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Can self-reported depression be helped by homeopaths?

A pragmatic cohort randomised controlled trial with qualitative interviews with patients.

Tables, figures and appendixes

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Table 2. Cochrane reviews of SSRIs in depression

Author, year	Condition	Comparator	Trials (n)	Patients (n)	Assessment period	Main results	Limitations
Arroll et al. 2009	Depression	Placebo	4	1,269	6 – 8 weeks	SSRIs effective in primary care; RR 1.28 (95% CI 1.15, 1.43); NNT median 7 (range 7-9); NNH range 20-90; standardised mean difference (SMD) 0.24 (95% CI 0.12, 0.35)	Most studies of short duration (6-8 weeks)
Cipriani et al. 2012	MDD	Other ADs	37		1 – 24 weeks	Citalopram (SSRI) more effective than paroxetine (SSRI) and reboxetine (SNRI), less effective than escitalopram (SSRI); more acceptable than tricyclics (TCA), reboxetine and venlafaxine (SNRI)	Risk of overestimation of treatment due to potential bias (sponsorship, publication)
Cipriani et al. 2010	MDD	Other ADs	59		1 – 24 weeks	Sertraline (SSRI) more effective than fluoxetine (SSRI); more acceptable/tolerable than amitriptyline and imipramine (TCA), paroxetine (SSRI), and mirtazapine (TeCA), but more likely to cause diarrhoea	Potential reporting bias: Studies did not report on all pre-specified outcomes and outcomes of clear relevance to patients and clinicians were not reported in any trials
Cipriani et al. 2009	MDD	Other ADs	22	4,000	1 – 24 weeks	Escitalopram (SSRI) more effective than citalopram (SSRI); less withdrawal than duloxetine (SNRI)	Insufficient evidence to compare to other ADs, risk of bias: allocation, blinding, reporting, information about outcomes
Magni et al. 2013	MDD	Other ADs	171	24,868	4 – 24 weeks	Fluoxetine (SSRI) poorer efficacy profile than sertraline (SSRI) and venlafaxine (SNRI), difference may be clinically meaningful	Insufficient evidence to firmly determine implications, risk of bias in the majority of trials, esp. due to incomplete outcome
Omori et al. 2010	MDD	Other ADs	54	5,122	2 – 10 weeks	Fluvoxamine (SSRI) more effective than other ADs, but with higher incidence of vomiting and nausea than imipramine, clomipramine and amitriptyline (TCAs)	High risk of reporting bias in most and incomplete data in over half of the trials
Purgato et al. 2014	MDD	Other ADs	115	26,134	1 – 24 weeks	Paroxetine (SSRI) more effective than reboxetine (SNRI) and less effective than mirtazapine (TeCA) at 1-4 weeks, less effective than citalopram at 6-12 weeks; no evidence of inferiority/superiority to other ADs; paroxetine less adverse events than amitriptyline, imipramine (TCAs) and older ADs, less well tolerated than agomelatin and St John's Wort	Unclear or high risk of bias in most studies due to poor reporting of allocation concealment and blinding of outcome assessment, incomplete reporting of outcomes; and many studies sponsored by the industry; comparison tolerability with St John's Wort (n=1)
Silva de Lima et al. 2005	Dysthymia	Placebo	4	878	4 – 12 weeks	SSRIs effective in treating dysthymia, similar to other ADs (TCAs, MOIs, other ADs); effectiveness over placebo: RR 0.68 (95% CI 0.56, 0.82) (risk of non-response), NNT 5 (95% CI 3.3, 9.0)	Quality of reports were poor with unclear or high risk of bias, with information omitted on study design, allocation concealment, analysis and generalisability
Silva de Lima et al. 2003	Dysthymia	Other ADs	5	791	4 – 12 weeks	Similar clinical response compared to other ADs, strength of evidence similar to TCAs, better than for other ADs; less side effects of sertraline (SSRI) than imipramine (TCA)	Quality of reporting poor in most studies, including information on allocation concealment only in 1 trial, no ITT-analysis, insufficient information on randomisation in 3 trials, other weaknesses in reporting (baseline data, drop-outs, post-randomisation exclusions, SDs)

Table 3. Cochrane reviews of SSRIs in depression for specific patient groups

Author, year	Condition	Comparator	Trials (n)	Patients (n)	Assessment period	Main results	Limitations
Bains et al. 2002	Depression in dementia	Other ADs	7	769	6 – 12 weeks	Weak evidence for effectiveness of SSRIs in dementia	Limited number of trials; only 1 trial reported randomisation method and used ITT-analysis, blinding not checked, 3 trials not reported placebo types
Baumeister et al. 2012	Depression in diabetes mellitus	Placebo & other ADs	5	241	3 – 24 weeks	Moderate and clinically significant effect on depression in diabetes patients at 3-6 months	Limited number of trials, low quality evidence with high/unclear risk of bias, incl. selection, performance, attrition and other bias, each form of bias in at min. half of the trials, heterogeneity of patients and interventions
Baumeister et al. 2011	Depression in coronary artery disease	Placebo	9		4 – 25 weeks	SSRIs had a small effect over placebo	Limited number of trials, low quality evidence with high/unclear risk of bias, incl. selection, performance, attrition and other bias, each form of bias in at min. half of the trials, heterogeneity of patients and interventions
Hackett et al. 2008	Depression after stroke	Placebo	7	704	6 – 26 weeks	ADs had a small effect over placebo, but also a higher rate of adverse effects. Pooled OR 0.47 (95% CI 0.22, 0.98) for binary outcome measures, OR 0.22 (95% CI 0.09, 0.52) for patients reporting min.50% reduction in mood scores.	Reviewers present results of the review for all medication collectively, incl. TCAs, SSRIs, other ADs, other medication. Unclear/high risk of bias (n=5) due to unclear details of randomisation/allocation concealment (n=4), no/insufficient information on blinding (n=5), unclear/no ITT-analysis (n=3)
Koch et al. 2011	Depression in multiple sclerosis	Placebo	1	42	12 weeks	Paroxetine (SSRI) non-significantly better than placebo for depression in MS patients, higher incidence of nausea/headache	Insufficient evidence from a single trial (with high attrition rate) to draw any firm conclusions
Mottram et al. 2006	Depression in elderly	Other ADs	32		4 – 24 weeks	SSRIs & TCAs equally efficacious for depressed elderly people, less withdrawal & side effects in SSRI compared to TCA groups	Risk of bias in most trials due to insufficient information on allocation concealment, “per protocol” analyses, heterogeneity of drugs/patient groups
Rabindranath et al. 2005	Depression in dialysis patients	Placebo	1	12	8 weeks	No conclusion can be drawn based on a single small trial	Only a single small trial
Wilkinson & Izmeth 2012	Depression in elderly	Placebo	3	539	6 – 36 weeks	SSRIs superior to placebo at 12 months, no difference at 6, 24 & 36 months	Risk of bias due to insufficient information on allocation concealment (n=1), blinding (n=1), other reasons (n=3). Not clear if ITT-analysis used (n=1), trials were heterogeneous
Wilson et al. 2001	Depression in elderly	Placebo	2	737	4 – 8 weeks	Some effect of SSRIs over placebo, OR 0.51 (95% CI 0.36, 0.72), NNT 8.45 (95% CI 8.38, 8.53)	Limited evidence from 2 trials, inadequate description of allocation concealment and randomisation procedure

Table 4. Cochrane reviews of TCAs in depression

Author, year	Condition	Comparator	Trials (n)	Patients (n)	Assessment period	Main results	Limitations
Arroll et al. 2009	Depression	Placebo	13	1,233	6 – 8 weeks	TCAs effective in primary care; RR 1.24 (95% CI 1.11, 1.38); NNT median 9 (range 7-16); NNH range 4-30; mean difference HDRS 3.17 (95% CI 2.39, 3.94); standardised mean difference (SMD) 0.49 (95% CI 0.32, 0.67)	Most studies of short duration (6-8 weeks)
Furukawa et al. 2003	Acute depression	Placebo, different dosage of TCAs	41 (TCAs vs placebo: 35; TCA vs TCA:6)	2,564 (TCAs vs placebo: 2,013, TCA vs TCA:551)	4 – 8 weeks	Low dosage TCA more likely than placebo to result in improvement: RR 1.65 (95% CI 1.36, 2.00) (4 weeks), RR 1.47 (95% CI 1.12, 1.94) (6-8 weeks). Standard dose TCA not better than low dose TCA, but higher drop-out rate due to side effects	Risk of bias as most trials (n=31) did not provide sufficient information to assess the randomisation procedure (allocation)
Guaiana et al. 2007	Depression	Other TCAs, SSRIs	194		2 weeks – 6 months	Amitriptyline (TCA) at least as efficacious as other TCAs or newer SSRIs, but with more side-effects	The quality of studies was on average assessed as medium to low, with no trial reporting on adequate concealment allocation method
Leucht et al. 2012	MDD	Other ADs	39	3,509	3 – 12 weeks	Amitriptyline (TCA) more efficacious than placebos (OR 2.67, 95% CI 2.21, 3.23), with more significant effect for severe depression (p=0.02), but with higher rate of side effects resulting in withdrawal (OR 4.15, 95% CI 2.71, 6.35)	Risk of bias due to poorly reported randomisation methods, allocation concealment and blinding, used of "per protocol" analysis in some trials
Moncrieff et al. 2004	Depression	Active Placebos	9	751	2 – 12 weeks	Small differences in favour of TCAs compared to active placebos (atropine mimicking TCA side effects): mean difference in effect size 0.39 (95% CI 0.24, 0.54), sensitivity analysis omitting a single strongly positive trial: effect size 0.17 (95% CI 0.00, 0.34)	Most studies used "per protocol" analysis
Silva de Lima et al. 2005	Dysthymia	Placebo	5	600	4 – 12 weeks	TCAs are effective in treating dysthymia, similarly to other ADs (SSRIs, MOIs & other ADs); effectiveness over placebo: RR 0.68 (95% CI 0.59, 0.78) (risk of non-response), NNT 4.3 (95% CI 3.2, 6.5)	Quality of reports were poor, with information omitted on study design, allocation concealment, analysis and generalisability
Silva de Lima et al. 2003	Dysthymia	Other ADs	7	1,205	4 – 12 weeks	Similar clinical response compared to other ADs, strength of evidence similar to SSRIs and better than for other ADs; more side effects of imipramine (TCA) compared to sertraline (SSRI) and MAOIs	The quality of reporting was poor in most studies, with no information on allocation concealment, no ITT-analysis in five trials, and in insufficient information on randomisation in four trials, as well as other weaknesses in reporting (baseline data, exclusions, standard deviations)

Table 5. Cochrane reviews of TCAs in depression for specific patient groups

Author, year	Condition	Comparator	Trials (n)	Patients (n)	Assessment period	Main results	Limitations
Baumeister et al. 2011	Depression in coronary artery disease	SSRI	1	81	4 – 25 weeks	Nortriptyline (TCA) comparable to paroxetine (SSRI) at 6 weeks	Single trial, unclear risk of selection bias (allocation concealment) and reporting bias (selective reporting), conflicting interests (funded by manufacturer)
Hackett et al. 2008	Depression after stroke	Placebo	3	129	6 – 26 weeks	ADs had a small effect over placebo, but also a higher rate of adverse effects	Reviewers present results of the review for all medication collectively, including TCAs, SSRIs, other ADs and other medication. Methodological weaknesses in all TCA trials, unclear or high risk of bias due to unclear details of randomisation (n=2), single blinded (n=2), no use of ITT-analysis (n=1), concealment of allocation unclear in all trials
Koch et al. 2011	Depression in multiple sclerosis	Placebo	1	28	12 weeks	Desipramine (TCA) non-significantly better than placebo for depression in MS patients, with adverse effects in 86% of desipramine patients	Insufficient evidence from a single trial (with high attrition rate) to draw any firm conclusions
Mottram et al. 2006	Depression in elderly	Other ADs	32		4 – 24 weeks	TCAs & SSRIs were equally efficacious for depressed elderly people, with more withdrawal and side effects in TCA compared to SSRI groups	Risk of bias in most trials due to insufficient information on allocation concealment, use of "per protocol" analyses, heterogeneity of drugs and patient groups
Wilkinson & Izmeth 2012	Depression in elderly	Placebo	3	197	6 – 36 weeks	TCA superior to placebo at 24 months (RR 0.70, 95% CI 0.50, 0.99), no difference at 6, 12 & 36 months	Some risk of bias, due to insufficient information on allocation concealment (n=2), blinding (n=1), incomplete outcome data (n=2), selective reporting (n=1), and other reasons (n=3). It was not clear if ITT-analysis had been used, trials were heterogeneous
Wilson et al. 2001	Depression in elderly	Placebo	7	428	4 – 8 weeks	Some effect of TCAs over placebo, OR 0.32 (95% CI 0.21, 0.47), NNT 3.97 (95% CI 3.88, 4.05)	Risk of bias due to inadequate description of allocation concealment and randomisation procedure

Table 6. Cochrane reviews of psychological therapies in depression

Author, year	Condition	Intervention	Comparator	Trials (n)	Patients (n)	Assessment period	Main results	Limitations
Akechi et al. 2008	Depression in incurable cancer patients	Supportive psychotherapy (n=5), hypnosis (n=2),relaxation, CBT, problem solving therapy (each n=1)	Treatment as usual	10 (meta	780 (meta-analysis 51	4 weeks – 12 months	Significant decrease in depression (SMD -0.44, 95% CI -0.08, -0.80) (6 trials)	No trial of clinically diagnosed depression, risk of bias, unclear selectio due to insufficient information on allocation concealment procedures (8 trials)
Barbato & D'Avanzo 2006	Depression	Marital therapy	Individual psychotherapy, drug therapy, minimal/no treatment	8	Varying , depends on comparison max. 167 fc depressive symptoms	7 weeks – 24 months	Better than no/minimal treatment (SMD 1.28, 95% 0.72, 1.85), no significant differences compared to individual psychotherapy (SMD 0.12, 95% CI -0.32, 0.56), lower drop-out rate than drug therapy	Methodological weaknesses in most studies, including small samples, risk of bias esp. resulting from unclear method of allocation concealment and unclear blinding of assessor in most studies significant heterogeneity among studies, probable use of per protocol analysis (and no ITT-analysis)
Baumeister et al. 2011	Depression in coronary artery disease	Psychological interventions	Usual care (7 studies) or waitlist (1)	8	3158	4 – 25 weeks	Small but clinically significant effect compared to usual care	Low methodological quality in 6 of 8 studies due to high or unclear risk of selection bias (n=4), attrition bias (n=5), reporting bias (n=6), small studies (n=3) or not reported number of participants (n=1), studies of higher quality were small
Baumeister et al. 2012	Depression in diabetes mellitus	Psychological interventions	Usual care	8	1122	3 – 24 weeks	Moderate and clinically significant effect compared to usual care	Risk of bias in all studies, esp. high risk of assessment bias due to lack of blinding of assessors (n=7), high or unclear risk of reporting bias (n=6), attrition bias (n=5), selection bias due to unclear description of random selection and allocation procedures (n=4)
Churchill et al. 2013	Depression	CBT	Treatment as usual (n=3), attention placebo (n=1)	4	224	2 – 18 weeks	Better than treatment as usual	Low quality evidence due to methodological weaknesses including risk of bias from unclear allocation method, non-blinded assessors, small sample sizes, heterogeneity of trials

Author, year	Condition	Intervention	Comparator	Trials (n)	Patients (n)		Main results	Limitations
Dennis et al. 2007	Depression during pregnancy	Interpersonal psychotherapy	Parenting education program	1	38	16 weeks	Reduced risk of depressive symptoms	Methodological weaknesses with risk of bias resulting from insufficient information on random allocation procedure, single trial
Hackett et al. 2008	Depression after stroke	Psychotherapy: CBT, counselling, motivational interviewing, psycho-education	Usual care	4	448	6 – 26 weeks	No evidence of benefit	No blinding of assessors (n=1), details of blinding unclear (n=1), small sample sizes (n=3)
Henken et al. 2007	Depression	Family therapy	Waitlist	6	519	8 – 15 weeks	Better than waitlist control, also in trials with lower risk of bias	Half of the trials were of low methodological quality, with risk of bias resulting from no/unclear allocation concealment, heterogeneous trials reducing generalisability of results
Hunot et al. 2013	Acute depression	Third wave CBT	CBT	3	144	12 – 16 weeks	No difference between approaches	High or unclear risk of bias, esp. no information on allocation of participants (n=2),unclear risk of bias due to attrition (n=1), no pre-published protocol (risk of reporting bias)
Lane et al. 2013	Depression in congenital heart disease	CBT, psycho-therapy, talking/ counselling therapy		0	0		No studies identified	
Lane et al. 2005	Depression in heart failure	Psychological interventions		0	0		No studies identified	
Orgeta et al. 2014	Depression in dementia and mild cognitive impairment	CBT, Interpersonal therapy, counselling	Educational programs, diagnostic feedback, services slightly above usual care	6	439	6 – 48 weeks	Positive effect on depression from psychological treatments for dementia. No studies identified for mild cognitive impairment	Unclear or high risk of bias (n=5), esp. due to unclear randomisation, blinding and selective reporting of results

