Childbirth                           | Global assessment, other obs. | O80     | Humphrey (49)           | Childbirth                | O80    | Occurrence of preterm labour |
| Dorfman (32)             | Childbirth                           | Occurrence of dystocia        | O80     | Demory (27)             | Childbirth                | O80    | Dystocia                     |
| Hofmeyr (43)             | Childbirth                           | Pain                          | O80     | Hopkinson (44)          | Childbirth                | O80    | Pain                         |
| Ives (45)                | Childbirth                           | Pain                          | O80     | Bettigole (12)          | Childbirth                | O80    | Pain                         |
| Berrebi (11)             | Breastfeeding                        | Pain                          | O92     | Louviere (56)           | Breastfeeding             | O92    | Pain                         |

| Musculoskeletal complaints |                                  |                              |     | Musculoskeletal complaints |                      |     |                              |
|----------------------------|----------------------------------|------------------------------|-----|----------------------------|----------------------|-----|------------------------------|
| Thiele (89)                | Haemarthrosis                    | Global assessment, physician | M25 | Ramesh (78)                | Injuries             | T14 | Global assessment, patient   |
| Mössinger (65)             | Cramps                           | Global assessment, patient   | R25 | Memeo (61)                 | Soft tissue injury   | T14 | Global assessment, patient   |
| Tveiten (91)               | Physical activity                | Soreness                     | M79 | Grossman (42)              | Physical activity    | M79 | Soreness                     |
| Vickers (95)               | Physical activity                | Soreness                     | M79 | Semark (91)                | Physical activity    | M79 | Soreness                     |
| Vickers (94)               | Physical activity                | Soreness                     | M79 | Thompson (101)             | Physical activity    | M79 | Soreness                     |
| Jawara (50)                | Physical activity                | Soreness                     | M79 | Barlas (6)                 | Physical activity    | M79 | Pain                         |
| Casanova (20)              | Myalgia                          | Global assessment, patient   | M79 | Weller (108)               | Physical activity    | M79 | Global assessment, patient   |
| Bohmer (15)                | Sports injury                    | Global assessment, patient   | T14 | Lacey (54)                 | Soft tissue injury   | T14 | Global assessment, physician |
| Schmidt (83)               | Subcutaneous mechanical injuries | Global assessment, patient   | T14 | Paddon-Jones (74)          | Muscle damage        | T14 | Soreness                     |
| Zell5)                     | Sprain                           | Joint angulation             | S93 | McLatchie (59)             | Ankle sprains        | S93 | Global assessment, physician |
| Dorfman (30)               | Infusion                         | Pain                         | T80 | Giner (39)                 | Arterial cannulation | T80 | Pain                         |
| Neurology                  |                                  |                              |     | Neurology                  |                      |     |                              |
| Brigo (16)                 | Migraine                         | Global assessment, patient   | G43 | Diamond (29)               | Migraine             | G43 | Global assessment, patient   |
| Straumsheim (87)           | Migraine                         | Frequency of attacks         | G43 | Storey (97)                | Migraine             | G43 | Frequency of attacks         |
| Whithmarsh (99)            | Migraine                         | Migraine attacks             | G43 | Goldstein (40)             | Migraine             | G43 | Migraine attacks             |
| Savage (81)                | Stroke                           | Death                        | I64 | Sacco (84)                 | Stroke               | I64 | Death                        |
| Savage (82)                | Stroke                           | Death                        | I64 | Horn (45)                  | Stroke               | I64 | Occurrence of poor outcome   |
| Master (59)                | Aphasia                          | Global assessment, physician | R47 | Huber (47)                 | Aphasia              | R47 | Global assessment, physician |
| Walach (96)                | Headache                         | Pain                         | R51 | Schmitt (89)               | Headache             | R51 | Pain                         |
| Chapman (21)               | Traumatic brain injury           | Activities                   | S06 | Narotam (68)               | Brain injury         | S07 | Global assessment, physician |
| Dexpert (28)               | Motion sickness                  | Global assessment, other     | T75 | Attias (4)                 | Seasickness          | T75 | Global assessment, patient   |
| Ponti (72)                 | Seasickness                      | Global assessment, patient   | T75 | Shupak (92)                | Seasickness          | T75 | Global assessment, patient   |
| Pollinosis and asthma      |                                  |                              |     | Pollinosis and asthma      |                      |     |                              |
| Mokkapatti (63)            | Conjunctivitis                   | Occurrence of conjunctivitis | H10 | Davis (24)                 | Conjunctivitis       | H10 | Global assessment, physician |
| Mössinger (67)             | Rhinitis                         | Global assessment, patient   | J00 | de Molina (26)             | Rhinitis             | J00 | Global assessment, patient   |
| Taylor (88)                | Allergic rhinitis                | Global assessment, patient   | J30 | Munk (67)                  | Allergic rhinitis    | J30 | Global assessment, patient   |
| Wiesenauer (100)           | Pollinosis                       | Ocular symptoms              | J30 | Althaus (3)                | Pollinosis           | J30 | Ocular symptoms              |
| Wiesenauer (101)           | Pollinosis                       | Ocular symptoms              | J30 | Taudorf (100)              | Pollinosis           | J30 | Ocular symptoms              |
| Wiesenauer (103)           | Pollinosis                       | Ocular symptoms              | J30 | Ciprandi (20)              | Pollinosis           | J30 | Global assessment, physician |
| Aabel (1)                  | Pollinosis                       | Global assessment, patient   | J30 | Bodtger (16)               | Pollinosis           | J30 | Global assessment, patient   |
| Reilly (77)                | Pollinosis                       | Global assessment, patient   | J30 | Brunet (17)                | Pollinosis           | J30 | Global assessment, patient   |
| Reilly (78)                | Pollinosis                       | Global assessment, patient   | J30 | Wuthrich (109)             | Pollinosis           | J30 | Global assessment, patient   |

