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Complete List of Authors:	Bruhn, Hanne; University of Aberdeen, Health Services Research Unit Bond, Christine; University of Aberdeen, Elliott, Alison; University of Aberdeen, General Practice and Primary Care Hannaford, Phil; University of Aberdeen Lee, Amanda; University of Aberdeen, Division of Applied Health Sciences McNamee, Paul; University of Aberdeen Smith, Blair; University of Dundee, Watson, Margaret; University of Aberdeen, General Practice and Primary Care Blyth, Annie; University of East Anglia, Norwich Medical School Wright, David; University of East Anglia, Infection Holland, Richard; University of East Anglia,
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Title page

Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial

Hanne Bruhn, Christine M Bond, Alison M Elliott, Philip C Hannaford, Amanda J Lee, Paul McNamee, Blair H Smith, Margaret C Watson, Annie Blyth, Richard Holland, David Wright

Centre for Healthcare Randomised Trials, Health Services Research Unit, University of Aberdeen, 3rd floor Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD, UK Hanne Bruhn, Trial Manager

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Christine M Bond, Professor of Primary Care: Pharmacy

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Alison M Elliott, Senior Research Fellow

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Philip C Hannaford, NHS Grampian Chair of Primary Care

Population Health, 1st floor, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK, Amanda J Lee, Professor of Medical Statistics

Health Economics Research Unit, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK, Paul McNamee, Reader

Mackenzie Building, Kirsty Semple Way, Ninewells Hospital and Medical School, Dundee, DD2 4RB, UK, Blair H Smith, Professor of Population Science

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Margaret C Watson, Senior Research Fellow

Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK, Annie Blyth, Research Associate

Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK, Richard Holland, Professor of Public Health Medicine

School of Pharmacy, University of East Anglia, Norwich Research Park, NR4 7TJ, UK, David Wright, Chair in Pharmacy Practice

Correspondence to: Professor CM Bond c.m.bond@abdn.ac.uk, Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK

Abstract

Objectives

To compare the effectiveness of pharmacist medication-review, with or without prescribing, with standard care, for patients with chronic pain.

Design

An exploratory randomised controlled trial.

Setting

Six general practices with prescribing pharmacists in Grampian (3) and East Anglia (3).

Participants

Patients on repeat prescribed pain medication(4815) were screened by GPs, and mailed invitations (1397). 196 were randomised and 180 (92%) completed. Exclusion criteria included: severe mental illness, terminally ill, cancer related pain, history of addiction

Randomisation and intervention

Patients were randomised using a remote telephone service to: (i) pharmacist medication-review with face-to-face pharmacist prescribing; or (ii) pharmacist medication-review with feedback to GP and no planned patient contact; or (iii) treatment as usual (TAU). Blinding was not possible.

Outcome measures

Primary outcomes were the Chronic Pain Grade (CPG) and the SF-12v2, together with Hospital Anxiety and Depression Scale (HADS). Outcomes were collected at 0,3,and 6 months. Ethical approval was obtained.

Results

In the prescribing arm (n=70) two patients were excluded/nine withdrew. In the review arm (n=63) one was excluded/three withdrew. In the TAU arm (n=63) four withdrew. Compared with baseline, patients had an improved CPG in the prescribing arm, 47.7% (21/44; p=0.003), and in the review arm, 38.6% (17/44; p=0.001), but not the TAU group, 31.3% (15/48; ns). The SF-12 PCS showed no effect in the prescribing or review arms but improvement in TAU

(p=0.02). The SF-12 MCS showed no effect for the prescribing or review arms and deterioration in the TAU arm (p=0.002). HADS scores improved within the prescribing arm for Depression (p=0.022) and Anxiety (p=0.007), between groups (p=0.022 and p=0.045 respectively)

Conclusion

This is the first RCT of pharmacist-prescribing in the UK, and suggests a benefit for patients with chronic pain. A larger trial is required.

Trial registration: www.isrctn.org/ISRCTN06131530. Medical Research Council funding.

Focus:

- Chronic pain, (lasting >3 months) affects up to half the adult population, most of whom are primarily managed in primary care but prescribing is often sub-optimal.
- Pharmacists now have prescribing rights but no published research has compared the effectiveness of their prescribing with that of GPs.
- The hypothesis was that pharmacist advice (with or without pharmacist prescribing) would lead to better outcomes than usual care

Key messages:

- The findings suggest improved pain related outcomes for patients receiving pain related care from a pharmacist prescriber
- A larger trial is called for.

Strengths and Limitations

- This the first randomised controlled trial of pharmacist prescribing in the UK looking at patient reported clinical outcomes
- The study was designed as an exploratory trial so no power calculation was done

Introduction

Chronic pain (pain lasting more than three months) affects up to half the adult United Kingdom (UK) population, and is considered severely limiting in about 15% of cases (1). Recovery is uncommon with nearly 80% of those identified with chronic pain at baseline still reporting chronic pain four years later (2). It adversely affects many aspects of a person's physical and psychological health, and social and economic well being (3-6).

In the UK, most patients with chronic pain present, and are managed, in primary care (7). Although non-pharmacological treatments are available, these are accessed by few patients, with mixed success (e.g. (8-10). Analgesics prescribed in primary care remain the mainstay of treatment (4), representing substantial workload and cost. Sub-optimal prescribing may lead to poor pain control and other adverse patient outcomes. One study found that the most common medications involved in adverse drug reaction-related emergency admissions involved non-steroidal anti-inflammatory drugs (NSAIDs) (11). Improved prescribing could result in better outcomes and remove the need for more costly, scarce, alternatives.

Pharmacists working in UK general practices are well-placed to improve pain pharmacotherapy because of their expertise in therapeutics, understanding of the poly-pharmacy regimens (12) frequently used in chronic pain management, and established relationships with other primary care colleagues. In the UK National Health Service (NHS), recent regulatory changes now allow accredited pharmacists (as well as some other health care professionals such as nurses) to prescribe prescription-only medicines (POMs) (13).

However, despite the increasing number of non-medical prescribers, including pharmacists, there has been no rigourous comparisons of the outcomes of non-medical versus GP prescribing. This information is needed to assess the clinical effectiveness of different care models.

This paper reports findings from an exploratory randomised controlled trial (RCT) comparing pharmacist medication review, with or without pharmacist prescribing, with standard care for patients with chronic pain. Development of the trial was informed by earlier feasibility work (14,15).

The hypothesis was that, in patients with chronic pain, pharmacist advice (with or without pharmacist prescribing) would lead to better patient functioning and/or better pain control at

six months than treatment as usual (TAU). The hypothesis was developed prior to data collection.

Methods

Regulatory Issues

Ethical approval was granted by the National Research Ethics Service Committee – North of Scotland (reference number 09/S0801/107). NHS Research and Development approval was granted by NHS Grampian and East Norfolk & Waveney Research Governance Committees. Patients gave informed consent before taking part.

Design

An open, exploratory RCT in which patients were randomised to one of three study arms. Participants were not blind to allocated treatment arm due to the nature of the intervention.

Recruitment of practices and independent prescribing pharmacists

Practices in Grampian, Scotland (n=18) and East Anglia, England (n=4) known to have an attached Royal Pharmaceutical Society of Great Britain registered independent pharmacist prescriber, were eligible to take part. From those indicating a willingness to participate, convenience sampling was used to identify six general practices: three in Grampian and three in East Anglia.

Patient inclusion and exclusion criteria

Patients registered with the recruited practices were eligible for inclusion if they were over 18 years of age, living in their own home, and receiving regular prescribed medication for pain. Patients were identified by a computerised search {5 McDermott, M. E. 2006} of the drug records of all individuals registered with the practice, to identify those who had received either two or more acute prescriptions, and/or one repeat prescription within the last 120 days, for an analgesic (British National Formulary (BNF section 4.7) and/or non-steroidal anti-inflammatory medication (NSAID) (BNF section 10.1.1). Medications which can be used for analgesia but whose primary indication is not chronic pain (e.g. triptans, anti-epileptics or anti-depressants) were excluded as these drugs identify few additional eligible patients (16). In accordance with trial criteria, GPs excluded and recorded reasons for patients who had: a

concomitant severe mental health problem or terminal illness; had suffered recent bereavement; had a known alcohol or drug addiction; suffered pain caused by cancer or other malignancy; were unable to give informed consent; other (unspecified) reasons.

Patient recruitment

Eligible patients were sent an invitation pack (letter, information sheet, consent form) by practice staff between March and June 2010. Consent forms were returned directly to the researchers, who sent out a baseline questionnaire. Patients returning completed questionnaires were randomised by the researcher using a telephone randomisation service with a random number allocation which ensured allocation concealment. The allocation sequence was 1:1:1.

Intervention

All participating pharmacists took part in a two-day course updating them about pain management. As part of the training, participants defined and agreed the treatment algorithm they would all use.

'Prescribing' arm: Pharmacists invited patients to a face-to-face consultation. Prior to the consultation, pharmacists completed a paper-based medication review of each patient's medical record and patients were asked to complete a pain diary to inform the consultation. A pharmaceutical care plan was agreed between the pharmacist and the patient. The plan assessed and documented relevant past medical history and current conditions; known allergies and adverse drug reactions; relevant laboratory results; pain-related medications prescribed in the previous 10 years; current pain related prescription medications; current symptoms; lifestyle issues, including units of alcohol consumed per week; recommendations for changes to medication (if any); whether non-pharmaceutical treatments had been considered; and, any other relevant issues. At the end of the consultation any required prescriptions for medicines were issued by the pharmacist. Due to Controlled Drug (CD) regulations in place at the time, prescribing for CDs was done using a supplementary prescribing Clinical Management Plan (17), rather than independent prescribing. Patients were followed up either by phone or face-to-face, at each pharmacist's discretion.

'Review arm': The pharmacists conducted a paper-based medication review focussed on pain-related prescription medications, before creating a pharmaceutical care plan which detailed

any recommendations for medication changes. The plan was passed to the patient's GP for implementation. The GPs were asked subsequently about actions taken as a result of the recommendations.

Treatment as usual (TAU): Patients received standard general practice care.

Outcome measures

There were two primary outcome measures: the Chronic Pain Grade (CPG) and the Medical Outcomes Study 12-item short form version 2 (SF-12v2). Use of both a pain specific and generic outcome measure was based on Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (18) and an earlier (18,19)feasibility study (15).

The CPG (20) is a seven item scale which assesses pain severity on two dimensions: disability and intensity. The scale classifies pain according to level of intensity and disability (I (low disability-low intensity) to IV (high disability-severely limiting)).

The SF-12v2 is a generic health and functioning scale (21), previously used in population-based studies of pain (22,23). A Physical (PCS) and Mental Component Score (MCS) was calculated, ranging from 0 to 100; a higher score indicates better functioning.

A secondary outcome measure was the {{}}Hospital Anxiety and Depression Scale (HADS) (24), a 14-item screening instrument which identifies the possible and probable caseness of anxiety (7 items (HADS-A)) and depression (7 items (HADS-D)); each item scored from 0 (not present) to 3 (highly present). Standard thresholds and previously used labels (25) were applied (no depression/anxiety (0-7), mild (8-10), moderate (11-15) or severe (>15)).

Data collection

Participant questionnaires

Questionnaires were posted to participants at baseline (pre-randomisation), and 3 and 6 months post-randomisation (follow-up was conducted between July 2010 and January 2011). Up to two reminders were sent. Questionnaire content included the outcome measures described above together with items on: demographic status (baseline only); screening items to confirm eligibility (baseline only); duration of pain condition (baseline only); location of pain;

Morisky Medication Adherence Scale 4 (MMAS-4) (26); participant satisfaction (11 statements derived from the feasibility study for the prescribing arm (3 months only) and additional comments by participants. The MMAS-4 provides a score of self-reported adherence to medication regimen. Scores range from 0 (low adherence) to 4 (high adherence).

Follow-up interviews with staff

Post-intervention, all pharmacists and all GPs in participating practices were invited to take part in semi-structured interviews, carried out face-to-face when possible, otherwise by telephone. Interviews were taped, transcribed verbatim and content analysis was carried out.

Sample size

As this was an exploratory trial to estimate the effect size for a larger trial, no formal sample size calculation was possible (27). We aimed to recruit 30 participants per practice (excluding those recruited for training purposes) i.e. 180 in total. This was deemed sufficient to give reliable effect size estimates for the primary outcome measures of chronic pain grade or health status.

Data management and analysis

Data were entered into identical SPSS databases at each site and accuracy checks carried out on 10% before databases were merged. Descriptive statistics included means and standard deviations (SD) for normally distributed continuous data, medians (interquartile range (IQR)) for skewed continuous data and percentages (n) for categorical data. Analysis was conducted on an intention-to-treat basis for participants with complete data on relevant measures using SPSS version 18.

Exploratory analyses for parametric data included the paired t-test for within-arm comparisons and one-way ANOVA for between arm comparisons. For non-parametric data it included the Wilcoxon Signed Rank test for within-arm comparisons and the Kruskal Wallis test for between arm comparisons. Categorical data was analysed using the marginal homogeneity test for within-arm comparisons and the Chi-squared test for between arm comparisons;analyses reported here are based on 6 month follow-up data (other than for participant experiences).

Results

Response rates and demography

Six of the seven practices approached participated. GPs excluded 12% (392/3281) of patients, mostly those with dementia. There was no statistically significant difference between participants and non-participants in terms of age, gender, and index of multiple deprivation. Figure 1 shows the flow of participants through the study. Overall, the consent rate was 25% (356/1397) and the recruitment rate was 14% (196/1397).

[INSERT FIGURE 1 HERE]

Eighty six percent of participants (251/289) returned baseline questionnaires, of whom 232 were randomised (36 participants were randomised to one of the two intervention arms for training purposes and were not included in any further analysis and 19 were not included as recruitment target had been met). The overall follow-up rate at 3 months was 86% (161/187)and at 6 months 84% (152/180).

As shown in Table 1, groups were similar at baseline for demographic and socioeconomic variables and pain data. Most participants were married, Caucasian and female, older (mean (SD) age 65 (12.6) years), had an annual income of <£25,000 and had suffered from pain for at least five years. Most (57%;103/181) reported being fully adherent to their medication regimen (MMAS-4, median 4.0 (IQR 3.0- 4.0)) (15 missing MMAS scores).

[INSERT TABLE 1 HERE]

In the prescribing arm, 78% (53/68) attended an initial prescribing consultation, 31 had at least one planned follow-up (generally conducted by phone) and 130 recommendations were made for 92% (49/53) of participants seen. Examples are shown in Box 1. The median time taken for the note-based record review was 35 minutes (IQR 20.0, 45.0), the consultation was 30 minutes (IQR 20.0, 40.0), careplan preparation 10 minutes (IQR 10.0, 20.0) and median duration of follow-ups was 10 minutes (IQR 5.0- 15.0).

[INSERT BOX 1 HERE]

In the review arm 97% (60/62) of participants' records were reviewed (note there was one post randomisation exclusion) for whom 197 recommendations were made. Where GP feedback was provided (n=48), they generally agreed with pharmacists' recommendations, which were fully implemented for 20 participants (two by the pharmacist following request by GP), partially for 19 participants and not at all for nine participants. The median time taken for the note-

based record review was 30 minutes (IQR24.3, 45.0), and careplan preparation was 10 minutes (IQR 5.0, 20.0).

Clinical outcome measures

Table 2 shows the mean (SD) or median (IQR) of the CPG for each arm at baseline and 6 month follow-up. Table 3 shows the SF-12 scores and Table 4 shows the HADS-A and HADS-D results.

[INSERT TABLE 2,3,4, HERE]

In the prescribing arm, there was a statistically significant within arm improvement for the CPG intensity (p=0.002) and disability (p=0.003) subscales, and between arms on the intensity sub-scale (p=0.02), but not the disability subscale (p=0.55) (Table 2). There was a significant within-arm improvement in overall CPG grade in the prescribing (p=0.003) and review arm (p=0.001), but not in the TAU arm. The SF-12 Physical Component Score showed a statistically significant within arm improvement in the TAU arm (p=0.02, Table 3), but not between trial arms. The SF-12 Mental Component Score showed a statistically significant deterioration in the TAU arm (p=0.002, Table 3), as did the HADS-D (p=0.03, Table 4). Analysis was also carried out on the non-categorised HADS scores which showed a statistically significant improvement within the prescribing arm for Depression (p=0.022) and Anxiety (p=0.007). These were both significant between groups (p=0.022 and p=0.045 respectively) (Table 5).

Acceptability of the pharmacist prescribing intervention

All six pharmacists and 56% of the GPs (23/41) were interviewed. All pharmacists and most GPs were positive about the intervention, although some GPs suggested that the pharmacists' recommendations had been minor and questioned the cost-effectiveness of the service. Patient participants were generally positive about the pharmacist prescribing service although some concerns were identified, as Illustrated by the quotes shown in Box 2.

[INSERT BOX 2 HERE]

Discussion

Principal findings

This exploratory RCT of pharmacist-led management of patients with chronic pain suggests that pharmacist prescribing (and possibly pharmacist review alone) may be effective in improving

pain-related outcomes and be acceptable to both patients and professionals. There was an indication of a positive effect on emotional health, but no measurable effect on general health.

Strengths and weaknesses

This was the first RCT to assess clinical and humanistic outcomes after pharmacist prescribing for any clinical condition compared to usual GP care, and the first RCT to specifically assess pharmacist-led management of chronic pain, compared with usual GP care. It was based on extensive development and feasibility work (14,15) in line with MRC framework for development and evaluation of complex interventions (28). A range of validated outcome measures was included, as well as a parallel qualitative process evaluation which demonstrated satisfaction and acceptability. The inclusion of six practices and their associated pharmacists from both Scotland and England increased the generalisability of the findings. Pharmacists agreed and used a common treatment algorithm which should have increased standardisation of treatment.

There were, however limitations. Although high follow-up response rates were achieved at both three (86%) and six months (85%) only 25% of eligible patients entered the trial. This low initial consent rate is in line with other studies (29,30), but may cause unknown biases including problems of generalisability. Rewording of participant recruitment documentation could address some of the concerns identified by participant feedback e.g. having too many people involved in one's care. More participants withdrew in the prescribing arm compared with the other two arms, which might be attributed to the need for an additional practice visit. The study was an exploratory trial so no formal power calculation was undertaken because of no prior knowledge of effect size. Due to the nature of the intervention, no participants were blind to their group allocation, and so some outcomes, especially the qualitative components, may have been affected by social desirability bias.

Our main outcome measures were self-reported, but this is the norm in pain studies as pain is a subjective experience (18). Furthermore we do not know how important the observed differences were to participants. Following precedents set in previous research (25), and because there is no consensus on an alternative measure (31) we used the HADS as a tool to classify people by severity of depression and anxiety. However it is strictly a screening tool, and

the four levels of severity have not been formally validated. We therefore also compared outcomes using it as a continuous scale.

Relationship with other studies

This study is important because no other RCT has evaluated pharmacist prescribing and few studies, and importantly no RCTs, have evaluated pharmacist interventions for pain. In pharmacist prescribing most research has focussed on reported experiences of professionals and patients, and not used validated outcome measures. Yet pharmacist prescribing is now widely practised. For pain, there have been a few small studies. Briggs et al (2008) (32) conducted a small before-and-after evaluation (involving 65 patients) of a nurse and pharmacist-led chronic pain clinic in primary care. Pain intensity Visual Analogue Scale scores reduced significantly over six months. Another evaluation of 26 patients using a medication review service provided jointly by a physiotherapist and pharmacist, reported improvement in pain control for 88% of patients (33).

The CPG was found to show a graded effect across the three arms, showing discrimination with both direction and strength of improvement, suggesting maximum benefit for those in the pharmacist prescribing arm. However, the reduction in overall score appears to be mediated by a change in the intensity of pain subscale rather than in pain-related disability. In contrast, the SF-12, a measure of general health and functionality showed no significant difference between intervention arms, reflecting either no effect or or lack of powerto detect an effect.

Whilst most participants in this study were already within the normal range on the HADS scale, and therefore had minimal chance of improvement, there were nonetheless suggestions of better ourcomes in participants in the prescribing arm. Including a range of instruments is in line with IMMPACT recommendations (34), which state that focus should be on the whole person, not just about pain. However, this needs to be balanced with minimising participant burden.

Explanations, implications, and future research

The number of pharmacists' recommendations per participant was higher in the review arm than in the prescribing arm. This might seem contradictory to the possible greater benefit found in the prescribing arm. However, in the prescribing arm pharmacists met the participant and may have more readily identified and dismissed suggestions previously tried. The

interview feedback highlighted that some recommendations for change, whilst sensible, had been tried already. This might also be the reason why there were only 60% of pharmacist recommendations with which the GP fully agreed. Self-reported adherence to medication at baseline was good. Despite this, the pharmacists still improved pain outcomes in the prescribing arm. This could have been due to changes in medications and/or participant education about optimal timing for administration of analgesic medicines. Further research is needed to confirm the beneficial effect of pharmacist prescribing and its sustainability.