Author, year	Condition	Intervention	Comparator	Trials (n)	Patients (n)	Assessment Period	Main results	Limitations
Rabindranath et al. 2005	Depression in dialysis patients	Psychological interventions		0	0		No studies identified	
Shinohara et al. 2013	Depression	Behavioural therapies	Other psychological therapies incl. CBT and psycho-dynamic therapies	25	955	5 – 24 weeks	Behavioural therapies not different to other psychological therapies (18 studies, n=690), CBT better than behavioural therapies (15 studies, n=544), behavioural therapies better than psychodynamic therapies (2 studies, n=110)	Unclear or high risk of bias and small sample size in most studies, studies showing evidence of differences between therapies were of low quality
Wilkinson & Izmeth 2012	Depression in elderly	Interpersonal therapy	Placebo medication	2	98	6 – 36 weeks	Study 1: No difference between Interpersonal therapy (IT) and placebo medication (1, 2 & 3 years), IT + antidepressant was better than IT alone and placebo alone, no difference between IT and antidepressants Study 2: No difference between psychological therapies + antidepressant compared to antidepressant alone	Small trials, risk of reporting bias (n=1), risk of detection bias due to lack of blinding of assessors (n=1)
Wilson et al. 2008	Depression in elderly	CBT, psychodynamic therapy	Active control interventions, waitlist	9	818	4 – 8 weeks	CBT more effective than waitlist control (5 trials, n=153) and active control interventions (3 studies, n unclear), No difference between CBT and psycho-dynamic therapy (3 studies, n=226)	Risk of bias esp. due to unclear allocation concealment procedure (all trials), small sample sizes

SMD: Standard mean difference (in outcome measure)

Table 7. Systematic review: Observational uncontrolled studies reporting on outcomes during and after treatment provided by homeopaths for patients suffering from diagnosed or self-reported depression

Author, year	Design	Sample	Intervention	Control	Outcome measures	Results	Comments to methods	Model validity
Adler et al. 2008	Case series, retro-spective	All new patients diagnosed with depression (DSM-IV according to SCID) over a 10 month period N=15 Onset of depression (median, IQR, range): 3 years (1-15, 0-22) Last episode lasting (median, IQR, range): 7 months (5-18, 1-60) Homeopathy clinic for depressive disorders, Jundiaí, Brazil	Individualised homeopathy for up to 4 consultations: 10 different homeopathic remedies were prescribed No other concurrent treatment Homeopath: 1	Before to after assessment	MADRS score at first three follow-up consultations Remission rates Patient-completed outcome measure	Statistically significant reduction in MADRS scores at 2nd, 3rd and 4th consultation Weeks Cons. mean (range) N 1 15 2 7.0 (4-22) 12 3 7.5 (4-14) 12 4 Not reported 5 Cons.: Consultation Weeks: Number of weeks since previous consultation N: Number of participants LOCF analysis More than 50% decrease in MADRS scores in 14 of 15 patients (93%) at 3rd consultation (mean 14-15 weeks) MADRS score (mean, SD): Baseline: 24.9 (5.8) 7 weeks: 9.7 (8.2) Change: p<0.0001 MADRS score significance sustained (mean, SD): 3.consultation: 6.5 (5.8) 4. consultation: 5.7 (5.6) Remission: n=13 (87%) One patient experienced clinical aggravation and was referred for antidepressant drug therapy.	Strengths: Diagnosed patients assessed with appropriate outcome measures. LOCF for missing data (2nd & 3rd consultation n=3) Low risk of attrition bias: Sufficient data, incl. co-morbidities (n=8). Limitations: Small sample. Retrospective. Single practitioner. Unclear risk of reporting bias: No pre-published protocol; same practitioner carried out treatment and assessments. Missing data for 2/3 of participants (n=10) at 4th consultation (one discontinued treatment due to significant improvement, another due to deterioration).	High model validity, including rationale for the intervention, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), appropriate and sufficiently sensitive outcome measures, and a follow-up period sufficient to detect an effect of the intervention.

SCID: Structured Clinical Interview. IQR: Interquartile range. MADRS: Montgomery & Åsberg Depression Rating Scale.

Author, year	Design	Sample	Intervention	Control	Outcome measures	Results	Comments to methods	Model validity
Attena et al. 2000	Uncon-trolled obser-vational study, prospec-tive	Diagnosed depression (out of 648 patients diagnosed with sub-acute and chronic conditions) n=24	Pluralist homeopathy (more than one remedy at the time) Follow-up at 3 and 6 months Homeopaths: 3	Before to after assessment	SF-36, question 2: How do you evaluate your health 1 year after you started treatment? Questionnaire completed over the telephone, called by a researcher (not a practitioner)	Marked improvement: n=13 (54.2%) Moderate improvement: n=8 (33.3%) No improvement/worse: n=3 (12.5%)	Strengths: Follow-up for at least 6 months and assessment after 1 year. Limitations: Small sample. Unclear risk of attrition and reporting bias: No pre-published protocol; limited data for depressed patients. Outcome measure not validated for depression. No information on potential confounding factors.	Low/unclear model validity: Unclear if a significant body of accredited homeopaths would support the rationale for the study, if treatment was consistent with homeopathic principles, and whether practitioners were suitably qualified and experienced. The main outcome was capable of detecting change and the length of the follow-up period was sufficient.
Clover 2000	Survey, prospec-tive	Diagnosed depression in patients with carcinoma of the breast (from 1000 patients with various complaints) n=14 Referral from GPs and hospital doctors Homeopathic hospital outpatient clinic, Tunbridge Wells, United Kingdom	Individualised homeopathic treatment: Details of treatment unknown (study period 12 months) Homeopaths: Unknown (>1)	Before to after assessment	7-point numerical self-reported rating scale at follow-up consultations Completed by patient with a clinic clerk after follow-up consultation in the absence of a doctor or nurse	7-point NRS at follow-up consultation: +3 n=9 64.3% +2: n=3 21.4% +1: n=1 7.1% 0: n=0 0.0% -1: n=1 7.1% -2/-3/-4: n=0 0.0% + indicates improvement, - indicates deterioration (for further details, see footnote) Participants: Response rate at follow-up consultations (n=2500): 55% (n=1372), no response 45% (n=822) Response rate for depressed patients not reported.	Limitations: Small sample. High risk of attrition bias: Missing data patients (45%), and consultation numbers. Unclear risk of reporting bias: No pre-published protocol. Number of practitioners unclear. Outcome measure not validated for depression. Limited information on potential confounding factors including other treatment (4% of all patients received acupuncture, but not specified for depression).	Insufficient information to assess model validity. Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).

7-point NRS: 7-point Numerical Rating Scale (Clover 2000): +3 Much better, +2 Better/Moderately better, +1 Slightly better, 0 No change, -1 Slightly worse, -2 Worse/Moderately worse, -3 Much worse.

Author, year	Design	Sample	Intervention	Control	Outcome measures	Results	Comments to methods	Model validity
Dempster 1998	Survey of random selection of patients, retro-spective	Diagnosed depression (random selection of 44 patients with various diagnosed mental health problems) n=12 Participants included: Depression n=8 Mild depression n=2 Post-natal depression n=2 Duration of depression: > 5 years (n=4) 4-5 years (n=1) 2-3 years (n=1) 1-2 years (n=1) 2-4 months (n=4) < 1 month (n=1) Referral from GPs NHS GP practice, West Yorkshire, United Kingdom	Individualised homeopathic treatment in a single practice, treatment for minimum 1 month Homeopath: 1	Before to after assessment	Self-reported improvement in depression given in percent, assessment 2-36 months after treatment Postal questionnaire completed by patient	Improvement in depression: Median 85%, Mode 90% (n=4). Interquartile range 55-90%. Range 10%-100% Improvement in long-standing depression (min.4 yrs) (n=5): 30%,80%,80%,90%,100% Improvement in recently developed depression (max.4 months) (n=4): 60%, 90%, 90%, 100% 8 of 11 patients stopped their medication (for depression n=6, uncertain n=2) (one was not taking any medication) Participants: Response rate depressed patients not reported. Response rate all patients 86% (n=44), no response 14% (n=7)	Strengths: Random selection of diagnosed patients. High external validity (similar to 'real world practice'). Limitations: Small sample. High risk of reporting bias: Not published in peer reviewed journal, no pre-published protocol. Retrospective. Single practitioner. Unclear risk of attrition bias: Patient response rate unclear. Limited information on confounding factors. Assessment period variable. Outcome measure not validated for depression. No information on potential confounding factors.	High model validity including rationale for the intervention provided and intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included). Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).
Mathie & Robinson 2006	Uncon-trolled obser-vational study, prospec-tive	Diagnosed depression (of 961 consecutive patients with various complaints) n=55 Referral: For NHS GPs (n=10) patients attended their doctor in the normal way; self-referral for private practitioners (n=2) 10 NHS and 2 private homeopathy GP practices, in England and Scotland, United Kingdom	Individualised homeopathic treatment Homeopaths: 14	Before to after assessment	7-point numerical self-reported rating scale at last follow-up consultation, max. 6 months Patient-completed outcome at consultation with homeopath	7-point NRS at latest follow-up consultation (n=55): Major or moderate improvement (+2 or +3): n=35, 63.6% Data not given for mild improvement (+1), no change/unsure (0) and deterioration (-1/-2/-3) Participants: With follow-up n=55 Drop-out n=2	Strengths: High external validity (similar to 'real world practice'). Limitations: Unclear risk of reporting bias: No pre-published protocol. Unclear risk of attrition bias: Data not reported for depressed patients, incl. drop-out, number of consultations and assessment period. Limited information on potential confounding factors, although plausible alternative explanation for clinical change recorded in 3.7% of all included patients. Outcome measure not validated for depression.	High model validity including rationale for the intervention provided and intervention used consistently with homeopathy principles, practitioners suitable and experienced. Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use). Uncertain if length of follow-up was sufficient.

7-point NRS: 7-point Numerical Rating Scale (Mathie & Robinson 2005): +3 Much better, +2 Better/Moderately better, +1 Slightly better, 0 No change, -1 Slightly worse, -2 Worse/Moderately worse, -3 Much worse.

Author, year	Design	Sample	Intervention	Control	Outcome measures	Results	Comments to methods	Model validity
Oberai et al. 2013	Uncon-trolled obser-vational study, prospec-tive	Diagnosed depression (ICD-10 criteria, min. 2 typical symptoms + 2 common symptoms, excluded if min. 25% improvement in HDRS after 1 week of placebo) n=83 Onset of depression episode (mean, SD): 1.92 years (1.02) Patients admitted to the institute indoor patient department. Central Research Institute, Kottayam, Kerala, India	Individualised homeopathic treatment, 6 months Number of homeopaths not specified	Before to during & after assessment	Primary: HDRS at 0, 3, 6 & 12 months Secondary: BDI, CGI-1, CGI-2 at 0, 3, 6 & 12 months Adverse events Outcome measures completed by patients and collected by investigators and consultant psychiatrist	Primary: HDRS baseline:17.98 (4.9) HDRS 12 months:5.8 (5.9) (mean, SD) HDRS 0, 3, 6 & 12 months (Repeated Measure ANOVA): p=0.001. Effect size = 0.74 Secondary: BDI baseline: 23.4 (6.9) BDI 12 months: 7.1 (8.7) (mean, SD) BDI 0, 3, 6 & 12 months (Repeated Measure ANOVA): p=0.001. Effect size = 0.72 CGI-1 baseline: 4 (3.2-5) CGI-1 12 months: 1 (1-2) (median, IQR) CGI-1 0, 3, 6 & 12 months (Friedman's tests) p=0.001. Effect size: 0.82 CGI-2 3 months: 2 (2-3) CGI-2 12 months: 1 (1-1) (median, IQR) CGI-2 3, 6 & 12 months (Friedman's tests) p=0.001. Effect size: 0.79 Adverse events: None	Strengths: Use of validated outcome measures. Repeated measures (4 time-points). Statistical analyses following ITT principle using LOCF. High external validity (similar to 'real world practice'). Limitations: Threshold BDI levels for mild, moderate and severe depression not reported. Overlap in categories used to report depression duration at baseline (1-5 years & 5-10 years). Unclear risk of attrition/reporting bias: Minor discrepancies between abstract, text and tables reporting on HDRS threshold levels and types of homeopathic medicines used. No rationale for use of parametric test for HDRS and BDI (unclear if data was normally distributed). Ethical: Patients appear not to have been asked for consent to 1 week run-in placebo treatment.	High model validity including rationale for the intervention provided, intervention used consistently with homeopathy principles, outcome measure reflects main effects expected, outcome measure is capable of detecting change, follow-up period likely to have been sufficient. Unclear: qualification and experience of practitioners, number of practitioners.

IQR: Interquartile range. NHS: National Health Service. HDRS: Hamilton Depression Rating Scale (17-point). BDI: Beck Depression Inventory (21-point).
CGI-1: Clinical Global Impression (scale 1-7). CGI-2: Clinical Global Improvement (scale 1-7) (Oberai et al. 2013).

Author, year	Design	Sample	Intervention	Control	Outcome measures	Results	Comments to methods	Model validity
Richards on 2001	Uncon-trolled obser-vational survey, prospec-tive	Diagnosed depression (out of 1100 consecutive medically diagnosed patients with various complaints) n=30 Referred from GPs Department of homeopathic medicine, Liverpool, United Kingdom	Individualised homeopathic treatment, mean 3.7 consultations (minimum 3), study period 1 year Homeopaths: 4?	Before to after assessment	GHHOS (self-reported) after treatment, after mean 3.7 consultations (min. 3) (study period 1 year) Patient-completed outcome handed to receptionist, clinic doctor completed a separate form recording the outcome score (unclear procedure)	GHOOS after treatment (after min. 3 consultations, mean 3.7): +2/+3/+4: n=15 50.0% +3/+4: n=8 26.7% +2: n=7 23.3% +1/0: n=15 50.0% -1/-2/-3/-4: n=0 0.0% + indicates improvement, - indicates deterioration (for further details, see footnote) Participants: Response rate for depressed patients not reported. Only patients with follow-up consultations included. Number of patients with no follow-up consultation not reported.	Strengths: High external validity Limitations: Small sample. Unclear risk of reporting bias: No pre-published protocol. Unclear risk of attrition/confirmation bias: No data for patients with no follow-up sessions, length of follow-up, drop-out rates not reported, unclear outcome recording procedure. No information on potential confounding factors. Outcome measure not validated for depression.	High model validity including rationale for the intervention provided, intervention used consistently with homeopathy principles, qualification and experience of practitioner (although number of practitioners uncertain), follow-up period likely to be sufficient. Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).
Sevar 2000	Uncon-trolled obser-vational study, prospec-tive	Diagnosed depression (out of 829 consecutive medically diagnosed patients with various complaints) n=64 Source of referral uncertain Private MD homeopathy clinic, Cumbria, United Kingdom	Individualised homeopathic treatment: First consultation 75 minutes, follow-up 30 minutes Homeopaths: 1	Before to after assessment	GHHOS (self-reported) after treatment, assessment period 6 months – 7 years Patient-reported outcome, data collected by homeopath	GHOOS after treatment (range 6 months – 7 years): +3/+4: n=40 62.5% +2: n=5 7.8% +1/0: n=10 15.6% -1/-2/-3/-4: n=0 0.0% Unknown: n=9 14.1% + indicates improvement, - indicates deterioration (for further details, see footnote) The 40 patients who experienced considerable improvement, were able to discontinue antidepressants Participants: Response rate 86% (n=55), No response 14% (n=9)	Strengths: High external validity (similar to 'real world practice'). Limitations: High risk of reporting bias: No pre-published protocol, same person treated + reported outcomes. Unclear risk of attrition bias: Missing data for depressed patients, incl. consultation numbers. No info on potential confounding factors. Outcome measure not validated for depression.	High model validity including rationale for the intervention provided, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), sufficient follow-up period. Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).

