The cohort multiple randomized controlled trial design (cmRCT)

Commentary

CEB Journal Club

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Scope

- Two example articles
- Feasibility of using cmRCT for evaluating treatment in low back pain
  - Study Design
  - Comments
- Using cmRCT for studing depressed patients treated by homeopaths
  - Study Design
  - Comments

1 Feasibility of using cmRCT for evaluating treatment in low back pain

Study Design

Comments

ELSEVIER

Journal of Clinical Epidemiology ■ (2014) ■

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Randomized cohort trial was shown to be feasible for evaluating treatments in low back pain

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Study design

Objective:

To investigate the feasibility of conducting a cohort, factorial randomized controlled trial (RCT) in the treatment of patients with low back pain (LBP)

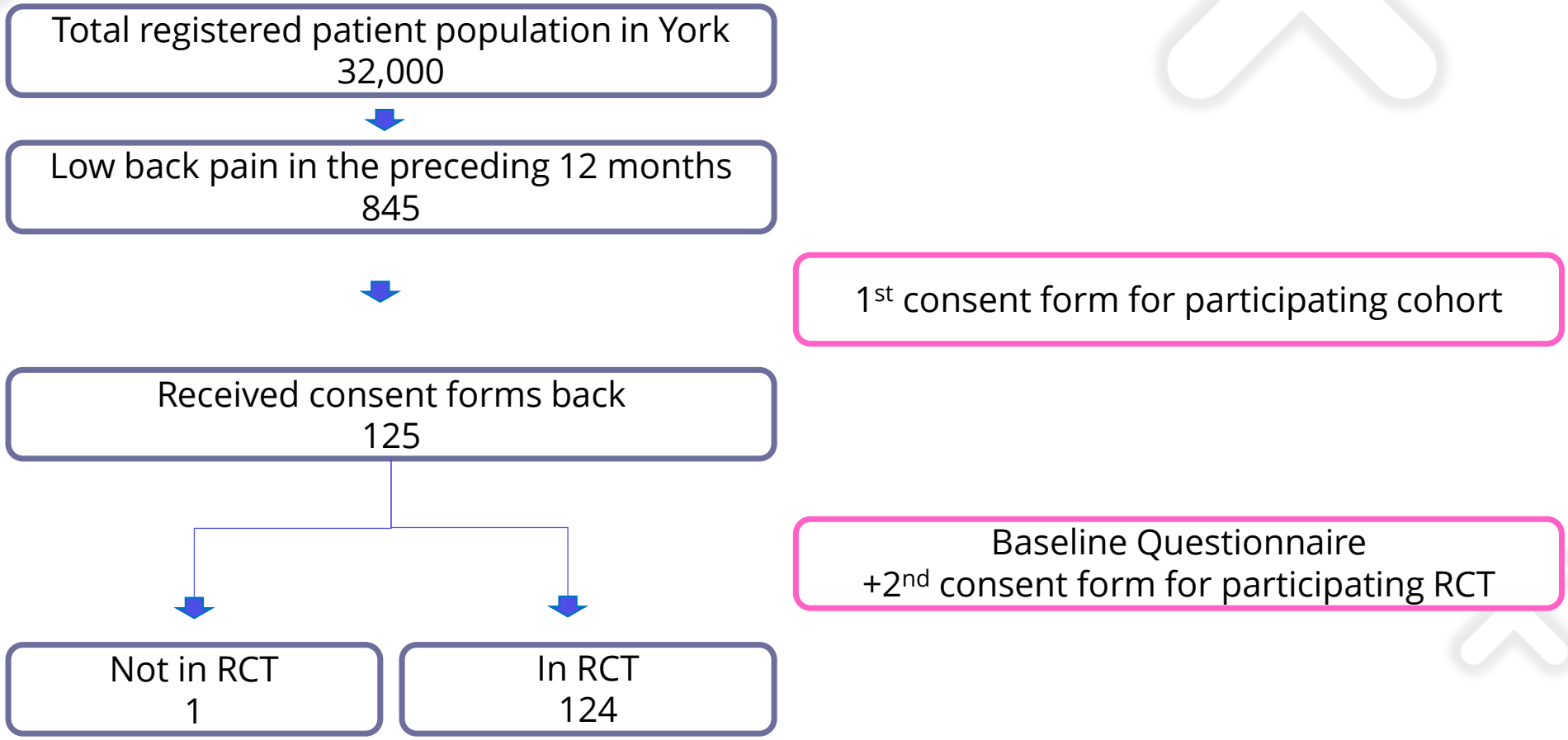
Study design and setting:

Pragmatic feasibility factorial RCT nested within an observational cohort study in two general practices in York, United Kingdom.