Conclusion

Our results suggest that pharmacist prescribing (and possibly pharmacist review alone) for patients with chronic pain is feasible, acceptable and leads to improvements in pain and other measures. A larger fully-powered trial is now needed to confirm these findings.

Data sharing statement

Consent was not obtained from participants for data sharing; the presented data are anonymised and there is no risk of individual identification. Requests for data should be made to the contact author who will provide this in a format in which risk of patient identification will be minimal.

Conflict of interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

HB and CB drafted the manuscript.

All authors:

1) made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

2) were involved in drafting the manuscript or revising it critically for important intellectual content; and

3) have given final approval of the version to be published.

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All authors had access to all of the study data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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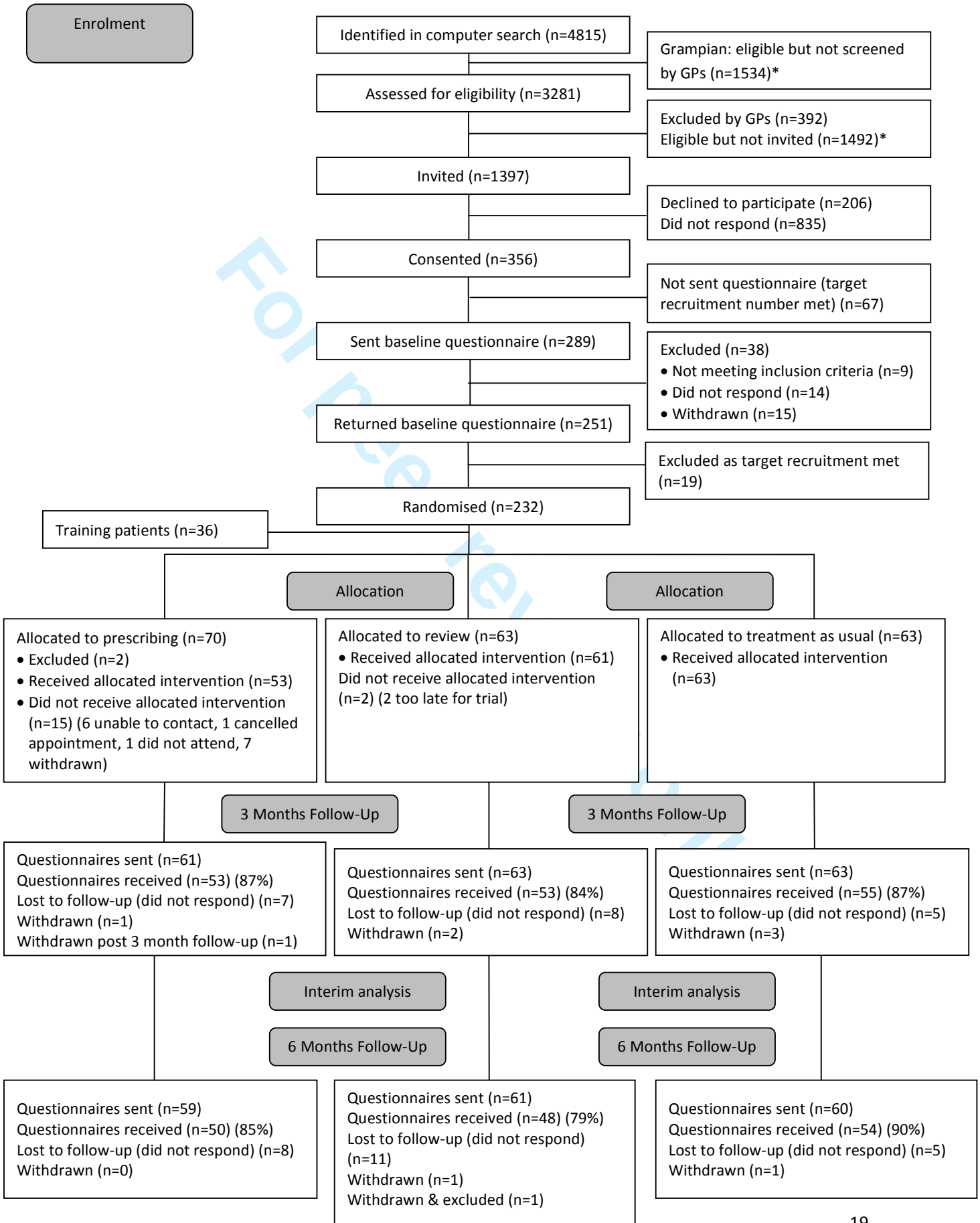
Figure 1: CONSORT Flow Diagram



*In Grampian, on the basis of response rates in the earlier feasibility study (241 screened patients resulted in 22 recruited) only a random sample of eligible participants were screened (15). In East Anglia all eligible patients were screened.

Table 1: Baseline demographic, socio-economic and pain data of patients by study arm, prescribing, review and treatment as usual (TAU)

	Prescribing* (n = 68)	**Review*** (n = 62)	**TAU*** (n = 63)
Age: mean (SD)	66.1 (12.1)	65.7 (14.2)	64.9 (11.6)
Missing	1	1	0
Gender (% female)	54.4 (37)	74.2 (46)	58.7 (37)
Marital status			
Married	43	30	41
Single	6	6	3
Divorced/widow	10	21	13
Other	6	4	6
Missing	3	1	0
Highest educational level achieved			
No qualifications	30	27	21
O grade or equivalent	12	6	14
Higher/A-level/NVQ3/SVQ3	6	8	7
Tertiary education/NVQ4/NVQ5	18	17	14
Other	2	1	4
Missing	0	3	3
Employment status			
Employed	16	14	9
Unemployed	3	5	1
Retired	38	35	34
Long term sick/disabled	7	5	9
Other	3	2	7
Missing	1	1	3
Household annual income before tax			
Less than £9,999	13	15	10
£10,000 - £14,999	14	18	22
£15,000 - £24,999	14	12	12
£25,000 – or more	22	11	8
Missing	5	6	11
Ethnic group			
Caucasian	67	62	61
Other	1		
Missing	0	0	2
Pain duration			
< 1 year	3	2	4
1 – 3 years	12	12	7
3 – 5 years	10	13	9
5 – 10 years	17	13	15
> 10 years	26	22	28
Pain localisation (%, n)			
Back	27.9 (19)	32.3 (20)	20.6 (13)
Neck, shoulders	7.4 (5)	9.7 (6)	9.5 (6)
Limbs or hips	42.6 (29)	30.6 (19)	50.8 (32)
Other	8.8 (6)	4.8 (3)	7.9 (5)
Missing	9	14	7

*Denominator based on numbers allocated to the specific arms, minus any exclusions due to protocol violations.

Table 2: Mean (standard deviation, SD) CPG intensity , median (interquartile range, IQR) CPG disability, and count CPG grade at baseline, 6 months follow-up and difference between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). P-values for within and between arm differences are also reported.

	Prescribing		Review		TAU		P (between groups)
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	
Baseline CPG intensity	47	66.1 (16.0)	45	68.4 (17.6)	54	65.4 (18.0)	
6 month follow-up CPG intensity		58.1 (19.5)		67.4 (21.7)		65.6 (19.6)	
Difference CPG intensity		-8.0 (16.3)		-1.0 (16.0)		0.2 (14.9)	0.02
P (within groups)		0.002		0.67		0.93	
		Median [IQR]		Median [IQR]		Median [IQR]	
Baseline CPG disability	48	60.0 [30.0; 75.8]	46	66.7 [45.0; 80.0]	53	56.7 [36.7; 80.0]	
6 Month follow-up CPG disability		40.0 [20.0; 60.0]		53.3 [29.2; 73.3]		50.0 [25.0; 80.0]	
Difference CPG disability		-8.3 [-23.3; 0.0]		-3.3 [-16.7; 10.0]		-3.3 [-21.7; 5.0]	0.55
P (within groups)		0.003		0.15		0.05	
Baseline CPG grade	44	Count (%)	44	Count (%)	48	Count (%)	
I		5 (11.4)		3 (6.8)		5 (10.4)	
II		16 (36.4)		9 (20.5)		13 (27.1)	
III		7 (15.9)		10 (22.7)		13 (27.1)	
VI		16 (36.4)		22 (50.0)		17 (35.4)	
6 month follow-up CPG grade							
I		13 (29.5)		8 (18.2)		6 (12.5)	
II		13 (29.5)		15 (34.1)		17 (35.4)	
III		8 (18.2)		8 (18.2)		11 (22.9)	
IV		10 (22.7)		13 (29.5)		14 (29.2)	
Difference CPG grade							
≤-1		21 (47.7)		17 (38.6)		15 (31.2)	
0		17 (38.6)		25 (56.8)		25 (52.1)	
≥1		6 (13.6)		2 (4.5)		8 (2.1)	0.16
P (within groups)		0.003		0.001		0.17	

*Number of participants in each group who completed the appropriate part of the CPG at both baseline and follow-up.

Table 3: Mean (standard deviation, SD) SF12 Physical Component Score (PCS) and median (interquartile range, IQR) Mental Component Score (MCS) at baseline and 6 month follow-up and difference between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.

	Prescribing		Review		TAU		
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	P (between groups)
Baseline SF12 PCS	41	33.5 (10.8)	43	32.59(11.38)	45	29.60 (9.71)	
6 month follow-up SF12 PCS		35.3 (10.8)		34.62 (11.26)		32.59 (9.14)	
Difference SF12 PCS		1.8 (7.5)		2.02 (7.56)		2.99 (8.11)	0.75
P (within groups)		0.12		0.09		0.02	
		Median [IQR]		Median (IQR)	45	Median (IQR)	
Baseline SF12 MCS	42	52.4 [42.0; 58.8]	43	47.9 [38.5; 59.9]		51.5 [41.3; 60.7]	
6 month follow-up SF12 MCS		49.6 [42.8; 58.1]		47.9 [38.9; 56.2]		44.7 [37.6; 55.8]	
Difference SF12 MCS		-0.4 [-3.7; 6.0]		-1.2 [-6.6; 4.2]		-3.0 [-10.0; 1.3]	0.04
P (within groups)		0.64		0.37		0.002	

* Number of participants in each group who completed the appropriate part of the SF-12 at both baseline and follow-up.

Table 4: The HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) count of patients according to severity (normal, mild, moderate or severe) and the difference in severity category between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.*

	n	**Prescribing**	n	**Review**	n	**TAU**	
Baseline HADS-D	44	Count (%)	45	Count (%)	53	Count (%)	P (between groups)
Normal		32 (72.7)		31 (68.9)		38 (71.7)	
Mild		8 (18.2)		11 (24.4)		7 (13.2)	
Moderate		3 (6.8)		3 (6.7)		8 (15.1)	
Severe		1 (2.3)		0		0	
6 month follow-up HADS-D							
Normal		32 (72.7)		32 (71.1)		32 (60.4)	
Mild		7 (15.9)		6 (13.3)		10 (18.9)	
Moderate		5 (11.4)		6 (13.3)		8 (15.1)	
Severe		0		1 (2.2)		3 (5.7)	
Difference HADS-D							
≤-1		5 (11.4)		4 (8.9)		2 (3.8)	
0		34 (77.3)		37 (82.0)		40 (75.5)	
≥1		5 (11.4)		4 (8.9)		11 (20.8)	Not valid**
P (within groups)		1.0		0.71		0.03	
Baseline HADS-A	44	Count (%)	43	Count (%)	48	Count (%)	
Normal		25 (56.8)		30 (69.8)		29 (60.4)	
Mild		8 (18.2)		7 (16.3)		9 (18.8)	
Moderate		8 (18.2)		5 (11.6)		8 (16.7)	
Severe		3 (6.8)		1 (2.3)		2 (4.2)	
6 month follow-up HADS-A							
Normal		27 (61.4)		29 (67.4)		32 (66.7)	
Mild		7 (15.9)		6 (14.0)		5 (10.4)	
Moderate		8 (18.2)		6 (14.0)		10 (20.8)	
Severe		2 (4.5)		2 (4.7)		1 (2.1)	
Difference HADS-A							
≤-1		6 (13.6)		3 (7.0)		10 (20.8)	
0		35 (79.5)		33 (76.7)		29 (60.4)	
≥1		3 (6.8)		7 (16.3)		9 (18.8)	0.14
P (within groups)		0.25		0.21		0.55	

* Number of participants in each group who completed the appropriate part of the HADS at both baseline and follow-up.

**Between arms p-value not valid due to low numbers in multiple cells, even after collapsing to three categories.

Table 5: Median HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) scores (interquartile range, IQR) at baseline and 6 month follow-up and difference between the two assessment point for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.

	Prescribing		Review		TAU		
	n	Median [IQR]	n	Median [IQR]	n	Median [IQR]	P (between groups)
Baseline HADS-D	42	5.0 [3.0;8.0]	44	4.5 [2.3; 8.0]	51	5.0 [3.0; 8.0]	
6 month follow-up HADS-D		4.0 [2.0; 8.0]		5.0 [2.0; 8.8]		5.0 [2.0; 10.0]	
Difference HADS-D		-1.0 [-2.0; 0.0]		0.0 [-1.0; 1.8]		0.0 [-1.0; 2.0]	0.02
P (within groups)		0.02		0.33		0.22	
Baseline HADS-A	44	7.0 [3.3; 10.8]	43	5.0 [3.0; 10.0]	48	6.0[4.0; 10.0]	
6 month follow-up HADS-A		5.0 [2.3; 9.8]		6.0 [3.0; 9.0]		7.0 [4.0; 10.0]	
Difference HADS-A		-1.0 [-2.0; 0.0]		0.0 [-2.0; 2.0]		0.5 [-3.0; 2.0]	0.05
P (within groups)		0.01		0.45		0.81	

* Number of participants in each group who completed the appropriate part of the HADS at both baseline and follow-up.

Box 1 Examples of pharmacist interventions in the prescribing arm

Changes to pain management: 'use paracetamol regularly', 'take tramadol if needed' 'add piroxicam gel PRN', 'given web links to self help groups'

Compliance aid: ' gave written times that this drug could be taken'

Addressing side effects/safety: 'take paracetamol after initial NSAID', 'take senna', 'ordered blood monitoring', 'stop use of two NSAIDS'

General health: 'discussed weight loss', 'invited to practice nurse for BP', 'glucose, lipids and lifestyle update',

Cost minimisation: 'change aspirin EC to plain',

BOX 2 Examples of quotes from Pharmacists (n=6), GPs (n=23) and patient participants (n=40) on the prescribing intervention

Pharmacists (from interviews):

Satisfying (n=6):'contact with patients', 'being able to help patients', 'being able to make a difference to long-standing pain'...'even in small ways'

Interesting (n=6):'learning about pain'

Challenging (n=6):'complex, chronically ill patients'

GPs (from interviews):

Support for the service (n=17): it's been a very positive thing'

Agreement with pharmacists' recommendations (n=23): 'oh very reasonable suggestions', 'tinkering round the edges', 'had been tried already'.

Trust in the practice pharmacist (n=23):'I respect his professional judgement'

Cost effectiveness (n=6): 'if there's limited resources do we want to spend the money on a pharmacist'.

Patients (from 3 month questionnaire):

Closed questions:

Proportion agreeing that:
The pharmacist was interested in them (89%; 39/44)
They were totally satisfied (85%; 39/46)
They were told about their treatment (82%; 38/46)
Their consultation was thorough (79%; 34/44)
They would have liked more time (9%;4/44)
They would have preferred to see their GP (9%; 4/44)
Too many people were now involved in their treatment (11%; 5/44).

Open text questions:

Positive (n=39): 'She was professional, relaxed, pleasant and interested. Excellent!'

Negative (n=1): 'A waste of time, altered my tablets which made my pain worse'.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10, figure 1(p.18)
	13b	For each group, losses and exclusions after randomisation, together with reasons	10, figure 1(p.18)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7-8
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	10, Table 1 (p20)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	See Tables 2,3,4,5 and page 9 (ITT)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	See pages 10/11, and Tables 2,3,4,5. P values reported
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13
Other information			
Registration	23	Registration number and name of trial registry	4

Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial

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Title page

Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial

Hanne Bruhn, Christine M Bond, Alison M Elliott, Philip C Hannaford, Amanda J Lee, Paul McNamee, Blair H Smith, Margaret C Watson, Annie Blyth, Richard Holland, David Wright

Centre for Healthcare Randomised Trials, Health Services Research Unit, University of Aberdeen, 3rd floor Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD, UK Hanne Bruhn, Trial Manager

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Christine M Bond, Professor of Primary Care: Pharmacy

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Alison M Elliott, Senior Research Fellow

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Philip C Hannaford, NHS Grampian Chair of Primary Care

Medical Statistics Team, Division of Applied Health Sciences, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK, Amanda J Lee, Professor of Medical Statistics

Health Economics Research Unit, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK, Paul McNamee, Reader

Mackenzie Building, Kirsty Semple Way, Ninewells Hospital and Medical School, Dundee, DD2 4RB, UK, Blair H Smith, Professor of Population Science

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Margaret C Watson, Senior Research Fellow

Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK, Annie Blyth, Research Associate

Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK, Richard Holland, Professor of Public Health Medicine

School of Pharmacy, University of East Anglia, Norwich Research Park, NR4 7TJ, UK, David Wright, Chair in Pharmacy Practice

Correspondence to: Professor CM Bond c.m.bond@abdn.ac.uk, Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK

Abstract

Objectives

To compare the effectiveness of pharmacist medication-review, with or without pharmacist prescribing, with standard care, for patients with chronic pain.

Design

An exploratory randomised controlled trial.

Setting

Six general practices with prescribing pharmacists in Grampian (3) and East Anglia (3).

Participants

Patients on repeat prescribed pain medication(4815) were screened by GPs, and mailed invitations (1397). 196 were randomised and 180 (92%) completed. Exclusion criteria included: severe mental illness, terminally ill, cancer related pain, history of addiction

Randomisation and intervention

Patients were randomised using a remote telephone service to: (i) pharmacist medication-review with face-to-face pharmacist prescribing; or (ii) pharmacist medication-review with feedback to GP and no planned patient contact; or (iii) treatment as usual (TAU). Blinding was not possible.

Outcome measures

Primary outcomes were the Chronic Pain Grade (CPG) and the SF-12v2, together with Hospital Anxiety and Depression Scale (HADS). Outcomes were collected at 0,3,and 6 months. Ethical approval was obtained.

Results

In the prescribing arm (n=70) two patients were excluded/nine withdrew. In the review arm (n=63) one was excluded/three withdrew. In the TAU arm (n=63) four withdrew. Compared with baseline, patients had an improved CPG in the prescribing arm, 47.7% (21/44; p=0.003), and in the review arm, 38.6% (17/44; p=0.001), but not the TAU group, 31.3% (15/48; ns). The SF-12 PCS showed no effect in the prescribing or review arms but improvement in TAU

(p=0.02). The SF-12 MCS showed no effect for the prescribing or review arms and deterioration in the TAU arm (p=0.002). HADS scores improved within the prescribing arm for Depression (p=0.022) and Anxiety (p=0.007), between groups (p=0.022 and p=0.045 respectively)

Conclusion

This is the first RCT of pharmacist-prescribing in the UK, and suggests there may be a benefit for patients with chronic pain. A larger trial is required.

Trial registration: www.isrctn.org/ISRCTN06131530. Medical Research Council funding.

Focus:

- Chronic pain, (lasting >3 months) affects up to half the adult population, most of whom are primarily managed in primary care but prescribing is often sub-optimal.
- Pharmacists now have prescribing rights but no published research has compared the effectiveness of their prescribing with that of GPs.
- The theory~~hypothesis~~ was that pharmacist advice (with or without pharmacist prescribing) would lead to better outcomes than usual care

Key messages:

- The findings suggest there may be improved pain related outcomes for patients receiving pain related care from a pharmacist prescriber
- A larger trial is called for.

Strengths and Limitations

- This the first randomised controlled trial of pharmacist prescribing in the UK looking at patient reported clinical outcomes
- The study was designed as an exploratory trial so no power calculation was done

Introduction

Chronic pain (pain lasting more than three months) affects up to half the adult United Kingdom (UK) population, and is considered severely limiting in about 15% of cases (1). Recovery is uncommon with nearly 80% of those identified with chronic pain at baseline still reporting chronic pain four years later (2). It adversely affects many aspects of a person's physical and psychological health, and social and economic well being (3-6).

In the UK, most patients with chronic pain present, and are managed, in primary care (7). Although non-pharmacological treatments are available, these are accessed by few patients, with mixed success (e.g. (8-10). Analgesics prescribed in primary care remain the mainstay of treatment (4), representing substantial workload and cost. Sub-optimal prescribing may lead to poor pain control and other adverse patient outcomes. One study found that the most common medications involved in adverse drug reaction-related emergency admissions involved non-steroidal anti-inflammatory drugs (NSAIDs) (11) which are commonly used to manage pain. Improved prescribing could result in better outcomes and remove the need for more costly, scarce, alternatives.