GHHOS: Glasgow Hospital Homeopathic Outcomes Scale, 9-point numerical rating scale including +4 Cured/Back to normal, +3 Major Improvement, +2 Moderate improvement, affecting daily living, +1 Slight improvement, no effect on daily living, 0 No change/Unsure, -1 Slight deterioration, no effect on daily living, -2 Moderate deterioration, affecting daily living, -3 Major deterioration ,-4 Disastrous deterioration.

Author, year	Design	Sample	Intervention	Control	Outcome measures	Results	Comments to methods	Model validity
Sevar 2005	Uncon-trolled obser-vational study, prospec-tive	Diagnosed depression (out of 455 consecutive medically diagnosed patients with various complaints) n=27 Source of referral uncertain Private MD homeopathy clinic, Cumbria, United Kingdom	Individualised homeopathic treatment: First consultation 75 minutes, follow-up 45 minutes (1st) or 30 minutes (other), mean 11 months (min. 6), mean 2.4 consultations (all 455 patients) Homeopaths: 1	Before to after assessment	GHHOS after treatment, mean 11 months (minimum 6) Combined patient- and clinician-reported outcome	GHOOS after treatment (mean 11 months, min. 6): +4: n=1 3.7% +3: n=16 59.3% +2: n=4 14.8% +1: n=1 3.7% 0: n=5 18.5% -1/-2/-3/-4: n=0 0.0% Unknown: n=0 0.0% + indicates improvement, - indicates deterioration (for further details, see footnote) 14 patients (52%) were able to significantly reduce or discontinue antidepressants Participants: Response rate 100% (n=27)	Strengths: High external validity (similar to 'real world practice'). Limitations: Small sample. High risk of reporting bias: No pre-published protocol, same person carried out treatment + reported outcomes Unclear risk of attrition bias: Missing data for depressed patients, incl. consultation numbers. High risk of confirmation bias: Outcome partially based on clinician's assessment. No information on confounding factors including other treatment, although non-significant difference in entire group (n=455) between 'homeopathy only' group (n=375) and combined treatment group (n=80). Outcome measure not validated for depression.	High model validity including rationale for the intervention provided, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), sufficient follow-up period. Unclear whether outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).

NHS: National Health Service. GHHOS: Glasgow Hospital Homeopathic Outcomes Scale, 9-point numerical rating scale including +4 Cured/Back to normal, +3 Major Improvement, +2 Moderate improvement, affecting daily living, +1 Slight improvement, no effect on daily living, 0 No change/Unsure, -1 Slight deterioration, no effect on daily living, -2 Moderate deterioration, affecting daily living, -3 Major deterioration ,-4 Disastrous deterioration.

Author, year	Design	Sample	Intervention	Control	Outcome measures	Results	Comments to methods	Model validity
Spence et al. 2005	Uncon-trolled obser-vational study, prospec-tive	Diagnosed depression (ICD-10, from 6,888 consecutive diagnosed patients in a university-hospital outpatient clinic) N=201 Referrals from GPs and hospital specialist consultants NHS university homeopathic hospital outpatient clinic, Bristol, United Kingdom	Individualised homeopathic treatment: First consultation 45 minutes, follow-up 15 minutes, mean total 3.6 consultations (for all patients), study period 6 years Homeopaths: 12	Before to after assessment	7-point numerical self-reported rating scale at follow-up consultations, length not given (study period 6 years) Patient-reported outcome, data collected by homeopath	<u>7-point NRS after mean 3.6 consultations</u>: +3 n=38 18.9% +2: n=69 34.3% +1: n=36 17.9% 0: n=46 22.9% -1: n=2 1.0% -2/-3/-4: n=0 0.0% + indicates improvement, - indicates deterioration (for further details, see footnote) <u>Participants</u>: 5% were unable to score (n=8) or the results were influenced by other factors (e.g. other treatment) (n=2)	<u>Strengths</u>: High external validity (similar to 'real world practice'). Large overall patient sample; several practitioners, treatment more representative of 'real world practice'. Potential confounding factors mentioned (although not for sub-group of depressed patients). <u>Limitations</u>: Unclear risk of confirmation and reporting bias: Patient-completed outcome, but data collected by practitioner, no pre-published protocol. Unclear risk of attrition bias: Limited data, including length of follow-up for depression patients not reported. Outcome measure not validated for depression.	High model validity including rationale for the intervention provided, intervention used consistently with homeopathy principles, qualification and experience of practitioners, sufficient follow-up period. It is unclear whether the outcome measure is sufficiently sensitive to identify changes in depressed patients (not validated for this use).

NHS: National Health Service. 7-point NRS: 7-point Numerical Rating Scale (Spence et al. 2006): +3 Major improvement, +2 Moderate improvement, +1 Mild improvement,

0 No change or unsure, -1 Mild deterioration, -2 Moderate deterioration, -3 Major deterioration.

Table 8. Systematic review: Pragmatic randomised controlled trials reporting on the effectiveness of standardised homeopathic medication for patients with diagnosed or self-reported depression

Author, year	Design	Sample	Intervention	Control	Outcome measures	Results	Risk of bias assessment, other comments to methods	Model validity
Wasilewski 2004	Pragmatic RCT	Depression in menopausal women (F32 n=135, F33 n=76) N=211 Homeopathic remedy (H) n=110 Fluvoxetine (F) n=101 Referral / recruitment unknown Neuropsychiatric clinic, Łódź, Poland	Homeopathic remedy (H) (same for all participants): Ignatia Homaccord (Heel GmbH) (Ignatia amara & Moschus moschiferus), 3x10 drops daily	Fluvoxamine (F) 50mg 3x daily	HDRS & BDI at 6 weeks	No significant between group differences in HDRS and BDI scores at 6 weeks. Participants: Included Completed All 211 182 H 110 100 F 101 82 Reduction in score at 6 weeks: HDRS BDI Min. 50% better H: 61% 66% n=68 (68.0%) F: 58% 65% n=53 (64.6%) All between group differences n.s. (p>0.05) Tolerability: Homeopathy significantly better tolerated than Fluvoxamine (p-value not given). Side-effects of Fluvoxamine were especially nausea/gastric symptoms (common side-effects for F). Drop-out due to side effects: Homeopathy n=2 Fluvoxamine n=12	Strengths: Reasonably large sample size of diagnosed participants. Fluvoxamine relevant control modality (similarly effective as other antidepressants). Limitations: No power calculation provided. Unclear risk of selection bias: No information on treatment allocation procedures, consultation length, and practitioner details. Unclear risk of attrition bias: Details of side-effects in homeopathy group not reported. Majority of participants (n=179) had a variety of comorbidities, but unclear how they were divided between treatment arms. Reduced HDRS/BDI scores only reported as percentages, not numbers provided, except for number of participants with min. 50% improvement. High risk of reporting bias: No pre-published protocol found. Authors state differences in tolerability was significant, but no p-value given.	Low/unclear model validity: Substantial number of experienced homeopaths would not support choice of intervention for this group of participants; intervention not based on the 'like treats like' principle or on the principle of isopathy; information on qualification and experience of practitioner missing. Outcome measure appropriate and sufficiently sensitive for measuring depression, but uncertain whether 6 weeks is sufficient to assess results.

SF-36: Short Form (36) Health Survey. Mulimen: consists of Ambra grisea, Calcium carbonicum, Cimicifuga racemosa, Gelsemium sempervirens, Hypericum perforatum, Kalium carbonicum, Sepia officinalis, Urtica dioica. F32: First depressive episode. F33: Recurrence of depressive episode. HDRS: Hamilton Depression Rating Scale. BDI: Beck Depression Inventor

Table 9. Systematic review: Placebo-controlled double-blinded trials reporting on the efficacy of homeopathic medicinal products used by patients suffering from diagnosed or self-reported depression

Author, year	**Design**	**Sample, condition, recruitment, setting, country**	**Intervention**	**Control**	**Outcome measures**	**Results**	**Risk of bias assessment, other comments to methods**	**Model validity, other comments to intervention**
Adler et al. 2011a	RCT, double-blinded, double-dummy, placebo-controlled, non-inferiority trial	Moderate to severe depression (DSM-IV according to SCID + MADRS score min.15) N=91 Homeopathic remedy+placebo for fluoxetine (H) n=48 Fluoxetine+placebo for homeopathic remedy (F) n=43 Referral from MDs within the public health system Depression outpatient clinic, São Paulo, Brazil	Individualised homeopathic remedy (H) (20 different medicines were used, all prescribed in Q-potencies, starting at Q2 + placebo for fluoxetine-hydrochlorine) for 8 weeks Homeopath: 1	Fluoxetine-hydrochlorine (F) 20 mg daily, increased to 40 mg daily after 4 weeks in case of no response + placebo for individualised homeopathic remedy for 8 weeks	Primary: MADRS at 4 & 8 weeks Secondary: Response & remission rates at 4 & 8 weeks Tolerability at 4 & 8 weeks	Homeopathy non-inferior to fluoxetine at 4 and 8 weeks Participants: Randomised Completed All 91 55 H 48 29 F 43 26 Full analysis set Between group difference for mean MADRS score non-significant at 4 weeks (95% CI -6.95, 0.86, p=0.65) and 8 weeks (95% CI -6.05, 0.77, p=0.97). Time effect for both groups p<0.001 Response rates for H / F were similar at 4 weeks: 63.9% / 65.8% 8 weeks: 84.6% / 82.8% Remission rates H / F similar: 4 weeks: 47.1% / 55.3%, p=0.42 8 weeks: 76.9% / 72.4%, p=0.72 Tolerability comparable Adverse events (AE): H: 10.7%, F: 21.4% Difference p=0.28 Discontinued due to AE: H: n=3. F: n=8 Difference p=0.07 Excluded due to worsening: H: n=5. F: n=1 Difference p=0.21	Overall low risk of bias, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of assessment, completeness of outcome data and reporting. High attrition rates (appr.40%) contribute to potential source of bias. Study well described, including study aim, design, participants, interventions, outcomes, statistics and results. Otherwise well-designed trial. No power calculation prior to study start, but trial was part of pilot suggesting non-inferiority of homeopathy compared to fluoxetine. Pre-fixed margin of non-inferiority (Δ) 1.45 (1/3-1/2 of the advantage of fluoxetine over placebo, and min. considered of clinical relevance). Attrition rates appr. 40% (both groups), but intention-to-treat analysis carried out. Only percentages (and not numbers) have been provided for secondary outcomes (response & remission rates).	Overall high model validity, including rationale for intervention, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), and appropriateness of outcome measures. It is possible that other experienced homeopaths would consider the assessment period to be too short, although a time-effect was found during the study period.

SCID: Structured Clinical Interview. MADRS: Montgomery & Åsberg Depression Rating Scale. Homeopathic remedies potentised (diluted & succussed) at following concentrations Q2=$2x10^{-16}$, Q3=$8x10^{-21}$, Q4=$1.6x10^{-25}$ (Q4 surpasses Avogadro's number). Tolerability measured using the side effect rating scale of the Scandinavian Society of Psychopharmacology.

Author, year	Design	Sample, condition, recruitment, setting, country	Intervention	Control	Outcome measures	Results	Risk of bias assessment, other comments to methods	Model validity, other comments to intervention
Adler et al. 2013	RCT, partially double-blinded (for verum vs placebo, but not for extensive vs shorter consul-tation), placebo-controlled, four-armed trial	Acute major depression (moderate episode) (diagnosed by psychiatrist, degree of depression HAM-D score 17-24 rated by psychologist) N=44 Extensive consultation (first 60-90 min, follow-up 30 min) + homeopathic remedy (H) n=16 Extensive consultation (first 60-90 min, follow-up 30 min) + placebo (P) n=7 Shorter consultation (first 30 min, follow-up 10 min) + homeopathic remedy (H) n=14 Shorter consultation (first 30 min, follow-up 10 min) + placebo (P) n=7 Co-operation with outpatient practices, radio & TV interviews, advertisement in newspapers and underground trains Integrative Medicine outpatient clinic of the Charité – Universitätsmedizin Berlin, Germany	Individualised homeopathic remedy (H) daily (20 different medicines were used, all prescribed in Q-potencies, starting at Q2 + extensive or shorter consultation) Homeopath: 1	Placebo daily	Primary: HAM-D at 6 weeks Secondary: HAM-D at 2 & 4 weeks BDI and SF-12 at 2, 4 & 6 weeks Adverse events Participants' treatment expec-tations	Data solely analysed descriptively without formal hypothesis testing due to insufficient sample size At 6 weeks: No relevant differences between homeopathic medicines and placebo on HAM-D and BDI Odds ratios: response, remission rates and SF-12 slightly better in homeopathic group compared to placebo, but large CI Odds ratios: response, remission rates and SF-12 slightly better in shorter compared to extensive consultation group, but large CI Adverse events: H: n=19 (of 30), 63.3% P: n=9 (of 14), 64.3% No serious adverse events No suicide ideation	Low risk of bias for comparison of homeopathy and placebo, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of assessment, completeness of outcome data and reporting. High risk of bias for comparison of extensive and short consultation as blinding of practitioners is impossible, although results were in favour of short consultations (opposite of what was expected by the practitioner and researchers) The main weakness of this trial is the fact that it was underpowered due insufficient number of participants (recruited 44 out of 228) Study well described, including study aim, design, participants, interventions, outcomes, statistics and results, although no hypothesis testing was carried out due to small sample size.	Overall high model validity, including rationale for intervention, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), and appropriateness of outcome measures. It is possible that other experienced homeopaths would consider the assessment period to be too short.

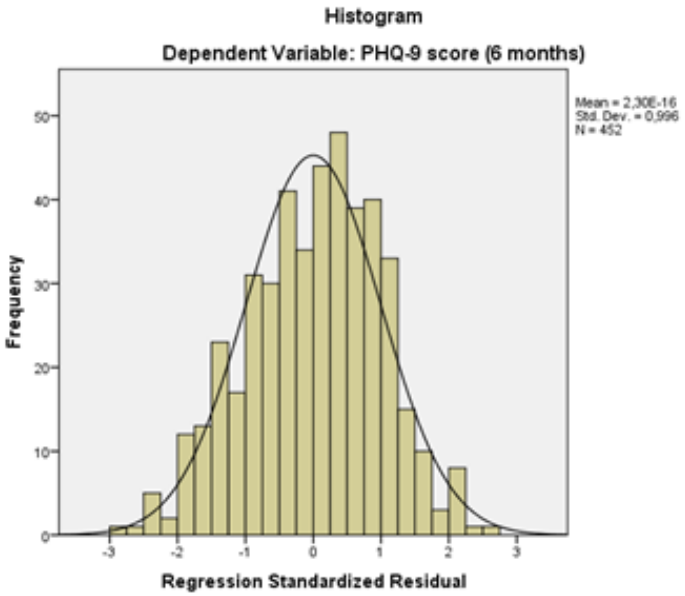
Homeopathic remedies potentised (diluted & succussed) at following concentrations Q2=$2x10^{-16}$, Q3=$8x10^{-21}$, Q4=$1.6x10^{-25}$ (Q4 surpasses Avogadro's number). HAM-D: Hamilton Depression Rating Scale. BDI: Beck Depression Inventory. SF-12: Short Form-12 Health Survey.