Study design of RCT

- **Intervention:**
  - Usual care
  - Usual care + the trial treatment
    - Acupuncture
    - Manual therapy: ex. Spinal mobilization, massage etc.
    - Combined
- **Outcome measurement:**
  - Primary: Roland Morris Disability Questionnaire (RMDQ)
  - Secondary: The Modified Oswestry Disability Index Questionnaire
  - Time: 3 months after randomization
- **Statistical Analysis (main):**
  - Intention-to-treat analysis

Setting and Consent form



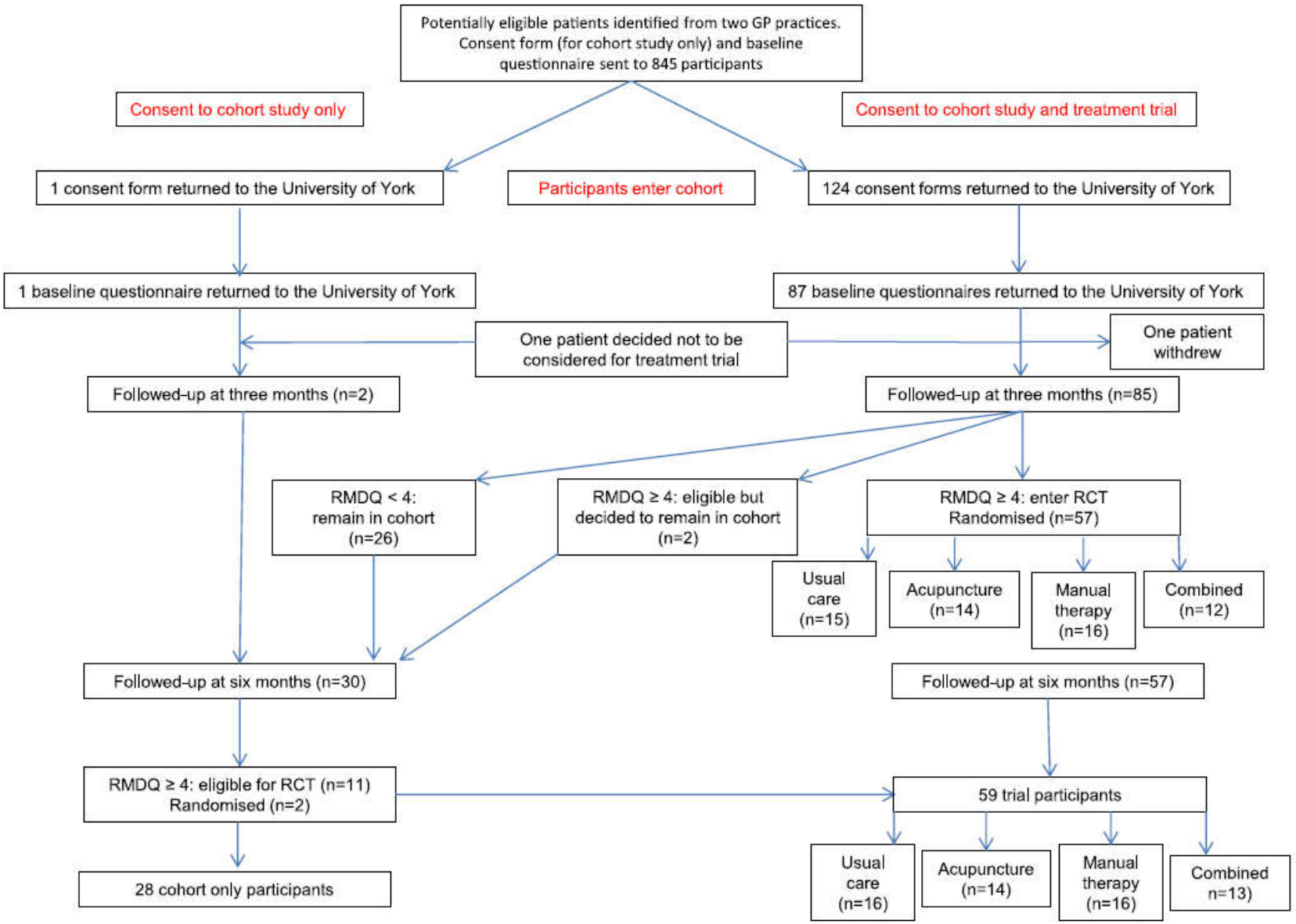
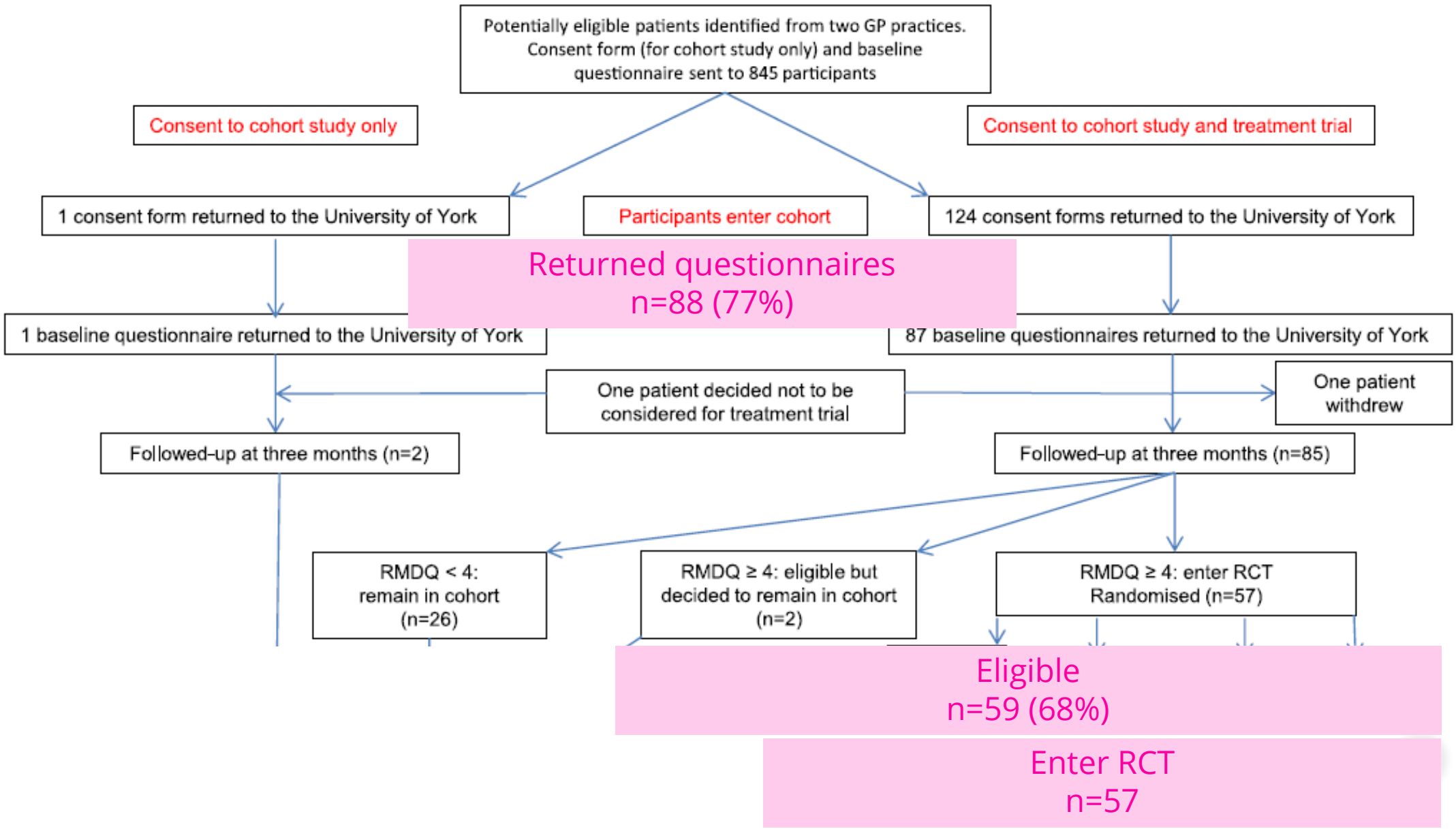
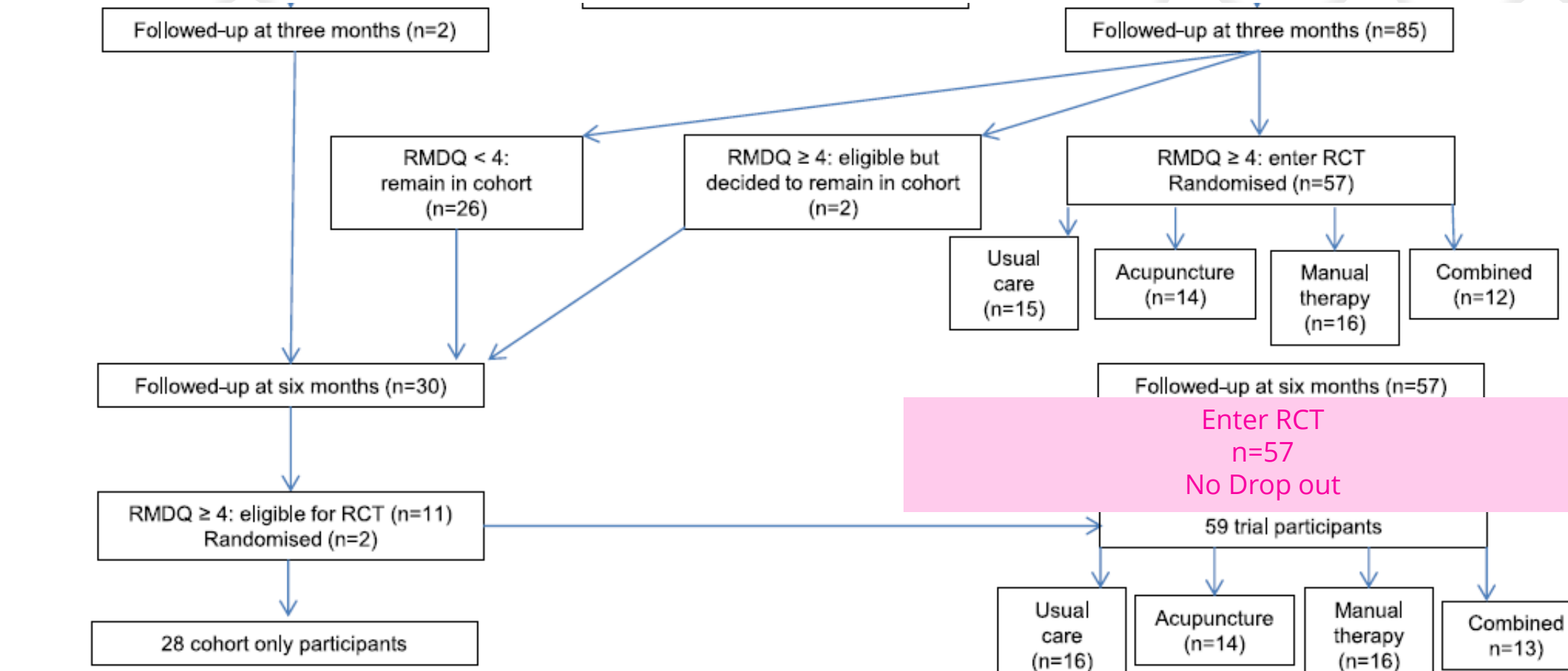