Pharmacists working in UK general practices are well-placed to improve pain pharmacotherapy because of their expertise in therapeutics, understanding of the poly-pharmacy regimens (12) frequently used in chronic pain management, and established relationships with other primary care colleagues. In the UK National Health Service (NHS), recent regulatory changes now allow accredited pharmacists (as well as some other health care professionals such as nurses) to prescribe prescription-only medicines (POMs) (13). Pharmacists can either be qualified as supplementary prescribers, in which case they operate within an agreed clinical management plan (CMP) in partnership with the doctor and patient, or as an independent prescriber, in which case they can either prescribe completely independently or within a CMP.

However, despite the increasing number of non-medical prescribers, including pharmacists, there has been no rigourous comparisons of the outcomes of non-medical versus GP prescribing. This information is needed to assess the clinical effectiveness of different care models.

This paper reports findings from an exploratory randomised controlled trial (RCT) comparing pharmacist medication review, with or without pharmacist prescribing, with standard care for

patients with chronic pain. Development of the trial was informed by earlier feasibility work (14,15).

The *a priori* theory was that, in patients with chronic pain, pharmacist advice (with or without pharmacist prescribing) would lead to better patient functioning and/or better pain control at six months than treatment as usual (TAU).

Methods

Regulatory Issues

Ethical approval was granted by the National Research Ethics Service Committee – North of Scotland (reference number 09/S0801/107). NHS Research and Development approval was granted by NHS Grampian and East Norfolk & Waveney Research Governance Committees. Patients gave informed consent before taking part.

Design

An open, exploratory RCT in which patients were randomised to one of three study arms. Participants were not blind to allocated treatment arm due to the nature of the intervention.

Recruitment of practices and independent prescribing pharmacists

Practices in the Grampian Health Board area, Scotland (n=18) and East Anglia region of England (n=4) known to have an attached Royal Pharmaceutical Society of Great Britain registered independent pharmacist prescriber, were eligible to take part. From those indicating a willingness to participate, convenience sampling was used to identify six general practices: three in Grampian and three in East Anglia.

Patient inclusion and exclusion criteria

Patients registered with the recruited practices were eligible for inclusion if they were over 18 years of age, living in their own home, and receiving regular prescribed medication for pain. Patients were identified by a computerised search (14) of the drug records of all individuals registered with the practice, to identify those who had received either two or more acute prescriptions, and/or one repeat prescription within the last 120 days, for an analgesic (British National Formulary (BNF section 4.7) and/or non-steroidal anti-inflammatory medication (NSAID) (BNF section 10.1.1). Medications which can be used for analgesia but whose primary indication is not chronic pain (e.g. triptans, anti-epileptics or anti-depressants) were excluded

as these drugs identify few additional eligible patients (16). In accordance with trial criteria, GPs excluded and recorded reasons for patients who had: a concomitant severe mental health problem or terminal illness; had suffered recent bereavement; had a known alcohol or drug addiction; suffered pain caused by cancer or other malignancy; were unable to give informed consent; other (unspecified) reasons.

Patient recruitment

Eligible patients were sent an invitation pack (letter, information sheet, consent form) by practice staff between March and June 2010. Consent forms were returned directly to the researchers, who sent out a baseline questionnaire. Patients returning completed questionnaires were randomised by the researcher using a telephone randomisation service with a random number allocation which ensured allocation concealment. The allocation sequence was 1:1:1.

Intervention

All participating pharmacists took part in a two-day course updating them about pain management. As part of the training, participants defined and agreed the treatment algorithm they would all use.

'Prescribing' arm: Pharmacists invited patients to a face-to-face consultation. Prior to the consultation, pharmacists completed a paper-based medication review of each patient's medical record and patients were asked to complete a pain diary to inform the consultation. A pharmaceutical care plan was agreed between the pharmacist and the patient. The plan assessed and documented relevant past medical history and current conditions; known allergies and adverse drug reactions; relevant laboratory results; pain-related medications prescribed in the previous 10 years; current pain related prescription medications; current symptoms; lifestyle issues, including units of alcohol consumed per week; recommendations for changes to medication (if any); whether non-pharmaceutical treatments had been considered; and, any other relevant issues. Copies of the pain diary and pharmaceutical care plan are available from the authors on request. At the end of the consultation any required prescriptions for medicines were issued by the pharmacist. Due to Controlled Drug (CD) regulations in place at the time, prescribing for CDs was done using a supplementary prescribing Clinical Management Plan (17), rather than independent prescribing. Patients were followed up either by phone or face-to-face, at each pharmacist's discretion.

'Review arm': The pharmacists conducted a paper-based medication review focussed on pain-related prescription medications, before creating a pharmaceutical care plan which detailed any recommendations for medication changes. The plan was passed to the patient's GP for implementation. The GPs were asked subsequently about actions taken as a result of the recommendations.

Treatment as usual (TAU): Patients received standard general practice care.

Outcome measures

There were two primary outcome measures: the Chronic Pain Grade (CPG) and the Medical Outcomes Study 12-item short form version 2 (SF-12v2). Use of both a pain specific and generic outcome measure was based on Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (18) and an earlier feasibility study (15).

The CPG (19) is a seven item scale which assesses pain severity on two dimensions: disability and intensity. The scale classifies pain according to level of intensity and disability (I (low disability-low intensity) to IV (high disability-severely limiting)).

The SF-12v2 is a generic health and functioning scale (20), previously used in population-based studies of pain (21, 22). A Physical (PCS) and Mental Component Score (MCS) was calculated, ranging from 0 to 100; a higher score indicates better functioning.

A secondary outcome measure was the Hospital Anxiety and Depression Scale (HADS) (23), a 14-item screening instrument which identifies the possible and probable caseness of anxiety (7 items (HADS-A)) and depression (7 items (HADS-D)); each item scored from 0 (not present) to 3 (highly present). Standard thresholds and previously used labels (24) were applied (no depression/anxiety (0-7), mild (8-10), moderate (11-15) or severe (>15)).

Data collection

Participant questionnaires

Questionnaires were posted to participants at baseline (pre-randomisation), and 3 and 6 months post-randomisation (follow-up was conducted between July 2010 and January 2011). Up to two reminders were sent. Questionnaire content included the outcome measures

described above together with items on: demographic status (baseline only); screening items to confirm eligibility (baseline only); duration of pain condition (baseline only); location of pain; Morisky Medication Adherence Scale 4 (MMAS-4) (25); participant satisfaction (11 statements derived from the feasibility study for the prescribing arm (3 months only) and additional comments by participants. The MMAS-4 provides a score of self-reported adherence to medication regimen. Scores range from 0 (low adherence) to 4 (high adherence).

Follow-up interviews with staff

Post-intervention, all pharmacists and all GPs in participating practices were invited to take part in semi-structured interviews, carried out face-to-face when possible, otherwise by telephone. Interviews were taped, transcribed verbatim and content analysis was carried out.

Sample size

As this was an exploratory trial to estimate the effect size for a larger trial, no formal sample size calculation was possible (26). We aimed to recruit 30 participants per practice (excluding those recruited for training purposes) i.e. 180 in total. This was deemed sufficient to give reliable effect size estimates for the primary outcome measures of chronic pain grade or health status.

Data management and analysis

Data were entered into identical SPSS databases at each site and accuracy checks carried out on 10% before databases were merged. Descriptive statistics included means and standard deviations (SD) for normally distributed continuous data, medians (interquartile range (IQR)) for skewed continuous data and percentages (n) for categorical data. Analysis was conducted on an intention-to-treat basis for participants with complete data on relevant measures using SPSS version 18.

Exploratory analyses for parametric data included the paired t-test for within-arm comparisons of mean difference between baseline and 6 months and one-way ANOVA for between arm comparisons of mean difference. For non-parametric data it included the Wilcoxon Signed Rank test for within-arm comparisons of median difference and the Kruskal Wallis test for between arm comparisons of median difference. Categorical data was analysed using the marginal homogeneity test for within-arm comparisons (with null hypotheis that the distribution of CPG grade or HADS group does not change between baseline and 6 month

follow-up) and the Chi-squared test for between arm comparisons; analyses reported here are based on 6 month follow-up data (other than for participant experiences). Within arm effect sizes, expressed in terms of a Pearson correlation coefficient (r) have been calculated using the formulas from Rosenthal (1991) (27). Effect sizes can be directly compared using Cohen's (1988) (28) criteria of r=0.1 (small effect); r=0.3 (medium effect) and r=0.5 (large effect).

Results

Response rates and demography

Six of the seven practices approached participated. GPs excluded 12% (392/3281) of patients, mostly those with dementia. There was no statistically significant difference between participants and non-participants in terms of age, gender, and index of multiple deprivation. Figure 1 shows the flow of participants through the study. Overall, the consent rate was 25% (356/1397) and the recruitment rate was 14% (196/1397).

[INSERT FIGURE 1 HERE]

Eighty six percent of participants (251/289) returned baseline questionnaires, of whom 232 were randomised (36 participants were randomised to one of the two intervention arms for training purposes and were not included in any further analysis and 19 were not included as recruitment target had been met). The overall follow-up rate at 3 months was 86% (161/187)and at 6 months 84% (152/180).

As shown in Table 1, groups were similar at baseline for demographic and socioeconomic variables and pain data. Most participants were married, Caucasian and female, older (mean (SD) age 65 (12.6) years), had an annual income of <£25,000 and had suffered from pain for at least five years. Most (57%;103/181) reported being fully adherent to their medication regimen (MMAS-4, median 4.0 (IQR 3.0- 4.0)) (15 missing MMAS scores).

[INSERT TABLE 1 HERE]

In the prescribing arm, 78% (53/68) attended an initial prescribing consultation, 31 had at least one planned follow-up (of which 34/37 were conducted by phone) and 130 recommendations were made for 92% (49/53) of participants seen. Examples are shown in Box 1. The median time taken for the note-based record review was 35 minutes (IQR 20.0, 45.0), the consultation

was 30 minutes (IQR 20.0, 40.0), careplan preparation 10 minutes (IQR 10.0, 20.0) and median duration of follow-ups was 10 minutes (IQR 5.0- 15.0).

[INSERT BOX 1 HERE]

In the review arm 97% (60/62) of participants' records were reviewed (note there was one post randomisation exclusion) for whom 197 recommendations were made. Where GP feedback was provided (n=48), they generally agreed with pharmacists' recommendations, which were fully implemented for 20 participants (two by the pharmacist following request by GP), partially for 19 participants and not at all for nine participants. The median time taken for the note-based record review was 30 minutes (IQR24.3, 45.0), and careplan preparation was 10 minutes (IQR 5.0, 20.0).

Clinical outcome measures

Table 2 shows the mean (SD) or median (IQR) of the CPG for each arm at baseline and 6 month follow-up. Table 3 shows the SF-12 scores and Table 4 shows the HADS-A and HADS-D results.

[INSERT TABLE 2,3,4, HERE]

In the prescribing arm, there was a statistically significant within arm improvement for the CPG intensity (p=0.002, effect size (r)=0.45) and disability (p=0.003, effect size (r)=0.43) subscales, and between arms on the intensity sub-scale (p=0.02), but not the disability subscale (p=0.55) (Table 2). There was a significant within-arm improvement in overall CPG grade in the prescribing (p=0.003) and review arm (p=0.001), but not in the TAU arm. The SF-12 Physical Component Score showed a statistically significant within arm improvement in the TAU arm (p=0.02, effect size (r)=0.35) (Table 3), but not between trial arms. The SF-12 Mental Component Score showed a statistically significant deterioration in the TAU arm (p=0.002, effect size (r)=0.45)(Table 3), as did the HADS-D (p=0.03, Table 4). Analysis was also carried out on the non-categorised HADS scores which showed a statistically significant improvement within the prescribing arm for Depression (p=0.022) and Anxiety (p=0.007). These were both significant between groups (p=0.022 and p=0.045 respectively) (Table 5).

Acceptability of the pharmacist prescribing intervention

All six pharmacists and 56% of the GPs (23/41) were interviewed. All pharmacists and most GPs were positive about the intervention, although some GPs suggested that the pharmacists'

recommendations had been minor and questioned the cost-effectiveness of the service. Patient participants were generally positive about the pharmacist prescribing service although some concerns were identified, as Illustrated by the quotes shown in Box 2.

[INSERT BOX 2 HERE]

Discussion

Principal findings

This exploratory RCT of pharmacist-led management of patients with chronic pain suggests that pharmacist prescribing (and possibly pharmacist review alone) may be effective in improving pain-related outcomes and be acceptable to both patients and most professionals. There was an indication of a positive effect on emotional health, but no measurable effect on general health.

Strengths and weaknesses

This was the first RCT to assess clinical and humanistic outcomes after pharmacist prescribing for any clinical condition compared to usual GP care, and the first RCT to specifically assess pharmacist-led management of chronic pain, compared with usual GP care. It was based on extensive development and feasibility work (14,15) in line with MRC framework for development and evaluation of complex interventions (29). A range of validated outcome measures was included, as well as a parallel qualitative process evaluation which assessed satisfaction and acceptability. The inclusion of six practices and their associated pharmacists from both Scotland and England increased the generalisability of the findings. Pharmacists received formal training and agreed and used a common treatment algorithm which should have increased standardisation of treatment. The preponderance of females (overall 62%) and average age of 65 years reflects the wider chronic pain population (1) as does the distribution of pain site (30, 31,)

There were, however limitations. Although high follow-up response rates were achieved at both three (86%) and six months (85%) only 25% of eligible patients entered the trial. This low initial consent rate is in line with other studies (32, 33), but may cause unknown biases including problems of generalisability, as does the solely Caucasian ethnicity. Concerns identified by participants during the formal feedback e.g. having too many people involved in one's care may have contributed to poor response rates and rewording of participant

recruitment documentation to reassure participants of the role of the pharmacist could address this. More participants withdrew in the prescribing arm compared with the other two arms, which might be attributed to the need for an additional practice visit. The study was an exploratory trial so no formal power calculation was undertaken. However, because there were no published MIDs available to estimate effect size for the outcomes in this population, it was important to present the actual clinical magnitude of change in outcome at 6 months alongside a statistical assessment of this change (p-value). This allows an assessment of both clinical and statistical significance simultaneously with the caveat that this is an exploratory study. With around 50 patients per arm, this was deemed sufficient numbers to examine the change in outcome measures with appropriate within and between group univariate statistical tests. Due to the nature of the intervention, no participants were blind to their group allocation, and so some outcomes, especially the qualitative components, may have been affected by social desirability bias.

Our main outcome measures were self-reported, but this is the norm in pain studies as pain is a subjective experience (18). Furthermore we do not know how important the observed differences were to participants. Following precedents set in previous research (25), and because there is no consensus on an alternative measure (34) we used the HADS as a tool to classify people by severity of depression and anxiety. However it is strictly a screening tool, and the four levels of severity have not been formally validated. We therefore also compared outcomes using it as a continuous scale.

Relationship with other studies

This study is important because no other RCT has evaluated pharmacist prescribing and few studies, and importantly no RCTs, have evaluated pharmacist interventions for pain. In pharmacist prescribing most research has focussed on reported experiences of professionals and patients, and not used validated outcome measures. Yet pharmacist prescribing is now widely practised. For pain, there have been a few small studies. Briggs et al (2008) (35) conducted a small before-and-after evaluation (involving 65 patients) of a nurse and pharmacist-led chronic pain clinic in primary care. Pain intensity Visual Analogue Scale scores reduced significantly over six months. Another evaluation of 26 patients using a medication review service provided jointly by a physiotherapist and pharmacist in the UK, reported improvement in pain control for 88% of patients (36).

The CPG was found to show a graded effect across the three arms, showing discrimination with both direction and strength of improvement, suggesting maximum benefit for those in the pharmacist prescribing arm. However, the reduction in overall score appears to be mediated by a change in the intensity of pain subscale rather than in pain-related disability. The effect size of 0.45 suggests this could be an important difference. In contrast, the SF-12, a measure of general health and functionality showed no significant difference between intervention arms, reflecting either no effect or or lack of powerto detect an effect.

Whilst most participants in this study were already within the normal range on the HADS scale, and therefore had minimal chance of improvement, there were nonetheless suggestions of better ourcomes in participants in the prescribing arm. Including a range of instruments is in line with IMMPACT recommendations (37), which state that focus should be on the whole person, not just about pain. However, this needs to be balanced with minimising participant burden.

Explanations, implications, and future research

The number of pharmacists' recommendations per participant was higher in the review arm than in the prescribing arm. This might seem contradictory to the possible greater benefit found in the prescribing arm. However, in the prescribing arm pharmacists met the participant and may have more readily identified and dismissed suggestions previously tried. The interview feedback highlighted that some recommendations for change, whilst sensible, had been tried already. This might also be the reason why there were only 60% of pharmacist recommendations with which the GP fully agreed. Self-reported adherence to medication at baseline was good. Despite this, the pharmacists still improved pain outcomes in the prescribing arm. This could have been due to changes in medications and/or participant education about optimal timing for administration of analgesic medicines. Further research is needed to confirm the beneficial effect of pharmacist prescribing and its sustainability.

Conclusion

Our results suggest that pharmacist prescribing (and possibly pharmacist review alone) for patients with chronic pain is feasible, acceptable and may lead to improvements in pain and other measures. A larger fully-powered trial is now needed to confirm these findings.

Data sharing statement

Consent was not obtained from participants for data sharing; the presented data are anonymised and there is no risk of individual identification. Requests for data should be made to the contact author who will provide this in a format in which risk of patient identification will be minimal.

Conflict of interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

HB and CB drafted the manuscript.

All authors:

1) made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

2) were involved in drafting the manuscript or revising it critically for important intellectual content; and

3) have given final approval of the version to be published.

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All authors had access to all of the study data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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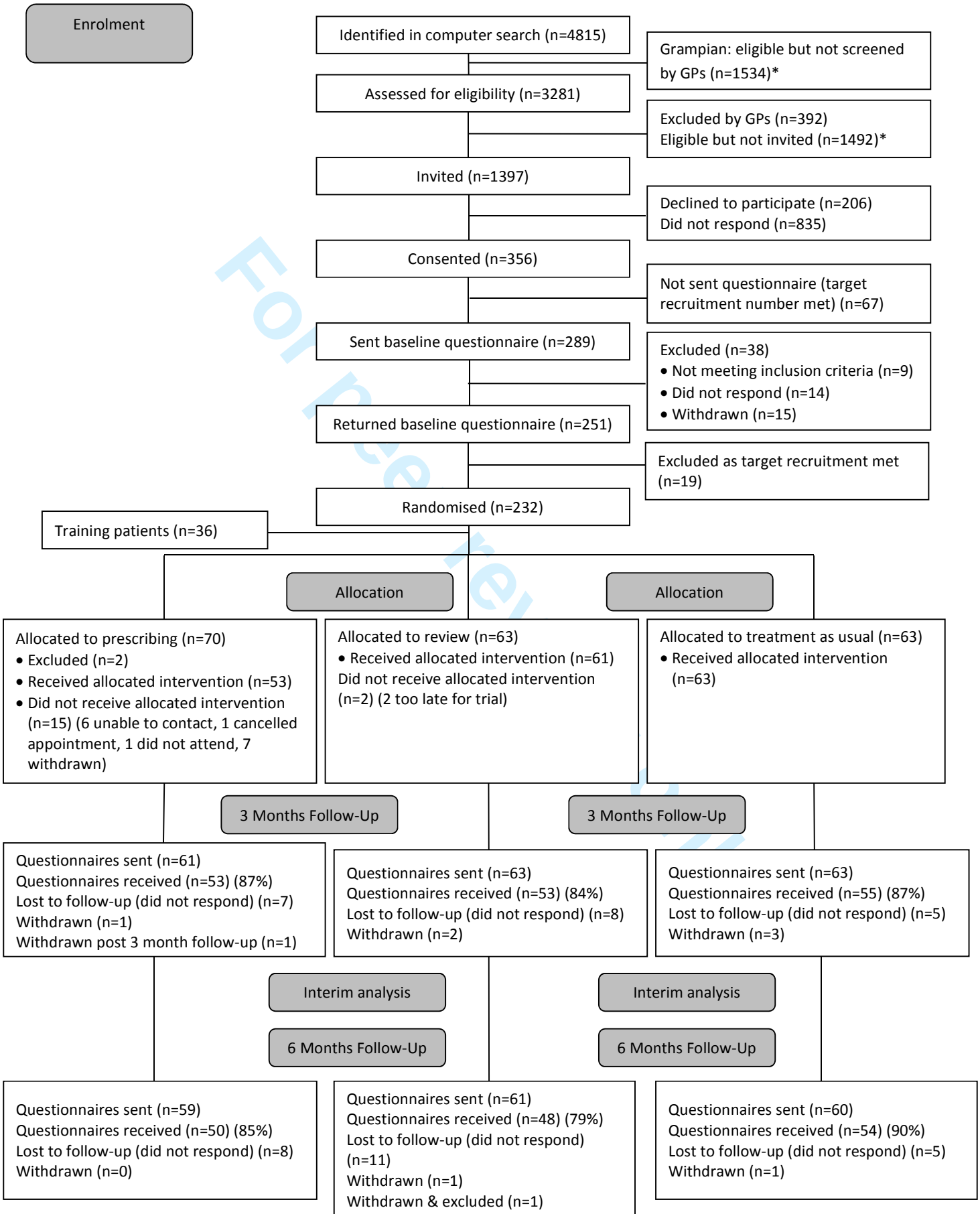
Figure 1: CONSORT Flow Diagram



*In the **Grampian Health Board area**, on the basis of response rates in the earlier feasibility study (241 screened patients resulted in 22 recruited) only a random sample of eligible participants were screened (15). In East Anglia all eligible patients were screened.