|                              |                                   |                                      |     |                              |                             |     |                                      |
|------------------------------|-----------------------------------|--------------------------------------|-----|------------------------------|-----------------------------|-----|--------------------------------------|
| Aabel (2)                    | Pollinosis                        | Global assessment, other             | J30 | Ciprandi (19)                | Pollinosis                  | J30 | Global assessment, other             |
| Wiesenauer (102)             | Pollinosis                        | Global assessment, other             | J30 | Moller (66)                  | Pollinosis                  | J30 | Global assessment, other             |
| Matusiewicz (61)             | Asthma                            | FEV1                                 | J45 | Bergmann (10)                | Asthma                      | J45 | FEV1                                 |
| Matusiewicz (61)             | Asthma                            | FEV1                                 | J45 | Boos (14)                    | Asthma                      | J45 | FEV1                                 |
| Matusiewicz (60)             | Asthma                            | FEV1/FVC                             | J45 | Reid (79)                    | Asthma                      | J45 | PEFR                                 |
| Freitas (37)                 | Asthma                            | Occurrence of asthma                 | J45 | Huerta Lopez (48)            | Asthma                      | J45 | Global assessment, physician         |
| Reilly (76)                  | Asthma                            | Global assessment, patient           | J45 | Stelmach (96)                | Asthma                      | J45 | Global assessment, other             |
| Respiratory tract infections |                                   |                                      |     | Respiratory tract infections |                             |     |                                      |
| Jacobs (47)                  | Otitis media                      | Global assessment, other             | H66 | Bertin (11)                  | Otitis media                | H66 | Pain                                 |
| Mössinger (68)               | Otitis media                      | Global assessment, physician         | H66 | Ruohola (83)                 | Otitis media                | H66 | Occurrence of acute otitis media     |
| Weiser (97)                  | Sinusitis                         | Global assessment, other             | J01 | Frachet (36)                 | Sinusitis                   | J01 | Global assessment, patient           |
| Mössinger (66)               | Pharyngitis                       | Duration of symptoms                 | J02 | Nelson (71)                  | Pharyngitis                 | J02 | Global assessment, other             |
| de Lange (27)                | Upper respiratory tract infection | Global assessment, other             | J06 | Hutton (50)                  | Common cold                 | J00 | Global assessment, other             |
| Diefenbach (29)              | Upper respiratory tract infection | Global assessment, patient           | J06 | Schlenter (88)               | Sinusitis                   | J01 | Headache                             |
| Attena (5)                   | Influenza like disease            | Occurrence of influenza like disease | J11 | Crawford (22)                | Influenza                   | J11 | Occurrence of influenza like disease |
| Brydak (17)                  | Influenza like disease            | Occurrence of influenza like disease | J11 | De Flora (25)                | Influenza like disease      | J11 | Occurrence of influenza like disease |
| Ferley (36)                  | Influenza like disease            | Occurrence of influenza like disease | J11 | Dolin (30)                   | Influenza                   | J11 | Occurrence of influenza like disease |
| Heilmann (42)                | Influenza like disease            | Occurrence of influenza like disease | J11 | Kaiser (52)                  | Influenza                   | J11 | Occurrence of influenza like disease |
| Davies (26)                  | Influenza like disease            | Occurrence of influenza like disease | J11 | Belshe (8)                   | Influenza                   | J11 | Occurrence of influenza              |
| Nolleveaux (69)              | Influenza like disease            | Occurrence of influenza like disease | J11 | Cohen (21)                   | Influenza                   | J11 | Occurrence of influenza              |
| Rottey (80)                  | Influenza like disease            | Occurrence of symptoms               | J11 | Peters (76)                  | Influenza                   | J11 | Occurrence of influenza              |
| Lecocq (57)                  | Influenza like disease            | Global assessment, patient           | J11 | Reuman (80)                  | Influenza                   | J11 | Occurrence of influenza              |
| Papp (71)                    | Influenza like disease            | Global assessment, patient           | J11 | Van Voris (104)              | Influenza                   | J11 | Global assessment, other             |
| Ferley (35)                  | Influenza like disease            | Global assessment, physician         | J11 | Nicholson (72)               | Influenza                   | J11 | Global assessment, other             |
| Casanova (19)                | Influenza like disease            | Temperature                          | J11 | Treanor (102)                | Influenza                   | J11 | Temperature                          |
| Friese (38)                  | Adenoid vegetations               | Global assessment, physician         | J35 | Scalfani (90)                | Adenotons. hypertrophy      | J35 | Global assessment, physician         |
| Hourst (44)                  | Respiratory tract infection       | Occurrence of symptoms               | J98 | Van Eygen (103)              | Respiratory tract infection | J98 | Occurrence of symptoms               |

