BMJ Open

# Efficacy of botulinum toxin A injection in pelvic floor muscles in chronic pelvic pain patients: a study protocol for a multicentre randomised controlled trial

Melle Spruijt ,[1,2] Manon Kerkhof,[3] Marian Rombouts,[4] Richard Brohet,[5] Wenche Klerkx[1,2]

**To cite:** Spruijt M, Kerkhof M, Rombouts M, *et al*. Efficacy of botulinum toxin A injection in pelvic floor muscles in chronic pelvic pain patients: a study protocol for a multicentre randomised controlled trial. *BMJ Open* 2023;**13**:e070705. doi:10.1136/bmjopen-2022-070705

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-070705).

Received 11 December 2022
Accepted 15 June 2023



[1]Department of Gynaecology, St Antonius Hospital, Nieuwegein, The Netherlands
[2]Department of Gynaecology, Radboud Universiteit Nijmegen, Nijmegen, The Netherlands
[3]Department of Gynaecology, Curilion Clinics, Haarlem, The Netherlands
[4]Department of Physical Therapy, Radboud Universiteit, Nijmegen, The Netherlands
[5]Department of Data Science, Isala Zwolle, Zwolle, The Netherlands

**Correspondence to**
Melle Spruijt;
m.spruijt@antoniusziekenhuis.nl

## ABSTRACT

**Introduction** Chronic pelvic pain (CPP) is a common multifactorial condition affecting 6%–27% of women aged 18–50 years worldwide. The aim of this randomised controlled trial (RCT) is to investigate the efficacy and safety of botulinum toxin A (BTA) injection compared with placebo injections in the pelvic floor muscles in women with CPP to improve pain, function and quality of life.

**Methods and analysis** This is a study protocol for a multicentre, double-blinded placebo controlled RCT conducted in five gynaecology departments across the Netherlands. A total of 94 women over 16 years, with at least 6 months of CPP without anatomical cause and pelvic floor hypertonicity refractory to first-line pelvic floor physical therapy will be included. Participants will be randomised equally to BTA or placebo, both following physical therapy and (re-)education on the pelvic floor at 4, 8, 12 and 26 weeks after intervention. Multiple validated questionnaires focusing on pain, quality of life and sexual function will be collected at baseline and during all follow-up visits. Statistical analysis includes mixed models for repeated measurements.

**Ethics and dissemination** Ethical approval (NL61409.091.17) was obtained from Radboud University Medical Research Ethics Committee (MREC) and Central Committee on Research involving human Subjects (CCMO). The findings will be presented through international conferences and peer-reviewed scientific journals.

**Trial registration number** EudraCT number (2017-001296-23), CCMO/METC number: NL61409.091.17.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ -First double-blinded randomised controlled trial assessing botulinum toxin A (BTA) treatment in combination with pelvic floor physical therapy and the Multiple Array Probe Leiden.
⇒ Six months follow-up with investigation of BTA effect after recovery of the impulse transmission.
⇒ Generalisation: multicentre study in secondary and tertiary care hospitals.
⇒ Inter clinician/physical therapist variability: five trained clinicians administering the injections and seven physical therapist treatment according to standardised protocol.
⇒ Possible dry-needling effect of placebo injections.

## INTRODUCTION

Worldwide around 6%–27% of the women suffer from chronic pelvic pain (CPP).[1] CPP is a multifactorial condition that may occur as a primary event or secondary to a physical, psychological or pathological factor. The pathophysiology is not well understood. Little is known on the influence of pelvic floor muscle spasms and myofascial trigger points in patients with CPP, although both may contribute to the development and/or maintenance of CPP.[2]

Around 85% of the women with CPP have dysfunction of the pelvic musculature.[3] A disproportionate release of acetylcholine and other neurogenic inflammatory substances (substance P, calcitonin gene-related peptide and glutamate) from the neuromuscular junction increases muscles tension, local hypoxia, tissue ischaemia and pain sensation. Moreover, these neuropeptides lower the threshold for pain nociception and thereby pain sensation, even when the primary cause of pain is dissolved.[4 5] The hypertonic pelvic floor can result in problems with urinary, sexual and defecatory function.