Fig. 1. CONSORT flow diagram. GP, General Practitioner; RCT, randomized controlled trial; RMDQ, Roland Morris Disability Questionnaire.


Potentially eligible patients identified from two GP practices. Consent form (for cohort study only) and baseline questionnaire sent to 845 participants
Consent to cohort study only
Consent to cohort study and treatment trial
1 consent form returned to the University of York
Participants enter cohort
124 consent forms returned to the University of York
Returned questionnaires n=88 (77%)
1 baseline questionnaire returned to the University of York
87 baseline questionnaires returned to the University of York
One patient decided not to be considered for treatment trial
One patient withdrew
Followed-up at three months (n=2)
Followed-up at three months (n=85)
RMDQ < 4: remain in cohort (n=26)
RMDQ ≥ 4: eligible but decided to remain in cohort (n=2)
RMDQ ≥ 4: enter RCT Randomised (n=57)
Eligible n=59 (68%)
Enter RCT n=57



Enter RCT
n=57
No Drop out

Still Follow-up in Cohort

Total RCT
n=59

Results of RCT

Not in RCT

RCT

Table 1. Characteristics of cohort-only and allocated trial treatment groups

Characteristic	Cohort only (n = 28)	Usual care (n = 16)	Acupuncture (n = 14)	Manipulation (n = 16)	Combined (n = 13)
Age (yr), mean (standard deviation)	46.3 (9.6)	46.3 (11.3)	45.6 (11.9)	43.9 (13.7)	50.1 (9.3)
Sex, male	8 (29)	5 (31)	4 (29)	9 (56)	5 (38)
Roland Morris Questionnaire (0–24, 0 = best)	1.8 (2.6)	11.4 (5.3)	8.8 (4.3)	8.0 (4.4)	7.0 (2.6)
Modified Oswestry Score (0–50, 0 = best)	11.6 (9.7)	29.5 (15.4)	29.6 (12.2)	24.0 (13.6)	19.2 (8.0)

+ Combined intervention groups tended to be approximately 5 years older than patients in the other trial arms

Results of RCT

Table 2. Results of regression analysis of treatments for low back pain at 3 months postrandomization