|                           |                                 |                              |     |                          |                                  |     |                                       |
|---------------------------|---------------------------------|------------------------------|-----|--------------------------|----------------------------------|-----|---------------------------------------|
| Torbicka (90)             | Respiratory tract infection     | Global assessment, physician | J98 | Rodriguez (81)           | Respiratory tract infection      | J98 | Global assessment, physician          |
| Bordes (13)               | Cough                           | Global assessment, patient   | R05 | Morrone (65)             | Cough                            | R05 | Global assessment, patient            |
| Surgery & anaesthesiology |                                 |                              |     | Surgery & anesthesiology |                                  |     |                                       |
| Kaziro (53)               | Tooth extraction                | Pain                         | K08 | Mehnert (60)             | Tooth extraction                 | K08 | Pain                                  |
| Chevreil (23)             | Postoperative ileus             | Time to first wind           | K91 | Benson (9)               | Postoperative ileus              | K91 | Time to first wind                    |
| Dorfman (31)              | Postoperative ileus             | Time to first wind           | K91 | Sadek (85)               | Postoperative ileus              | K91 | Time to first wind                    |
| Estrangnin (34)           | Postoperative ileus             | Occurrence of first wind     | K91 | Boghaert (13)            | Postoperative Ileus              | K91 | Occurrence of first wind              |
| Aulagnier (6)             | Postoperative ileus             | Global assessment, patient   | K91 | Taguchi (99)             | Postoperative ileus              | K91 | Occurrence of first wind              |
| Valero (93)               | Postoperative infection         | Postoperative infection      | T81 | Crowley (23)             | Postoperative infection          | T81 | Occurrence of postoperative infection |
| Ramelet (75)              | Surgery                         | Occurrence of haematomas     | Y83 | Oertli (73)              | Surgery                          | Y83 | Occurrence of haematomas              |
| Jeffrey (51)              | Hand surgery                    | Pain                         | Z09 | Schaffer (87)            | Surgery                          | Y83 | Pain                                  |
| Stevinson (86)            | Hand surgery                    | Pain                         | Z09 | Hoernecke (43)           | Hand surgery                     | Z09 | Pain                                  |
| Hart (41)                 | Hysterectomy                    | Pain                         | Z90 | Ilkjaer (51)             | Hysterectomy                     | Z90 | Pain                                  |
| Alibeu (3)                | Postoperative agitation         | Agitation                    | Z98 | Mendel (62)              | Postoperative agitation          | Z98 | Agitation                             |
| Kennedy (54)              | Postoperative chest problems    | Occurrence of complications  | Z98 | Negro (70)               | Postoperative lung complications | J95 | Occurrence of complications           |
| Miscellaneous             |                                 |                              |     | Miscellaneous            |                                  |     |                                       |
| Labreque (55)             | Warts                           | Global assessment, physician | B07 | Eron (34)                | Condylomata acuminata            | A63 | Global assessment, physician          |
| Kainz (52)                | Warts                           | Area of warts                | B07 | Yazar (110)              | Warts                            | B07 | Global assessment, other              |
| Schmidt (84)              | Fasting                         | body weight                  | E66 | Enzi (32)                | Obesity                          | E66 | Body weight                           |
| Werk (98)                 | Overweight                      | BMI                          | E66 | Bahadori (5)             | Obesity                          | E66 | BMI                                   |
| Cialdella (24)            | Substitution of benzodiazepines | Global assessment, physician | F13 | Petrovic (77)            | Benzodiazepine withdrawal        | F13 | Global assessment, other              |
| McCutcheon (62)           | Anxiety                         | Anxiety                      | F41 | Frattola (37)            | Anxiety                          | F41 | Anxiety                               |
| Awdry (7)                 | Post viral fatigue syndrome     | Global assessment, patient   | G93 | Vercoulen (105)          | Chronic fatigue syndrome         | G93 | Global assessment, patient            |
| Ernst (33)                | Varicosis                       | Pain                         | I83 | Dominguez (31)           | Venous insufficiency             | I87 | Pain                                  |
| Oberbaum (70)             | Stomatitis                      | Global assessment, other     | K12 | Adamietz (1)             | Mucositis                        | K12 | Global assessment, other              |
| Balzarini (8)             | Radiodermatitis                 | Global assessment, physician | L58 | Lievens (55)             | Radiotherapy                     | K12 | Mucositis                             |
| Gibson (40)               | Rheumatoid Arthritis            | Global assessment, patient   | M06 | Boureau (15)             | Rheumatoid Arthritis             | M06 | Global assessment, patient            |
| Andrade (4)               | Rheumatoid Arthritis            | Global assessment, physician | M06 | Smolen (94)              | Rheumatoid Arthritis             | M06 | Global assessment, physician          |
| Leaman (56)               | Burns                           | Pain                         | T30 | Patterson (75)           | Burns                            | T30 | Pain                                  |
| Bourgeois (14)            | Infusion                        | Pain                         | T80 | Taddio (98)              | Injection                        | T80 | Pain                                  |