First-line CPP treatment usually consists of pelvic floor physiotherapy possibly in combination with psychological and/or sexuological consultation. Current literature on physiotherapy interventions shows some beneficial effects. However, there is no evidence supporting this treatment due to methodological problems and lack of standardisation in definition and treatment of CPP.[6] When first-line treatment fails, more invasive interventions should be considered. The injection of botulinum toxin A (BTA) may represent a reasonable second-line intervention.[7] The

inhibition of the release of acetylcholine by BTA results in a localised, partial and reversible chemical denervation of the muscle. This causes localised muscle weakness or paralysis.[4] In addition, BTA was found to block the release of neurogenic inflammatory substances (substance P and glutamate) in afferent C-fibres, leading to peripheral desensitisation and to, indirectly, reduced central sensitisation.[4] There is conflicting evidence that injection of BTA in the hypertonic pelvic floor muscles decreases pelvic pain in patients with therapy resistant CPP[7–9] . It is important to emphasise the limitations of the current literature, including: small sample sizes, not taking pretreatment physical therapy intervention into account and different BTA treatment protocols.

The aim of this randomised controlled trial is to investigate the efficacy and safety of pelvic floor BTA injection in women with CPP. We hypothesise that patients randomised to BTA injection in combination with pelvic floor muscle therapy will result insignificantly more pain reduction, better overall function and higher quality of life than those randomised to placebo injection.

## METHODS AND ANALYSIS

### Study design

This study protocol (V.12, August 2022) describes the design of a double-blinded randomised placebo-controlled trial (1:1 treatment ratio) conducted in five gynaecology departments (four hospitals and one medical clinic) across the Netherlands. Participants will be treated in the Radboud University Medical Center, St. Antonius Hospital, Amphia Hospital, Isala Hospital and Curilion women's health clinic.

Participants will be followed for 26 weeks after treatment. The schedule of enrolment, interventions and assessments during the study period is shown is figure 1.

### Eligibility criteria

#### Population

We will include women with CPP with (primary of secondary) pelvic floor muscle hypertonicity refractory to first line pelvic floor physiotherapy. CPP is defined by the International Continence Society (ICS):patients with >6 months or recurrent episodes of abdomino-perineo-pelvic pain, hypersensitivity or discomfort often associated with elimination changes, and sexual dysfunction in the absence of organic aetiology.

### Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

- Female, >16 years.
- CPP according to the ICS with or without dyspareunia.
- Vaginal examination with one finger possible.
- Pelvic floor hypertonicity measured through physical examination by registered pelvic floor physiotherapist and the Multiple Array Probe Leiden (MAPLe). MAPLe is a medical device, which identifies individual muscle activity on different sides and depths in the pelvic floor.[10]
- Unsuccessful previous physical therapy with registered physical therapist.