Table 1: Baseline demographic, socio-economic and pain data of patients by study arm, prescribing, review and treatment as usual (TAU)

	Prescribing* (n = 68)	**Review*** (n = 62)	**TAU*** (n = 63)
Age: mean (SD)	66.1 (12.1)	65.7 (14.2)	64.9 (11.6)
Missing	1	1	0
Gender (% female)	54.4 (37)	74.2 (46)	58.7 (37)
Marital status			
Married	43	30	41
Single	6	6	3
Divorced/widow	10	21	13
Other	6	4	6
Missing	3	1	0
Highest educational level achieved			
No qualifications	30	27	21
O grade or equivalent	12	6	14
Higher/A-level/NVQ3/SVQ3	6	8	7
Tertiary education/NVQ4/NVQ5	18	17	14
Other	2	1	4
Missing	0	3	3
Employment status			
Employed	16	14	9
Unemployed	3	5	1
Retired	38	35	34
Long term sick/disabled	7	5	9
Other	3	2	7
Missing	1	1	3
Household annual income before tax			
Less than £9,999	13	15	10
£10,000 - £14,999	14	18	22
£15,000 - £24,999	14	12	12
£25,000 – or more	22	11	8
Missing	5	6	11
Ethnic group			
Caucasian	67	62	61
Other	1		
Missing	0	0	2
Pain duration			
< 1 year	3	2	4
1 – 3 years	12	12	7
3 – 5 years	10	13	9
5 – 10 years	17	13	15
> 10 years	26	22	28
Pain localisation (%, n)			
Back	27.9 (19)	32.3 (20)	20.6 (13)
Neck, shoulders	7.4 (5)	9.7 (6)	9.5 (6)
Limbs or hips	42.6 (29)	30.6 (19)	50.8 (32)
Other	8.8 (6)	4.8 (3)	7.9 (5)
Missing	9	14	7

*Denominator based on numbers allocated to the specific arms, minus any exclusions due to protocol violations.

Table 2: Mean (standard deviation, SD) CPG intensity , median (interquartile range, IQR) CPG disability, and count CPG grade at baseline, 6 months follow-up and difference between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). P-values for within and between arm differences are also reported.

	Prescribing		Review		TAU		P (between groups***)
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	
Baseline CPG intensity	47	66.1 (16.0)	45	68.4 (17.6)	54	65.4 (18.0)	
6 month follow-up CPG intensity		58.1 (19.5)		67.4 (21.7)		65.6 (19.6)	
Difference CPG intensity		-8.0 (16.3)		-1.0 (16.0)		0.2 (14.9)	
P (within groups**)		0.002		0.67		0.93	0.02
Effect size (r)		0.45		0.07		0.01	
		Median [IQR]		Median [IQR]		Median [IQR]	
Baseline CPG disability	48	60.0 [30.0; 75.8]	46	66.7 [45.0; 80.0]	53	56.7 [36.7; 80.0]	
6 Month follow-up CPG disability		40.0 [20.0; 60.0]		53.3 [29.2; 73.3]		50.0 [25.0; 80.0]	
Difference CPG disability		-8.3 [-23.3; 0.0]		-3.3 [-16.7; 10.0]		-3.3 [-21.7; 5.0]	
P (within groups**)		0.003		0.15		0.05	0.55
Effect size (r)		0.43		0.20		0.26	
Baseline CPG grade	44	Count (%)	44	Count (%)	48	Count (%)	
I		5 (11.4)		3 (6.8)		5 (10.4)	
II		16 (36.4)		9 (20.5)		13 (27.1)	
III		7 (15.9)		10 (22.7)		13 (27.1)	
VI		16 (36.4)		22 (50.0)		17 (35.4)	
6 month follow-up CPG grade							
I		13 (29.5)		8 (18.2)		6 (12.5)	
II		13 (29.5)		15 (34.1)		17 (35.4)	
III		8 (18.2)		8 (18.2)		11 (22.9)	
IV		10 (22.7)		13 (29.5)		14 (29.2)	
Difference CPG grade							
≤-1		21 (47.7)		17 (38.6)		15 (31.2)	
0		17 (38.6)		25 (56.8)		25 (52.1)	
≥1		6 (13.6)		2 (4.5)		8 (2.1)	0.16
P (within groups***)		0.003		0.001		0.17	

*Number of participants in each group who completed the appropriate part of the CPG at both baseline and follow-up.

** From paired t-test, Wilcoxon signed rank test or marginal homogeneity test as appropriate

*** From ANOVA on mean difference, Kruskall-Wallis on median difference or chi-squared test on difference in CPG grade as appropriate

Table 3: Mean (standard deviation, SD) SF12 Physical Component Score (PCS) and median (interquartile range, IQR) Mental Component Score (MCS) at baseline and 6 month follow-up and difference between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.

	Prescribing		Review		TAU		
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	P (between groups***)
Baseline SF12 PCS	41	33.5 (10.8)	43	32.59(11.38)	45	29.60 (9.71)	
6 month follow-up SF12 PCS		35.3 (10.8)		34.62 (11.26)		32.59 (9.14)	
Difference SF12 PCS		1.8 (7.5)		2.02 (7.56)		2.99 (8.11)	
P (within groups**)		0.12		0.09		0.02	0.75
Effect size (r)		0.24		0.26		0.35	
		Median [IQR]		Median (IQR)	45	Median (IQR)	
Baseline SF12 MCS	42	52.4 [42.0; 58.8]	43	47.9 [38.5; 59.9]		51.5 [41.3; 60.7]	
6 month follow-up SF12 MCS		49.6 [42.8; 58.1]		47.9 [38.9; 56.2]		44.7 [37.6; 55.8]	
Difference SF12 MCS		-0.4 [-3.7; 6.0]		-1.2 [-6.6; 4.2]		-3.0 [-10.0; 1.3]	
P (within groups**)		0.64		0.37		0.002	0.04
Effect size (r)		0.07		0.14		0.46	

* Number of participants in each group who completed the appropriate part of the SF-12 at both baseline and follow-up.

** From paired t-test or Wilcoxon signed rank test as appropriate

*** From ANOVA on mean difference or Kruskall-Wallis test on median difference as appropriate

Table 4: The HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) count of patients according to severity (normal, mild, moderate or severe) and the difference in severity category between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.*

	n	**Prescribing**	n	**Review**	n	**TAU**	
Baseline HADS-D	44	Count (%)	45	Count (%)	53	Count (%)	P (between groups***)
Normal		32 (72.7)		31 (68.9)		38 (71.7)	
Mild		8 (18.2)		11 (24.4)		7 (13.2)	
Moderate		3 (6.8)		3 (6.7)		8 (15.1)	
Severe		1 (2.3)		0		0	
6 month follow-up HADS-D							
Normal		32 (72.7)		32 (71.1)		32 (60.4)	
Mild		7 (15.9)		6 (13.3)		10 (18.9)	
Moderate		5 (11.4)		6 (13.3)		8 (15.1)	
Severe		0		1 (2.2)		3 (5.7)	
Difference HADS-D							
≤-1		5 (11.4)		4 (8.9)		2 (3.8)	
0		34 (77.3)		37 (82.0)		40 (75.5)	
≥1		5 (11.4)		4 (8.9)		11 (20.8)	0.32
P (within groups**)		1.0		0.71		0.03	
Baseline HADS-A	44	Count (%)	43	Count (%)	48	Count (%)	
Normal		25 (56.8)		30 (69.8)		29 (60.4)	
Mild		8 (18.2)		7 (16.3)		9 (18.8)	
Moderate		8 (18.2)		5 (11.6)		8 (16.7)	
Severe		3 (6.8)		1 (2.3)		2 (4.2)	
6 month follow-up HADS-A							
Normal		27 (61.4)		29 (67.4)		32 (66.7)	
Mild		7 (15.9)		6 (14.0)		5 (10.4)	
Moderate		8 (18.2)		6 (14.0)		10 (20.8)	
Severe		2 (4.5)		2 (4.7)		1 (2.1)	
Difference HADS-A							
≤-1		6 (13.6)		3 (7.0)		10 (20.8)	
0		35 (79.5)		33 (76.7)		29 (60.4)	
≥1		3 (6.8)		7 (16.3)		9 (18.8)	0.14
P (within groups**)		0.25		0.21		0.55	

* Number of participants in each group who completed the appropriate part of the HADS at both baseline and follow-up.

** From marginal homogeneity test

*** From chi-squared test on difference in HADS

Table 5: Median HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) scores (interquartile range, IQR) at baseline and 6 month follow-up and difference between the two assessment point for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.

	Prescribing		Review		TAU		
	n	Median [IQR]	n	Median [IQR]	n	Median [IQR]	P (between groups)
Baseline HADS-D	42	5.0 [3.0;8.0]	44	4.5 [2.3; 8.0]	51	5.0 [3.0; 8.0]	
6 month follow-up HADS-D		4.0 [2.0; 8.0]		5.0 [2.0; 8.8]		5.0 [2.0; 10.0]	
Difference HADS-D		-1.0 [-2.0; 0.0]		0.0 [-1.0; 1.8]		0.0 [-1.0; 2.0]	0.02
P (within groups)		0.02		0.33		0.22	
Baseline HADS-A	44	7.0 [3.3; 10.8]	43	5.0 [3.0; 10.0]	48	6.0[4.0; 10.0]	
6 month follow-up HADS-A		5.0 [2.3; 9.8]		6.0 [3.0; 9.0]		7.0 [4.0; 10.0]	
Difference HADS-A		-1.0 [-2.0; 0.0]		0.0 [-2.0; 2.0]		0.5 [-3.0; 2.0]	0.05
P (within groups)		0.01		0.45		0.81	

* Number of participants in each group who completed the appropriate part of the HADS at both baseline and follow-up.

Box 1 Examples of pharmacist interventions in the prescribing arm

Changes to pain management: 'use paracetamol regularly', 'take tramadol if needed' 'add piroxicam gel PRN', 'given web links to self help groups'

Compliance aid: ' gave written times that this drug could be taken'

Addressing side effects/safety: 'take paracetamol after initial NSAID', 'take senna', 'ordered blood monitoring', 'stop use of two NSAIDS'

General health: 'discussed weight loss', 'invited to practice nurse for BP', 'glucose, lipids and lifestyle update',

Cost minimisation: 'change aspirin EC to plain',

BOX 2 Examples of quotes from Pharmacists (n=6), GPs (n=23) and patient participants (n=40) on the prescribing intervention

Pharmacists (from interviews):

Satisfying (n=6):'contact with patients', 'being able to help patients', 'being able to make a difference to long-standing pain'...'even in small ways'

Interesting (n=6):'learning about pain'

Challenging (n=6):'complex, chronically ill patients'

GPs (from interviews):

Support for the service (n=17): it's been a very positive thing'

Agreement with pharmacists' recommendations (n=23): 'oh very reasonable suggestions', 'tinkering round the edges', 'had been tried already'.

Trust in the practice pharmacist (n=23):'I respect his professional judgement'

Cost effectiveness (n=6): 'if there's limited resources do we want to spend the money on a pharmacist'.

Patients (from 3 month questionnaire):

Closed questions:

Proportion agreeing that:
The pharmacist was interested in them (89%; 39/44)
They were totally satisfied (85%; 39/46)
They were told about their treatment (82%; 38/46)
Their consultation was thorough (79%; 34/44)
They would have liked more time (9%;4/44)
They would have preferred to see their GP (9%; 4/44)
Too many people were now involved in their treatment (11%; 5/44).

Open text questions:

Positive (n=39): 'She was professional, relaxed, pleasant and interested. Excellent!'

Negative (n=1): 'A waste of time, altered my tablets which made my pain worse'.

Title page

Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial

Hanne Bruhn, Christine M Bond, Alison M Elliott, Philip C Hannaford, Amanda J Lee, Paul McNamee, Blair H Smith, Margaret C Watson, Annie Blyth, Richard Holland, David Wright

Centre for Healthcare Randomised Trials, Health Services Research Unit, University of Aberdeen, 3rd floor Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD, UK Hanne Bruhn, Trial Manager

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Christine M Bond, Professor of Primary Care: Pharmacy

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Alison M Elliott, Senior Research Fellow

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Philip C Hannaford, NHS Grampian Chair of Primary Care

Medical Statistics Team, Division of Applied Health Sciences~~Population Health, 1st floor~~, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK, Amanda J Lee, Professor of Medical Statistics

Health Economics Research Unit, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK, Paul McNamee, Reader

Mackenzie Building, Kirsty Semple Way, Ninewells Hospital and Medical School, Dundee, DD2 4RB, UK, Blair H Smith, Professor of Population Science

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Margaret C Watson, Senior Research Fellow

Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK, Annie Blyth, Research Associate

Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK, Richard Holland, Professor of Public Health Medicine

School of Pharmacy, University of East Anglia, Norwich Research Park, NR4 7TJ, UK, David Wright, Chair in Pharmacy Practice

Correspondence to: Professor CM Bond c.m.bond@abdn.ac.uk, Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK

Abstract

Objectives

To compare the effectiveness of pharmacist medication-review, with or without pharmacist prescribing, with standard care, for patients with chronic pain.

Design

An exploratory randomised controlled trial.

Setting

Six general practices with prescribing pharmacists in Grampian (3) and East Anglia (3).

Participants

Patients on repeat prescribed pain medication(4815) were screened by GPs, and mailed invitations (1397). 196 were randomised and 180 (92%) completed. Exclusion criteria included: severe mental illness, terminally ill, cancer related pain, history of addiction

Randomisation and intervention

Patients were randomised using a remote telephone service to: (i) pharmacist medication-review with face-to-face pharmacist prescribing; or (ii) pharmacist medication-review with feedback to GP and no planned patient contact; or (iii) treatment as usual (TAU). Blinding was not possible.

Outcome measures

Primary outcomes were the Chronic Pain Grade (CPG) and the SF-12v2, together with Hospital Anxiety and Depression Scale (HADS). Outcomes were collected at 0,3,and 6 months. Ethical approval was obtained.

Results

In the prescribing arm (n=70) two patients were excluded/nine withdrew. In the review arm (n=63) one was excluded/three withdrew. In the TAU arm (n=63) four withdrew. Compared with baseline, patients had an improved CPG in the prescribing arm, 47.7% (21/44; p=0.003), and in the review arm, 38.6% (17/44; p=0.001), but not the TAU group, 31.3% (15/48; ns). The SF-12 PCS showed no effect in the prescribing or review arms but improvement in TAU

(p=0.02). The SF-12 MCS showed no effect for the prescribing or review arms and deterioration in the TAU arm (p=0.002). HADS scores improved within the prescribing arm for Depression (p=0.022) and Anxiety (p=0.007), between groups (p=0.022 and p=0.045 respectively)

-Conclusion

This is the first RCT of pharmacist-prescribing in the UK, and suggests ~~a~~ there may be a ~~-~~benefit for patients with chronic pain. A larger trial is required.

Trial registration: www.isrctn.org/ISRCTN06131530. Medical Research Council funding.

Focus:

- Chronic pain, (lasting >3 months) affects up to half the adult population, most of whom are primarily managed in primary care but prescribing is often sub-optimal.
- Pharmacists now have prescribing rights but no published research has compared the effectiveness of their prescribing with that of GPs.
- The theory~~hypothesis~~ was that pharmacist advice (with or without pharmacist prescribing) would lead to better outcomes than usual care

Key messages:

- The findings suggest there may be improved pain related outcomes for patients receiving pain related care from a pharmacist prescriber
- A larger trial is called for.

Strengths and Limitations

- This the first randomised controlled trial of pharmacist prescribing in the UK looking at patient reported clinical outcomes
- The study was designed as an exploratory trial so no power calculation was done

Introduction

Chronic pain (pain lasting more than three months) affects up to half the adult United Kingdom (UK) population, and is considered severely limiting in about 15% of cases (1). Recovery is uncommon with nearly 80% of those identified with chronic pain at baseline still reporting chronic pain four years later (2). It adversely affects many aspects of a person's physical and psychological health, and social and economic well being (3-6).

In the UK, most patients with chronic pain present, and are managed, in primary care (7). Although non-pharmacological treatments are available, these are accessed by few patients, with mixed success (e.g. (8-10). Analgesics prescribed in primary care remain the mainstay of treatment (4), representing substantial workload and cost. Sub-optimal prescribing may lead to poor pain control and other adverse patient outcomes. One study found that the most common medications involved in adverse drug reaction-related emergency admissions involved non-steroidal anti-inflammatory drugs (NSAIDs) (11) which are commonly used to manage pain. Improved prescribing could result in better outcomes and remove the need for more costly, scarce, alternatives.

Pharmacists working in UK general practices are well-placed to improve pain pharmacotherapy because of their expertise in therapeutics, understanding of the poly-pharmacy regimens (12) frequently used in chronic pain management, and established relationships with other primary care colleagues. In the UK National Health Service (NHS), recent regulatory changes now allow accredited pharmacists (as well as some other health care professionals such as nurses) to prescribe prescription-only medicines (POMs) (13). Pharmacists can either be qualified as supplementary prescribers, in which case they operate within an agree-d clinical management plan (CMP) in partnership with the doctor and patient, or as an independent prescriber, in which case they can either prescribe completely independently or within a CMP.

However, despite the increasing number of non-medical prescribers, including pharmacists, there has been no rigourous comparisons of the outcomes of non-medical versus GP prescribing. This information is needed to assess the clinical effectiveness of different care models.

This paper reports findings from an exploratory randomised controlled trial (RCT) comparing pharmacist medication review, with or without pharmacist prescribing, with standard care for

patients with chronic pain. Development of the trial was informed by earlier feasibility work (14,15).

The *a priori* theory ~~hypothesis~~ was that, in patients with chronic pain, pharmacist advice (with or without pharmacist prescribing) would lead to better patient functioning and/or better pain control at six months than treatment as usual (TAU). ~~The hypothesis was developed prior to data collection.~~

Comment [g1]: Think we need to stay away from word hypothesis since it implies a powered study

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Methods

Regulatory Issues

Ethical approval was granted by the National Research Ethics Service Committee – North of Scotland (reference number 09/S0801/107). NHS Research and Development approval was granted by NHS Grampian and East Norfolk & Waveney Research Governance Committees. Patients gave informed consent before taking part.

Design

An open, exploratory RCT in which patients were randomised to one of three study arms. Participants were not blind to allocated treatment arm due to the nature of the intervention.

Recruitment of practices and independent prescribing pharmacists

Practices in the Grampian Health Board area, Scotland (n=18) and East Anglia region of~~,~~ England (n=4) known to have an attached Royal Pharmaceutical Society of Great Britain registered independent pharmacist prescriber, were eligible to take part. From those indicating a willingness to participate, convenience sampling was used to identify six general practices: three in Grampian and three in East Anglia.

Patient inclusion and exclusion criteria

Patients registered with the recruited practices were eligible for inclusion if they were over 18 years of age, living in their own home, and receiving regular prescribed medication for pain. Patients were identified by a computerised search (14) ~~{5 McDermott, M. E. 2006}~~ of the drug records of all individuals registered with the practice, to identify those who had received either two or more acute prescriptions, and/or one repeat prescription within the last 120 days, for an analgesic (British National Formulary (BNF section 4.7) and/or non-steroidal anti-

inflammatory medication (NSAID) (BNF section 10.1.1). Medications which can be used for analgesia but whose primary indication is not chronic pain (e.g. triptans, anti-epileptics or anti-depressants) were excluded as these drugs identify few additional eligible patients (16). In accordance with trial criteria, GPs excluded and recorded reasons for patients who had: a concomitant severe mental health problem or terminal illness; had suffered recent bereavement; had a known alcohol or drug addiction; suffered pain caused by cancer or other malignancy; were unable to give informed consent; other (unspecified) reasons.