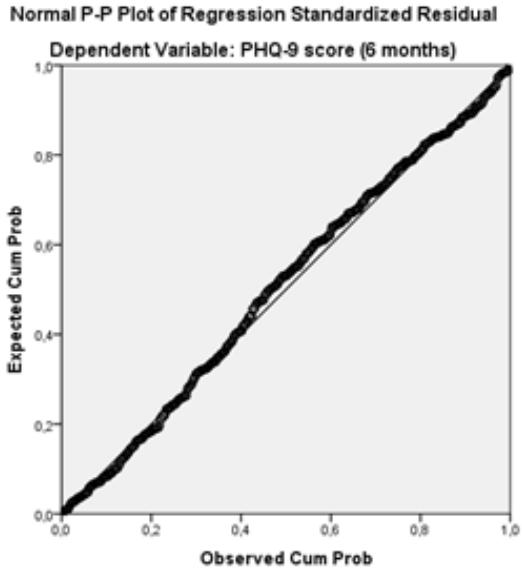
Author, year	Design	Sample, condition, recruitment, setting, country	Intervention	Control	Outcome measures	Results	Risk of bias assessment, other comments to methods	Model validity, other comments to intervention
Macías-Cortés et al. 2015	RCT, double-blinded, double-dummy, placebo-controlled trial	Moderate to severe depression (diagnosed according to DSM-IV, degree of depression HRSD score 14-24) in peri- and post-menopausal women N=133 Homeopathic remedy + placebo for fluoxetine (H) n=44 Fluoxetine + placebo for homeopathic remedy (F) n=46 Placebo for homeopathic remedy + placebo for Fluoxetine (P) n=43 Internet advertisements, community groups, liaison with health professionals, posters at study site, brochures for hospital population Hospital Juárez de México, Ministry of Health	Individualised homeopathic remedy (H) (all prescribed in liquid C30 or C200 potency, taken 2x daily) Homeopath: 1 Consultation at baseline, 4 & 6 weeks	Control 1: Fluoxetine 20 mg daily + placebo for individualised homeopathic remedy for 6 weeks Control 2: Placebo for Fluoxetine + placebo for individualised homeopathic remedy for 6 weeks	<u>Primary</u>: HRSD (17-item) at 4 & 6 weeks Clinically significant: min. 3 points Responder: min. 50% decrease Remission: 7 points or less Adverse events at 4 & 6 weeks <u>Secondary</u>: BDI at 4 & 6 weeks GS at 4 & 6 weeks	<u>At 6 weeks</u>:* HDRS: Homeopathy group better than placebo by 5.0 points ($p<0.001$) Fluoxetine was better than placebo by 3.2 points ($p<0.001$) Results were also significant using Bonferroni correction ($p<0.01$) No statistically significant differences between homeopathic medicines or fluoxetine and placebo BDI (ITT-analysis using Bonferroni correction $p=0.130$) Homeopathy significantly better than placebo and fluoxetine on GS (climacteric scale) ($p=0.002$) Response 6 weeks (min. 50 % decrease on HRSD): H: 54.4 %, F: 41.3 %, P: 11.6 % ($p<0.001$) Remission at 6 weeks (min. 7 point reduction on HRSD): H: 15.9 %, F: 15.2 %, P: 4.7 % ($p=0.194$) <u>Adverse events</u> (AE): Nine different types of AE: Insomnia (n=6, 13.6%), dyspepsia (n=6, 13.6%), nausea (n=5, 11.4%), fatigue (n=5, 11.4%), anxiety (n=4, 9.1%), dizziness (n=4, 9.1%), diarrhoea (n=3, 6.8%), headache (n=3, 6.8%), constipation (n=2, 4.5%). Prevalence similar to fluoxetine and placebo patients (p-values 0.062 to 0.999). All AE mild and tolerable with no interruption of medication , except 1 fluoxetine patient with increased anxiety & insomnia No serious adverse events	Low risk of bias for comparison of homeopathy and placebo, including random sequence generation, allocation concealment, blinding of assessment, completeness of outcome data and reporting. The authors report that participants and personnel were blinded, but it is unclear whether any tests had been carried out to assess successfulness of blinding. Symptom assessment was however carried out by a blinded investigator (clinical psychologist) Study well described, including study aim, design, participants, interventions, outcomes, statistics and results, including a sample size calculation. Multiple imputation for missing data	Overall high model validity, including rationale for intervention, intervention used consistently with homeopathy principles, suitability of qualified and experienced practitioner (although only a single homeopath included), and appropriateness of outcome measures. It is possible that other experienced homeopaths would consider the assessment period to be too short.

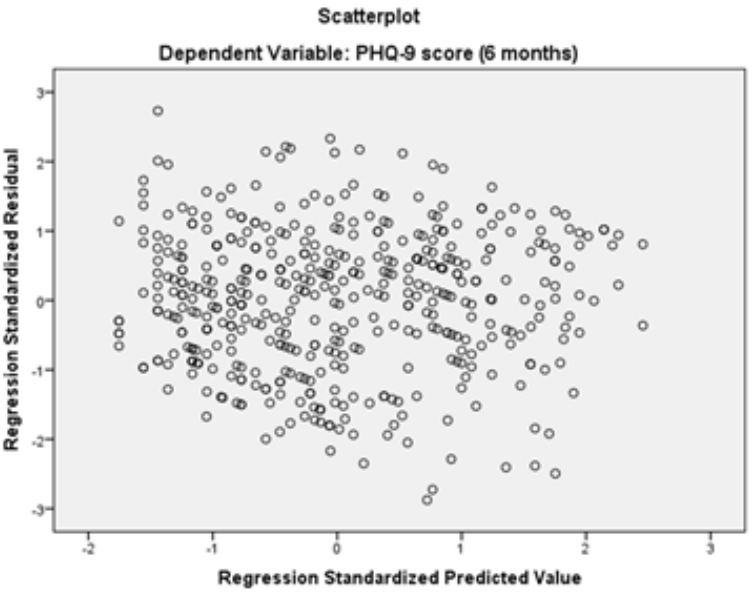
* Results were also statistically significant at 4 weeks, but only 6-week results are presented in the table.
HRSD: Hamilton Rating Scale for Depression (17-item) Homeopathic remedies potentised (diluted & succussed) at following concentrations $C30=1x10^{-60}$, $C200=1x10^{-400}$ (both surpass Avogadro's number).
BDI: Beck Depression Inventory. GS: Green Climacteric Scale (vasomotor, somatic and psychological symptoms, and sexual function).

Figures 3, 4 and 5. Histogram, Normal P-Plot of regression Standardized Residual and Scatterplot for Regression Standardized/Residual Regression Standardized Predicted

Figures 3, 4 and 5. Histogram, Normal P-Plot of Regression Standardized Residual and Scatterplot for Regression Standardized Residual/Regression Standardized Predicted Value

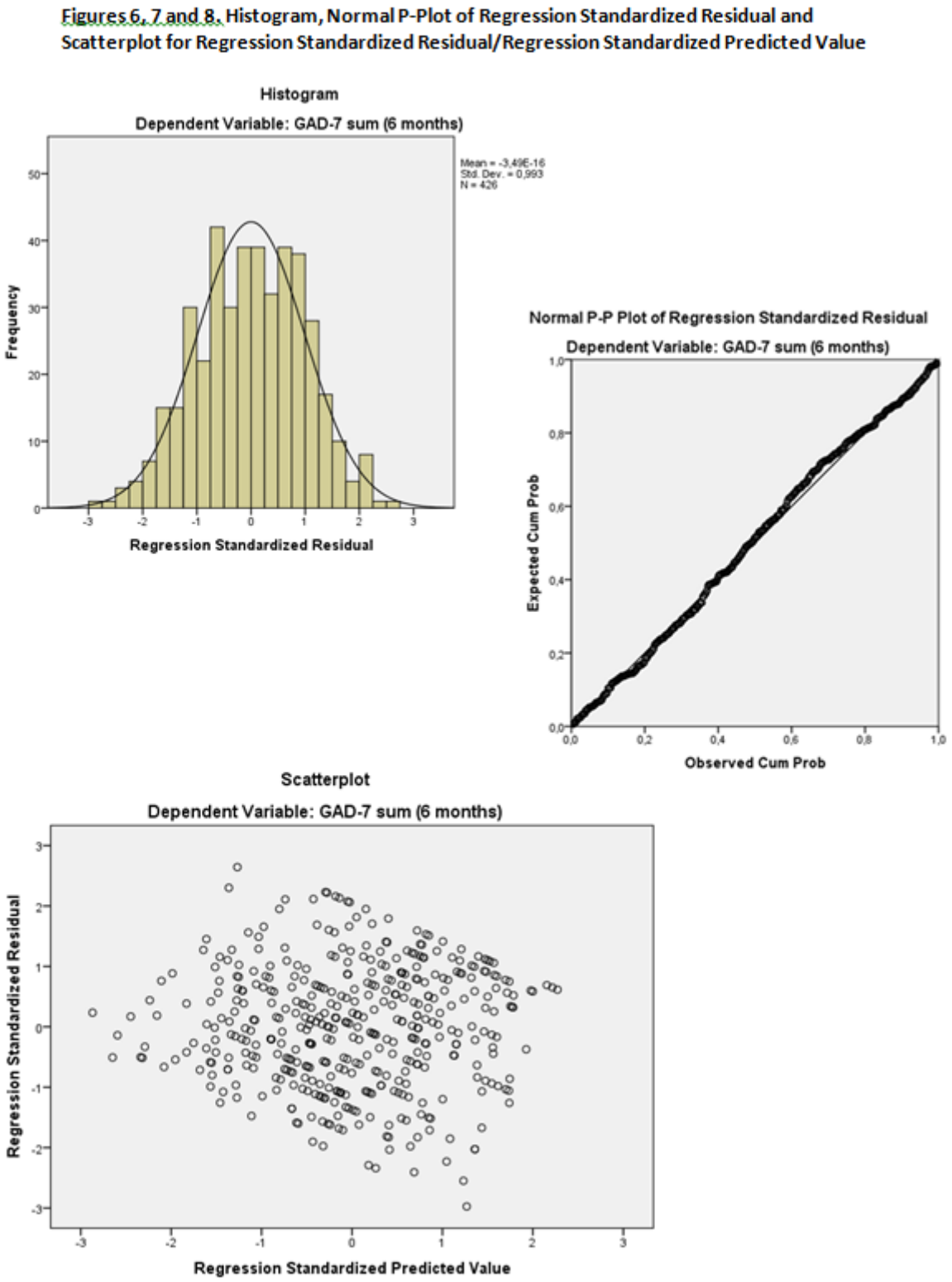






Value

Figures 6, 7 and 8. Histogram, Normal P-Plot of Regression Standardized Residual and Scatterplot for Regression Standardized Residual/Regression Standardized Predicted value



Appendix 1. Viksveen et al. 2012

NIHR CLAHRC
for South Yorkshire

NHS
National Institute for
Health Research

South Yorkshire Cohort

Health data for Clifton Medical Centre, Rotherham and South Yorkshire

South Yorkshire Cohort data of March 2012, analysed June 2012

Viksveen P, Young TA, Relton C, Bissell P.

Introduction and main points

This is an informal report which contains data for Clifton Medical Centre (CMC) collected from the South Yorkshire Cohort (SYC). It includes comparison with other SYC Rotherham and South Yorkshire practices. P-values have been calculated to determine any potential differences between CMC and all Rotherham and all South Yorkshire practices (results considered statistically significant when p=/<0.05). Calculations have been adjusted for gender, age group and deprivation score. Results are based on data collected up until March 2012. A more complete overview may be provided by the end of 2012.

Patients invited to participate in SYC: age 16 – 85 years
Results from Health Questionnaire (7 pages) mailed out 10 June & 10 August 2010.
Deprivation score (IMD Score): 30.83 (Rotherham 32.3, England 19.9)

Weight: One out of five CMC patients was obese and 57.5 % were overweight. CMC patients were more overweight ($p = 0.0002$) and obese ($p < 0.0001$) than SYC patients overall, but not compared to Rotherham patients overall. The prevalence of obesity in Rotherham was lower compared to 2005 estimates presented by Health Survey England (HSE) (20% versus 28%). Forty-three percent of CMC patients were concerned about their weight, and about half of all patients had increased exercise and tried to eat healthy food, whereas four out of ten controlled their food portion size. Some had joined specific slimming clubs and a limited number used weight loss medication or meal replacements. Weight strategies for CMC patients were not significantly different to Rotherham or SYC patients overall, with the exception of a trend of higher use of weight loss medication other than Alli ($p = 0.1$).

Long-standing illness: About 54% of CMC patients suffered from self-reported long-standing illness. Compared to Rotherham and SYC practices there were no differences in long-standing illness overall or for diabetes, but more CMC patients were anxious (12.0% versus 10.0 % / 9.8 %) ($p = 0.02$ / $p = 0.005$) and depressed (11.0% versus 8.9% / 9.4%) ($p < 0.001$ / $p = 0.04$). Three out of ten had moderate or extreme anxiety or depression on the day they completed the Health Questionnaire, which was more compared to Rotherham and SYC practice patients overall ($p = 0.01$ / 0.008). There was a trend towards a lower frequency of hypertension compared to all Rotherham practices ($p = 0.09$) and a trend towards higher frequency for heart disease compared to SYC patients overall ($p = 0.06$).

Long-standing depression: The most typical / average depressed patient (CMC, Rotherham and SYC) was female and between 35 and 54 years. She had a life satisfaction score of about 5 (scale 0-10), which is considerably lower than for other patients, and she had had twice as many consultations with a GP compared to other patients.

For detailed results, see next pages.

Long-standing illness

	CMC	Rotherham	South Yorkshire	P-values
Long-standing illness (all)	54.4 %	54.6 %	53.3 %	0.87 / 0.41
Anxiety	12.0 %	10.0 %	9.8 %	0.02 / 0.005
Depression	11.0 %	8.9 %	9.4 %	< 0.0001 / 0.04
Diabetes	5.6 %	5.5 %	5.4 %	0.90 / 0.80
Hypertension	13.8 %	15.6 %	14.3 %	0.09 / 0.80
Heart disease	5.3 %	4.9 %	4.3 %	0.46 / 0.06

Anxiety & depression	CMC	Rotherham	South Yorkshire	P-values
Moderate or extreme (EQ-5D)	30.1 %	26.7 %	26.9 %	0.01 / 0.008

(Note: P-values have not been calculated for the following)

Life satisfaction Numerical rating scale (0-10)

	CMC	Rotherham	South Yorkshire
Depressed (mean)	4.9	5.0	4.9
Non-depressed (mean)	7.2	7.4	7.3

GP consultations	CMC	Rotherham	South Yorkshire
Depressed (mean)	2.2	2.2	2.5
Non-depressed (mean)	1.1	1.1	1.2

Note: Analysis for non-depressed patients do NOT include all (i.e. also depressed) patients, only non-depressed patients.

Long-standing DEPRESSION

	CMC	Rotherham	South Yorkshire
Female	54.2 %	60.9 %	57.2 %
Age groups			
<= 24 years	7.2 %	7.9 %	9.1 %
25-34 years	12.6 %	11.2 %	14.8 %
35-44 years	21.6 %	20.0 %	21.1 %
45-54 years	26.3 %	22.9 %	22.7 %
55-64 years	17.4 %	20.0 %	17.9 %
65-74 years	8.4 %	11.4 %	9.9 %
>= 75 years	6.6 %	6.7 %	4.4 %

Results

Clifton Medical Centre (CMC)
Total responses received: 1.547 patients
Female: 60.4 %

Weight

	CMC	Rotherham	South Yorkshire	P-values
Minimum **overweight**	57.5 %	56.1 %	52.3 %	0.33 / 0.0002
Minimum **obese**	20.8 %	19.6 %	18.2 %	0.30 / < 0.0001

BMI groups	CMC	Rotherham	South Yorkshire	P-values
50+	0.1 %	0.1 %	0.1 %	0.72 / 0.77
Morbidly obese	2.1 %	1.9 %	1.8 %	0.49 / 0.35
Obese	18.2 %	17.7 %	16.2 %	0.40 / 0.02
Overweight	36.6 %	36.5 %	34.2 %	0.93 / 0.07
Normal	39.5 %	41.8 %	45.4 %	0.12 / < 0.001
Underweight	3.0 %	2.2 %	2.3 %	0.06 / 0.07

Note: According to Health Survey England (HSE) 2005 the estimated prevalence of obesity for adults in Rotherham was 28.3 % (national estimate 24.2 %). *Ref: NHS Rotherham. Joint Strategic Needs Assessment. July 2011.*

	CMC	Rotherham	South Yorkshire	P-values
Weight is a concern for me	43.4 %	41.7 %	41.9 %	0.27 / 0.27

Weight strategies	CMC	Rotherham	South Yorkshire	P-values
Exercise & food				
Increasing exercise	47.5 %	46.2 %	46.6 %	0.36 / 0.50
Healthy eating	47.2 %	47.9 %	47.9 %	0.63 / 0.58
Controlling portion size	41.3 %	40.5 %	40.7 %	0.60 / 0.68
Slimming clubs				
Slimming world	7.6 %	7.8 %	8.1 %	0.82 / 0.53
Weight Watchers	12.0 %	11.9 %	10.8 %	1.00 / 0.16
Rosemary Conley D&F	1.9 %	1.7 %	1.4 %	0.63 / 0.15
Lighterlife	0.5 %	0.4 %	0.5 %	0.70 / 0.97
OTC weight loss medication				
Alli (Orlistat)	2.7 %	2.2 %	2.2 %	0.26 / 0.19
Other	2.4 %	1.9 %	1.8 %	0.28 / 0.10
Meal replacements				
Lighterlife	0.8 %	0.6 %	0.8 %	0.40 / 0.89
Other	3.0 %	2.9 %	2.8 %	0.73 / 0.68

Appendix 2. Literature search results for systematic reviews of homeopathy.