Indications and outcomes: free text from Shang 2005. ICD-10 3-digit codes and matching of studies within each indication group provided by authors of this systematic review.

### 2.1.2 Methodological quality, heterogeneity

Four components of methodological quality were assessed, of which three (double blinding, adequate generation of allocation sequence, intention-to-treat analysis) did not differ among the two trial sets, while the proportion trials with adequate concealment of allocation was higher among HOM trials (44.5%,  $n = 49/110$ ) than CON trials (19.1%,  $n = 21/110$ ) ( $p < 0.0001$ ). Likewise, the proportion of high-quality trials was higher for HOM trials (19.1%) than CON trials (8.2%) ( $p = 0.0294$ ) (Table 1). Heterogeneity was significantly (F test,  $p = 0.011$ ) less pronounced among HOM trials (I-squared 65%) than CON trials (I-squared 77%) (Table 4).

Table 4 Tests for statistical heterogeneity

| Intervention          | Chi-squared               | I-squared |
|-----------------------|---------------------------|-----------|
| Homoeopathy           | 309, df 109, $p < 0.0001$ | 65%       |
| Conventional medicine | 481, df 109, $p < 0.0001$ | 77%       |

### 2.1.3 Funnel plot inspection and associated statistical tests

In both trial sets funnel plots were asymmetric, trials with higher standard error having larger effects. Likewise, Egger's test was significant for both trial sets, with less asymmetry for HOM trials than for CON trials (asymmetry coefficients 0.17 and 0.21, respectively, Table 5).