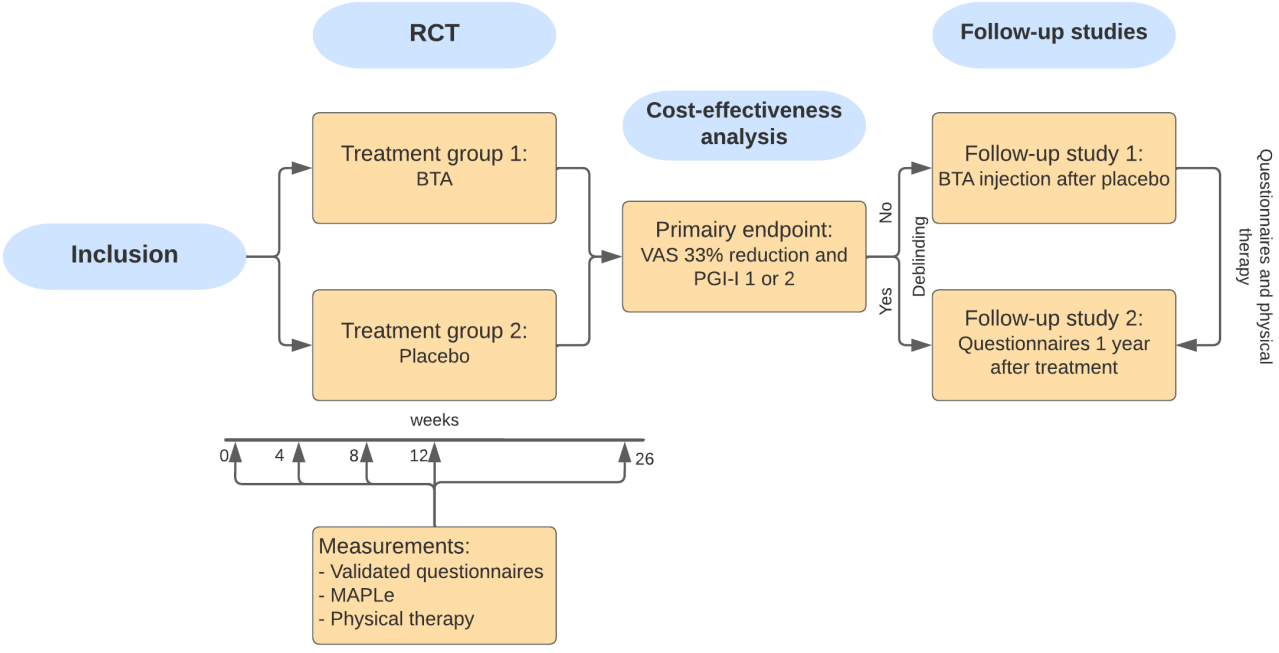


**Figure 1** Flow chart study protocol. BTA, botulinum toxin A; PGI-I, Patient Global Impression of Improvement; RCT, randomised controlled trial; MAPLe, Multiple Array Probe Leiden; VAS, Visual Analogue Scale.

- Good understanding of Dutch language.
- Willing to provide informed consent.

### Exclusion criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

- (Wish for) pregnancy/lactation during study period.
- Previous pelvic floor BTA treatment.
- Known hypersensitivity to BTA.
- History of neuromuscular or bleeding disorders.

### Recruitment

Recruitment will take place in all clinical study centres and associated hospitals, or outpatient clinics that also offer clinical care to this patient population. In addition, patient organisations will provide information about this clinical trial.

Women fulfilling the inclusion criteria will be informed about the clinical trial and receive oral and written information about the study. When the patient is willing to participate, the informed consent form must be signed prior to randomisation.

### Blinding and randomisation

This trial is a double-blinded, randomised placebo-controlled trial (1:1 treatment ratio) in which participants and clinicians will be unaware of the randomisation allocation until the end of follow-up.

We will prepare 94 closed envelopes (for the 94 study participants) containing a 1:1 randomisation for BTA or placebo. Each participating centre will receive of closed envelopes and will appoint an independent health professional, a medical doctor, research nurse or medical assistant, responsible for preparing the investigational product for administration. The independent professional will randomly select an envelope after patient inclusion.

Participants will be deblinded in case of emergency in collaboration with the investigators or after acquiring the primary endpoint.

### Study medication and preparation

The investigational medicinal product (IMP) will either be BTA 100 IU or 0.9% NaCl (placebo).

The BTA and placebo will be supplied from site stock, where it is stored according to Good Distribution Practice, recommended, respectively, in Dutch hospital pharmacies and outpatient clinics. The drugs will become IMPs only when they are made ready for administration.

The independent health professional, not involved in the study or treatment of the patient, will prepare the syringe with the IMP under aseptic conditions just before administration. The independent health professional will dissolve 100 IU BTA in 6cc 0.9% NaCl in a syringe or only 6cc 0.9% NaCl in a syringe, depending on the treatment arm. This process will always be verified by a second, independent person (controller) to assure that the process is done correctly.

### Patient and public involvement

This research protocol was developed and implemented without patient or public involvement.

Neither patients nor the public will be invited to interpret the results, as well as the writing or editing of final manuscript. As previously mentioned, the patient organisation is only involved in recruitment of participants.

### Interventions

#### Treatment

The syringe containing the IMP will be handled to the administrator just before injection. For the intravaginal injection with either BTA or placebo, patients will be placed in lithotomy position and the vulva will be swabbed with antiseptic. The patient and the administrator are blinded to the content of the syringes. Points of maximal pain at palpation in the pelvic floor muscles are identified by digital vaginal palpation. Landmarks identify the insertion of the puborectal muscles left and right at the pubic bone, halfway the puborectal muscle left and right and the most distal part of the puborectal muscle and the iliococcygeal muscle left and right. If all six points are painful at palpation, all six points will be injected with IMP with an Iowa trumpet needle. The syringes will be emptied over the different injection sites of hypertonicity (2–6 sites, 1–3 mL per site). Injections sites will be checked for haemostasis with a (small) speculum.