Systematic literature search included titles results
Sources searched: Cochrane Library, EMBASE, MEDLINE, PubMed, own archives, reference lists, contact with other researchers.
Date: 20.02.15
Titles: 349 (duplicates removed).
Relevant titles included: 124. Reviews: 123
Note: Cooper & Relton 2010b is not a separate review, but an update of Cooper & Relton 2010a

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Appendix 3. Databases and other resource website addresses for systematic review.

AMED: Allied and Complementary Medicine http://www.ovid.com/site/catalog/databases/12.jsp
BHL: British Homeopathic Library http://hominform.soutron.net/Catalogues/Search.aspx
http://www.hlisd.org/LibraryDetail.aspx?libraryid=3106
(BHL has been closed since the literature search was carried out)
BMC CAM: BMC Complementary and Alternative Medicine www.biomedcentral.com/1472-6882
CAMbase: http://cambase.dmz.uni-wh.de/opencam/index_en.html
CAMEOL Database: http://www.rccm.org.uk/node/115
CAM Quest: http://www.cam-quest.org/en/
CCDAN: Cochrane Depression Anxiety and Neurosis Review Group trial register
http://ccdan.cochrane.org/
CINAHL: http://www.ebscohost.com/cinahl/
ClinicaTrials.gov: http://clinicaltrials.gov/ct2/search
Cochrane LIBRARY:
http://onlinelibrary.wiley.com/o/cochrane/cochrane_search_fs.html?newSearch=true
CSA (Sociological Abstracts): http://www.csa.com/
CORE-Hom: https://www.hri-research.org/resources/research-databases/core-hom/
DARE: Database of Abstracts of Reviews of Effects: http://www.crd.york.ac.uk/crdweb/
EMBASE: http://www.embase.com/
EU Clinical Trials Register: https://www.clinicaltrialsregister.eu/index.html
HomBRex-Database: http://www.carstens-stiftung.de/hombrex/index.php
HRI: Homeopathy Research Institute: http://homeoinst.org/database
(Database has changed into CORE-Hom since the literature search was carried out)
HTA: Health Technology Assessment database http://www.crd.york.ac.uk/crdweb/
IJHDR: International Journal of High Dilution Research
http://www.feg.unesp.br/~ojs/index.php/ijhdr/index
Interhomeopathy www.interhomeopathy.org
MEDLINE: http://www.proquest.com/en-US/catalogs/databases/detail/medline_ft.shtml
NCBI: National Center for Biotechnology Information http://www.ncbi.nlm.nih.gov/
NHS EED: NHS Economic Evaluation Database http://www.crd.york.ac.uk/crdweb/
PubMed: http://www.ncbi.nlm.nih.gov/pubmed
PsycINFO: http://www.apa.org/pubs/databases/psycinfo/index.aspx
ReferenceWorks: http://www.kenthomeopathic.com/referenceworks.html
Scopus: SciVerse Scopus http://www.scopus.com/home.url
TRIP: Turning Research Into Practice: http://www.tripdatabase.com/
Web of Science: http://thomsonreuters.com/products_services/science/science_products/a-z/web_of_science/
Zetoc: Z39.50-compliant access to the British Library's Electronic Table of Contents http://zetoc.mimas.ac.uk/

Appendix 4. MEDLINE search result.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present: http://www.proquest.com/en-US/catalogs/databases/detail/medline_ft.shtml

SUMMARY

Best search string: hom*eopat* AND depress*
Nothing added by adding: potentised, dysthymia, other terms or other ways of spelling words
Result: 92
Time limit: 1982 – current
Date: 13.07.12

SEARCH BUILDER

1. exp homeopathy/ 3895
2. homeopathy.mp. 4414
3. 1 OR 2 4414
4. homeopath 62
5. 2 OR 4 4427
6. homeopathic 1805
7. 5 OR 6 4929
8. homeopat* 4971
9. 7 OR 8 4971
10. homoeopathy 359
11. homoeopath 16
12. 8 OR 9 370
13. homoeopathic 317
14. 12 OR 13 619
15. homoeopat* 703
16. 14 OR 15 703
17. homeopat* OR homeopat* 5117
18. hom*eopat* 5117
17. potentised 11
18. potentized 67
19. 15 OR 16 78
20. potenti?ed 79
21. 19 OR 20 79
22. hom*eopat* OR potenti?ed

Highest search result: hom*eopat* OR potenti?ed 5125

1. exp depression/ 65900
2. depression 244303
3. 1 OR 2 244303
4. depressed 74060
5. 2 OR 4 290118
6. depressive 104477
7. 5 OR 6 323189
8. depress* 351348
9. 7 OR 8 351348
10. depressive disorder 73259
11. 8 OR 10 351348
12. exp dysthymic disorder/ 917
13. dysthymic 1621
14. 12 OR 13 1621
15. dysthymia 1625
16. 13 OR 15 2737
17. dysthym*2776
18. 16 OR 17 2776
21. depress* OR dysthym* 351680

Highest search result: depress* OR dysthym* 351680

Combined search (homeopathy and depression terms)
(hom*eopat* OR potenti?ed) AND (depress* OR dysthym*) 92
(hom*eopat* OR potenti?ed) AND (depress*) 92
(hom*eopat*) AND (depress*) 92

Appendix 5. Letter to patients for screening and baseline data collection.

The University Of Sheffield.

Date: 17.09.2013

Dear ,

You have previously completed and returned the Health Questionnaire we sent to you. You were one of 2 000 people who reported sometimes feeling anxious or depressed. We would like to learn more about your experiences. We would be grateful if you could complete the enclosed the Mood and Health Questionnaire. What we learn will help us understand how we can improve the health of people living in South Yorkshire.

It will take about 15 minutes to complete the questionnaire. When you have completed the questionnaire, please put it in the envelope and post it to the researchers at the University of Sheffield. **You do not need a stamp**.

All your answers will be made anonymous and used only for research purposes. It is completely up to you whether you fill in the questionnaire. You can withdraw from this study at any time in the future.

If you have any queries or require further information about this study please contact Petter Viksveen or Dr. Clare Relton at: ScHARR, University of Sheffield, FREEPOST – SF1314, Sheffield, S1 1AY. Tel: 0114 222 0796. Email: p.viksveen@sheffield.ac.uk

Thank you.

Yours sincerely
Dr. Clare Relton and Petter Viksveen
Researchers at the University of Sheffield

Appendix 6. Mood and Health Questionnaire

NHS

Mood and Health Questionnaire

South Yorkshire Cohort

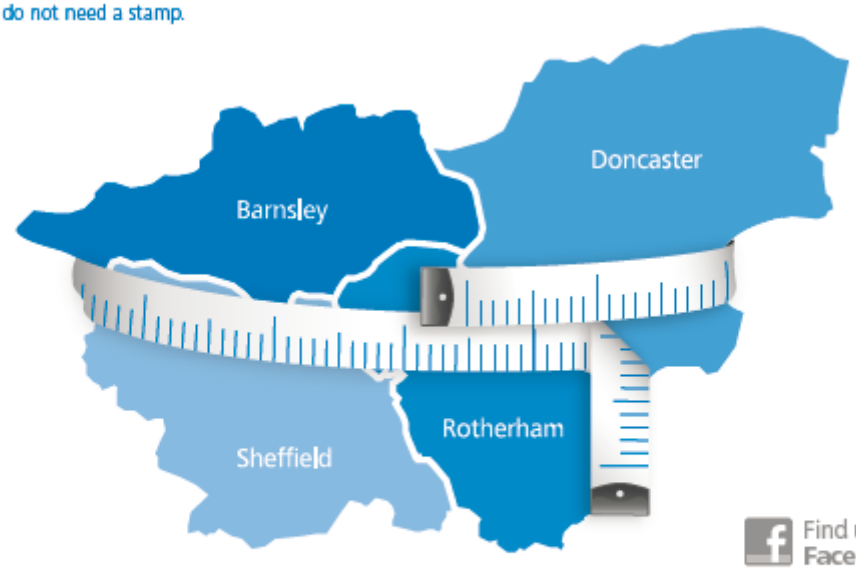
Thank you for completing the previous Health Questionnaire we sent you. You were one of 2,000 people who reported feeling anxious or depressed sometimes. We would like to hear more about your experience and would be grateful if you could complete this questionnaire.

The questionnaire will take about 15 minutes to complete. When you have completed the questionnaire, please put it in the envelope and post it to the researchers at the University of Sheffield. You do not need a stamp.

The information will be treated confidentially and will not be used for any other purpose than for the South Yorkshire Cohort project.

If you have any queries or require further information about this study please contact Petter Viksveen or Dr Clare Relton at: ScHARR, University of Sheffield, FREEPOST - SF1314, Sheffield, S1 1AY.

Tel: 0114 222 0796
Email: p.viksveen@sheffield.ac.uk



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Your health

Here are some simple questions about your health in general. By ticking one answer in each group below, please indicate which statements best describe your own health state TODAY.

Mobility	Please tick one:
I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐
Self-care	Please tick one:
I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
Usual Activities	Please tick one:
I have no problems with performing my usual activities (e.g. work, study, housework, family or leisure activities)	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐
Pain / Discomfort	Please tick one:
I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐
Anxiety / Depression	Please tick one:
I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

Long standing conditions

Do you have any long-standing illness, health problem, condition or disability? ☐ Yes ☐ No

If yes, please tick all that apply:

		When did this first start?	When did the current episode start?
Tiredness / Fatigue	☐		
Insomnia	☐		
Anxiety / Nerves	☐		
Depression	☐		
Other: *Please describe*	☐		

2

Your mood

Over the last 2 weeks, how often have you been bothered by any of the following problems?
Put a circle around the number that corresponds to your answer.

	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Over the last 2 weeks, how often have you been bothered by any of the following problems?
Put a circle around the number that corresponds to your answer.

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
10. If you checked off any problems (above), how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people	0	1	2	3

Your medication

Are you currently taking any medication? (Either prescribed by your doctor, or that you buy yourself).

☐ Yes ☐ No

Please list all your medication below, including vitamins and mineral supplements, dietary supplements or diet pills, herbal or homeopathic remedies.

Name & strength of tablet, medicine, ointment, drops, inhaler or injection	Is this prescribed for you? *Please tick:*	What is this for?
(Example) Co-codamol 8mg/500mg tablets	☐ Yes ☑ No	*Joint pain*
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

In the past, have you taken any medication or treatment for feelings of depression? ☐ Yes ☐ No

Name of medicine or treatment	Is this prescribed for you? *Please tick:*	When did you first take this?
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

About you

In the last 3 MONTHS, how many times have you visited the following:

Hospital	Accident and Emergency (A&E)	☐☐ times
	Hospital - day case	☐☐ times
	Hospital - outpatients	☐☐ times
	Hospital - in-patients (*nights*)	☐☐ nights
Other healthcarers	GP	☐☐ times
	Nurse	☐☐ times
	Physiotherapist	☐☐ times
	Dietitian	☐☐ times
	Midwife	☐☐ times
	Mental health worker	☐☐ times
	Psychotherapist	☐☐ times
Other carers	Counsellor	☐☐ times
	Care worker	☐☐ times
	Social worker	☐☐ times
	Health visitor	☐☐ times
	Community health champion	☐☐ times
	Health trainer	☐☐ times
Alternative therapist	Acupuncturist	☐☐ times
	Chiropractor	☐☐ times
	Herbalist	☐☐ times
	Homeopath	☐☐ times
	Osteopath	☐☐ times

Other *Please describe*	
	☐☐ times

How many children do you have (under the age of 18)? ☐☐ children

What age is your youngest child? ☐☐ years. Are you currently pregnant? ☐ Yes ☐ No

Your height ☐ feet ☐☐ inches **OR** ☐☐☐ cm

Your weight ☐☐ stone ☐☐ lbs **OR** ☐☐☐ kgs

Are you currently employed? ☐ Yes ☐ No

During the last 3 MONTHS, how many days have you taken off from paid work as a result of ill health? ☐☐ days

During the last 3 MONTHS, on how many days has your ill health prevented you from carrying out your: Household tasks: ☐☐ days Leisure activities: ☐☐ days

Alcohol: How many days in the last WEEK did you drink alcohol? ☐ days

How many units of alcohol did you drink in the last WEEK? ☐☐ units

A unit of alcohol is equal to ½ a pint of ordinary beer, lager or cider, 1 single measure of spirits, 1 small glass of wine or 1 measure of fortified wine.

Are you currently involved in another study to do with your health?

☐ Yes ☐ No

If yes, which one / what is it about? .....

5

About you

Thank you for your answers. These will be combined with hundreds of others. What we learn will help us understand how we can improve the health of people living in South Yorkshire.

May we contact you again?

☐ Yes ☐ No

Please fill in your **forename**, **surname** and **address** **if different** to those printed to the left:

Forename (print)

Surname (print)

Address

Postcode

Please fill in your preferred contact details below:

Telephone

Mobile phone*

Email*

*Optional

Signature .....

Thank you for completing the Health Questionnaire. Please put it in the prepaid envelope and post it to the researchers. NO STAMP NEEDED.

If you have any queries or require further information about this study please contact Petter Viksveen or Dr Clare Relton at: ScHARR, University of Sheffield, FREEPOST - SF1314, Sheffield S1 1AY

Tel: 0114 222 0796 **Email:** p.viksveen@sheffield.ac.uk

Appendix 7. Mood and Health Questionnaire – follow-up

NHS

Mood and Health Questionnaire

Yorkshire Health Study

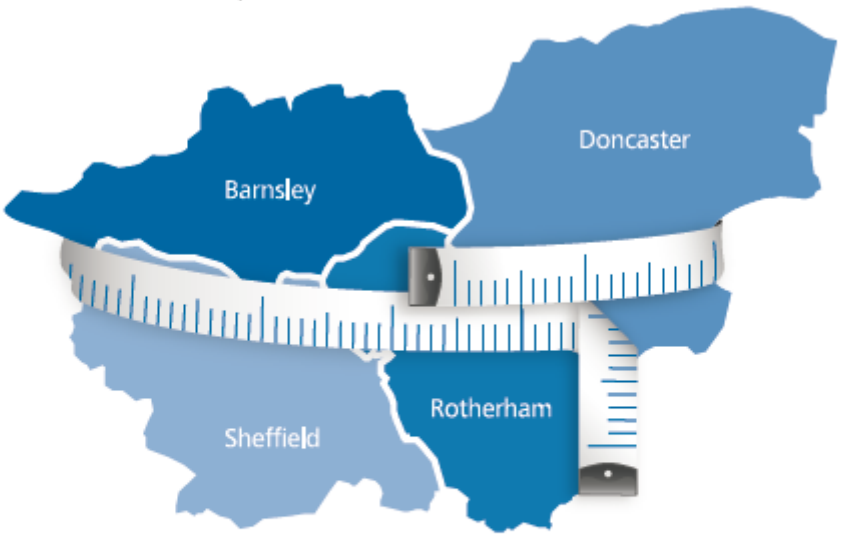
Thank you for completing the previous Mood and Health Questionnaire we sent you. You were one of 2,000 people who reported feeling anxious or depressed sometimes. We would like to hear more about your experience and would be grateful if you could complete this questionnaire.

The questionnaire will take about 15 minutes to complete. When you have completed the questionnaire, please put it in the envelope and post it to the researchers at the University of Sheffield. You do not need a stamp.

The information will be treated confidentially and will not be used for any other purpose than for the Yorkshire Health Study.

If you have any queries or require further information about this study please contact Petter Viksveen or Dr Clare Relton at: ScHARR, Regent Court, 30 Regent Street, Sheffield S1 4DA.