Table 5 Tests for funnel plot asymmetry

| Trials                | Funnel plot asymmetry? | Egger's test                   |              |
|-----------------------|------------------------|--------------------------------|--------------|
|                       |                        | Asymmetry coefficient (95%-CI) | p-value      |
| Homoeopathy           | Yes                    | 0.17 (0.10-0.32)               | $p < 0.0001$ |
| Conventional medicine | Yes                    | 0.21 (0.11-0.40)               | $p < 0.0001$ |

### 2.1.4 Associations between methodological quality or subgroups and effect estimates

Univariate associations between quality components and diagnostic categories, respectively, and effect estimates were tested in both trial sets. Among HOM trials, significant associations were found for 3 of 7 single quality components (Medline-indexed, double-blinding, adequate generation of allocation sequence) as well as for high-quality trials. Among CON trials, the same eight tests showed no significant associations. In both trial sets, there were no significant associations between indication group and effect estimates. Furthermore, for HOM trials no significant associations were found between homoeopathy type and effect estimates (Table 6).

Table 6 Univariate associations between subgroups and effect estimates

| Methodological quality                     | Homoeopathy      |             |              | Conventional medicine |             |              |
|--------------------------------------------|------------------|-------------|--------------|-----------------------|-------------|--------------|
|                                            | ROR (95%-CI)     | p-value     | Significant? | ROR (95%-CI)          | p-value     | Significant? |
| English language                           | 0.73 (0.53-1.00) | $p = 0.05$  | No           | 0.67 (0.40-1.14)      | $p = 0.114$ | No           |
| Medline-indexed                            | 0.69 (0.50-0.94) | $p = 0.019$ | Yes          | 1.03 (0.61-1.75)      | $p = 0.906$ | No           |
| Double-blinding                            | 0.44 (0.22-0.87) | $p = 0.017$ | Yes          | 0.63 (0.36-1.11)      | $p = 0.107$ | No           |
| Adequate generation of allocation sequence | 0.76 (0.48-0.95) | $p = 0.024$ | Yes          | 0.98 (0.65-1.46)      | $p = 0.913$ | No           |
| Adequate concealment                       | 0.78 (0.57-1.07) | $p = 0.117$ | No           | 0.76 (0.48-1.16)      | $p = 0.193$ | No           |
| Intention-to-treat                         | 1.25 (0.87-1.80) | $p = 0.225$ | No           | 1.14 (0.78-1.66)      | $p = 0.506$ | No           |
| High quality trials                        | 0.62 (0.43-0.90) | $p = 0.011$ | Yes          | 0.61 (0.34-1.09)      | $p = 0.095$ | No           |
| Other subgroups                            |                  |             |              |                       |             |              |
| Duration of follow-up                      | No data          | $p = 0.862$ | No           | No data               | $p = 0.594$ | No           |
| Indication group ( $n = 8$ )               | No data          | $p = 0.660$ | No           | No data               | $p = 0.360$ | No           |

ROR: Rate of odds ratios. 95%-CI: 95% confidence interval

In multivariate analyses, as summarised by the authors “the standard error of the log odds ratio (asymmetry coefficient) was the dominant variable in both groups. Coefficients of other variables, including study quality, were attenuated and became non-significant” (Shang 2005, pp. 729-730).

### 2.1.5 Primary outcomes of this systematic review

Meta-analytic effect estimates were not available for either of the two trial sets.

## 2.2 High-quality trials

### 2.2.1 Descriptive data

A total of 21 HOM and 9 CON trials were of high quality (individual trials listed in Table 7).