As found by Adelowo *et al*,[9] no local or general anaesthetic is needed and with intact sensations, the hypertonicity can be better evaluated for location of injection. Placement of the treatment medication is possible if patients can undergo vaginal examination with one finger. After administration, patients will be discharged the same day if in good clinical condition. Before discharge an emergency number is provided in case of serious adverse events (SAEs). One week after injection, patients will be contacted to evaluate possible side effects.

The physical therapy protocol was developed by the five affiliated physical therapists at a consensus meeting. Each participating physical therapist involved in the study will take care of approximately 20 participants and will accompany the patient throughout the study. Patients will receive 30 min physical therapy sessions by an experienced pelvic floor therapist at 4, 8, 12 and 26 weeks after injection and more often if needed. Education on the pelvic floor muscles will be the main focus of treatment. During these sessions, pelvic floor muscle therapy is performed using a standardised protocol of biofeedback guided exercises comprising rest, maximal voluntary contraction, submaximum contraction, endurance, relaxation and coordination exercises. In every session, visual feedback of the EMG signals by the MAPLe, verbal instructions and exercises will be used to teach patients how to control the pelvic floor muscles. This includes relaxation and coordination exercises combined with abdominal breathing. In addition, toilet behaviour and life style instructions will be provided to optimise the use of the pelvic floor muscles in daily life. The treatment will

be further individualised to match the patient's ability and specific needs. If necessary, the physical therapist will apply internal manual techniques including vaginal stretch exercises and trigger point releases. Patients are encouraged to insert a finger or, if possible, a dilator with increasing diameter. Patients will practise these techniques at home, alone or with their partner, using a customised home exercise programme.[11 12]

### Outcome measures

At baseline, multiple clinical and sociodemographic data will be obtained from all women: age, body mass index, use of pain medication or other medication, menstrual status, parity, use of cigarettes and alcohol, previous surgery (laparoscopic/vaginal/abdominal), negative sexual experience, sexual activity, comorbidities and relationship status.

### Primary outcomes

Decrease of CPP, measured by a decrease in Visual Analogue Scale score (VAS score 0–10) with 33%[13 14] and a Patient Global Impression of Improvement score (PGI-I) of 1 or 2 (better or much better) at 26 weeks after injection will be the primary outcome.

### Secondary outcomes

- Patient expectation: evaluate whether patients pretest expectations influences trail results by validated questionnaires: Pain Catastrophising Scale, Hospital Anxiety and Depression Scale and Patients were asked about their expectations regarding the effect of treatment in the following areas: Pelvic Floor Impact Questionnaire (PFIQ-7), quality of life (EQ-5D), PGI-I and VAS score.
- Patient-reported outcomes measured with validated questionnaires: pelvic floor distress inventory-20, PFIQ-7, quality of life (EQ-5D), painDETECT, sexual function (PISQ-IR).
- Pelvic floor muscle activity (microvolt) measured by the MAPLe device.[10]
- Cost-effectiveness analysis in case the study shows a statistically significant difference.

## Adverse event

Adverse events are defined as any undesirable experience occurring during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the participant or observed by the investigator or his staff will be recorded. In case of a life-threatening situation, resulting in death, permanent disability or damage, will be categorised as an SAE. An elective hospital admission will not be considered as an SAE. The investigator shall report SAEs to the sponsor without undue delay after obtaining knowledge of the events.

## Follow-up

At baseline, 4, 8, 12 and 26 weeks after injection, validated questionnaires will be supplied to the participants and pelvic floor hypertonicity will be measured with the MAPLe device. After 26 weeks, the primary endpoints by VAS and PGI-I will be measured.