Patient recruitment

Eligible patients were sent an invitation pack (letter, information sheet, consent form) by practice staff between March and June 2010. Consent forms were returned directly to the researchers, who sent out a baseline questionnaire. Patients returning completed questionnaires were randomised by the researcher using a telephone randomisation service with a random number allocation which ensured allocation concealment. The allocation sequence was 1:1:1.

Intervention

All participating pharmacists took part in a two-day course updating them about pain management. As part of the training, participants defined and agreed the treatment algorithm they would all use.

'Prescribing' arm: Pharmacists invited patients to a face-to-face consultation. Prior to the consultation, pharmacists completed a paper-based medication review of each patient's medical record and patients were asked to complete a pain diary to inform the consultation. A pharmaceutical care plan was agreed between the pharmacist and the patient. The plan assessed and documented relevant past medical history and current conditions; known allergies and adverse drug reactions; relevant laboratory results; pain-related medications prescribed in the previous 10 years; current pain related prescription medications; current symptoms; lifestyle issues, including units of alcohol consumed per week; recommendations for changes to medication (if any); whether non-pharmaceutical treatments had been considered; and, any other relevant issues. Copies of the pain diary and pharmaceutical care plan are available from the authors on request. At the end of the consultation any required prescriptions for medicines were issued by the pharmacist. Due to Controlled Drug (CD) regulations in place at the time, prescribing for CDs was done using a supplementary

prescribing Clinical Management Plan (17), rather than independent prescribing. Patients were followed up either by phone or face-to-face, at each pharmacist's discretion.

'Review arm': The pharmacists conducted a paper-based medication review focussed on pain-related prescription medications, before creating a pharmaceutical care plan which detailed any recommendations for medication changes. The plan was passed to the patient's GP for implementation. The GPs were asked subsequently about actions taken as a result of the recommendations.

Treatment as usual (TAU): Patients received standard general practice care.

Outcome measures

There were two primary outcome measures: the Chronic Pain Grade (CPG) and the Medical Outcomes Study 12-item short form version 2 (SF-12v2). Use of both a pain specific and generic outcome measure was based on Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (18) and an earlier ~~(18,19)~~feasibility study (15).

The CPG (19~~20~~) is a seven item scale which assesses pain severity on two dimensions: disability and intensity. The scale classifies pain according to level of intensity and disability (I (low disability-low intensity) to IV (high disability-severely limiting)).

The SF-12v2 is a generic health and functioning scale (20~~21~~), previously used in population-based studies of pain (21, 22~~22,23~~). A Physical (PCS) and Mental Component Score (MCS) was calculated, ranging from 0 to 100; a higher score indicates better functioning.

A secondary outcome measure was the ~~{(}~~Hospital Anxiety and Depression Scale (HADS) (23~~24~~), a 14-item screening instrument which identifies the possible and probable caseness of anxiety (7 items (HADS-A)) and depression (7 items (HADS-D)); each item scored from 0 (not present) to 3 (highly present). Standard thresholds and previously used labels (24~~5~~) were applied (no depression/anxiety (0-7), mild (8-10), moderate (11-15) or severe (>15)).

Data collection

Participant questionnaires

Questionnaires were posted to participants at baseline (pre-randomisation), and 3 and 6 months post-randomisation (follow-up was conducted between July 2010 and January 2011). Up to two reminders were sent. Questionnaire content included the outcome measures described above together with items on: demographic status (baseline only); screening items to confirm eligibility (baseline only); duration of pain condition (baseline only); location of pain; Morisky Medication Adherence Scale 4 (MMAS-4) (256); participant satisfaction (11 statements derived from the feasibility study for the prescribing arm (3 months only) and additional comments by participants. The MMAS-4 provides a score of self-reported adherence to medication regimen. Scores range from 0 (low adherence) to 4 (high adherence).

Follow-up interviews with staff

Post-intervention, all pharmacists and all GPs in participating practices were invited to take part in semi-structured interviews, carried out face-to-face when possible, otherwise by telephone. Interviews were taped, transcribed verbatim and content analysis was carried out.

Sample size

As this was an exploratory trial to estimate the effect size for a larger trial, no formal sample size calculation was possible (267). We aimed to recruit 30 participants per practice (excluding those recruited for training purposes) i.e. 180 in total. This was deemed sufficient to give reliable effect size estimates for the primary outcome measures of chronic pain grade or health status.

Data management and analysis

Data were entered into identical SPSS databases at each site and accuracy checks carried out on 10% before databases were merged. Descriptive statistics included means and standard deviations (SD) for normally distributed continuous data, medians (interquartile range (IQR)) for skewed continuous data and percentages (n) for categorical data. Analysis was conducted on an intention-to-treat basis for participants with complete data on relevant measures using SPSS version 18.

Exploratory analyses -for parametric data included the paired t-test for within-arm comparisons of mean difference between baseline and 6 months and one-way ANOVA for between arm comparisons of mean difference. For non-parametric data it included the Wilcoxon Signed Rank test for within-arm comparisons of median difference and the Kruskal Wallis test for

between arm comparisons of median difference. Categorical data was analysed using the marginal homogeneity test for within-arm comparisons ~~of~~ (with null hypotheis that the distribution of CPG grade or HADS group does not change between baseline and 6 month follow-up) and the Chi-squared test for between arm comparisons; analyses reported here are based on 6 month follow-up data (other than for participant experiences). Within arm effect sizes, expressed in terms of a Pearson correlation coefficient (r) have been calculated using the formulas from Rosenthal (1991) (27). Effect sizes can be directly compared using Cohen's (1988) (28) criteria of r=0.1 (small effect); r=0.3 (medium effect) and r=0.5 (large effect).

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Results

Response rates and demography

Six of the seven practices approached participated. GPs excluded 12% (392/3281) of patients, mostly those with dementia. There was no statistically significant difference between participants and non-participants in terms of age, gender, and index of multiple deprivation. Figure 1 shows the flow of participants through the study. Overall, the consent rate was 25% (356/1397) and the recruitment rate was 14% (196/1397).

[INSERT FIGURE 1 HERE]

Eighty six percent of participants (251/289) returned baseline questionnaires, of whom 232 were randomised (36 participants were randomised to one of the two intervention arms for training purposes and were not included in any further analysis and 19 were not included as recruitment target had been met). The overall follow-up rate at 3 months was 86% (161/187)and at 6 months 84% (152/180).

As shown in Table 1, groups were similar at baseline for demographic and socioeconomic variables and pain data. Most participants were married, Caucasian and female, older (mean (SD) age 65 (12.6) years), had an annual income of <£25,000 and had suffered from pain for at least five years. Most (57%;103/181) reported being fully adherent to their medication regimen (MMAS-4, median 4.0 (IQR 3.0- 4.0)) (15 missing MMAS scores).

[INSERT TABLE 1 HERE]

In the prescribing arm, 78% (53/68) attended an initial prescribing consultation, 31 had at least one planned follow-up (of which 34/37 were ~~generally~~ conducted by phone) and 130

recommendations were made for 92% (49/53) of participants seen. Examples are shown in Box 1. The median time taken for the note-based record review was 35 minutes (IQR 20.0, 45.0), the consultation was 30 minutes (IQR 20.0, 40.0), careplan preparation 10 minutes (IQR 10.0, 20.0) and median duration of follow-ups was 10 minutes (IQR 5.0- 15.0).

[INSERT BOX 1 HERE]

In the review arm 97% (60/62) of participants' records were reviewed (note there was one post randomisation exclusion) for whom 197 recommendations were made. Where GP feedback was provided (n=48), they generally agreed with pharmacists' recommendations, which were fully implemented for 20 participants (two by the pharmacist following request by GP), partially for 19 participants and not at all for nine participants. The median time taken for the note-based record review was 30 minutes (IQR24.3, 45.0), and careplan preparation was 10 minutes (IQR 5.0, 20.0).

Clinical outcome measures

Table 2 shows the mean (SD) or median (IQR) of the CPG for each arm at baseline and 6 month follow-up. Table 3 shows the SF-12 scores and Table 4 shows the HADS-A and HADS-D results.

[INSERT TABLE 2,3,4, HERE]

In the prescribing arm, there was a statistically significant within arm improvement for the CPG intensity (p=0.002, effect size (r)=0.45) and disability (p=0.003, effect size (r)=0.43) subscales, and between arms on the intensity sub-scale (p=0.02), but not the disability subscale (p=0.55) (Table 2). There was a significant within-arm improvement in overall CPG grade in the prescribing (p=0.003) and review arm (p=0.001), but not in the TAU arm. The SF-12 Physical Component Score showed a statistically significant within arm improvement in the TAU arm (p=0.02, effect size (r)=0.35) (Table 3), but not between trial arms. The SF-12 Mental Component Score showed a statistically significant deterioration in the TAU arm (p=0.002, effect size (r)=0.45)(Table 3), as did the HADS-D (p=0.03, Table 4). Analysis was also carried out on the non-categorised HADS scores which showed a statistically significant improvement within the prescribing arm for Depression (p=0.022) and Anxiety (p=0.007). These were both significant between groups (p=0.022 and p=0.045 respectively) (Table 5).

Acceptability of the pharmacist prescribing intervention

All six pharmacists and 56% of the GPs (23/41) were interviewed. All pharmacists and most GPs were positive about the intervention, although some GPs suggested that the pharmacists' recommendations had been minor and questioned the cost-effectiveness of the service. Patient participants were generally positive about the pharmacist prescribing service although some concerns were identified, as Illustrated by the quotes shown in Box 2.

[INSERT BOX 2 HERE]

Discussion

Principal findings

This exploratory RCT of pharmacist-led management of patients with chronic pain suggests that pharmacist prescribing (and possibly pharmacist review alone) may be effective in improving pain-related outcomes and be acceptable to both patients and most professionals. There was an indication of a positive effect on emotional health, but no measurable effect on ~~-~~general health.

Strengths and weaknesses

This was the first RCT to assess clinical and humanistic outcomes after pharmacist prescribing for any clinical condition compared to usual GP care, and the first RCT to specifically assess pharmacist-led management of chronic pain, compared with usual GP care. It was based on extensive development and feasibility work (14,15) in line with MRC framework for development and evaluation of complex interventions (~~28~~29). A range of validated outcome measures was included, as well as a parallel qualitative process evaluation which ~~demonstrated~~ assessed satisfaction and acceptability. The inclusion of six practices and their associated pharmacists from both Scotland and England increased the generalisability of the findings. Pharmacists received formal training and agreed and used a common treatment algorithm which should have increased standardisation of treatment~~.~~. The preponderance of females (overall 62%) and average age of 65 years reflects the wider chronic pain population (1) as does the distribution of pain site (30, 31,~~29,30~~)

There were, however limitations. Although high follow-up response rates were achieved at both three (86%) and six months (85%) only 25% of eligible patients entered the trial. This low initial consent rate is in line with other studies (32, 33~~31,32~~~~29,30~~), but may cause unknown biases including problems of generalisability, as does the solely Caucasian~~.~~ ethnicity. Concerns

identified by participants during the formal feedback e.g. having too many people involved in one's care may have contributed to poor response rates and rRewording of participant recruitment documentation to reassure participants of the role of the pharmacist could address this. ~~some of the concerns identified by participant feedback e.g. having too many people involved in one's care.~~ More participants withdrew in the prescribing arm compared with the other two arms, which might be attributed to the need for an additional practice visit. The study was an exploratory trial so no formal power calculation was undertaken. However, because there were no published MIDs available to estimate effect size for the outcomes in this population, it was important to present the actual clinical magnitude of change in outcome at 6 months alongside a statistical assessment of this change (p-value). This allows an assessment of both clinical and statistical significance simultaneously with the caveat that this is an exploratory study. With around 50 patients per arm, this was deemed sufficient numbers to examine the change in outcome measures with appropriate within and between group univariate statistical tests. ~~because of no prior knowledge of effect size.~~ Due to the nature of the intervention, no participants were blind to their group allocation, and so some outcomes, especially the qualitative components, may have been affected by social desirability bias.

Our main outcome measures were self-reported, but this is the norm in pain studies as pain is a subjective experience (18). Furthermore we do not know how important the observed differences were to participants. Following precedents set in previous research (25), and because there is no consensus on an alternative measure (3431) we used the HADS as a tool to classify people by severity of depression and anxiety. However it is strictly a screening tool, and the four levels of severity have not been formally validated. We therefore also compared outcomes using it as a continuous scale.

Relationship with other studies

This study is important because no other RCT has evaluated pharmacist prescribing and few studies, and importantly no RCTs, have evaluated pharmacist interventions for pain. In pharmacist prescribing most research has focussed on reported experiences of professionals and patients, and not used validated outcome measures. Yet pharmacist prescribing is now widely practised. For pain, there have been a few small studies. Briggs et al (2008) (3542) conducted a small before-and-after evaluation (involving 65 patients) of a nurse and pharmacist-led chronic pain clinic in primary care. Pain intensity Visual Analogue Scale scores

reduced significantly over six months. Another evaluation of 26 patients using a medication review service provided jointly by a physiotherapist and pharmacist in the UK, reported improvement in pain control for 88% of patients (36~~53~~).

The CPG was found to show a graded effect across the three arms, showing discrimination with both direction and strength of improvement, suggesting maximum benefit for those in the pharmacist prescribing arm. However, the reduction in overall score appears to be mediated by a change in the intensity of pain subscale rather than in pain-related disability. The effect size of 0.45 suggests this could be an important difference. In contrast, the SF-12, a measure of general health and functionality showed no significant difference between intervention arms, reflecting either no effect or or lack of powerto detect an effect.

Whilst most participants in this study were already within the normal range on the HADS scale, and therefore had minimal chance of improvement, there were nonetheless suggestions of better ourcomes in participants in the prescribing arm. Including a range of instruments is in line with IMMPACT recommendations (37~~64~~), which state that focus should be on the whole person, not just about pain. However, this needs to be balanced with minimising participant burden.

Explanations, implications, and future research

The number of pharmacists' recommendations per participant was higher in the review arm than in the prescribing arm. This might seem contradictory to the possible greater benefit found in the prescribing arm. However, in the prescribing arm pharmacists met the participant and may have more readily identified and dismissed suggestions previously ~~-~~tried. The interview feedback highlighted that some recommendations for change, whilst sensible, had been tried already. This might also be the reason why there were only 60% of pharmacist recommendations with which the GP fully agreed. Self-reported adherence to medication at baseline was good. Despite this, the pharmacists still improved pain outcomes in the prescribing arm. This could have been due to changes in medications and/or participant education about optimal timing for administration of analgesic medicines. Further research is needed to confirm the beneficial effect of pharmacist prescribing and its sustainability.

Conclusion

Our results suggest that pharmacist prescribing (and possibly pharmacist review alone) for patients with chronic pain is feasible, acceptable and may lead to improvements~~...acceptable and leads to improvements~~ in pain and other measures. A larger fully-powered trial is now needed to confirm these findings.

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Data sharing statement

Consent was not obtained from participants for data sharing; the presented data are anonymised and there is no risk of individual identification. Requests for data should be made to the contact author who will provide this in a format in which risk of patient identification will be minimal.

Conflict of interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

HB and CB drafted the manuscript.

All authors:

1) made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

2) were involved in drafting the manuscript or revising it critically for important intellectual content; and

3) have given final approval of the version to be published.

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All authors had access to all of the study data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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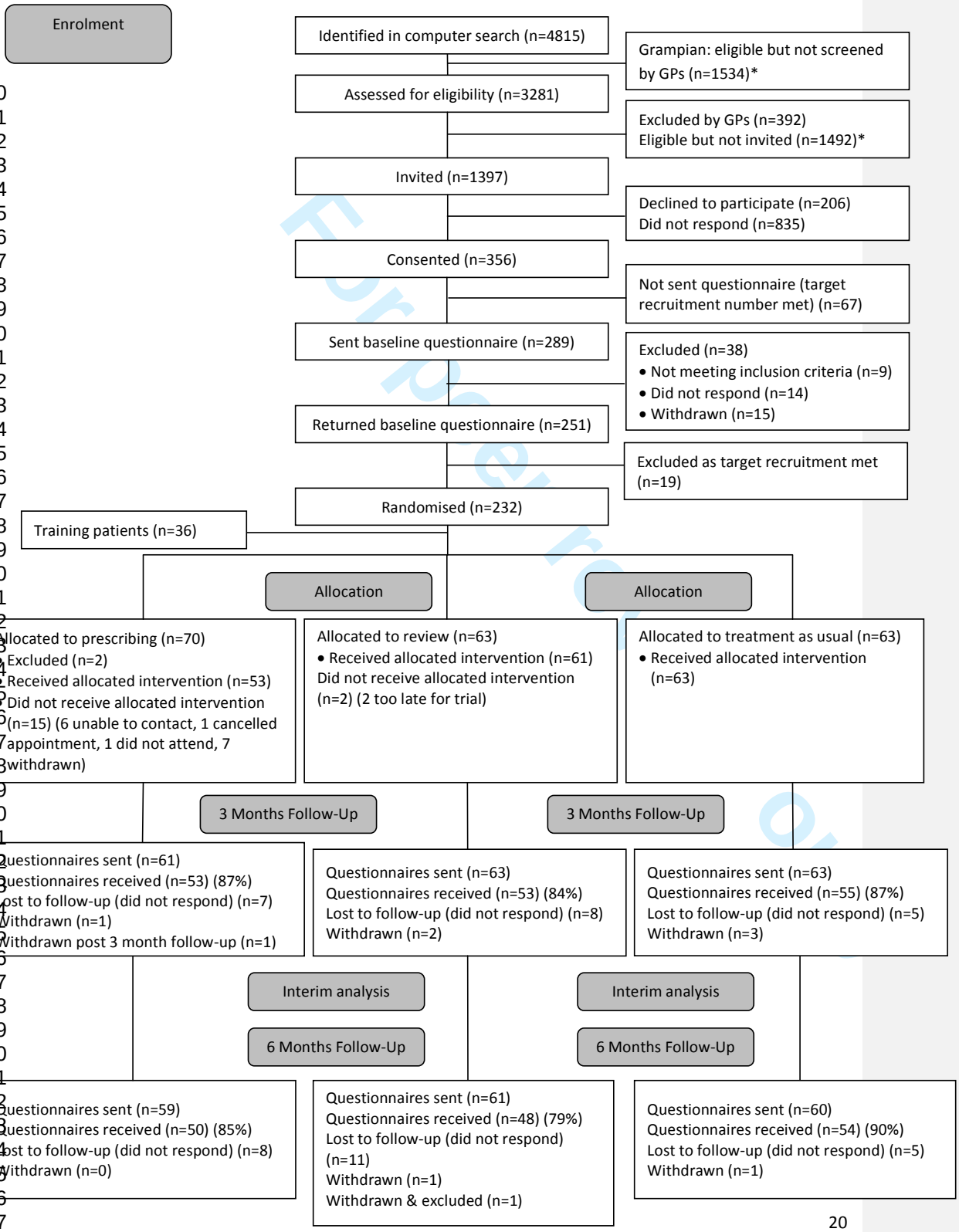
Figure 1: CONSORT Flow Diagram



*In the **Grampian Health Board area**~~Grampian~~, on the basis of response rates in the earlier feasibility study (241 screened patients resulted in 22 recruited) only a random sample of eligible participants were screened (15). In East Anglia all eligible patients were screened.

Table 1: Baseline demographic, socio-economic and pain data of patients by study arm, prescribing, review and treatment as usual (TAU)

	Prescribing* (n = 68)	**Review*** (n = 62)	**TAU*** (n = 63)
Age: mean (SD)	66.1 (12.1)	65.7 (14.2)	64.9 (11.6)
Missing	1	1	0
Gender (% female)	54.4 (37)	74.2 (46)	58.7 (37)
Marital status			
Married	43	30	41
Single	6	6	3
Divorced/widow	10	21	13
Other	6	4	6
Missing	3	1	0
Highest educational level achieved			
No qualifications	30	27	21
O grade or equivalent	12	6	14
Higher/A-level/NVQ3/SVQ3	6	8	7
Tertiary education/NVQ4/NVQ5	18	17	14
Other	2	1	4
Missing	0	3	3
Employment status			
Employed	16	14	9
Unemployed	3	5	1
Retired	38	35	34
Long term sick/disabled	7	5	9
Other	3	2	7
Missing	1	1	3
Household annual income before tax			
Less than £9,999	13	15	10
£10,000 - £14,999	14	18	22
£15,000 - £24,999	14	12	12
£25,000 – or more	22	11	8
Missing	5	6	11
Ethnic group			
Caucasian	67	62	61
Other	1		
Missing	0	0	2
Pain duration			
< 1 year	3	2	4
1 – 3 years	12	12	7
3 – 5 years	10	13	9
5 – 10 years	17	13	15
> 10 years	26	22	28
Pain localisation (%, n)			
Back	27.9 (19)	32.3 (20)	20.6 (13)
Neck, shoulders	7.4 (5)	9.7 (6)	9.5 (6)
Limbs or hips	42.6 (29)	30.6 (19)	50.8 (32)
Other	8.8 (6)	4.8 (3)	7.9 (5)
Missing	9	14	7

*Denominator based on numbers allocated to the specific arms, minus any exclusions due to protocol violations.