Outcome measure	Usual care (UC)	Acupuncture	Additional difference attributed to acupuncture over UC[a] (95% CI)	Manual therapy	Additional difference attributed to manual therapy over UC[a] (95% CI)	Acupuncture and manual therapy	Additional difference attributed to acupuncture and manual therapy combined over UC[a] (95% CI)
Roland Morris Questionnaire (0–24, 0 = best)	7.4 (6.2) $n = 14$	7.1 (4.6) $n = 13$	0.6 (−3.8, 5.0) $P = 0.78$	5.5 (6.3) $n = 13$	0.4 (−4.2, 4.9) $P = 0.87$	2.8 (2.7) $n = 12$	−2.1 (−6.3, 2.0)[b] $P = 0.30$
Modified Oswestry Score (0–50, 0 = best)	25.4 (22.1) $n = 13$	22.6 (11.7) $n = 13$	−2.5 (−13.9, 8.9)[b] $P = 0.65$	20.6 (11.4) $n = 14$	0.0 (−10.3, 10.3) $P = 1.0$	10.8 (7.4) $n = 12$	−5.2 (−17.3, 6.9)[b] $P = 0.38$

Abbreviation: CI, confidence interval.

[a] Estimated by analysis of covariance with adjustment for screening score.

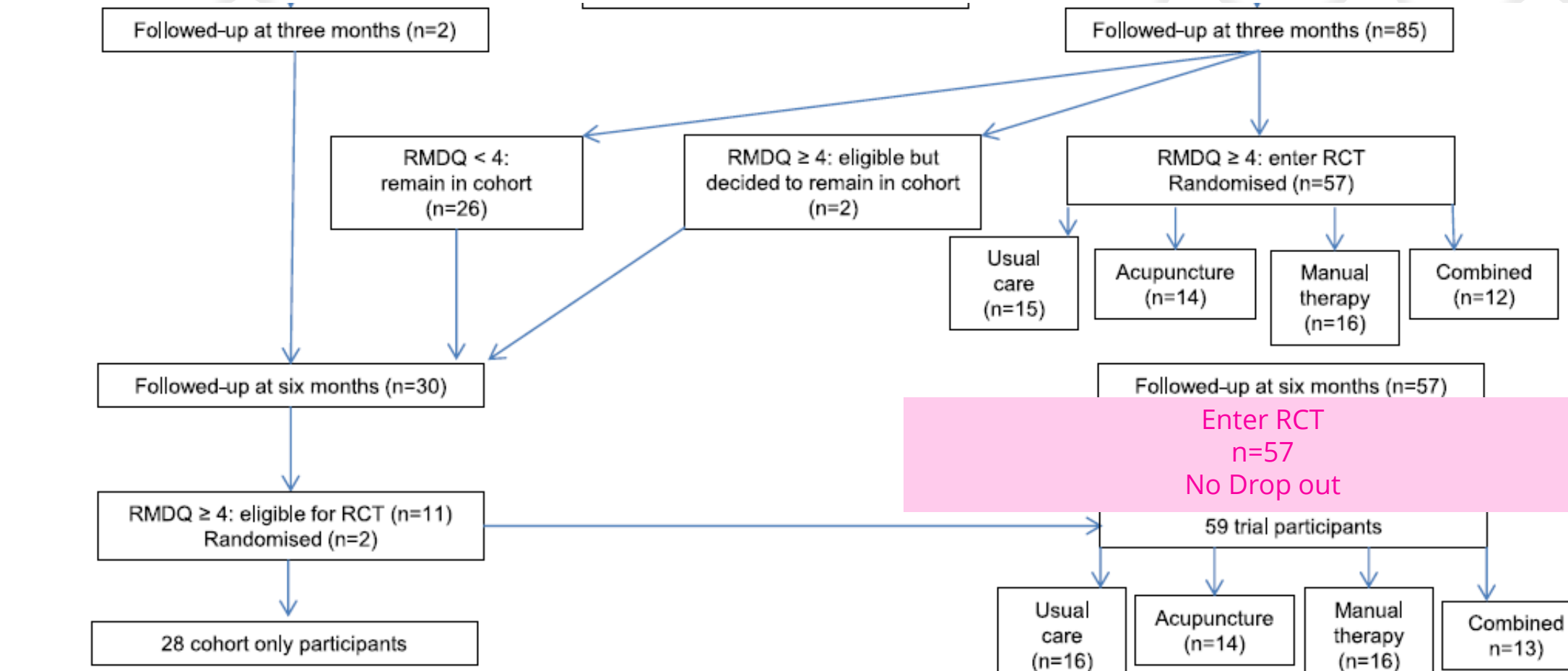
[b] Negative differences represent a favorable outcome for the relevant intervention over usual care.