Table 7 High-quality trials of homoeopathy and conventional medicine, listed in order of descending sample size

| Homoeopathy trials (n = 21) |                  |                        |     | Conventional medicine trials (n = 9) |                  |                          |     |
|-----------------------------|------------------|------------------------|-----|--------------------------------------|------------------|--------------------------|-----|
| No.                         | Author (trial #) | Indication group       | N   | No.                                  | Author (trial #) | Indication group         | N   |
| 1                           | Rottey (80)      | Influenza like disease | 501 | 1                                    | Horn (45)        | Stroke                   | 454 |
| 2                           | Vickers (94)     | Physical activity      | 400 | 2                                    | Nicholson (72)   | Influenza                | 319 |
| 3                           | Papp (71)        | Influenza like disease | 334 | 3                                    | Reuman (80)      | Influenza                | 316 |
| 4                           | Schmidt (84)     | Fasting                | 208 | 4                                    | Crowley (23)     | Postoperative infection  | 273 |
| 5                           | Labreque (55)    | Warts                  | 162 | 5                                    | Kaplan (53)      | Diarrhoea                | 256 |
| 6                           | Jacobs (46)      | Diarrhoea              | 116 | 6                                    | De Flora (25)    | Influenza like disease   | 248 |
| 7                           | Weiser (97)      | Sinusitis              | 104 | 7                                    | Möller (66)      | Pollinosis               | 146 |
| 8                           | Walach (96)      | Headache               | 98  | 8                                    | Humphrey (49)    | Childbirth               | 89  |
| 9                           | Jacobs (49)      | Diarrhoea              | 81  | 9                                    | Gade (38)        | Irritable bowel syndrome | 54  |
| 10                          | Jacobs (47)      | Otitis media           | 75  |                                      |                  |                          |     |
| 11                          | Hart (41)        | Hysterectomy           | 73  |                                      |                  |                          |     |
| 12                          | Wiesenauer (102) | Pollinosis             | 72  |                                      |                  |                          |     |
| 13                          | Zell (105)       | Sprain                 | 69  |                                      |                  |                          |     |
| 14                          | Böhmer (15)      | Sports injury          | 67  |                                      |                  |                          |     |
| 15                          | Vickers (95)     | Physical activity      | 57  |                                      |                  |                          |     |
| 16                          | Jawara (50)      | Physical activity      | 50  |                                      |                  |                          |     |
| 17                          | Chapman (21)     | Traumatic brain injury | 50  |                                      |                  |                          |     |
| 18                          | Tveiten (91)     | Physical activity      | 46  |                                      |                  |                          |     |
| 19                          | Stevinson (86)   | Hand surgery           | 42  |                                      |                  |                          |     |
| 20                          | Lepaisant (58)   | Premenstrual syndrome  | 36  |                                      |                  |                          |     |
| 21                          | Chapman (22)     | Premenstrual syndrome  | 10  |                                      |                  |                          |     |

“Large” high-quality trials (highlighted in yellow) identified in <sup>3</sup>.

Among these, sample size was significantly lower in HOM trials than in CON trials (median 73.0 and 256.0 patients, respectively; median difference 154.0 patients, 95%-CI 17.0-223.0;  $p = 0.022$ , Table 8).

Table 8 Sample size of high-quality trials of homoeopathy and conventional medicine, respectively

| Sample size         | Homoeopathy (n = 21) | Conventional medicine (n = 9) | Mann-Whitney U-test                                                           |
|---------------------|----------------------|-------------------------------|-------------------------------------------------------------------------------|
| Median              | 73.0                 | 256.0                         | $p = 0.022$ ,<br>median difference<br>(CON – HOM) 154.0,<br>95%-CI 17.0-223.0 |
| Interquartile range | 50.0-139.0           | 117.5-317.8                   |                                                                               |
| Total range         | 10-501               | 54-454                        |                                                                               |
| Mean (SD)           | 126.2 (129.8)        | 239.4 (125.3)                 |                                                                               |

Analysed by the authors of this systematic review

Following sample restriction to high-quality trials, the distribution of indications in the two trial subsets (Table 2) was altered, with 73% ( $n = 22/30$ ) of trials unmatched (Table 9, also described in Rutten 2008<sup>4</sup>, p.171).