Table 2: Mean (standard deviation, SD) CPG intensity , median (interquartile range, IQR) CPG disability, and count CPG grade at baseline, 6 months follow-up and difference between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). P-values for within and between arm differences are also reported.

	Prescribing		Review		TAU		P (between groups***)
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	
Baseline CPG intensity	47	66.1 (16.0)	45	68.4 (17.6)	54	65.4 (18.0)	
6 month follow-up CPG intensity		58.1 (19.5)		67.4 (21.7)		65.6 (19.6)	
Difference CPG intensity		-8.0 (16.3)		-1.0 (16.0)		0.2 (14.9)	0.02
P (within groups**)		0.002		0.67		0.93	0.02
Effect size (r)		0.45		0.07		0.01	
		Median [IQR]		Median [IQR]		Median [IQR]	
Baseline CPG disability	48	60.0 [30.0; 75.8]	46	66.7 [45.0; 80.0]	53	56.7 [36.7; 80.0]	
6 Month follow-up CPG disability		40.0 [20.0; 60.0]		53.3 [29.2; 73.3]		50.0 [25.0; 80.0]	
Difference CPG disability		-8.3 [-23.3; 0.0]		-3.3 [-16.7; 10.0]		-3.3 [-21.7; 5.0]	0.55
P (within groups**)		0.003		0.15		0.05	0.55
Effect size (r)		0.43		0.20		0.26	
Baseline CPG grade	44	Count (%)	44	Count (%)	48	Count (%)	
I		5 (11.4)		3 (6.8)		5 (10.4)	
II		16 (36.4)		9 (20.5)		13 (27.1)	
III		7 (15.9)		10 (22.7)		13 (27.1)	
VI		16 (36.4)		22 (50.0)		17 (35.4)	
6 month follow-up CPG grade							
I		13 (29.5)		8 (18.2)		6 (12.5)	
II		13 (29.5)		15 (34.1)		17 (35.4)	
III		8 (18.2)		8 (18.2)		11 (22.9)	
IV		10 (22.7)		13 (29.5)		14 (29.2)	
Difference CPG grade							
≤-1		21 (47.7)		17 (38.6)		15 (31.2)	
0		17 (38.6)		25 (56.8)		25 (52.1)	
≥1		6 (13.6)		2 (4.5)		8 (2.1)	0.16
P (within groups***)		0.003		0.001		0.17	

*Number of participants in each group who completed the appropriate part of the CPG at both baseline and follow-up.

** From paired t-test, Wilcoxon signed rank test or marginal homogeneity test as appropriate

*** From ANOVA on mean difference, Kruskall-Wallis on median difference or chi-squared test on difference in CPG grade as appropriate

Table 3: Mean (standard deviation, SD) SF12 Physical Component Score (PCS) and median (interquartile range, IQR) Mental Component Score (MCS) at baseline and 6 month follow-up and difference between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.

	Prescribing		Review		TAU		
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	P (between groups***)
Baseline SF12 PCS	41	33.5 (10.8)	43	32.59(11.38)	45	29.60 (9.71)	
6 month follow-up SF12 PCS		35.3 (10.8)		34.62 (11.26)		32.59 (9.14)	
Difference SF12 PCS		1.8 (7.5)		2.02 (7.56)		2.99 (8.11)	~~0.75~~
P (within groups**)		0.12		0.09		0.02	0.75
Effect size (r)		0.24~~x~~		0.26~~x~~		0.35~~x~~	
		Median [IQR]		Median (IQR)	45	Median (IQR)	
Baseline SF12 MCS	42	52.4 [42.0; 58.8]	43	47.9 [38.5; 59.9]		51.5 [41.3; 60.7]	
6 month follow-up SF12 MCS		49.6 [42.8; 58.1]		47.9 [38.9; 56.2]		44.7 [37.6; 55.8]	
Difference SF12 MCS		-0.4 [-3.7; 6.0]		-1.2 [-6.6; 4.2]		-3.0 [-10.0; 1.3]	~~0.04~~
P (within groups**)		0.64		0.37		0.002	0.04
Effect size (r)		0.07~~x~~		0.14~~x~~		0.46~~x~~	

* Number of participants in each group who completed the appropriate part of the SF-12 at both baseline and follow-up.

** From paired t-test or Wilcoxon signed rank test as appropriate

*** From ANOVA on mean difference or Kruskall-Wallis test on median difference as appropriate

Table 4: The HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) count of patients according to severity (normal, mild, moderate or severe) and the difference in severity category between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.*

	n	**Prescribing**	n	**Review**	n	**TAU**	
Baseline HADS-D	44	Count (%)	45	Count (%)	53	Count (%)	P (between groups***)
Normal		32 (72.7)		31 (68.9)		38 (71.7)	
Mild		8 (18.2)		11 (24.4)		7 (13.2)	
Moderate		3 (6.8)		3 (6.7)		8 (15.1)	
Severe		1 (2.3)		0		0	
6 month follow-up HADS-D							
Normal		32 (72.7)		32 (71.1)		32 (60.4)	
Mild		7 (15.9)		6 (13.3)		10 (18.9)	
Moderate		5 (11.4)		6 (13.3)		8 (15.1)	
Severe		0		1 (2.2)		3 (5.7)	
Difference HADS-D							
≤-1		5 (11.4)		4 (8.9)		2 (3.8)	
0		34 (77.3)		37 (82.0)		40 (75.5)	
≥1		5 (11.4)		4 (8.9)		11 (20.8)	0.32~~Not valid**~~
P (within groups**)		1.0		0.71		0.03	
Baseline HADS-A	44	Count (%)	43	Count (%)	48	Count (%)	
Normal		25 (56.8)		30 (69.8)		29 (60.4)	
Mild		8 (18.2)		7 (16.3)		9 (18.8)	
Moderate		8 (18.2)		5 (11.6)		8 (16.7)	
Severe		3 (6.8)		1 (2.3)		2 (4.2)	
6 month follow-up HADS-A							
Normal		27 (61.4)		29 (67.4)		32 (66.7)	
Mild		7 (15.9)		6 (14.0)		5 (10.4)	
Moderate		8 (18.2)		6 (14.0)		10 (20.8)	
Severe		2 (4.5)		2 (4.7)		1 (2.1)	
Difference HADS-A							
≤-1		6 (13.6)		3 (7.0)		10 (20.8)	
0		35 (79.5)		33 (76.7)		29 (60.4)	
≥1		3 (6.8)		7 (16.3)		9 (18.8)	0.14
P (within groups**)		0.25		0.21		0.55	

* Number of participants in each group who completed the appropriate part of the HADS at both baseline and follow-up.

~~**Between arms p-value not valid due to low numbers in multiple cells, even after collapsing to th~~

** From marginal homogeneity test

*** From chi-squared test on difference in HADS

~~ree categories.~~

Table 5: Median HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) scores (interquartile range, IQR) at baseline and 6 month follow-up and difference between the two assessment point for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.

	Prescribing		Review		TAU		
	n	Median [IQR]	n	Median [IQR]	n	Median [IQR]	P (between groups)
Baseline HADS-D	42	5.0 [3.0;8.0]	44	4.5 [2.3; 8.0]	51	5.0 [3.0; 8.0]	
6 month follow-up HADS-D		4.0 [2.0; 8.0]		5.0 [2.0; 8.8]		5.0 [2.0; 10.0]	
Difference HADS-D		-1.0 [-2.0; 0.0]		0.0 [-1.0; 1.8]		0.0 [-1.0; 2.0]	0.02
P (within groups)		0.02		0.33		0.22	
Baseline HADS-A	44	7.0 [3.3; 10.8]	43	5.0 [3.0; 10.0]	48	6.0[4.0; 10.0]	
6 month follow-up HADS-A		5.0 [2.3; 9.8]		6.0 [3.0; 9.0]		7.0 [4.0; 10.0]	
Difference HADS-A		-1.0 [-2.0; 0.0]		0.0 [-2.0; 2.0]		0.5 [-3.0; 2.0]	0.05
P (within groups)		0.01		0.45		0.81	

* Number of participants in each group who completed the appropriate part of the HADS at both baseline and follow-up.

Box 1 Examples of pharmacist interventions in the prescribing arm

Changes to pain management: 'use paracetamol regularly', 'take tramadol if needed' 'add piroxicam gel PRN', 'given web links to self help groups'

Compliance aid: ' gave written times that this drug could be taken'

Addressing side effects/safety: 'take paracetamol after initial NSAID', 'take senna', 'ordered blood monitoring', 'stop use of two NSAIDS'

General health: 'discussed weight loss', 'invited to practice nurse for BP', 'glucose, lipids and lifestyle update',

Cost minimisation: 'change aspirin EC to plain',

BOX 2 Examples of quotes from Pharmacists (n=6), GPs (n=23) and patient participants (n=40) on the prescribing intervention

Pharmacists (from interviews):

Satisfying (n=6):'contact with patients', 'being able to help patients', 'being able to make a difference to long-standing pain'...'even in small ways'

Interesting (n=6):'learning about pain'

Challenging (n=6):'complex, chronically ill patients'

GPs (from interviews)*:*

Support for the service (n=17): it's been a very positive thing'

Agreement with pharmacists' recommendations (n=23): 'oh very reasonable suggestions', 'tinkering round the edges', 'had been tried already'.

Trust in the practice pharmacist (n=23):'I respect his professional judgement'

Cost effectiveness (n=6): 'if there's limited resources do we want to spend the money on a pharmacist'.

Patients (from 3 month questionnaire):

Closed questions:

Proportion agreeing that:
The pharmacist was interested in them (89%; 39/44)
They were totally satisfied (85%; 39/46)
They were told about their treatment (82%; 38/46)
Their consultation was thorough (79%; 34/44)
They would have liked more time (9%;4/44)
They would have preferred to see their GP (9%; 4/44)
Too many people were now involved in their treatment (11%; 5/44).

Open text questions:

Positive (n=39): 'She was professional, relaxed, pleasant and interested. Excellent!'

Negative (n=1): 'A waste of time, altered my tablets which made my pain worse'.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10, figure 1(p.18)
	13b	For each group, losses and exclusions after randomisation, together with reasons	10, figure 1(p.18)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7-8
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	10, Table 1 (p20)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	See Tables 2,3,4,5 and page 9 (ITT)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	See pages 10/11, and Tables 2,3,4,5. P values reported
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13
Other information			
Registration	23	Registration number and name of trial registry	4

Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial

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Title page

Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial

Hanne Bruhn, Christine M Bond, Alison M Elliott, Philip C Hannaford, Amanda J Lee, Paul McNamee, Blair H Smith, Margaret C Watson, Annie Blyth, Richard Holland, David Wright

Centre for Healthcare Randomised Trials, Health Services Research Unit, University of Aberdeen, 3rd floor Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD, UK Hanne Bruhn, Trial Manager

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Christine M Bond, Professor of Primary Care: Pharmacy

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Alison M Elliott, Senior Research Fellow

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Philip C Hannaford, NHS Grampian Chair of Primary Care

Medical Statistics Team, Division of Applied Health Sciences, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK, Amanda J Lee, Professor of Medical Statistics

Health Economics Research Unit, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK, Paul McNamee, Reader

Division of Population Health Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD2 4RB, UK, Blair H Smith, Professor of Population Science

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Margaret C Watson, Senior Research Fellow

Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK, Annie Blyth, Research Associate

Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK, Richard Holland, Professor of Public Health Medicine

School of Pharmacy, University of East Anglia, Norwich Research Park, NR4 7TJ, UK, David Wright, Chair in Pharmacy Practice

Correspondence to: Professor CM Bond c.m.bond@abdn.ac.uk, Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK

Abstract

Objectives

To compare the effectiveness of pharmacist medication-review, with or without pharmacist prescribing, with standard care, for patients with chronic pain.

Design

An exploratory randomised controlled trial.

Setting

Six general practices with prescribing pharmacists in Grampian (3) and East Anglia (3).

Participants

Patients on repeat prescribed pain medication(4815) were screened by GPs, and mailed invitations (1397). 196 were randomised and 180 (92%) completed. Exclusion criteria included: severe mental illness, terminally ill, cancer related pain, history of addiction

Randomisation and intervention

Patients were randomised using a remote telephone service to: (i) pharmacist medication-review with face-to-face pharmacist prescribing; or (ii) pharmacist medication-review with feedback to GP and no planned patient contact; or (iii) treatment as usual (TAU). Blinding was not possible.

Outcome measures

Outcomes were the SF-12v2, the Chronic Pain Grade (CPG), the HUI3 and the Hospital Anxiety and Depression Scale (HADS). Outcomes were collected at 0,3,and 6 months.

Ethical approval was obtained.

Results

In the prescribing arm (n=70) two patients were excluded/nine withdrew. In the review arm (n=63) one was excluded/three withdrew. In the TAU arm (n=63) four withdrew. Compared with baseline, patients had an improved CPG in the prescribing arm, 47.7% (21/44; p=0.003), and in the review arm, 38.6% (17/44; p=0.001), but not the TAU group, 31.3% (15/48; ns). The

SF-12 PCS showed no effect in the prescribing or review arms but improvement in TAU (p=0.02). The SF-12 MCS showed no effect for the prescribing or review arms and deterioration in the TAU arm (p=0.002). HADS scores improved within the prescribing arm for Depression (p=0.022) and Anxiety (p=0.007), between groups (p=0.022 and p=0.045 respectively).

Conclusion

This is the first RCT of pharmacist-prescribing in the UK, and suggests there may be a benefit for patients with chronic pain. A larger trial is required.

Trial registration: www.isrctn.org/ISRCTN06131530. Medical Research Council funding.

Focus:

- Chronic pain, (lasting >3 months) affects up to half the adult population, most of whom are primarily managed in primary care but prescribing is often sub-optimal.
- Pharmacists now have prescribing rights but no published research has compared the effectiveness of their prescribing with that of GPs.
- The hypothesis was that pharmacist advice (with or without pharmacist prescribing) would lead to better outcomes than usual care

Key messages:

- The findings suggest there may be improved pain related outcomes for patients receiving pain related care from a pharmacist prescriber
- A larger trial is called for.

Strengths and Limitations

- This the first randomised controlled trial of pharmacist prescribing in the UK looking at patient reported clinical outcomes
- The study was designed as an exploratory trial so no power calculation was done

Introduction

Chronic pain (pain lasting more than three months) affects up to half the adult United Kingdom (UK) population, and is considered severely limiting in about 15% of cases (1). Recovery is uncommon with nearly 80% of those identified with chronic pain at baseline still reporting chronic pain four years later (2). It adversely affects many aspects of a person's physical and psychological health, and social and economic well being (3-6).

In the UK, most patients with chronic pain present, and are managed, in primary care (7). Although non-pharmacological treatments are available, these are accessed by few patients, with mixed success (e.g. (8-10). Analgesics prescribed in primary care remain the mainstay of treatment (4), representing substantial workload and cost. Sub-optimal prescribing may lead to poor pain control and other adverse patient outcomes. One study found that the most common medications involved in adverse drug reaction-related emergency admissions involved non-steroidal anti-inflammatory drugs (NSAIDs) (11) which are commonly used to manage pain. Improved prescribing could result in better outcomes and remove the need for more costly, scarce, alternatives.

Pharmacists working in UK general practices are well-placed to improve pain pharmacotherapy because of their expertise in therapeutics, understanding of the poly-pharmacy regimens (12) frequently used in chronic pain management, and established relationships with other primary care colleagues. In the UK National Health Service (NHS), recent regulatory changes now allow accredited pharmacists (as well as some other health care professionals such as nurses) to prescribe prescription-only medicines (POMs) (13). Pharmacists can either be qualified as supplementary prescribers, in which case they operate within an agreed clinical management plan (CMP) in partnership with the doctor and patient, or as an independent prescriber, in which case they can either prescribe completely independently or within a CMP.

However, despite the increasing number of non-medical prescribers, including pharmacists, there has been no rigourous comparisons of the outcomes of non-medical versus GP prescribing. This information is needed to assess the clinical effectiveness of different care models.

This paper reports findings from an exploratory randomised controlled trial (RCT) comparing pharmacist medication review, with or without pharmacist prescribing, with standard care for

patients with chronic pain. Development of the trial was informed by earlier feasibility work (14,15).

The *a priori* hypothesis was that, in patients with chronic pain, pharmacist advice (with or without pharmacist prescribing) would lead to better patient functioning and/or better pain control at six months than treatment as usual (TAU).

Methods

Regulatory Issues

Ethical approval was granted by the National Research Ethics Service Committee – North of Scotland (reference number 09/S0801/107). NHS Research and Development approval was granted by NHS Grampian and East Norfolk & Waveney Research Governance Committees. Patients gave informed consent before taking part.

Design

An open, exploratory RCT in which patients were randomised to one of three study arms. Participants were not blind to allocated treatment arm due to the nature of the intervention.

Recruitment of practices and independent prescribing pharmacists

Practices in the Grampian Health Board area, Scotland (n=18) and East Anglia region of England (n=4) known to have an attached Royal Pharmaceutical Society of Great Britain registered independent pharmacist prescriber, were eligible to take part. From those indicating a willingness to participate, convenience sampling was used to identify six general practices: three in Grampian and three in East Anglia.

Patient inclusion and exclusion criteria

Patients registered with the recruited practices were eligible for inclusion if they were over 18 years of age, living in their own home, and receiving regular prescribed medication for pain. Patients were identified by a computerised search (14) of the drug records of all individuals registered with the practice, to identify those who had received either two or more acute prescriptions, and/or one repeat prescription within the last 120 days, for an analgesic (British National Formulary (BNF section 4.7) and/or non-steroidal anti-inflammatory medication (NSAID) (BNF section 10.1.1). Medications which can be used for analgesia but whose primary indication is not chronic pain (e.g. triptans, anti-epileptics or anti-depressants) were excluded

as these drugs identify few additional eligible patients (16). In accordance with trial criteria, GPs excluded and recorded reasons for patients who had: a concomitant severe mental health problem or terminal illness; had suffered recent bereavement; had a known alcohol or drug addiction; suffered pain caused by cancer or other malignancy; were unable to give informed consent; other (unspecified) reasons.

Patient recruitment

Eligible patients were sent an invitation pack (letter, information sheet, consent form) by practice staff between March and June 2010. Consent forms were returned directly to the researchers, who sent out a baseline questionnaire. Patients returning completed questionnaires were randomised by the researcher using a telephone randomisation service with a random number allocation which ensured allocation concealment. The allocation sequence was 1:1:1.

Intervention

All participating pharmacists took part in a two-day course updating them about pain management. As part of the training, participants defined and agreed the treatment algorithm they would all use.

'Prescribing' arm: Pharmacists invited patients to a face-to-face consultation. Prior to the consultation, pharmacists completed a paper-based medication review of each patient's medical record and patients were asked to complete a pain diary to inform the consultation. A pharmaceutical care plan was agreed between the pharmacist and the patient. The plan assessed and documented relevant past medical history and current conditions; known allergies and adverse drug reactions; relevant laboratory results; pain-related medications prescribed in the previous 10 years; current pain related prescription medications; current symptoms; lifestyle issues, including units of alcohol consumed per week; recommendations for changes to medication (if any); whether non-pharmaceutical treatments had been considered; and, any other relevant issues. Copies of the pain diary and pharmaceutical care plan are available from the authors on request. At the end of the consultation any required prescriptions for medicines were issued by the pharmacist. Due to Controlled Drug (CD) regulations in place at the time, prescribing for CDs was done using a supplementary prescribing Clinical Management Plan (17), rather than independent prescribing. Patients were followed up either by phone or face-to-face, at each pharmacist's discretion.

'Review arm': The pharmacists conducted a paper-based medication review focussed on pain-related prescription medications, before creating a pharmaceutical care plan which detailed any recommendations for medication changes. The plan was passed to the patient's GP for implementation. The GPs were asked subsequently about actions taken as a result of the recommendations.

Treatment as usual (TAU): Patients received standard general practice care.

Outcome measures

A core aim of this exploratory randomised controlled trial (RCT) was to finalise the selction of outcome measures for a subsequent multi-centred RCT. In the Current Controlled Trials Registration (ISRCTNO6131530) we specified both primary and secondary outcome measures (primary: SF12, HUI ; secondary: CPG, HADS) based on our judgement following the earlier feasibility study (15). However in practice, all outcomes were considered equal and no single measure was defined as the primary outcome, for example, for the purpose of a sample size calculation (see below). These four outcome measures are described below. Inclusion of both pain specific and generic outcome measures was based on Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (18) and an earlier feasibility study (15).