Feasibility of conducting cRCT

- Response rate to initial mail out = 15%
- Attrition rate = 0% (up to 3 months)
- Attrition rate = 1% (up to 6 months)
  - 1 change to cohort (before entering the RCT)
  - 1 they did not think they would benefit from treatment because of reduce symptoms and therefore asked not to be considered for the treatment trial.
- 3 people expressly stated that they would not consider one of the treatment options
- Other trials
  - UK BEAM attrition rates of 25%
  - a cognitive behavior treatment trial for LBP attrition rates of 22%
  - a trial of yoga for LBP attrition rates of 13%

Other benefits

- using the design for a chronic remitting/relapsing condition like back pain, is that some participants, who initially were not eligible because of low symptom scores, became eligible at a later date and could be randomized.
- by including the cohort of low symptom patients, we could, if the trial had been large enough, have supplemented the randomized analysis by including the cohort in a regression discontinuity analysis.



Enter RCT
n=57
No Drop out

Still Follow-up in Cohort

Total RCT
n=59

Limitation

- Small sample size
- Excluded patients with age > 65
- Additional cost and workforce to follow-up non-RCT cohort
  - Not cost-effective use of research resources

2 Using cmRCT for studing depressed patients treated by homeopaths

Study Design

Comments

Study design

Objective:

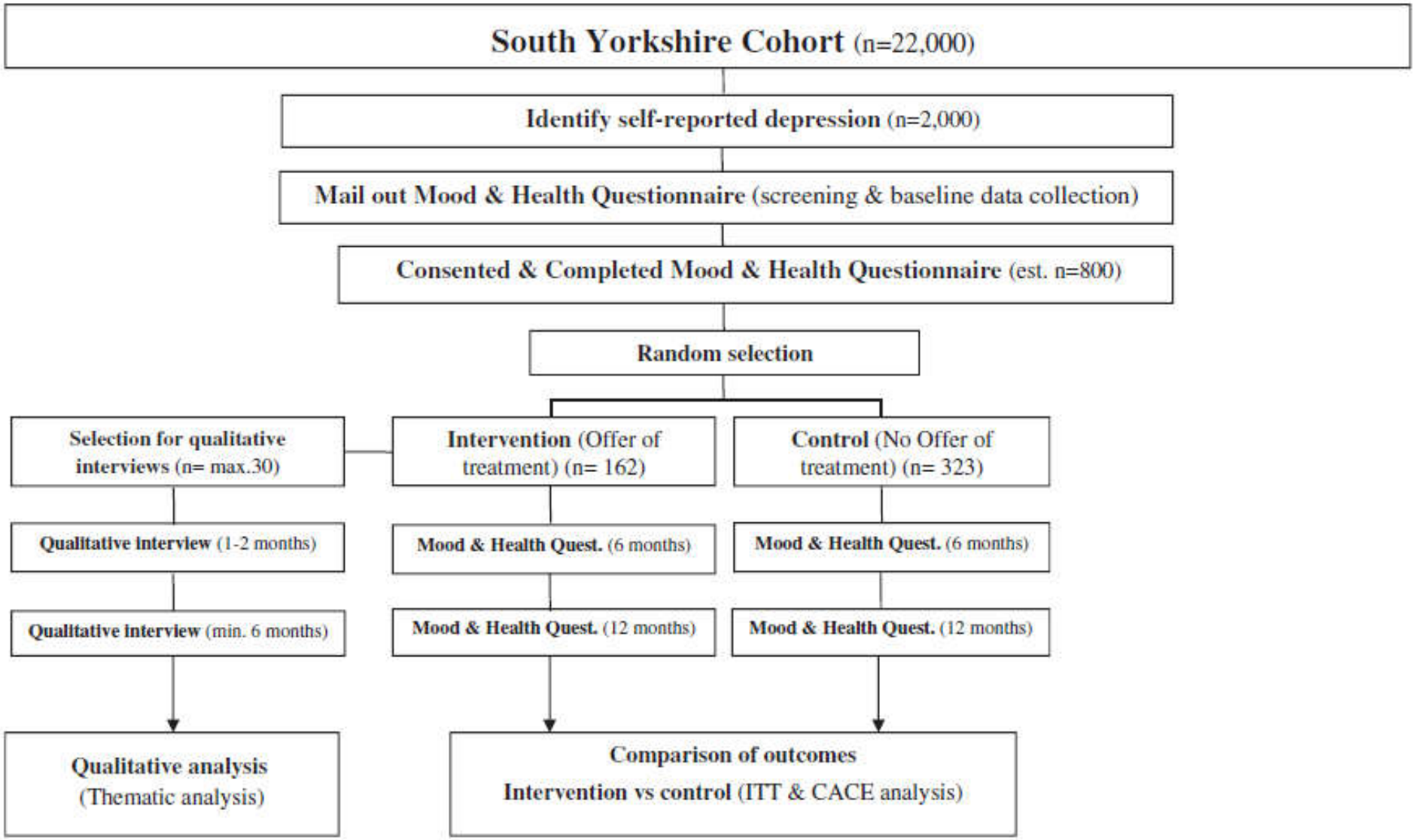
To test the effectiveness of adjunctive treatment by homeopaths compared to usual care alone, over a period of 12 months in patients with self-reported depression.