## Follow-up study 1

Participants who do not meet the primary endpoint, 33% reduction in VAS score or a PGI-I of 1 or 2, will be deblinded and if in the placebo arm, asked to participate in the follow-up study. In this follow-up study 1, a BTA injection will be placed in the hypertonic pelvic floor muscles as described before. Physical therapy, MAPLe measurements, and validated questionnaires will be registered for the following 26 weeks (at t=30, 34, 38 and 52 weeks) after primary injection.

## Follow-up study 2

All patients will be asked to participate in follow-up study 2. In follow-up study 2, patients are asked to fill in questionnaires including PGI-I and VAS scores 1 year after treatment. If placebo group patients are participating in follow-up study 1, they will fill out questionnaires 1 year after BTA treatment, t=78 weeks after primary placebo injection.

At 78 weeks after primary injection, the study is closed for all participants. Finally, if significant results are obtained, a cost-effectiveness analysis will be performed.

## Sample size

The study will be powered to detect a reduction of 33% in VAS score (primary outcome) from baseline to 26 weeks follow-up. A 33% reduction in VAS score is considered clinically relevant. To demonstrate this difference, 47 patients in each of the intervention groups is needed according to the ANNCOVA (analysis of covariance) procedure (assuming a common SD of 4, power=80%, alpha level=0.05). We plan to recruit a total of 94 patients.

## Potential risks and benefits

According to the NFU 'Guideline Quality assurance of research involving human subjects (update December 2020), the risk of this study is considered minimal. However, patients can have direct problems from the injection (bleeding, infection) which will be treated accordingly (tamponade, possibly antibiotic treatment), or problems related to a temporary hypertonic or hypotonic pelvic floor (temporarily urinary or faecal incontinence, constipation). An anaphylactic reaction may occur very rarely after injection with BTA. Epinephrine and other antianaphylactic measures will be available at the outpatient clinic.

Benefits to be investigated are diminished or decreased amount or episodes of CPP, ability to have (painless) intercourse, more control of pelvic floor musculature and thereby better control on urinary and defecatory function and eventually a better quality of life.

## Withdrawal of individual participants

Participants can leave the study at any time for any reason if they wish to do so without any consequences. The

investigator can decide to withdraw a participant from the study for (urgent) medical reasons.

If withdrawal occurs before injection, these patients will be replaced to reach the power. If withdrawal occurs after injection, analyses will be done with an intention-to-treat analyses and missing data will be imputed if possible.

### Data management

The data collected for the trial will consist of baseline characteristics, physical examination, questionnaires and MAPLe measurements. All participant-identifiable data, such as informed consent forms, will be stored in the investigator site files, accessible only to delegated members of the study team. All outcome data will be stored in CASTOR electronic file using a participant identification code. When it is necessary to be able to trace data to an individual participant, a participant identification code list is used to link the data to the participant. The code is chronologically the number of inclusion. The key to the code will be safeguarded by an independent person. The handling of personal data should comply with the Dutch Personal Data Protection Act.

### Premature termination of the study

Criteria for premature termination of the study will be adverse events in more than 50% of the participants. The ethical committee will be informed and data will be published to inform other study groups on this unwanted and unexpected outcome.

### Statistical analysis

Descriptive statistics will be used for clinical variables at inclusion for the treatment and the placebo groups. Results will be presented as a mean (SD), a median (range) or proportion (%). Continuous variables will be analysed with the Student's t-test. Categorical data will be analysed with the $\chi^2$ or Fisher's exact test. Statistical significance will be determined as $p<0.05$.

To evaluate the effect of BTA on the VAS score during follow-up, all statistical analysis will be performed according to intention to treat. This means that women, who did not complete all at the 26-week visit, will be censored at the last visit on which all assessments were completed. We will run a mixed model for repeated measures. The most important advantage of this approach is that if an observation is missing at one time point, only that time point will be dropped. The remaining data will be retained. Missing data will be examined and if necessary randomly imputated. Another advantage is that time-varying variables can be easily evaluated and post-hoc tests for repeated measures factors can be performed.

Primary and secondary outcomes at follow-up (4, 8, 12 and 26 weeks postinjection) will be compared with baseline for both treatment groups separately. For the subjective and objective outcome measurements, as well as the occurrence of possible side effects the treatment group and the placebo group will be compared with the use of time-to-event methods for interval censored data. The Kaplan-Meier analysis is used to estimate the success rates at 26 weeks of follow-up.