The SF-12v2 is a generic health and functioning scale (19), previously used in population-based studies of pain (20,21). A Physical (PCS) and Mental Component Score (MCS) was calculated, ranging from 0 to 100; a higher score indicates better functioning.

The Health Utilities Index (HUI3) is a preference-based system for measuring comprehensive health status and health-related quality of life (HRQL) (22). It provides descriptive evidence and a score for each dimension of health (vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition) and a HRQL score for overall health. Each dimension has 3- 6 levels. Owing to the cost of the additional license fee to score data from this measure, this instrument was not subsequently analysed.

The CPG (23) is a seven item scale which assesses pain severity on two dimensions: disability and intensity. The scale classifies pain according to level of intensity and disability (I (low disability-low intensity) to IV (high disability-severely limiting)).

The Hospital Anxiety and Depression Scale (HADS) (24) is a 14-item screening instrument which identifies the possible and probable caseness of anxiety (7 items (HADS-A)) and depression (7 items (HADS-D)); each item scored from 0 (not present) to 3 (highly present). Standard thresholds and previously used labels (25) were applied (no depression/anxiety (0-7), mild (8-10), moderate (11-15) or severe (>15)).

Data collection

Participant questionnaires

Questionnaires were posted to participants at baseline (pre-randomisation), and 3 and 6 months post-randomisation (follow-up was conducted between July 2010 and January 2011). Up to two reminders were sent. Questionnaire content included the outcome measures described above together with items on: demographic status (baseline only); screening items to confirm eligibility (baseline only); duration of pain condition (baseline only); location of pain; Morisky Medication Adherence Scale 4 (MMAS-4) (26); participant satisfaction (11 statements derived from the feasibility study for the prescribing arm (3 months only) and additional comments by participants. The MMAS-4 provides a score of self-reported adherence to medication regimen. Scores range from 0 (low adherence) to 4 (high adherence).

Follow-up interviews with staff

Post-intervention, all pharmacists and all GPs in participating practices were invited to take part in semi-structured interviews, carried out face-to-face when possible, otherwise by telephone. Interviews were taped, transcribed verbatim and content analysis was carried out.

Sample size

As this was an exploratory trial to estimate the effect size for a larger trial, no formal sample size calculation was possible (27). We aimed to recruit 30 participants per practice (n=180) (with an additional six per practice for training purposes i.e. 216 in total. This was deemed sufficient to give reliable effect size estimates for the outcome measures of health status or chronic pain grade..

Data management and analysis

Data were entered into identical SPSS databases at each site and accuracy checks carried out on 10% before databases were merged. Descriptive statistics included means and standard deviations (SD) for normally distributed continuous data, medians (interquartile range (IQR))

for skewed continuous data and percentages (n) for categorical data. Analysis was conducted on an intention-to-treat basis for participants with complete data on relevant measures using SPSS version 18.

Exploratory analyses for parametric data included the paired t-test for within-arm comparisons of mean difference between baseline and 6 months and one-way ANOVA for between arm comparisons of mean difference. For non-parametric data it included the Wilcoxon Signed Rank test for within-arm comparisons of median difference and the Kruskal Wallis test for between arm comparisons of median difference. Categorical data was analysed using the marginal homogeneity test for within-arm comparisons (with null hypotheis that the distribution of CPG grade or HADS group does not change between baseline and 6 month follow-up) and the Chi-squared test for between arm comparisons; analyses reported here are based on 6 month follow-up data (other than for participant experiences). Within arm effect sizes, expressed in terms of a Pearson correlation coefficient (r) have been calculated using the formulas from Rosenthal (1991) (28). Effect sizes can be directly compared using Cohen's (1988) (29) criteria of r=0.1 (small effect); r=0.3 (medium effect) and r=0.5 (large effect).

Results

Response rates and demography

Six of the seven practices approached participated. GPs excluded 12% (392/3281) of patients, mostly those with dementia. There was no statistically significant difference between participants and non-participants in terms of age, gender, and index of multiple deprivation. Figure 1 shows the flow of participants through the study. Overall, the consent rate was 25% (356/1397) and the recruitment rate was 14% (196/1397).

[INSERT FIGURE 1 HERE]

Eighty six percent of participants (251/289) returned baseline questionnaires, of whom 232 were randomised (36 participants were randomised to one of the two intervention arms for training purposes and were not included in any further analysis and 19 were not included as recruitment target had been met). The overall follow-up rate at 3 months was 86% (161/187)and at 6 months 84% (152/180).

As shown in Table 1, groups were similar at baseline for demographic and socioeconomic variables and pain data. Most participants were married, Caucasian and female, older (mean (SD) age 65 (12.6) years), had an annual income of <£25,000 and had suffered from pain for at least five years. Most (57%;103/181) reported being fully adherent to their medication regimen (MMAS-4, median 4.0 (IQR 3.0- 4.0)) (15 missing MMAS scores).

[INSERT TABLE 1 HERE]

In the prescribing arm, 78% (53/68) attended an initial prescribing consultation, 31 had at least one planned follow-up (of which 34/37 were conducted by phone) and 130 recommendations were made for 92% (49/53) of participants seen. Examples are shown in Box 1. The median time taken for the note-based record review was 35 minutes (IQR 20.0, 45.0), the consultation was 30 minutes (IQR 20.0, 40.0), careplan preparation 10 minutes (IQR 10.0, 20.0) and median duration of follow-ups was 10 minutes (IQR 5.0- 15.0).

[INSERT BOX 1 HERE]

In the review arm 97% (60/62) of participants' records were reviewed (note there was one post randomisation exclusion) for whom 197 recommendations were made. Where GP feedback was provided (n=48), they generally agreed with pharmacists' recommendations, which were fully implemented for 20 participants (two by the pharmacist following request by GP), partially for 19 participants and not at all for nine participants. The median time taken for the note-based record review was 30 minutes (IQR24.3, 45.0), and careplan preparation was 10 minutes (IQR 5.0, 20.0).

Clinical outcome measures

Table 2 shows the mean (SD) or median (IQR) of the CPG for each arm at baseline and 6 month follow-up. Table 3 shows the SF-12 scores and Table 4 shows the HADS-A and HADS-D results.

[INSERT TABLE 2,3,4, HERE]

In the prescribing arm, there was a statistically significant within arm improvement for the CPG intensity (p=0.002, effect size (r)=0.45) and disability (p=0.003, effect size (r)=0.43) subscales, and between arms on the intensity sub-scale (p=0.02), but not the disability subscale (p=0.55) (Table 2). There was a significant within-arm improvement in overall CPG grade in the

prescribing (p=0.003) and review arm (p=0.001), but not in the TAU arm. The SF-12 Physical Component Score showed a statistically significant within arm improvement in the TAU arm (p=0.02, effect size (r)=0.35) (Table 3), but not between trial arms. The SF-12 Mental Component Score showed a statistically significant deterioration in the TAU arm (p=0.002, effect size (r)=0.45)(Table 3), as did the HADS-D (p=0.03, Table 4). Analysis was also carried out on the non-categorised HADS scores which showed a statistically significant improvement within the prescribing arm for Depression (p=0.022) and Anxiety (p=0.007). These were both significant between groups (p=0.022 and p=0.045 respectively) (Table 5).

Acceptability of the pharmacist prescribing intervention

All six pharmacists and 56% of the GPs (23/41) were interviewed. All pharmacists and most GPs were positive about the intervention, although some GPs suggested that the pharmacists' recommendations had been minor and questioned the cost-effectiveness of the service. Patient participants were generally positive about the pharmacist prescribing service although some concerns were identified, as Illustrated by the quotes shown in Box 2.

[INSERT BOX 2 HERE]

Discussion

Principal findings

This exploratory RCT of pharmacist-led management of patients with chronic pain suggests that pharmacist prescribing (and possibly pharmacist review alone) may be effective in improving pain-related outcomes and be acceptable to both patients and most professionals. There was an indication of a positive effect on emotional health, but no measurable effect on general health.

Strengths and weaknesses

This was the first RCT to assess clinical and humanistic outcomes after pharmacist prescribing for any clinical condition compared to usual GP care, and the first RCT to specifically assess pharmacist-led management of chronic pain, compared with usual GP care. It was based on extensive development and feasibility work (14,15) in line with MRC framework for development and evaluation of complex interventions (30). A range of validated outcome measures was included, as well as a parallel qualitative process evaluation which assessed satisfaction and acceptability. The inclusion of six practices and their associated pharmacists

from both Scotland and England increased the generalisability of the findings. Pharmacists received formal training and agreed and used a common treatment algorithm which should have increased standardisation of treatment. The preponderance of females (overall 62%) and average age of 65 years reflects the wider chronic pain population (1) as does the distribution of pain site (31,32)

There were, however limitations. Although high follow-up response rates were achieved at both three (86%) and six months (85%) only 25% of eligible patients entered the trial. This low initial consent rate is in line with other studies (33,34), but may cause unknown biases including problems of generalisability, as does the solely Caucasian ethnicity. Concerns identified by participants during the formal feedback e.g. having too many people involved in one's care may have contributed to poor response rates and rewording of participant recruitment documentation to reassure participants of the role of the pharmacist could address this. More participants withdrew in the prescribing arm compared with the other two arms, which might be attributed to the need for an additional practice visit. The study was an exploratory trial so no formal power calculation was undertaken**.** However, because there were no published MIDs available to estimate effect size for the outcomes in this population, it was important to present the actual clinical magnitude of change in outcome at 6 months alongside a statistical assessment of this change (p-value). This allows an assessment of both clinical and statistical significance simultaneously with the caveat that this is an exploratory study. With around 50 patients per arm, this was deemed sufficient numbers to examine the change in outcome measures with appropriate within and between group univariate statistical tests**.** Due to the nature of the intervention, no participants were blind to their group allocation, and so some outcomes, especially the qualitative components, may have been affected by social desirability bias.

Our outcome measures were self-reported, but this is the norm in pain studies as pain is a subjective experience (18). Furthermore we do not know how important the observed differences were to participants. Following precedents set in previous research (25), and because there is no consensus on an alternative measure (35) we used the HADS as a tool to classify people by severity of depression and anxiety. However it is strictly a screening tool, and the four levels of severity have not been formally validated. We therefore also compared outcomes using it as a continuous scale.

Relationship with other studies

This study is important because no other RCT has evaluated pharmacist prescribing and few studies, and importantly no RCTs, have evaluated pharmacist interventions for pain. In pharmacist prescribing most research has focussed on reported experiences of professionals and patients, and not used validated outcome measures. Yet pharmacist prescribing is now widely practised. For pain, there have been a few small studies. Briggs et al (2008) (36) conducted a small before-and-after evaluation (involving 65 patients) of a nurse and pharmacist-led chronic pain clinic in primary care. Pain intensity Visual Analogue Scale scores reduced significantly over six months. Another evaluation of 26 patients using a medication review service provided jointly by a physiotherapist and pharmacist in the UK, reported improvement in pain control for 88% of patients (37).

The CPG was found to show a graded effect across the three arms, showing discrimination with both direction and strength of improvement, suggesting maximum benefit for those in the pharmacist prescribing arm. However, the reduction in overall score appears to be mediated by a change in the intensity of pain subscale rather than in pain-related disability. The effect size of 0.45 suggests this could be an important difference. In contrast, the SF-12, a measure of general health and functionality showed no significant difference between intervention arms, reflecting either no effect or or lack of powerto detect an effect.

Whilst most participants in this study were already within the normal range on the HADS scale, and therefore had minimal chance of improvement, there were nonetheless suggestions of better ourcomes in participants in the prescribing arm. Including a range of instruments is in line with IMMPACT recommendations (38), which state that focus should be on the whole person, not just about pain. However, this needs to be balanced with minimising participant burden.

Explanations, implications, and future research

The number of pharmacists' recommendations per participant was higher in the review arm than in the prescribing arm. This might seem contradictory to the possible greater benefit found in the prescribing arm. However, in the prescribing arm pharmacists met the participant and may have more readily identified and dismissed suggestions previously tried. The interview feedback highlighted that some recommendations for change, whilst sensible, had been tried already. This might also be the reason why there were only 60% of pharmacist

recommendations with which the GP fully agreed. Self-reported adherence to medication at baseline was good. Despite this, the pharmacists still improved pain outcomes in the prescribing arm. This could have been due to changes in medications and/or participant education about optimal timing for administration of analgesic medicines. Further research is needed to confirm the beneficial effect of pharmacist prescribing and its sustainability.

Conclusion

Our results suggest that pharmacist prescribing (and possibly pharmacist review alone) for patients with chronic pain is feasible, acceptable and may lead to improvements in pain and other measures. A larger fully-powered trial is now needed to confirm these findings.

Data sharing statement

Consent was not obtained from participants for data sharing; the presented data are anonymised and there is no risk of individual identification. Requests for data should be made to the contact author who will provide this in a format in which risk of patient identification will be minimal.

Conflict of interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

HB and CB drafted the manuscript.

All authors:

1) made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

2) were involved in drafting the manuscript or revising it critically for important intellectual content; and

3) have given final approval of the version to be published.

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All authors had access to all of the study data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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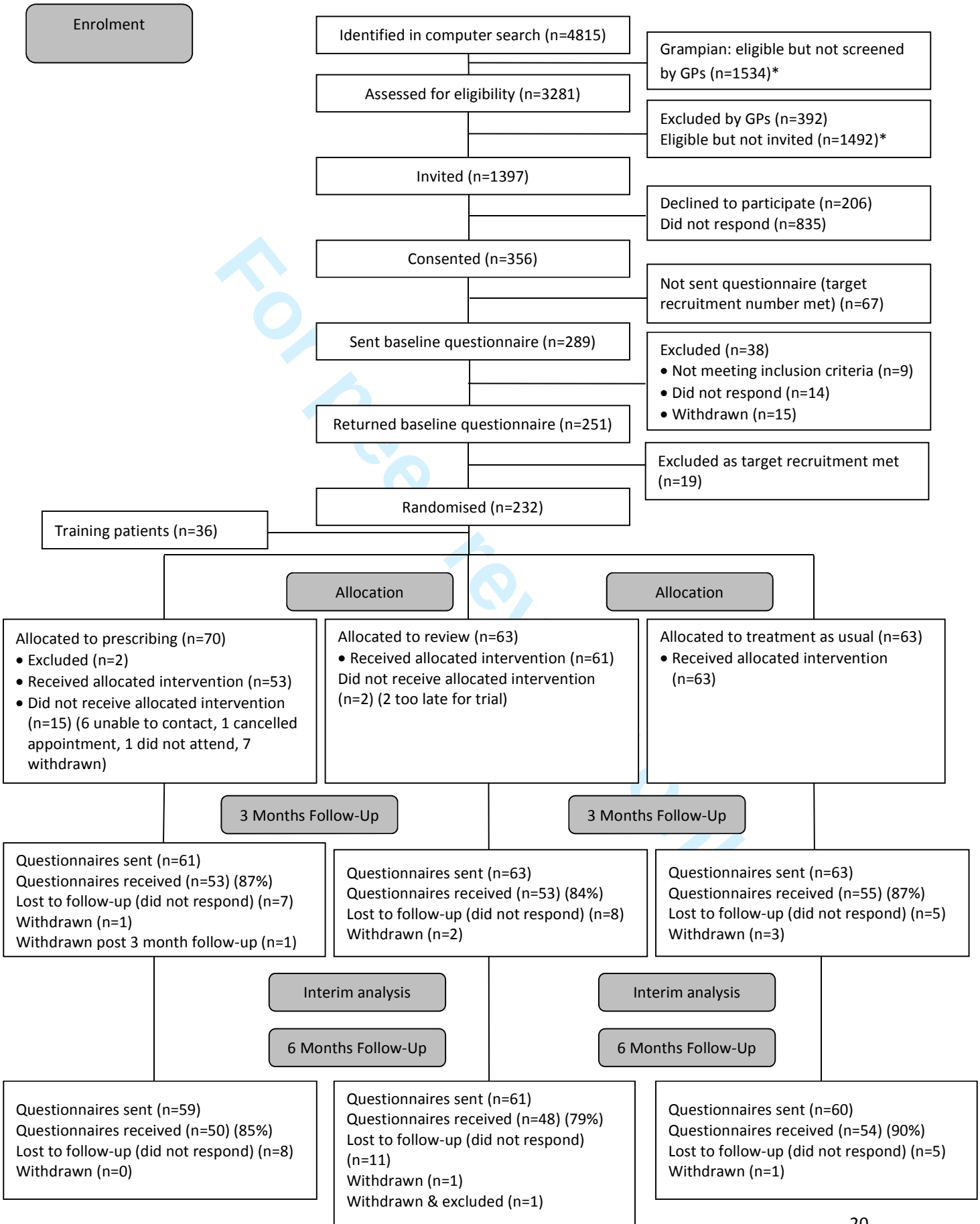
Figure 1: CONSORT Flow Diagram



*In the **Grampian Health Board area**, on the basis of response rates in the earlier feasibility study (241 screened patients resulted in 22 recruited) only a random sample of eligible participants were screened (15). In East Anglia all eligible patients were screened.

Table 1: Baseline demographic, socio-economic and pain data of patients by study arm, prescribing, review and treatment as usual (TAU)

	Prescribing* (n = 68)	**Review*** (n = 62)	**TAU*** (n = 63)
Age: mean (SD)	66.1 (12.1)	65.7 (14.2)	64.9 (11.6)
Missing	1	1	0
Gender (% female)	54.4 (37)	74.2 (46)	58.7 (37)
Marital status			
Married	43	30	41
Single	6	6	3
Divorced/widow	10	21	13
Other	6	4	6
Missing	3	1	0
Highest educational level achieved			
No qualifications	30	27	21
O grade or equivalent	12	6	14
Higher/A-level/NVQ3/SVQ3	6	8	7
Tertiary education/NVQ4/NVQ5	18	17	14
Other	2	1	4
Missing	0	3	3
Employment status			
Employed	16	14	9
Unemployed	3	5	1
Retired	38	35	34
Long term sick/disabled	7	5	9
Other	3	2	7
Missing	1	1	3
Household annual income before tax			
Less than £9,999	13	15	10
£10,000 - £14,999	14	18	22
£15,000 - £24,999	14	12	12
£25,000 – or more	22	11	8
Missing	5	6	11
Ethnic group			
Caucasian	67	62	61
Other	1		
Missing	0	0	2
Pain duration			
< 1 year	3	2	4
1 – 3 years	12	12	7
3 – 5 years	10	13	9
5 – 10 years	17	13	15
> 10 years	26	22	28
Pain localisation (%, n)			
Back	27.9 (19)	32.3 (20)	20.6 (13)
Neck, shoulders	7.4 (5)	9.7 (6)	9.5 (6)
Limbs or hips	42.6 (29)	30.6 (19)	50.8 (32)
Other	8.8 (6)	4.8 (3)	7.9 (5)
Missing	9	14	7

*Denominator based on numbers allocated to the specific arms, minus any exclusions due to protocol violations.

Table 2: Mean (standard deviation, SD) CPG intensity , median (interquartile range, IQR) CPG disability, and count CPG grade at baseline, 6 months follow-up and difference between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). P-values for within and between arm differences are also reported.

	Prescribing		Review		TAU		P (between groups***)
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	
Baseline CPG intensity	47	66.1 (16.0)	45	68.4 (17.6)	54	65.4 (18.0)	
6 month follow-up CPG intensity		58.1 (19.5)		67.4 (21.7)		65.6 (19.6)	
Difference CPG intensity		-8.0 (16.3)		-1.0 (16.0)		0.2 (14.9)	
P (within groups**)		0.002		0.67		0.93	0.02
Effect size (r)		0.45		0.07		0.01	
		Median [IQR]		Median [IQR]		Median [IQR]	
Baseline CPG disability	48	60.0 [30.0; 75.8]	46	66.7 [45.0; 80.0]	53	56.7 [36.7; 80.0]	
6 Month follow-up CPG disability		40.0 [20.0; 60.0]		53.3 [29.2; 73.3]		50.0 [25.0; 80.0]	
Difference CPG disability		-8.3 [-23.3; 0.0]		-3.3 [-16.7; 10.0]		-3.3 [-21.7; 5.0]	
P (within groups**)		0.003		0.15		0.05	0.55
Effect size (r)		0.43		0.20		0.26	
Baseline CPG grade	44	Count (%)	44	Count (%)	48	Count (%)	
I		5 (11.4)		3 (6.8)		5 (10.4)	
II		16 (36.4)		9 (20.5)		13 (27.1)	
III		7 (15.9)		10 (22.7)		13 (27.1)	
VI		16 (36.4)		22 (50.0)		17 (35.4)	
6 month follow-up CPG grade							
I		13 (29.5)		8 (18.2)		6 (12.5)	
II		13 (29.5)		15 (34.1)		17 (35.4)	
III		8 (18.2)		8 (18.2)		11 (22.9)	
IV		10 (22.7)		13 (29.5)		14 (29.2)	
Difference CPG grade							
≤-1		21 (47.7)		17 (38.6)		15 (31.2)	
0		17 (38.6)		25 (56.8)		25 (52.1)	
≥1		6 (13.6)		2 (4.5)		8 (2.1)	0.16
P (within groups***)		0.003		0.001		0.17	

*Number of participants in each group who completed the appropriate part of the CPG at both baseline and follow-up.