Table 9 Matching by indication for high-quality trials of homoeopathy and conventional medicine, respectively

| Indications, free text<br>(ICD-10, 3-digit codes) | Homoeopathy |         | Conventional medicine |         | Total |         | Unmatched |         |
|---------------------------------------------------|-------------|---------|-----------------------|---------|-------|---------|-----------|---------|
|                                                   | N           | Percent | N                     | Percent | N     | Percent | N         | Percent |
| Childbirth (O80)                                  | 0           | 0%      | 1                     | 11%     | 1     | 3%      | 1         | 3%      |
| Diarrhoea (A09)                                   | 2           | 10%     | 1                     | 11%     | 3     | 10%     | 1         | 3%      |
| Fasting (E66)                                     | 1           | 5%      | 0                     | 0%      | 1     | 3%      | 1         | 3%      |
| Hand surgery (Z09)                                | 1           | 5%      | 0                     | 0%      | 1     | 3%      | 1         | 3%      |
| Headache (R51)                                    | 1           | 5%      | 0                     | 0%      | 1     | 3%      | 1         | 3%      |
| Hysterectomy (Z90)                                | 1           | 5%      | 0                     | 0%      | 1     | 3%      | 1         | 3%      |
| Influenza OR Influenza-like disease (J11)         | 2           | 10%     | 3                     | 33%     | 5     | 17%     | 1         | 3%      |
| Irritable bowel syndrome (K58)                    | 0           | 0%      | 1                     | 11%     | 1     | 3%      | 1         | 3%      |
| Otitis media (H66)                                | 1           | 5%      | 0                     | 0%      | 1     | 3%      | 1         | 3%      |
| Physical activity (M79)                           | 4           | 19%     | 0                     | 0%      | 4     | 13%     | 4         | 13%     |
| Pollinosis (J30)                                  | 1           | 5%      | 1                     | 11%     | 2     | 7%      | 0         | 0%      |
| Postoperative infection (T81)                     | 0           | 0%      | 1                     | 11%     | 1     | 3%      | 1         | 3%      |
| Premenstrual syndrome (N94)                       | 2           | 10%     | 0                     | 0%      | 2     | 7%      | 2         | 7%      |
| Sinusitis (J01)                                   | 1           | 5%      | 0                     | 0%      | 1     | 3%      | 1         | 3%      |
| Sports injury (T14)                               | 1           | 5%      | 0                     | 0%      | 1     | 3%      | 1         | 3%      |
| Sprain (S93)                                      | 1           | 5%      | 0                     | 0%      | 1     | 3%      | 1         | 3%      |
| Stroke (I64)                                      | 0           | 0%      | 1                     | 11%     | 1     | 3%      | 1         | 3%      |
| Traumatic brain injury (S06)                      | 1           | 5%      | 0                     | 0%      | 1     | 3%      | 1         | 3%      |
| Warts (B07)                                       | 1           | 5%      | 0                     | 0%      | 1     | 3%      | 1         | 3%      |
| TOTAL                                             | 21          | 100%    | 9                     | 100%    | 30    | 100%    | 22        | 73%     |

Coding of indications and matching according to Table 3

## 2.2.2 Primary outcomes of this systematic review

Effect estimates were available for high-quality HOM trials (analysed in Lüdtke 2008<sup>5</sup>), showing a significant positive effect of homoeopathy, compared to placebo (Article, Table 12). For high-quality CON trials, no meta-analytic effect estimate was available.

## 2.3 Large high-quality trials

### 2.3.1 Descriptive data

Following sample restriction to “large” (Shang 2005, abstract) or “larger” (Shang 2005 p.730) high-quality trials, a total of 8 HOM and 6 CON trials remained. These trials were identified by the authors<sup>3</sup> and are highlighted in yellow in Table 7.

No criteria for “large/larger” trials were stated. It was not explained why the third largest high-quality CON trial (Reuman, CON trial no. 80,  $n = 316$  patients) was not included among the “large/larger” trials. – In this case we made an exception to the principle of not reading individual trial publications when conducting a SR of SR (cf. Article, Section ‘Data collection process’): the Reuman trial publication<sup>6</sup> presented two placebo-controlled randomised trials of the same drug, thereof one four-armed trial with altogether  $n = 78$  patients and one three-armed trial with a very similar sample size ( $n = 318$  or  $n = 317$  patients for amantadine 100 mg or 200 mg vs placebo, respectively) to the reported sample size of  $n = 316$  and results compatible with those reported in Shang 2005. We could thus confirm that this trial did have the third largest sample size among the high-quality CON trials (Table 7).

Median sample sizes were 185.0 and 264.5 for HOM and CON trials, respectively; the difference was not significant ( $p = 0.491$ , Table 10).