Tel: 0114 222 0796
Email: p.viksveen@sheffield.ac.uk



The University Of Sheffield.

Sheffield Hallam University

NHS National Institute for Health Research

Your health

Here are some simple questions about your health in general. By ticking one answer in each group below, please indicate which statements best describe your own health state TODAY.

Mobility	Please tick one:
I have no problems in walking about	☐
I have some problems in walking about	☐
I am confined to bed	☐
Self-care	Please tick one:
I have no problems with self-care	☐
I have some problems washing or dressing myself	☐
I am unable to wash or dress myself	☐
Usual Activities	Please tick one:
I have no problems with performing my usual activities (e.g. work, study, housework, family or leisure activities)	☐
I have some problems with performing my usual activities	☐
I am unable to perform my usual activities	☐
Pain / Discomfort	Please tick one:
I have no pain or discomfort	☐
I have moderate pain or discomfort	☐
I have extreme pain or discomfort	☐
Anxiety / Depression	Please tick one:
I am not anxious or depressed	☐
I am moderately anxious or depressed	☐
I am extremely anxious or depressed	☐

Long standing conditions

Do you have any long-standing illness, health problem, condition or disability? ☐ Yes ☐ No

If yes, please tick all that apply:

Tiredness / Fatigue	☐	High blood pressure	☐
Pain	☐	Heart disease	☐
Insomnia	☐	Osteoarthritis	☐
Anxiety / Nerves	☐	Stroke	☐
Depression	☐	Cancer	☐
Memory problems	☐	Other *(please state)*:	☐
Diabetes	☐		
Breathing problems e.g. chronic bronchitis, asthma or emphysema	☐		

2

Your mood

Over the last 2 weeks, how often have you been bothered by any of the following problems?
Put a circle around the number that corresponds to your answer.

	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Over the last 2 weeks, how often have you been bothered by any of the following problems?
Put a circle around the number that corresponds to your answer.

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
10. If you checked off any problems (above), how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people	0	1	2	3

Your medication

Are you currently taking any medication? (Either prescribed by your doctor, or that you buy yourself).

☐ Yes ☐ No

Please list all your medication below, including vitamins and mineral supplements, dietary supplements or diet pills, herbal or homeopathic remedies.

Name & strength of tablet, medicine, ointment, drops, inhaler or injection	Is this prescribed for you? *Please tick*:	What is this for?
(Example) Co-codamol 8mg/500mg tablets	☐ Yes ☑ No	*Joint pain*
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	
	☐ Yes ☐ No	

4

About you

In the last 3 MONTHS, how many times have you visited the following:

Hospital	Accident and Emergency (A&E)	☐☐ times
	Hospital - day case	☐☐ times
	Hospital - outpatients	☐☐ times
	Hospital - in-patients (*nights*)	☐☐ nights
Other healthcarers	GP	☐☐ times
	Nurse	☐☐ times
	Physiotherapist	☐☐ times
	Dietitian	☐☐ times
	Midwife	☐☐ times
	Mental health worker	☐☐ times
	Psychotherapist	☐☐ times
Other carers	Counsellor	☐☐ times
	Care worker	☐☐ times
	Social worker	☐☐ times
	Health visitor	☐☐ times
	Community health champion	☐☐ times
	Health trainer	☐☐ times
Alternative therapist	Acupuncturist	☐☐ times
	Chiropractor	☐☐ times
	Herbalist	☐☐ times
	Homeopath	☐☐ times
	Osteopath	☐☐ times

Other *Please describe:*	
	☐☐ times

Are you currently employed? ☐ Yes ☐ No

During the last 3 MONTHS, how many days have you taken off from paid work as a result of ill health? ☐☐ days

During the last 3 MONTHS, on how many days has your ill health prevented you from carrying out your:

Household tasks: ☐☐ days

Leisure activities: ☐☐ days

Alcohol: How many days in the last WEEK did you drink alcohol? ☐ days

How many units of alcohol did you drink in the last WEEK? ☐☐ units

A unit of alcohol is equal to ½ a pint of ordinary beer, lager or cider, 1 single measure of spirits, 1 small glass of wine or 1 measure of fortified wine.

5

About you

Thank you for your answers. These will be combined with hundreds of others. What we learn will help us understand how we can improve the health of people living in South Yorkshire.

May we contact you again?

☐ Yes ☐ No

Please fill in your **forename**, **surname** and **address** **if different** to those printed to the left:

Forename (print)

Surname (print)

Address

Postcode

Please fill in your preferred contact details below:

Telephone

Mobile phone*

Email*

*Optional

Signature .....

Thank you for completing the Mood and Health Questionnaire. Please put it in the prepaid envelope and post it to the researchers. NO STAMP NEEDED.

If you have any queries or require further information about this study please contact Petter Viksveen or Dr Clare Relton at: ScHARR, Regent Court, 30 Regent Street, Sheffield S1 4DA.

Tel: 0114 222 0796 **Email:** p.viksveen@sheffield.ac.uk

Appendix 8. Offer group – Treatment offer letter

Offer group – Treatment offer letter (version 8, date 14.07.2012)

Date:

Dear Mr., Mrs., Ms.

You may remember that you recently completed and returned the Mood and Health Questionnaire. Thank you for your help. You reported some degree of anxiety and/or depression. You are one of 162 participants who have been randomly selected to be offered treatment by a homeopath. The treatment is free and we will reimburse your travel costs to consultations.

Homeopathy is a form of complementary and alternative medicine used by many patients. It is used for different conditions, including anxiety and depression. Treatment includes consultations and taking homeopathic medicines. In previous studies some patients reported improvement. Little or no side-effects have been reported by patients. Researchers at the University of Sheffield would like to learn more about your experience with such treatment.

You will be contacted by telephone by a researcher to hear if you want to participate. You can then also ask any questions you may have.

Please read the enclosed **Participant Information Sheet** for further information.

If you decide to participate then please sign the enclosed **Consent Form** and return it to us in the enclosed envelope. No stamp is needed.

You may then contact one of the following practitioners to agree the date and time of your first consultation:
Name of practitioner, contact details

If you have any questions or require further information about this study please contact Petter Viksveen or Dr. Clare Relton at: ScHARR, University of Sheffield, FREEPOST – SF1314, Sheffield, S1 1AY. Tel: 0114 222 0796. Email: p.viksveen@sheffield.ac.uk

Thank you.

Yours sincerely
Dr. Clare Relton and Petter Viksveen
Researchers at the University of Sheffield

Appendix 9. Offer group – Participant Information Sheet

The University Of Sheffield.

School Of Health And Related Research.

Offer group – Participant Information Sheet (version 10, date 25.06.2013)

You have been invited to take part in a study of homeopathic treatment. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. The aim of this study is to find out whether treatment by a homeopath is effective for people who report symptoms of depression.

Why have I been chosen for this study?
You have been chosen because you reported some degree of anxiety and/or depression when you filled in the Mood and Health Questionnaire.

What will I be asked to do?
You are being asked to have a course of homeopathic treatment. This will consist of consultations with a homeopath roughly once every 1-3 months for a maximum period of 9 months. Your homeopath will prescribe homeopathic remedies for you. Homeopathy is a form of complementary and alternative medicine used by many patients. It is used for different conditions, including anxiety and depression. Previous patients have reported little or no side-effects of such treatment. Researchers at the University of Sheffield would like to learn more about your experience with such treatment.

The treatment is free and we will reimburse your travel costs to consultations.

Participating in this study does not affect any other treatment you may be using. You should continue to take any medication or treatment provided by your GP or other health practitioners. Any standard medication you are taking must be continued as prescribed by your GP/specialist. All homeopaths in this study are qualified, registered and experienced practitioners. They have agreed to contact your GP should this become necessary. In such a case they will discuss this with you first. Your GP will be informed if you agree to participate in this project.

Do I have to take part in this research?
No, it is up to you to choose whether you want to take part. If you decide to take part, you will be asked to sign the attached Consent From. You have the right to withdraw from this study at any given time. This will not affect any other treatment you are receiving. You do not need to give a reason for this (but you may be asked if you are willing to give a reason.)

Will the information I give be kept private?
Yes. All information you provide will be kept strictly confidential. Once we have collected the information, all the data will be made anonymous. As an individual you will not be identifiable in the results of the study. The data will be kept for 5 years or until the end of the South Yorkshire Cohort study.

What will happen to the results of this research?
The results of this research will be published in a health science journal and in a PhD report at the University of Sheffield. If you would like, we will give you a report of the findings of the study.

Who is organising and funding the research?
This study is part of a programme carried out by the principal investigator, Petter Viksveen, at the University of Sheffield. The project has received funding from various sources. The project will pay the homeopaths who provide the treatment and your travel costs.

Who has reviewed the study?
This study has been reviewed by Independent Scientific Reviewers and researchers at the University of Sheffield.

What if I have any concerns or questions or wish to file a complaint?
If you have any concerns, including any experienced negative effects following treatment, if you have any questions or require further information about this study, or wish to file a complaint, please contact Petter Viksveen or Dr. Clare Relton at: ScHARR, University of Sheffield, FREEPOST – SF1314, Sheffield, S1 1AY. Tel: 0114 222 0796. Email: p.viksveen@sheffield.ac.uk Complaints may also be filed directly to the University of Sheffield by contacting Mrs. Kirsty Woodhead at k.woodhead@sheffield.ac.uk

Thank you for reading this.

Appendix 10. Consent form

The University Of Sheffield.

Consent Form

Centre number: ScHARR (to be filled in by researcher)

Study number: 12/YH/0379 (to be filled in by researcher)

Participant Identification Number: (to be filled in by researcher)

1. I hereby confirm that I have read and understand the information in the "Offer group – Participant Information Sheet" and have been given the opportunity to ask researchers at the University of Sheffield any questions I may have.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason.

3. I understand that the information I provide will be treated confidentially and will only be looked at by the researchers involved in this project.

4. I understand that any standard medication must be continued as prescribed by my GP/specialist.

_____	_____	_____
Your name (capital letters)	Your signature	Date

Please return the signed consent form to: Petter Viksveen at: ScHARR – Regent Court, FREEPOST – SF1314, Sheffield, S1 1AY.

Appendix 11. Adverse Events Assessment Guidelines for the DEPSY project

Adverse Events Assessment Guidelines for the DEPSY project (version 3, 13.03.2013)

Introduction

This document has been developed for the pragmatic cohort randomized controlled trial of the clinical and cost effectiveness of treatment of depression by homeopaths (DEPSY) at the School of Health and Related Research (ScHARR), University of Sheffield, and which is embedded in the South Yorkshire Cohort (SYC). The aim of the DEPSY project is to assess the acceptability and comparative clinical and cost effectiveness of adjunctive treatment provided by homeopaths in addition to usual care for patients who have self-reported depression (DEPSY). A random selection of patients in the South Yorkshire Cohort (SYC) will be offered treatment by homeopaths. Homeopaths must report adverse events to the research management team. Patients are also informed in the Patient Information Sheet that they may report adverse events directly to the research team.

These Adverse Event (AE) guidelines are mainly based on the Common Terminology Criteria for Adverse Events (CTCAE) (U.S. Department of Health and Human Services 2010, v.4.03), the Standard Operating Procedure developed by the Clinical Trials Research Unit (CTRU) at the University of Sheffield (2012) and existing homeopathy literature. This document supplements the DEPSY risk assessment guidelines (full title: "How to identify and deal with clinical risk issues: Guidelines for homeopaths providing treatment in the DEPSY project.")

What is an adverse event?

Many definitions of adverse events exist. The CTCAE guidelines define an adverse event (AE) as (p.1): "… any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure."

Different grades of adverse events

Adverse events may be categorised in various ways. The CTCAE guidelines use the following 5 categories (p.1) (semi-colon indicates 'or') (definitions are also consistent with European Commission (2011) guidelines):

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only. Intervention not indicated.

Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL (ADL = Activities of Daily Living) (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; resulting in significant disability or incapacity; limiting self-care ADL (ADL = Activities of Daily Living) (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden), or congenital anomaly or birth defect; or events that may require intervention to prevent any of the mentioned consequences.

Grade 4: Life-threatening consequences; urgent intervention indicated. This refers to events where the subject was at risk of death, not where the event hypothetically could have caused death.

Grade 5: Death related to AE.

These grades help us to differentiate between adverse events and serious adverse events.

Adverse events in homeopathy and homeopathic aggravations

Homeopathic remedies are known mostly to be highly diluted products. They are therefore normally considered to be safe (Bornhöft et al. 2006) and not to represent a risk of toxicological effects or interactions with conventional drugs (Woodward 2005). Nevertheless, adverse events following homeopathic treatment have been reported by various authors (e.g. Dantas & Rampes 2000, Grabia & Ernst 2003, Haidvogl et al. 2007). These adverse events have been characterised as transient and mild (Dantas & Rampes 2000) or mild to moderate (Grabia & Ernst 2003). No observational studies or clinical trials have reported serious adverse events (ECCH 2009). Dantas & Rampes (2000) found that adverse events were most commonly: headaches, tiredness, skin eruptions, dizziness, bowel dysfunctions such as diarrhoea or loose stools, and aggravations of patients' pre-existing symptoms. More recently adverse events after homeopathic medicines have been reported in patients with mental health problems (Pilkington et al. 2005, 2006). However, these adverse events were not serious and did not result in withdrawal from treatment.

Aggravations of patients' pre-existing symptoms are commonly referred to as 'homeopathic aggravations' in the homeopathy literature. They involve a temporary worsening of patients' already existing symptoms and occur relatively soon after taking a homeopathic medicine (Thompson et al. 2004). These temporary reactions are normally considered favourable and part of patients' curative process (Endrizzi et al. 2005, Thompson et al. 2004).

What should homeopaths in the DEPSY project do?

The main reason for reporting adverse events in the DEPSY project is to ensure patients' safety. It is therefore important that homeopaths check for adverse events at each consultation and report any changes in patients which might be considered to be serious adverse reactions (regardless of whether or not the adverse event is viewed by the homeopath as a potentially curative 'homeopathic

aggravation'). Homeopaths should report any event which would satisfy at least the grade 3 criteria as defined in the CTCAE guidelines. This would include:

- any severe or medically significant reactions, even though they may not be life-threatening
- reactions resulting in hospitalisation or prolongation of hospitalisation
- reactions limiting patients ability for self-care, including daily living activities such as bathing, dressing and undressing, feeding themself, using the toilet, taking medications

Homeopaths should also report any development into level 3 – Moderate to severe, or more, as defined in the DEPSY Risk Guidelines.

When in doubt, homeopaths should contact the management team (see emails below). The DEPSY Management Team will then determine what should be done, including the need to report the event to the Head of the School of Health and Related Research (ScHARR), the sponsor (University of Sheffield), the DEPSY Steering Committee and the and the Regional Ethics Committee; and whether there is a need to contact the patient and/or her/his GP.

Adverse events should be reported using the Adverse Event & Risk form included in the DEPSY Risk Guidelines. The form should be completed within 24 hours of the event and should be emailed to the Chief Investigator, Petter Viksveen at p.viksveen@sheffield.ac.uk and Dr Clare Relton at c.relton@sheffield.ac.uk (PLEASE EMAIL **BOTH**).

What should the DEPSY Management Team do?

The Management Team will receive reports from homeopaths and patients about adverse events. The Management Team will report to the Head of the School of Health and Related Research (ScHARR) at the University of Sheffield within 1-5 days (depending on severity) of the occurrence of the event. They will **report serious adverse events (SAE) within 48 hours to the Head of the School of Health and Related Research (ScHARR), the sponsor (University of Sheffield), the DEPSY Steering Committee and the and the Regional Ethics Committee; and when needed the patient and/or her/his GP.**

The Management Team will complete the University of Sheffield Adverse Event Report Form and will in line with the Standard Operating Procedure developed by the Clinical Trials Research Unit (CTRU) at the University of Sheffield (2012) include their assessment of the seriousness, frequency and intensity of the Adverse Event; concomitant treatment; the assessed relationship to treatment by homeopath; any actions taken and the outcome. **When in doubt, the Management Team will discuss the issue with the Head of the School of Health and Related Research (ScHARR).**

Seriousness: Death; life threatening; inpatient hospitalisation; prolonged hospitalisation; persistent or significant disability/incapacity; congenital abnormality/birth defect.

Frequency: Isolated; intermittent; continuous; unknown.

Intensity: Mild; moderate; severe.