Study design and setting:

A pragmatic trial using the “cohort multiple randomised controlled trial” design

Study design of RCT

- **Intervention:**
  - Offer Homeopaths
  - Not offer Homeopaths
  - (but patient could choose to receive Homeopaths or not)
- **Outcome measurement:**
  - Primary: Patient Health Questionnaire (PHQ-9)
    - Time: 6 months after randomization
  - Secondary: Generalised Anxiety Disorder (GAD-7)
    - Time: 6, 12 months after randomization
    - Also PHQ-9 at 12 month
- **Statistical Analysis (main):**
  - Intention-to-treat analysis
  - Complier average causal effect (CACE) using Instrumental variable (IV)


South Yorkshire Cohort (n=22,000)
Identify self-reported depression (n=2,000)
Mail out Mood & Health Questionnaire (screening & baseline data collection)
Consented & Completed Mood & Health Questionnaire (est. n=800)
Random selection
Selection for qualitative interviews (n= max.30)
Intervention (Offer of treatment) (n= 162)
Control (No Offer of treatment) (n= 323)
Qualitative interview (1-2 months)
Mood & Health Quest. (6 months)
Mood & Health Quest. (6 months)
Qualitative interview (min. 6 months)
Mood & Health Quest. (12 months)
Mood & Health Quest. (12 months)
Qualitative analysis
(Thematic analysis)
Comparison of outcomes
Intervention vs control (ITT & CACE analysis)

Accepted offer
74/185 (40%)

@6 months
Response rate for Rx group
65/74 (88%)

@6 months
Response rate for Not Rx group
60/111 (54%)