Table 10 Sample size of “large” high-quality trials of homoeopathy and conventional medicine, respectively

| Sample size         | Homoeopathy (n = 8) | Conventional medicine (n = 6) | Mann-Whitney U-test                                                            |
|---------------------|---------------------|-------------------------------|--------------------------------------------------------------------------------|
| Median              | 185.0               | 264.5                         | p = 0.491<br>median difference (HOM – CON)<br>-59.5 (95% CI -175.0 to + 144.5) |
| Interquartile range | 107.0-385.5         | 222.5-352.75                  |                                                                                |
| Total range         | 98-501              | 146-454                       |                                                                                |
| Mean (SD)           | 240.38 (152.92)     | 282.67 (101.35)               |                                                                                |

Analysed by the authors of this systematic review.

The 14 trials covered 10 different indications, with 57% (n = 8/14) of trials unmatched (Table 11).

Table 11 Shang 2005: Large high-quality trials of homoeopathy and conventional medicine, ordered by indication

| Indications (free text)  | Homoeopathy |         | Conventional medicine |         | Total |         | Unmatched |                  |
|--------------------------|-------------|---------|-----------------------|---------|-------|---------|-----------|------------------|
|                          | N           | Percent | N                     | Percent | N     | Percent | N         | Percent of Total |
| Diarrhoea                | 1           | 13%     | 1                     | 17%     | 2     | 14%     | 0         | 0%               |
| Headaches                | 1           | 13%     | 0                     | 0%      | 1     | 7%      | 1         | 7%               |
| Muscle soreness          | 1           | 13%     | 0                     | 0%      | 1     | 7%      | 1         | 7%               |
| Plantar warts            | 1           | 13%     | 0                     | 0%      | 1     | 7%      | 1         | 7%               |
| Post operative infection | 0           | 0%      | 1                     | 17%     | 1     | 7%      | 1         | 7%               |
| Prevention of influenza  | 1           | 13%     | 1                     | 17%     | 2     | 14%     | 0         | 0%               |
| Sinusitis                | 1           | 13%     | 0                     | 0%      | 1     | 7%      | 1         | 7%               |
| Stroke (venous)          | 0           | 0%      | 1                     | 17%     | 1     | 7%      | 1         | 7%               |
| Treatment of influenza   | 1           | 13%     | 2                     | 33%     | 3     | 21%     | 1         | 7%               |
| Weight loss              | 1           | 13%     | 0                     | 0%      | 1     | 7%      | 1         | 7%               |
| TOTAL                    | 8           | 100%    | 6                     | 100%    | 14    | 100%    | 8         | 57%              |

### 2.3.2 Combined sensitivity analyses

Effect estimates for large high-quality trials showed no significant difference between intervention and placebo for the 8 largest HOM trials and a positive significant effect compared to placebo for the 1<sup>st</sup>, 2<sup>nd</sup> and 4<sup>th</sup> to 7<sup>th</sup> largest CON trials (Table 12).

Table 12 Effect estimates after sample restriction to “large” high-quality trials

| Intervention          | N trials |                          | Odds ratio (95% confidence interval) | Significant? |
|-----------------------|----------|--------------------------|--------------------------------------|--------------|
|                       | All      | After sample restriction |                                      |              |
| Homoeopathy           | 110      | 8                        | 0.88 (0.65-1.19)                     | No           |
| Conventional medicine | 110      | 6                        | 0.58 (0.39-0.85)                     | Yes          |

An odds ratio < 1 favours the intervention

## 2.4 The largest trials

Meta-regression analyses of “predicted effect in trials as large as the largest trials” (cf. Article, Section ‘Secondary outcomes’) showed no significant difference between intervention and placebo for HOM trials and a positive significant effect compared to placebo for CON trials (Table 13).

Table 13 Predicted effects in trials as large as the largest trials

| Intervention          | Odds ratio (95% confidence interval) | Significant? |
|-----------------------|--------------------------------------|--------------|
| Homoeopathy           | 0.96 (0.73-1.25)                     | No           |
| Conventional medicine | 0.67 (0.48-0.91)                     | Yes          |

Meta-regression analyses. An odds ratio < 1 favours the intervention

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