Concomitant treatment: Any treatment other than the treatment provided by the homeopath.

Assessed relationship to treatment by homeopath: Definite; probable; possible; unlikely; unrelated; not assessable.

Action taken: None; reduce dose; treatment withdrawn; specific treatment; other.

Outcome: Recovered; improved; unchanged; deterioration; persisted; death.

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Appendix 12. How to identify and deal with clinical risk issues: Guidelines for homeopaths providing treatment in the DEPSY project.

How to identify and deal with clinical risk issues: Guidelines for homeopaths providing treatment in the DEPSY project (version 7, 16.02.2013)

Introduction

This document has been developed for homeopaths who treat patients included in the pragmatic cohort randomized controlled trial of the clinical and cost effectiveness of treatment of depression by homeopaths (DEPSY) project at the School of Health and Related Research (ScHARR), University of Sheffield, and which is embedded in the South Yorkshire Cohort (SYC). The aim of the project is to assess the acceptability and comparative clinical and cost effectiveness of adjunctive treatment provided by homeopaths in addition to usual care for patients who have self-reported depression (DEPSY). A random selection of patients in the South Yorkshire Cohort (SYC) will be offered treatment by homeopaths.

This document is mainly based on the clinical risk protocol developed by Sheffield Mind (2011, undated), and supplemented by the guidelines for management of depression developed by the National Collaborating Centre for Mental Health (NCCMH 2006). It includes issues that have been considered particularly important for homeopaths in the DEPSY project. Practitioners are encouraged to read the full Sheffield Mind and NCCMH guidelines. These documents will be provided by the Chief Investigator.

A special thanks to Sheffield Mind for permission to use their documents for this project.

Confidentiality

- Take the patient's wishes into consideration, but make aware that if the concern is serious enough it may be necessary to breach confidentiality
- Discuss limits of confidentiality at the start of treatment and again when dealing with a risk issue
- Make decisions regarding breaching confidentiality after discussion with your supervisor and/or the Chief Investigator of the research project

Your competency

- Work within the limits of your competency
- Work according to a recognised and enforceable code of ethics developed by your professional organisation
- Make sure you have regular supervision, depending on your need and level of experience

Monitoring and measuring the level and urgency of risk

Ask patients directly about their mental health, in order to identify any potential risk factors. When communicating with patients, make sure you use everyday language so that your patients understand.

When a risk issue is identified or there is a perceived change in the level of a known risk:

- Engage with the patient and explore risk with the patient
- Be willing to explore the patient's feelings and introduce the idea that positive change is possible
- Know where to find information that will help you and the patient make decisions about risk
- Share anonymised information with your supervisor and/or the project Chief Investigator
- Record fully and accurately the issue and action taken, using a clinical risk assessment form (Appendix A) with dates, times, people involved, actions taken, and outcomes of actions
- Provide regular reports to the Chief Investigator, who will forward it to the Steering Committee and the Project Team to monitor levels and frequency of risk situations and plan accordingly

What is clinical risk?

Clinical risk is the possibility of something negative happening as a direct result of the behaviour of a patient or people in their surroundings. It includes information received from or about a person that may have a negative impact on the patient or anyone the patient is in contact with.

Risk means situations and circumstances that could result in:

- Suicide
- Significant self-harm
- A person being harmed by others
- A person causing harm to others
- A significant deterioration in a person's mental health

Harm can be physical or emotional/psychological.

Warning signs

The following may be possible indications of risk:

- Suicidal ideation
- Evidence of starting to self-harm or increase in existing self-harming behaviour
- Patients reporting violence or threats of violence from others
- Patients reporting that they want to or do cause harm to others
- Situations disclosed that suggest children or vulnerable adults may be at risk
- Sudden changes in behaviour (especially in response to life challenges or therapy)
- Beginning or increasing substance misuse (including alcohol and tobacco)
- Erratic attendance for treatment
- Increase in negative behaviours
- Changes in sleeping/eating patterns
- Becoming increasingly isolated
- Patients on the edge of collapse/at risk to self
- Patients who are unresponsive in therapy
- Patients stopping prescribed medication
- Unexpected improvement, sudden or spontaneous recovery of depressed mood
- Failure to improve

Patients at risk and factors that may increase the level of risk

Consider patients' individual histories, including any medical, family and psychosocial issues. Assess:

- The presence or absence of any protective factors
- What the patient is saying and how this fits with known risk factors
- Expressed or documented concerns from significant others, and your supervisor's or the project Chief Investigator's assessment

Even when patients are not known to be high risk, situations can occur and/or develop which increase the level of risk.

Patient risk factors

- Suicidal ideation or previous suicide attempts
- Self-harm or history of self-harming
- History of violence and/or aggression from or towards others
- Psychiatric diagnosis and symptoms, severe enduring mental health problems (e.g. depression, eating disorders) and long term physical ill health
- Depth of depressive feelings, inability to resist negative thoughts
- Hopelessness about the present and future, sense of helplessness in a crisis
- Lack of confidence and low self-esteem
- Isolation, self-neglect
- Lack of coping/problem solving skills
- Inability to resist attempts at exploitation
- Impulsiveness, past and/or current high risk behaviours
- Unsettled and/or chaotic lifestyles
- Increase in aggressive behaviour/anger management problems
- Difficulties in establishing and maintaining meaningful relationships with others
- Misuse of drugs and/or alcohol

Contextual factors

- Family history
- Being in a high risk group (i.e. demographics, age, gender, occupation)
- Vulnerable adults
- History of difficult relationships with a vulnerable adult or child
- History of violence and/or aggression from others or towards others
- Moving into an abusive/exploitative relationship
- Lack of social support or the unwillingness/inability to use support networks
- Lack of stability in personal circumstances (family, job, accommodation)
- Changes in circumstance (relationship crisis, loss of job/home/role/a loved one, recent discharge from hospital or release from prison)
- Increases in external pressures (stress, bullying, debt, work pressures)

Clinical assessment tool

Level 1: Mild

Assessment criteria:
- Reactive depression with no past history
- Possible use of anti-depressants
- Relationship breakdown with no significant history
- Coming to term with life changes
- Symptoms might be amenable to cognitive work

Risk: No significant risk issues.

Level 2: Mild, moderate to severe

Assessment criteria:
Any criteria from level 1 plus:
- Likely use of anti-depressants
- Current relationship difficulties
- Recent life change that is causing fundamental review of life direction
- Family difficulties in the past, but patient currently has some supportive relationships

Risk: Possible risk issues in the past but no longer current.

Level 3: Moderate to severe

Assessment criteria:
Any criteria from level 1 & 2 plus:
- Moderate levels of risk requiring active monitoring and management
- Longer term mental health difficulties such as depression, anxiety, panic disorder
- Likely to have had previous hospital admissions
- History of sexual abuse or family violence
- Current serious relationship problems
- Relational difficulties with self/others due to early experience, but some support in community
- Possible eating difficulties
- Likely involvement of other agencies
- Aged under 19

Risk: Possible self-harm/suicide ideation but engaged with sense of containment. **Suggest patient could also be seen by her/his General Practitioner (GP).**

Level 4: Severe

Assessment criteria:
Any criteria from previous levels plus:
- Likely suicide ideation and previous attempts on life
- Likely history of self-harm
- Long term severe mental illness
- Serious health problems of possible psychosomatic origin
- Some psychosis if stabilised and managed
- More serious neglect or abuse in childhood
- Less support within and/or poor functioning in the community
- Possible child protection issues
- Other agencies involved but poor engagement likely

Risk: Possible self-harm/suicide ideation but willing to address this with the practitioner. **The patient should also be seen by her/his General Practitioner (GP) and/or a mental health specialist.**

Level 5: Severe – possible inpatient/crisis team

Assessment criteria:
Any of the previous criteria plus:

- Significant risk issues
- Serious suicide attempts
- Long term self-harm
- Dissociation
- Complex eating disorder
- Possible diagnosis of personality disorder
- Serious attachment difficulties
- Several hospitalisations

Risk: Urgent concern about risk of self-harm/suicide or harm to others. **The patient should be seen by her/his General Practitioner (GP) and/or a mental health specialist, and possibly be treated by a crisis team.**

Procedures for managing clinical risk

Consider if patients in risk have adequate social support and whether they know who to contact in case their condition deteriorates. Contact patients who do not attend follow-up consultations. Respect patients' decision in case they choose to withdraw from the study, but make an effort to check if their mental state of health has deteriorated and, if necessary, recommend them to contact their General Practitioner (GP) and/or Mental Health Team.

Severe and/or urgent risk

Risk issues in one-to-one consultations rarely need immediate action.
However, if during a consultation patients attempt to harm themselves or the therapist:

- Press the panic button (if there is one in the room, check this beforehand)
- Stay calm and reassuring
- Express concern clearly and use the time to gather as much information as possible
- Determine the urgency of the situation and discuss how to proceed
- Involve another practitioner if needed
- Make a judgement, together with the patient if possible, about whether they are safe to leave
- Make referral to another service such as the GP or Community Mental Health Team if needed
- If the patient is not safe to leave the building alone, seek permission from her/him to contact a relative, friend and/or the appropriate agency
- If all other avenues have been explored, call an ambulance
- If in doubt, dissuade the patient from leaving the building alone
- If the patient insists on leaving and there is sufficient concern about their safety, contact the police
- If the event takes place over email or telephone: Obtain as much detail as possible, in particular name and contact details, where the person is at that moment, contact persons, GP/healthcare practitioner details; and offer to talk to them or recommend someone who they may contact

To learn more about emergencies, become familiar with http://www.sheffieldmentalhealth.org.uk

High level of risk, but less urgent

- Gather as much information about the situation as possible
- Monitor all ongoing risk issues regularly and carefully
- Consider involving other agencies, GP, etc.
- Pay attention to the patient's wishes, the confidentiality and information sharing policies
- Inform the Chief Investigator of all ongoing risk issues
- Share information with relevant others when appropriate, and with the patient's permission

Who you may contact

For any issues that arise during and outside consultations, consider discussing these with your personal supervisor. You should make arrangements for supervision according to your own needs throughout the project. You have the responsibility to organise and finance this yourself. Treatment of patients should only start once such an arrangement has been made. Please inform the Chief Investigator once you have identified a supervisor.

General questions on safety or other questions related to the research project: Contact the Chief Investigator: Petter Viksveen, at p.viksveen@sheffield.ac.uk or tel. 0114 222 0796 or + 47 51 11 32 15.

Clinical risk issues

- If **not urgent**: Contact the Chief Investigator, who will either answer your question or recommend an appropriate person you may contact: Petter Viksveen, at p.viksveen@sheffield.ac.uk or tel. 0114 222 0796 or + 47 51 11 32 15.

- In case of **severe risk** or **urgent matters**: Contact the **Manager or another person at the clinic** where consultations are being carried out AND the **Chief Investigator** (CI) of the project: Petter Viksveen, at p.viksveen@sheffield.ac.uk or + 47 51 11 32 15 **AND** Dr Clare Relton c.relton@sheffield.ac.uk or tel. 0114 222 0796. (For further details on reporting of adverse events and risks, see Appendix A). In case you are unable to reach Petter Viksveen or Dr Clare Relton, contact the administrator at ScHARR (same phone number 0114 222 0796).

- In case **immediate help** is needed: Call **another practitioner or person at the clinic** for assistance and/or call **emergency/ambulance services** and/or **police** at **999** or **112**, as appropriate.

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Appendix A: Adverse Event & Risk form for DEPSY

An adverse event is an unfavourable event that includes, but is broader than, unintended errors and mistakes which arise as a result of research activity and result in one or more research participants having symptoms or being cause physical or psychological harm or serious distress. For further information – refer to the DEPSY Adverse Events Guidelines.

Please complete this form within 24 hours of the event occurring and email it to Chief Investigator Petter Viksveen at p.viksveen@sheffield.ac.uk **AND to Dr Clare Relton at** c.relton@sheffield.ac.uk **They need to report it to the Head of the School of Health and Related Research (ScHARR) at the University of Sheffield within 1-5 days (depending on severity) of the occurrence of the event. They will report serious adverse events (SAE) within 48 hours to the sponsor (Head of Operations Section, University of Sheffield), the Chair of the Steering Committee of the DEPSY project and the Regional Ethics Committee (REC). They will also report SAE to the patient's GP.**

Date:
Homeopath's name and contact details:
Patient's name, date of birth and contact details:
Patient's GP name and contact details:
Details: When did the event take place? Where did the event take place? What happened and what was the impact of the event? Do you have any thoughts on why the event occurred?
Action taken:
Follow up required (incl. any action(s) taken or planned to limit the risk of an event re-occurring):

Appendix 13. Interview guide I 120620 rev 121017

Project title (abbreviated): Depression in South Yorkshire (DEPSY)
Principal investigator: Petter Viksveen, Postgraduate Research Student, ScHARR, University of Sheffield. p.viksveen@sheffield.ac.uk
Aim: To explore the positive and negative experiences with homeopathic treatment in patients who have taken or who are taking antidepressant drugs.
Qualitative interview method: Semi-structured face-to-face interviews after 1st consultation + after a minimum of 2 follow-up consultations and 6 months.
Time: 2012 – 2013

INTERVIEW GUIDE I (1st interview) (version 2, date 20.06.2012)

Introduction: This is the guide for the first out of two interviews to be carried out as part of this project. The first interview will be carried out after patients have had their first consultation with a homeopath. Interviews will aim at lasting 30-60 minutes, including time for welcoming and closing the interview, but timeframes will be flexible. The length of the interview will be audio-recorded.

Introduction of interview to participants:
- Welcome participant and explain the purpose of the interview, which is to learn from the participant's experience with homeopathic treatment.
- Explain to the participant why and how she/he was chosen.
- Explain the procedure of the interview, including the use of audio-recording equipment.
- Inform the participant of ethical issues, including anonymity and confidentiality (who will have access to data and assure that the final results will not contain any information that may identify the participant), and the right to withdraw from the project at any given time, until the data have been analysed.
- Ask the participant if she/he has any questions, before the start of the interview.
- PI introduces himself, including his name, University affiliation and role in project.
- Check the participant's name and contact details.
- Ask the participant to sign the consent form.

Semi-structured interview:
- Invite the participant to tell about her/his experience (in general). Stay open to issues she/he may raise (e.g. general experiences of her/his depression), let her/him 'tell her/his story'.
- As much as possible pose open-ended questions (as opposed to closed and leading questions), include 'what' and 'how' questions, and avoid 'why' questions.
- Probe arising issues to understand them in depth.
- Actively listen by confirming understanding of the participants' responses, incl. feeding back the interviewer's understanding to allow the participant to confirm, adjust or correct.
- As much as possible use participants' own words and give time and room to reflect to allow for her/him to make 'new discoveries'.
- Pay attention to arising conflicting issues and aim to clarify and sort them out.
- Redirect the interview in case responses are not relevant.
- Interviewer should stay friendly, interested and neutral (no approval or disapproval).
- Questions posed to participants during the first interview may include:
  - What was your experience during and after the first consultation?
  - In which way was this similar or different to other treatment you have previously received?

    - What was your experience when you took the homeopathic medicine?
    - In which way was this similar or different to when you take antidepressant drugs?
- Follow-up questions will be kept as open as possible, such as:
    - Can you tell me more about …?
    - Can you give a more detailed description of …?
    - Do you have any examples of …?

Closing of interview:
- As the end of the interview approaches, the interviewer will ask
    - If there are any other issues the participant would like to mention.
    - If the participant has any question with regards to the interview.
    - If they have any comments with regards to the experience of the interview.

The participant's travel expenses will be reimbursed, based on average public transportation costs. Participants sign for reimbursed expenses.

Questions posed to participants during the second interview may include:
- How has your health developed over the past months?
- What was your experience with homeopathic treatment?
- In which way was this similar or different to your experiences with other forms of treatment that you have received?
- What was your experience when taking homeopathic medicines?
- In which way was this similar or different to when you take antidepressant drugs?
- How do you evaluate whether your homeopathic treatment is working?
- How do you think it's working? Extend this section. How do they hold different views of depression and treatment in their head?
- Views of risks of treatment, conventional and homeopathic
- Ask which drugs they were on, what treatment have they had
- How do people reflect on how they choose treatment?
- Open with general question about their depression
- Questions on consultation
- What do they know about homeopathy? How do they assess existing 'evidence'… The debate about homeopathy … There is a lot of debate these days about whether homeopathy works or not. What do you think about this? Did you check any information/sources before you went for treatment?