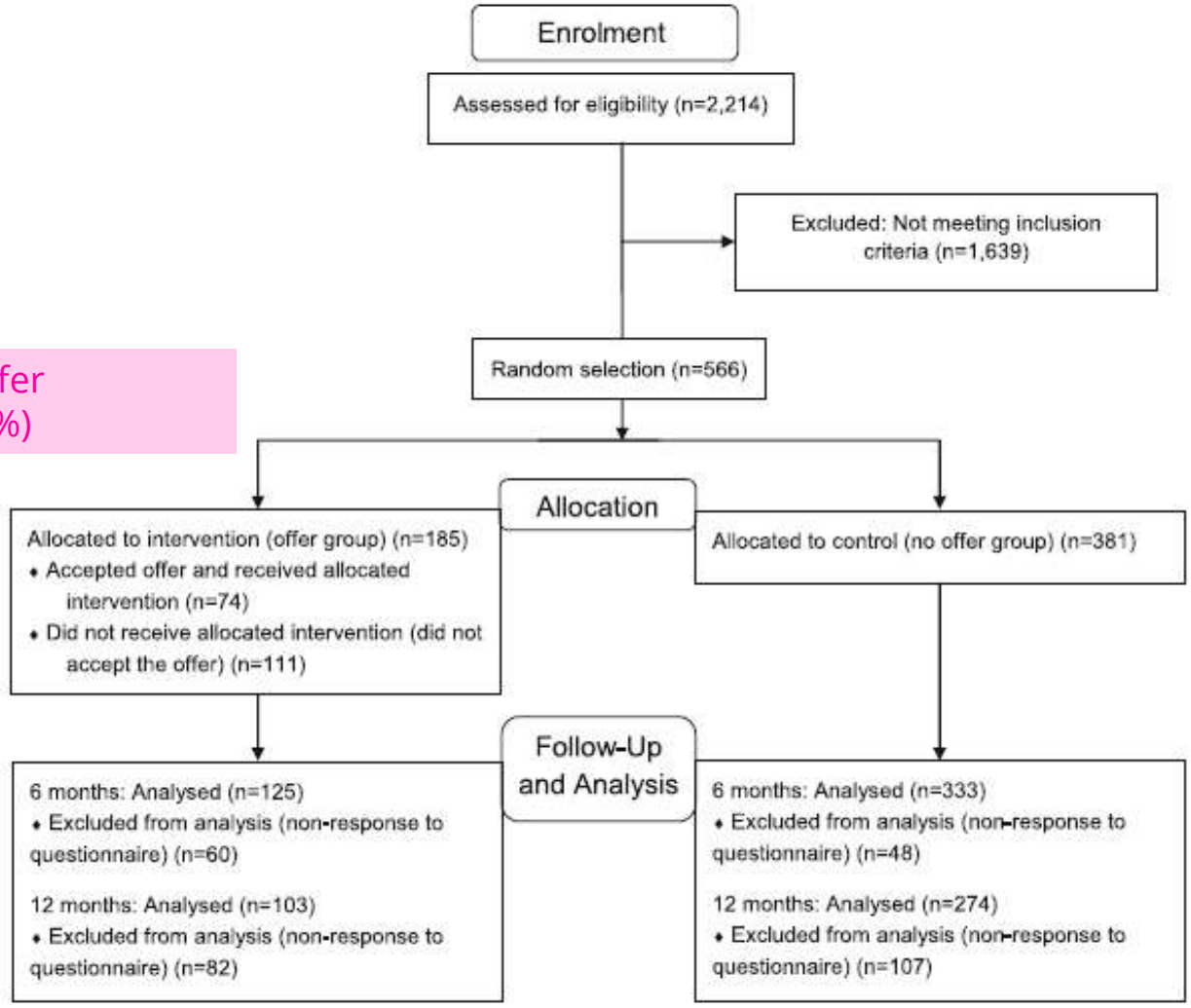


Fig. 1 Consolidated standards of reporting trials (CONSORT) flow-diagram: recruitment, randomisation and flow of patients

Acceptability

- Of 185 patients, 74 (40%) took up the offer of treatment and had at least one consultation with a homeopath.

- 90.5% (n = 67) had more than one consultation
- 75.7% (n = 56) had 5–12 consultations
- 9.5% (n = 7) only had one consultation.

Results

- Primary outcome: PHQ-9 at 6 months
  - Offer group: 1.4 points improvement (95% CI 0.2, 2.5, p = 0.019)
  - small standardized effect size in the offer group (Cohen's d = 0.30).
- PHQ-9 at 12 months
  - mean difference 1.4 points, 95% CI 0.3, 2.5, p = 0.015,
  - Cohen's d = 0.30
- Primary IV analysis
  - Offer group: 2.6 points improvement (95% CI 0.5, 4.7, p = 0.018) in favour of patients who received treatment by a homeopath
  - moderate standardized effect size (Cohen's d = 0.57).
  - Results were maintained at 12 months
  - (mean difference 2.4 points, 95% CI 0.9, 4.0, p = 0.002,
  - Cohen's d = 0.53).

Discussion

Recruitment

+ Trials often struggle to reach recruitment goals on time, and many trials fail entirely to recruit a sufficient number of participants, especially trials in depression and also other pragmatic trials.

Discussion

Attrition

- it was estimated that a realistic response rate would be 60% for health mental research
  - @6 months
  - Response rate for Rx group 65/74 (88%)
  - Response rate for Not Rx group 60/111 (54%)

    (overall 68% in offer group)
  - 87% response rate for control group
- In trials using the cmRCT design, some patients in the Offer group may be uninterested in responding to questionnaires if they either have no interest in or dislike the intervention.
- This will not be an issue for patients in the No offer group, because they are unaware of the intervention.

Discussion

Acceptability

+ Compared to “regular” RCTs, the use of the cmRCT design provides the additional benefit of testing the acceptability of the intervention.
+ Treatment uptake in this particular trial was good, given that this was not a clinical treatment-seeking population and the controversy surrounding homeopathy in the UK over the past few years.

Discussion

Analysis

+ Regular ITT analyses represent the effect of an “offer” of treatment, although we do not suggest there is an effect simply of being offered the intervention.
+ ITT analyses will “water down” any potential effect of interventions in cmRCT trials with low acceptance or compliance rates.
+ Therefore, IV analysis should be applied to test the effectiveness of the received intervention.

+ Informing patients that they may receive placebo does not occur in everyday practice and it affects their experiences, their behaviors and the results.

Discussion

Generalizability

+ The standard procedure for RCTs is that treatment is decided by chance, and information is not tailored to the individual patient but is generic, regardless of whether the patient is offered the treatment.
+ In trials with the cmRCT design, only those randomly selected to be offered the intervention are provided with information about the intervention. Hence, patients in the No offer group are not informed about interventions they cannot receive.
+ Thus, cmRCT is more comparable to real-world practice and contributes therefore to increasing the generalizability of results.

Thank you!!