IBM SPSS Statistics for Windows, V.26.0. will be used for all statistical analysis.

## ETHICS AND DISSEMINATION

Ethical approval was obtained from Radboud University Medical Research Ethics Committee (MREC) and Central Committee on Research involving human Subjects (CCMO). The findings will be presented through international conferences and peer-reviewed scientific journals. Informed consent material is only available in Dutch and will be obtained from each participant before randomisation. The researchers will provide direct access to source data and documents in case of trial-related monitoring, audits or regulatory inspections.

### Trial status

Recruitment started between January 2019 and October 2019. The estimated end date of the last recruitment for this study is March 2023.

**Contributors** WK conceived the trial and led the development of all procedures including intervention design and data management. MK, MR and MS participated in the design of the study and recruitment of participants. RB designed the statistical analysis plan and will oversee statistical analysis. MS oversees data collection, will perform data analysis and will draft the first version of the manuscript. All authors provided critical intellectual input to the manuscript and read and approved the final draft.

**Funding** This study is funded by the local research fund of St. Antonius Hospital and the local research fund of Isala Hospital. Additionally, BTA is funded by Allergan. A grant number was not applicable.

**Disclaimer** The funders have no role in the design of the study, implementation, data management, analysis and manuscript, or on the decision to submit results for publication.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.



**ORCID iD**

Melle Spruijt http://orcid.org/0000-0001-6509-8270

## REFERENCES

1 Ahangari A. Prevalence of chronic pelvic pain among women: an updated review. *Pain Physician* 2014;17:E141–7.
1 Fall M, Baranowski AP, Elneil S, *et al*. EAU guidelines on chronic pelvic pain. *Eur Urol* 2010;57:35–48.
3 Meister MR, Sutcliffe S, Badu A, *et al*. Pelvic floor Myofascial pain severity and pelvic floor disorder symptom bother: is there a correlation. *Am J Obstet Gynecol* 2019;221:235.
4 Aoki KR. Evidence for antinociceptive activity of botulinum toxin type a in pain management. *Headache* 2003;43:S9–15.
5 Jafri MS. Mechanisms of Myofascial pain. *Int Sch Res Notices* 2014;2014:523924.

6 Fuentes-Márquez P, Cabrera-Martos I, Valenza MC. Physiotherapy interventions for patients with chronic pelvic pain: a systematic review of the literature. *Physiother Theory Pract* 2019;35:1131–8.
7 Jarvis SK, Abbott JA, Lenart MB, *et al*. Pilot study of botulinum toxin type a in the treatment of chronic pelvic pain associated with spasm of the Levator ani muscles. *Aust N Z J Obstet Gynaecol* 2004;44:46–50.
8 Abbott JA, Jarvis SK, Lyons SD, *et al*. Botulinum toxin type a for chronic pain and pelvic floor spasm in women: a randomized controlled trial. *Obstet Gynecol* 2006;108:915–23.
9 Adelowo A, Hacker MR, Shapiro A, *et al*. Botulinum toxin type a (BOTOX) for refractory Myofascial pelvic pain. *Female Pelvic Med Reconstr Surg* 2013;19:288–92.
1 Voorham-van der Zalm PJ, Voorham JC, van den Bos TWL, *et al*. Reliability and differentiation of pelvic floor muscle Electromyography measurements in healthy volunteers using a new device: the multiple array probe Leiden (Maple). *Neurourol Urodyn* 2013;32:341–8.
11 Reissing ED, Armstrong HL, Allen C. Pelvic floor physical therapy for lifelong Vaginismus: a retrospective chart review and interview study. *J Sex Marital Ther* 2013;39:306–20.
12 Voorham JC, De Wachter S, Van den Bos TWL, *et al*. The effect of EMG Biofeedback assisted pelvic floor muscle therapy on symptoms of the overactive bladder syndrome in women: A randomized controlled trial. *Neurourol Urodyn* 2017;36:1796–803.
13 Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a Reanalysis of two clinical trials of postoperative pain. *J Pain* 2003;4:407–14.
14 Farrar JT, Portenoy RK, Berlin JA, *et al*. Defining the clinically important difference in pain outcome measures. *Pain* 2000;88:287–94.