Patients' responses may be followed up by additional probing questions, as considered appropriate by the interviewer, in order to obtain as clear and detailed understanding of patients' thoughts, views, feelings and experiences, as possible. Follow-up questions will be kept as open as possible and will therefore primarily be along the following lines:
- Can you tell me more about …?
- Can you give a more detailed description of …?
- Do you have any examples of …?

Appendix 14. Interview guide II 120620

Project title (abbreviated): Depression in South Yorkshire (DEPSY)
Principal investigator: Petter Viksveen, Postgraduate Research Student, ScHARR, University of Sheffield. p.viksveen@sheffield.ac.uk
Aim: To explore the positive and negative experiences with homeopathic treatment in patients who have taken or who are taking antidepressant drugs.
Qualitative interview method: Semi-structured face-to-face interviews after 1st consultation + after a minimum of 2 follow-up consultations and 6 months.
Time: 2012 – 2013

INTERVIEW GUIDE II (2nd interview) (version 2, date 20.06.2012)

Introduction: This is the guide for the second out of two interviews to be carried out as part of this project. The second interview will be carried out after patients have had a minimum of two follow-up consultations with a homeopath, a minimum of 6 months after their first consultation. Interviews will aim at lasting 30-60 minutes, including time for welcoming and closing the interview, but timeframes will be flexible. The length of the interview will be audio-recorded.

Introduction of interview to participants:
- Welcome participant and explain the purpose of the interview, which is to learn from the participant's long-term experience with homeopathic treatment.
- Explain to the participant why and how she/he was chosen.
- Explain the procedure of the interview, including the use of audio-recording equipment.
- Inform the participant of ethical issues, including anonymity and confidentiality (who will have access to data and assure that the final results will not contain any information that may identify the participant), and the right to withdraw from the project at any given time, until the data have been analysed.
- Ask the participant if she/he has any questions, before the start of the interview.
- PI introduces himself, including his name, University affiliation and role in project.
- Check the participant's name and contact details.
- Ask the participant to sign the consent form.

Semi-structured interview:
- Invite the participant to tell about her/his experience (in general). Stay open to issues she/he may raise (e.g. general experiences of her/his depression), let her/him 'tell her/his story'.
- As much as possible pose open-ended questions (as opposed to closed and leading questions), include 'what' and 'how' questions, and avoid 'why' questions.
- Probe arising issues to understand them in depth.
- Actively listen by confirming understanding of the participants' responses, incl. feeding back the interviewer's understanding to allow the participant to confirm, adjust or correct.
- As much as possible use participants' own words and give time and room to reflect to allow for her/him to make 'new discoveries'.
- Pay attention to arising conflicting issues and aim to clarify and sort them out.
- Redirect the interview in case responses are not relevant.
- Interviewer should stay friendly, interested and neutral (no approval or disapproval).
- Questions posed to participants during the second interview may include:
  - How has your health developed over the past months?
  - How has your mood been?

- What is your experience with homeopathic treatment?
- In which way was this similar or different to your experiences with other forms of treatment that you have received?
- What is your experience with the homeopathic consultation?
- In which way was this similar or different to other treatment you've received?
- What is your experience with taking homeopathic medicines?
- In which way was this similar or different to when you take antidepressant drugs?
- If you have experienced any changes, how do you think it works?
- In which way do you think this is similar or different to how antidepressant drugs work?
- Do you see any risks involved with homeopathic treatment?
- Do you see any risks involved with antidepressant treatment?
- What kind of antidepressant drugs have you been taking?

- Follow-up questions will be kept as open as possible, such as:
  - Can you tell me more about …?
  - Can you give a more detailed description of …?
  - Do you have any examples of …?

Closing of interview:

- As the end of the interview approaches, the interviewer will ask
  - If there are any other issues the participant would like to mention.
  - If the participant has any question with regards to the interview.
  - If they have any comments with regards to the experience of the interview.

The participant's travel expenses will be reimbursed, based on average public transportation costs. Participants sign for reimbursed expenses.

Appendix 15. Letter to patients – Invitation for qualitative interviews

The University Of Sheffield.

School Of Health And Related Research.

Letter to patients – Invitation for qualitative interviews (version 9, date 03.07.2012)

Date:

Dear Mr., Mrs., Ms.

You are one of over a hundred people who received treatment by a homeopath. We would be interested in learning more about your experiences. We are therefore inviting you to participate in an interview with a researcher at the University of Sheffield. What we learn will help us understand how we can improve the health of people living in South Yorkshire. It is up to you to choose whether you want to take part in this interview. Before you decide, please take time to read the following information carefully.

During the interview we will particularly focus on your health and your experiences with homeopathic treatment. You will be free to choose how to respond to questions. The interview will last from 30 to 60 minutes and will be audio-recorded. All information you provide will be kept strictly confidential and your answers will be made anonymous. It will only be used for research purposes. The data will be kept for 5 years or until the end of the South Yorkshire Cohort study. You can withdraw from this study at any time in the future. The results of this research will be published in a health science journal and in a PhD report at the University of Sheffield. If you would like, we will give you a report of the findings of the study

Your transportation expenses will be refunded.

If you choose to accept the offer, then please sign the attached consent form. You will be contacted by telephone by a researcher to hear if you want to participate. You can then also ask any questions you may have.

If you have any queries or require further information about this study please contact Petter Viksveen or Dr. Clare Relton at: ScHARR, University of Sheffield, FREEPOST – SF1314, Sheffield, S1 1AY. Tel: 0114 222 0796. Email: p.viksveen@sheffield.ac.uk

Thank you.

Yours sincerely
Dr. Clare Relton and Petter Viksveen
Researchers at the University of Sheffield

Appendix 16. Consent form

The University Of Sheffield.

School Of Health And Related Research.

Consent Form (version 1, date 26.06.2012)

Centre number:	(to be filled in by researcher)
Study number:	(to be filled in by researcher)
Participant Identification Number:	(to be filled in by researcher)

1. I hereby confirm that I have read and understand the information in the "Letter to patients – Invitation for qualitative interviews" and have been given the opportunity to ask researchers at the University of Sheffield any questions I may have.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason.

3. I understand that the information I provide will be treated confidentially and will only be looked at by the researchers involved in this project.

_____	_____	_____
Your name (capital letters)	Your signature	Date

Please return the signed consent form to: Petter Viksveen at: ScHARR, University of Sheffield, FREEPOST – SF1314, Sheffield, S1 1AY.

Appendix 17. Health & Human-Interventional Studies Research Governance Committee, Report on the visit to ScHARR to discuss the DEPSY clinical trial

Health & Human-Interventional Studies Research Governance Committee

Report on the visit to ScHARR to discuss the DEPSY clinical trial (16th January 2013)

To:
Mr Petter Viksveen (Principal Investigator)
Dr Clare Relton (1st Supervisor)
Professor Jon Nicholl (Head of Department and 2nd Supervisor)
cc.
Dr Cindy Cooper, Chair of the University's Health & Human-Interventional Studies Research Governance Committee
Professor Martin Thornhill, member of the University's Health & Human-Interventional Studies Research Governance Committee

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1. Preliminary statement

On 16th January 2013, Dr Cooper and Professor Thornhill from the University's Health & Human-Interventional Studies Research Governance Committee and the Committee's Secretary (Miss Nicola Donkin) (referred to as the QA (quality assurance) team), met with Mr Petter Viksveen, Dr Relton and Professor Jon Nicholl (present for the summarising section only) in order to discuss 'A pragmatic cohort randomized controlled trial of the clinical and cost effectiveness of treatment of depression by homeopaths (DEPSY)'. The DEPSY trial has been classed as potentially medium risk according to its risk assessment.

The meeting aimed to quality assure DEPSY's quality control systems in order that the University can be reasonable confident that DEPSY will comply with its protocol and will safeguard the dignity, rights, safety and well-being of the participants.

2. Format of the visit

The QA team asked the DEPSY team a series of questions relating to the following seven areas:

a) Governance arrangements (strategic)
b) Appropriately qualified staff and researchers
c) Day-to-day management arrangements (operational)
d) Protocol compliance
e) Dignity, rights, safety and well-being of the participants
f) Data integrity and record-keeping
g) Procedure in place should a participant make a complaint about the trial

A summary of the discussion relating to each of the areas is outlined below, followed by a list of the recommendations made by the QA team for the DEPSY clinical trial.

a) Governance arrangements (strategic)
It was confirmed that the trial had a Steering Committee (SC) consisting of: Professor Simon Gilbody (Chair), Professor Paul Bissell, Professor Stephen Walters, Dr Clare Relton, Bridget Strong (Sheffield Mind), user representative Mrs Carmen Calvo-Rodriguez and Petter Viksveen (PI). The QA team noted that this was satisfactory but that they must ensure that the Steering Committee remains independent and cannot be outnumbered by the Management Group members. There must be a minimum of three independent people on the SC, including at least one lay member and two academics. It was confirmed that the SC had not yet met but that a meeting will now take place. The QA team noted that the SC must ratify the protocol at its first meeting, and in advance of any

participant recruitment taking place. Formal Terms of Reference for the SC should also be agreed at its first meeting.

The Management Committee consists of Dr Clare Relton (1st supervisor), Professor Paul Bissell (advisor) and Mr Petter Viksveen (PI). They have not met formally but have been taking notes of the supervision meetings. The QA team recommended that more formal minutes are taken of such meetings. It was confirmed that Professor Jon Nicholl (Head of ScHARR) had recently taken on the role of 2nd supervisor.

The protocol states (p. 12) that research governance approval will be sought from Sheffield PCT. The DEPSY team confirmed that it will now be sought from Barnsley PCT. Mr Viksveen is currently in the process of obtaining an NHS Research Passport.

The DEPSY team confirmed that there is a £129K budget for the research project which includes funding the PI's study costs. The European Central Council of Homeopaths (ECCH) has agreed that their Treasurer will monitor the budgets (ECCH only made a small donation to the project funds). The DEPSY team confirmed that homeopaths would be paid according to the number of participants that they treat; the payment is coming from the trial's funds rather than a central university account so there are no university contracts involved. Agreement regarding payment is set out in the letter between the PI and the homeopaths. The QA team queried whether the letter would be legally binding if any disputes arose. The DEPSY team stated that if homeopaths did not deliver then they would not be paid and that they did have a back-up list of homeopaths to contact.

b) Appropriately qualified staff and researchers

The QA team reviewed the Delegation of Duties Log. It was recommended that there is clarification regarding to whom the particular roles may be delegated, and that this is approved by the supervisory team. As the project is recruiting via the South Yorkshire Cohort (SYC) the level of involvement with the Clinical Trials Research Unit must also be agreed.

The DEPSY team confirmed that all homeopathy consultations will take place in GP Practices; to date, four GP Practices have agreed to participate and the DEPSY team now plan to ask all 40 SYC GP Practices. Participants will be able to choose which Practice to attend and GPs will be kept informed of their patient's participation.

The homeopaths will be providing the package of care and will therefore be responsible for reporting adverse events (not the GPs). The DEPSY team confirmed that all homeopaths would be attending a half-day training session run by Sheffield Mind which would provide information on the protocol and guidance on reporting adverse events. Each homeopath will also be provided with an adverse event reporting form. The QA team recommended that the definition of an 'adverse event' be considered as it currently states events are 'unexpected' but in reality some may be anticipated. It is very important that it is made clear to homeopaths in the training exactly what should be reported, and that this is included in written guidelines to ensure clarity. There must then be a clear procedure for deciding which adverse events are serious and potentially linked to the intervention, and how these are dealt with. There should be two named people on the adverse event form in case of absence of the PI. The QA team recommended that homeopaths check at each consultation if there have been any adverse events and that this check is documented. All homeopaths should receive the training on the protocol and guidance on risk/adverse events before participating in the project.

The DEPSY team confirmed that the practice of homeopathy is not controlled by any statutory regulation but that they have checked that all participating homeopaths are registered with The Society of Homeopaths. The QA team recommended that their registration be checked annually.

c) Day-to-day management arrangements (operational)

The DEPSY team confirmed that key decisions (such as protocol changes) would be recorded in the minutes of supervisory meetings and in reports to the Steering Committee. It was confirmed that Dr Relton would act on anything requiring attention in Mr Viksveen's absence.

Regular meetings will be held in order to ensure that homeopaths understand their responsibilities and remain up-to-date with the project. The QA team noted that these would be very useful for monitoring and an opportunity to remind the homeopaths of any changes to protocol. The QA team agreed with Dr Relton's suggestions that the homeopaths be paid a nominal fee (in the region of £10–20) for attending these meetings to ensure commitment.

d) Protocol compliance

The DEPSY team confirmed that any substantial amendments would be submitted to the NHS REC; it would be up to the sponsor to decide if the amendment was minor or substantial. Any amendments to the protocol will be circulated to the homeopaths by email; the QA team recommended that confirmation of receipt and understanding of the changes be received in writing.

If any deviation is made from the protocol then this will be recorded by the homeopath. Due to the methodology of the project, if a participant withdraws from care then they are not withdrawing from the trial; they will still receive the questionnaire as these are not provided by the homeopaths.

e) Dignity, rights, safety and well-being of the participants

The DEPSY team will send an initial questionnaire and use the responses to decide if participants are eligible based upon inclusion/exclusion criteria. The DEPSY team will also review SYC patient notes to provide an extra check in case participants don't report certain conditions on their questionnaire. The risk assessment which will be provided by homeopaths will provide an additional checkpoint. If a participant does give cause for concern, either via questionnaire responses or interactions with the homeopath, there must be clear procedures for managing the risk (e.g. referral to/alerting the GP).

Mr Viksveen confirmed that he has a great deal of experience of interacting with mental health patients so is confident in dealing with any issues that may arise during the qualitative interviews.

The DEPSY team will keep copies of all informed consent documentation to ensure this has been provided by every participants.

f) Data integrity and record-keeping

To ensure patient confidentiality all records will be kept on a university password-protected computer or within a locked filing cabinet. The homeopaths are bound by the confidentiality and data protection policy of The Society of Homeopaths; the QA team recommended that they are reminded of this policy.

g) Procedure in place should a participant make a complaint about the trial

The information on the procedure for a participant to make a complaint about the trial is not currently on the participant information sheet; the QA team stressed that this must be added. It should also be made clear that adverse events can be reported directly to the DEPSY team.

List of recommendations

i. The Steering Committee must always include at least three independent members who consist of at least two academic members and at least one lay member.
ii. The Steering Committee must meet before participant recruitment begins. At the meeting the protocol must be ratified and formal Terms of Reference agreed.
iii. Formal minutes of all supervision meetings should be made, as these are essentially meetings of the Management Committee.
iv. The protocol should be kept up-to-date to ensure it reflects all changes made to the project.
v. It should be agreed with the supervisory team to whom the duties listed on the Delegation of Duties Log may be delegated.

vi. The management of data relating to South Yorkshire Cohort participants must be agreed with the Clinical Trials Research Unit.

vii. All homeopaths must be provided with clear guidance on the protocol to ensure that they adhere to it.

viii. The training for homeopaths must clearly outline adverse event reporting, and there must be two named contacts for reporting in case of absence. Homeopaths should check at each consultation if there have been any adverse events and should document this check.

ix. There must also be clear procedures for deciding what constitutes a serious adverse event and for dealing with such events. This should be added to the protocol.

x. The registration of participating homeopaths to The Society of Homeopaths should be checked annually.

xi. Records of key decisions must always be made.

xii. The team should consider whether to pay homeopaths a nominal fee for attending regular 'catch-up' meetings.

xiii. Confirmation of receipt and understanding of protocol amendments should be obtained from the homeopaths in writing.

xiv. Homeopaths should be reminded of the need to abide by the confidentiality and data protection policy of The Society of Homeopaths.

xv. The procedure for a participant to make a complaint about the clinical trial must be added to the participant information sheet. It should also be noted how participants can directly report adverse events.

xvi. If a participant does give cause for concern, either via the questionnaire or through interaction with the homeopath, there must be a clear procedure for managing the risk (e.g. referral to/alerting the GP).

xvii. The above-noted procedures should be set up as Standard Operating Procedures which are separate to the protocol.

It was agreed that the above recommendations will be implemented before participant recruitment begins. The responsibility for ensuring these are undertaken before participant recruitment is delegated to Professor Jon Nicholl, as Head of School.