** From paired t-test, Wilcoxon signed rank test or marginal homogeneity test as appropriate

*** From ANOVA on mean difference, Kruskall-Wallis on median difference or chi-squared test on difference in CPG grade as appropriate

Table 3: Mean (standard deviation, SD) SF12 Physical Component Score (PCS) and median (interquartile range, IQR) Mental Component Score (MCS) at baseline and 6 month follow-up and difference between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.

	Prescribing		Review		TAU		
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	P (between groups***)
Baseline SF12 PCS	41	33.5 (10.8)	43	32.59(11.38)	45	29.60 (9.71)	
6 month follow-up SF12 PCS		35.3 (10.8)		34.62 (11.26)		32.59 (9.14)	
Difference SF12 PCS		1.8 (7.5)		2.02 (7.56)		2.99 (8.11)	
P (within groups**)		0.12		0.09		0.02	0.75
Effect size (r)		0.24		0.26		0.35	
		Median [IQR]		Median (IQR)	45	Median (IQR)	
Baseline SF12 MCS	42	52.4 [42.0; 58.8]	43	47.9 [38.5; 59.9]		51.5 [41.3; 60.7]	
6 month follow-up SF12 MCS		49.6 [42.8; 58.1]		47.9 [38.9; 56.2]		44.7 [37.6; 55.8]	
Difference SF12 MCS		-0.4 [-3.7; 6.0]		-1.2 [-6.6; 4.2]		-3.0 [-10.0; 1.3]	
P (within groups**)		0.64		0.37		0.002	0.04
Effect size (r)		0.07		0.14		0.46	

* Number of participants in each group who completed the appropriate part of the SF-12 at both baseline and follow-up.

** From paired t-test or Wilcoxon signed rank test as appropriate

*** From ANOVA on mean difference or Kruskall-Wallis test on median difference as appropriate

Table 4: The HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) count of patients according to severity (normal, mild, moderate or severe) and the difference in severity category between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.*

	n	**Prescribing**	n	**Review**	n	**TAU**	
Baseline HADS-D	44	Count (%)	45	Count (%)	53	Count (%)	P (between groups***)
Normal		32 (72.7)		31 (68.9)		38 (71.7)	
Mild		8 (18.2)		11 (24.4)		7 (13.2)	
Moderate		3 (6.8)		3 (6.7)		8 (15.1)	
Severe		1 (2.3)		0		0	
6 month follow-up HADS-D							
Normal		32 (72.7)		32 (71.1)		32 (60.4)	
Mild		7 (15.9)		6 (13.3)		10 (18.9)	
Moderate		5 (11.4)		6 (13.3)		8 (15.1)	
Severe		0		1 (2.2)		3 (5.7)	
Difference HADS-D							
≤-1		5 (11.4)		4 (8.9)		2 (3.8)	
0		34 (77.3)		37 (82.0)		40 (75.5)	
≥1		5 (11.4)		4 (8.9)		11 (20.8)	0.32
P (within groups**)		1.0		0.71		0.03	
Baseline HADS-A	44	Count (%)	43	Count (%)	48	Count (%)	
Normal		25 (56.8)		30 (69.8)		29 (60.4)	
Mild		8 (18.2)		7 (16.3)		9 (18.8)	
Moderate		8 (18.2)		5 (11.6)		8 (16.7)	
Severe		3 (6.8)		1 (2.3)		2 (4.2)	
6 month follow-up HADS-A							
Normal		27 (61.4)		29 (67.4)		32 (66.7)	
Mild		7 (15.9)		6 (14.0)		5 (10.4)	
Moderate		8 (18.2)		6 (14.0)		10 (20.8)	
Severe		2 (4.5)		2 (4.7)		1 (2.1)	
Difference HADS-A							
≤-1		6 (13.6)		3 (7.0)		10 (20.8)	
0		35 (79.5)		33 (76.7)		29 (60.4)	
≥1		3 (6.8)		7 (16.3)		9 (18.8)	0.14
P (within groups**)		0.25		0.21		0.55	

* Number of participants in each group who completed the appropriate part of the HADS at both baseline and follow-up.

** From marginal homogeneity test

*** From chi-squared test on difference in HADS

Table 5: Median HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) scores (interquartile range, IQR) at baseline and 6 month follow-up and difference between the two assessment point for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.

	Prescribing		Review		TAU		
	n	Median [IQR]	n	Median [IQR]	n	Median [IQR]	P (between groups)
Baseline HADS-D	42	5.0 [3.0;8.0]	44	4.5 [2.3; 8.0]	51	5.0 [3.0; 8.0]	
6 month follow-up HADS-D		4.0 [2.0; 8.0]		5.0 [2.0; 8.8]		5.0 [2.0; 10.0]	
Difference HADS-D		-1.0 [-2.0; 0.0]		0.0 [-1.0; 1.8]		0.0 [-1.0; 2.0]	0.02
P (within groups)		0.02		0.33		0.22	
Baseline HADS-A	44	7.0 [3.3; 10.8]	43	5.0 [3.0; 10.0]	48	6.0[4.0; 10.0]	
6 month follow-up HADS-A		5.0 [2.3; 9.8]		6.0 [3.0; 9.0]		7.0 [4.0; 10.0]	
Difference HADS-A		-1.0 [-2.0; 0.0]		0.0 [-2.0; 2.0]		0.5 [-3.0; 2.0]	0.05
P (within groups)		0.01		0.45		0.81	

* Number of participants in each group who completed the appropriate part of the HADS at both baseline and follow-up.

Box 1 Examples of pharmacist interventions in the prescribing arm

Changes to pain management: 'use paracetamol regularly', 'take tramadol if needed' 'add piroxicam gel PRN', 'given web links to self help groups'

Compliance aid: ' gave written times that this drug could be taken'

Addressing side effects/safety: 'take paracetamol after initial NSAID', 'take senna', 'ordered blood monitoring', 'stop use of two NSAIDS'

General health: 'discussed weight loss', 'invited to practice nurse for BP', 'glucose, lipids and lifestyle update',

Cost minimisation: 'change aspirin EC to plain',

BOX 2 Examples of quotes from Pharmacists (n=6), GPs (n=23) and patient participants (n=40) on the prescribing intervention

Pharmacists (from interviews):

Satisfying (n=6):'contact with patients', 'being able to help patients', 'being able to make a difference to long-standing pain'...'even in small ways'

Interesting (n=6):'learning about pain'

Challenging (n=6):'complex, chronically ill patients'

GPs (from interviews):

Support for the service (n=17): it's been a very positive thing'

Agreement with pharmacists' recommendations (n=23): 'oh very reasonable suggestions', 'tinkering round the edges', 'had been tried already'.

Trust in the practice pharmacist (n=23):'I respect his professional judgement'

Cost effectiveness (n=6): 'if there's limited resources do we want to spend the money on a pharmacist'.

Patients (from 3 month questionnaire):

Closed questions:

Proportion agreeing that:
The pharmacist was interested in them (89%; 39/44)
They were totally satisfied (85%; 39/46)
They were told about their treatment (82%; 38/46)
Their consultation was thorough (79%; 34/44)
They would have liked more time (9%;4/44)
They would have preferred to see their GP (9%; 4/44)
Too many people were now involved in their treatment (11%; 5/44).

Open text questions:

Positive (n=39): 'She was professional, relaxed, pleasant and interested. Excellent!'

Negative (n=1): 'A waste of time, altered my tablets which made my pain worse'.

Title page

Pharmacist-led management of chronic pain in primary care: results from a randomised controlled exploratory trial

Hanne Bruhn, Christine M Bond, Alison M Elliott, Philip C Hannaford, Amanda J Lee, Paul McNamee, Blair H Smith, Margaret C Watson, Annie Blyth, Richard Holland, David Wright

Centre for Healthcare Randomised Trials, Health Services Research Unit, University of Aberdeen, 3rd floor Health Sciences Building, Foresterhill, Aberdeen, AB25 2ZD, UK Hanne Bruhn, Trial Manager

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Christine M Bond, Professor of Primary Care: Pharmacy

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Alison M Elliott, Senior Research Fellow

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Philip C Hannaford, NHS Grampian Chair of Primary Care

Medical Statistics Team, Division of Applied Health Sciences~~Population Health, 1st floor~~, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK, Amanda J Lee, Professor of Medical Statistics

Health Economics Research Unit, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, AB25 2ZD, UK, Paul McNamee, Reader

~~Mackenzie Building, Kirsty Semple Way~~Division of Population Health Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee, DD2 4RB, UK, Blair H Smith, Professor of Population Science

Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK, Margaret C Watson, Senior Research Fellow

Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK, Annie Blyth, Research Associate

Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, UK, Richard Holland, Professor of Public Health Medicine

School of Pharmacy, University of East Anglia, Norwich Research Park, NR4 7TJ, UK, David Wright, Chair in Pharmacy Practice

Correspondence to: Professor CM Bond c.m.bond@abdn.ac.uk, Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth West Block, Foresterhill, Aberdeen, AB25 2ZD, UK

Abstract

Objectives

To compare the effectiveness of pharmacist medication-review, with or without pharmacist prescribing, with standard care, for patients with chronic pain.

Design

An exploratory randomised controlled trial.

Setting

Six general practices with prescribing pharmacists in Grampian (3) and East Anglia (3).

Participants

Patients on repeat prescribed pain medication(4815) were screened by GPs, and mailed invitations (1397). 196 were randomised and 180 (92%) completed. Exclusion criteria included: severe mental illness, terminally ill, cancer related pain, history of addiction

Randomisation and intervention

Patients were randomised using a remote telephone service to: (i) pharmacist medication-review with face-to-face pharmacist prescribing; or (ii) pharmacist medication-review with feedback to GP and no planned patient contact; or (iii) treatment as usual (TAU). Blinding was not possible.

Outcome measures

~~Primary O~~outcomes were the SF-12v2, the Chronic Pain Grade (CPG), the HUI3 and the ~~SF-12v2, together with~~ Hospital Anxiety and Depression Scale (HADS). Outcomes were collected at 0,3,and 6 months.

Ethical approval was obtained.

Results

In the prescribing arm (n=70) two patients were excluded/nine withdrew. In the review arm (n=63) one was excluded/three withdrew. In the TAU arm (n=63) four withdrew. Compared with baseline, patients had an improved CPG in the prescribing arm, 47.7% (21/44; p=0.003),

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and in the review arm, 38.6% (17/44; p=0.001), but not the TAU group, 31.3% (15/48; ns). The SF-12 PCS showed no effect in the prescribing or review arms but improvement in TAU (p=0.02). The SF-12 MCS showed no effect for the prescribing or review arms and deterioration in the TAU arm (p=0.002). HADS scores improved within the prescribing arm for Depression (p=0.022) and Anxiety (p=0.007), between groups (p=0.022 and p=0.045 respectively).

-Conclusion

This is the first RCT of pharmacist-prescribing in the UK, and suggests ~~a~~ there may be a ~~-~~benefit for patients with chronic pain. A larger trial is required.

Trial registration: www.isrctn.org/ISRCTN06131530. Medical Research Council funding.

Focus:

- Chronic pain, (lasting >3 months) affects up to half the adult population, most of whom are primarily managed in primary care but prescribing is often sub-optimal.
- Pharmacists now have prescribing rights but no published research has compared the effectiveness of their prescribing with that of GPs.
- The ~~theory~~~~hypothesis~~hypothesis was that pharmacist advice (with or without pharmacist prescribing) would lead to better outcomes than usual care

Key messages:

- The findings suggest there may be improved pain related outcomes for patients receiving pain related care from a pharmacist prescriber
- A larger trial is called for.

Strengths and Limitations

- This the first randomised controlled trial of pharmacist prescribing in the UK looking at patient reported clinical outcomes
- The study was designed as an exploratory trial so no power calculation was done

Introduction

Chronic pain (pain lasting more than three months) affects up to half the adult United Kingdom (UK) population, and is considered severely limiting in about 15% of cases (1). Recovery is uncommon with nearly 80% of those identified with chronic pain at baseline still reporting chronic pain four years later (2). It adversely affects many aspects of a person's physical and psychological health, and social and economic well being (3-6).

In the UK, most patients with chronic pain present, and are managed, in primary care (7). Although non-pharmacological treatments are available, these are accessed by few patients, with mixed success (e.g. (8-10). Analgesics prescribed in primary care remain the mainstay of treatment (4), representing substantial workload and cost. Sub-optimal prescribing may lead to poor pain control and other adverse patient outcomes. One study found that the most common medications involved in adverse drug reaction-related emergency admissions involved non-steroidal anti-inflammatory drugs (NSAIDs) (11) which are commonly used to manage pain. Improved prescribing could result in better outcomes and remove the need for more costly, scarce, alternatives.

Pharmacists working in UK general practices are well-placed to improve pain pharmacotherapy because of their expertise in therapeutics, understanding of the poly-pharmacy regimens (12) frequently used in chronic pain management, and established relationships with other primary care colleagues. In the UK National Health Service (NHS), recent regulatory changes now allow accredited pharmacists (as well as some other health care professionals such as nurses) to prescribe prescription-only medicines (POMs) (13). Pharmacists can either be qualified as supplementary prescribers, in which case they operate within an agree-d clinical management plan (CMP) in partnership with the doctor and patient, or as an independent prescriber, in which case they can either prescribe completely independently or within a CMP.

However, despite the increasing number of non-medical prescribers, including pharmacists, there has been no rigourous comparisons of the outcomes of non-medical versus GP prescribing. This information is needed to assess the clinical effectiveness of different care models.

This paper reports findings from an exploratory randomised controlled trial (RCT) comparing pharmacist medication review, with or without pharmacist prescribing, with standard care for

patients with chronic pain. Development of the trial was informed by earlier feasibility work (14,15).

The *a priori* ~~theory~~ ~~hypothesis~~hypothesis was that, in patients with chronic pain, pharmacist advice (with or without pharmacist prescribing) would lead to better patient functioning and/or better pain control at six months than treatment as usual (TAU). ~~The hypothesis was developed prior to data collection.~~

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Methods

Regulatory Issues

Ethical approval was granted by the National Research Ethics Service Committee – North of Scotland (reference number 09/S0801/107). NHS Research and Development approval was granted by NHS Grampian and East Norfolk & Waveney Research Governance Committees. Patients gave informed consent before taking part.

Design

An open, exploratory RCT in which patients were randomised to one of three study arms. Participants were not blind to allocated treatment arm due to the nature of the intervention.

Recruitment of practices and independent prescribing pharmacists

Practices in the Grampian Health Board area, Scotland (n=18) and East Anglia region of~~,~~ England (n=4) known to have an attached Royal Pharmaceutical Society of Great Britain registered independent pharmacist prescriber, were eligible to take part. From those indicating a willingness to participate, convenience sampling was used to identify six general practices: three in Grampian and three in East Anglia.

Patient inclusion and exclusion criteria

Patients registered with the recruited practices were eligible for inclusion if they were over 18 years of age, living in their own home, and receiving regular prescribed medication for pain. Patients were identified by a computerised search (14) ~~{5 McDermott, M. E. 2006}~~ of the drug records of all individuals registered with the practice, to identify those who had received either two or more acute prescriptions, and/or one repeat prescription within the last 120 days, for an analgesic (British National Formulary (BNF section 4.7) and/or non-steroidal anti-

inflammatory medication (NSAID) (BNF section 10.1.1). Medications which can be used for analgesia but whose primary indication is not chronic pain (e.g. triptans, anti-epileptics or anti-depressants) were excluded as these drugs identify few additional eligible patients (16). In accordance with trial criteria, GPs excluded and recorded reasons for patients who had: a concomitant severe mental health problem or terminal illness; had suffered recent bereavement; had a known alcohol or drug addiction; suffered pain caused by cancer or other malignancy; were unable to give informed consent; other (unspecified) reasons.

Patient recruitment

Eligible patients were sent an invitation pack (letter, information sheet, consent form) by practice staff between March and June 2010. Consent forms were returned directly to the researchers, who sent out a baseline questionnaire. Patients returning completed questionnaires were randomised by the researcher using a telephone randomisation service with a random number allocation which ensured allocation concealment. The allocation sequence was 1:1:1.

Intervention

All participating pharmacists took part in a two-day course updating them about pain management. As part of the training, participants defined and agreed the treatment algorithm they would all use.

'Prescribing' arm: Pharmacists invited patients to a face-to-face consultation. Prior to the consultation, pharmacists completed a paper-based medication review of each patient's medical record and patients were asked to complete a pain diary to inform the consultation. A pharmaceutical care plan was agreed between the pharmacist and the patient. The plan assessed and documented relevant past medical history and current conditions; known allergies and adverse drug reactions; relevant laboratory results; pain-related medications prescribed in the previous 10 years; current pain related prescription medications; current symptoms; lifestyle issues, including units of alcohol consumed per week; recommendations for changes to medication (if any); whether non-pharmaceutical treatments had been considered; and, any other relevant issues. Copies of the pain diary and pharmaceutical care plan are available from the authors on request. At the end of the consultation any required prescriptions for medicines were issued by the pharmacist. Due to Controlled Drug (CD) regulations in place at the time, prescribing for CDs was done using a supplementary

prescribing Clinical Management Plan (17), rather than independent prescribing. Patients were followed up either by phone or face-to-face, at each pharmacist's discretion.

'Review arm': The pharmacists conducted a paper-based medication review focussed on pain-related prescription medications, before creating a pharmaceutical care plan which detailed any recommendations for medication changes. The plan was passed to the patient's GP for implementation. The GPs were asked subsequently about actions taken as a result of the recommendations.

Treatment as usual (TAU): Patients received standard general practice care.

Outcome measures

A core aim of this exploratory randomised controlled trial (RCT) was to finalise the selction of outcome measures for a subsequent multi-centred RCT. In the Current Controlled Trials Registration (ISRCTNO6131530) we specified both primary and secondary outcome measures (primary: SF12, HUI ; secondary: CPG, HADS) based on our judgement following the earlier feasibility study (15). However in practice, all outcomes were considered equal and no single measure was defined as the primary outcome, for example, for the purpose of a sample size calculation (see below). These four outcome measures are described below.

~~There were two primary outcome measures: the Chronic Pain Grade (CPG) and the Medical Outcomes Study 12-item short form version 2 (SF-12v2). Use~~ Inclusion of both ~~a~~ pain specific and generic outcome measures was based on Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations (18) and an earlier ~~(18,19)~~feasibility study (15).

The SF-12v2 is a generic health and functioning scale (19), previously used in population-based studies of pain (20,21). A Physical (PCS) and Mental Component Score (MCS) was calculated, ranging from 0 to 100; a higher score indicates better functioning.

The Health Utilities Index (HUI3) is a preference-based system for measuring comprehensive health status and health-related quality of life (HRQL) (22). It provides descriptive evidence and a score for each dimension of health (vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition) and a HRQL score for overall health. Each dimension has 3- 6 levels. Owing to the cost of the additional license fee to score data from this measure, this instrument was not subsequently analysed.

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The CPG (~~19~~22~~3~~0) is a seven item scale which assesses pain severity on two dimensions: disability and intensity. The scale ~~-~~classifies pain according to level of intensity and disability (I (low disability-low intensity) to IV (high disability-severely limiting)).

~~The SF-12v2 is a generic health and functioning scale (~~2021~~), previously used in population-based studies of pain (~~21, 22~~22,23). A Physical (PCS) and Mental Component Score (MCS) was calculated, ranging from 0 to 100; a higher score indicates better functioning.~~

~~A secondary outcome measure was~~The ~~the~~ ~~{{}}~~Hospital Anxiety and Depression Scale (HADS) ~~(23~~24(24)~~),~~ is a 14-item screening instrument which identifies the possible and probable caseness of anxiety (7 items (HADS-A)) and depression (7 items (HADS-D)); each item scored from 0 (not present) to 3 (highly present). Standard thresholds and previously used labels (2~~5~~45~~5~~) were applied (no depression/anxiety (0-7), mild (8-10), moderate (11-15) or severe (>15)).

Data collection

Participant questionnaires

Questionnaires were posted to participants at baseline (pre-randomisation), and 3 and 6 months post-randomisation (follow-up was conducted between July 2010 and January 2011). Up to two reminders were sent. Questionnaire content included the outcome measures described above together with items on: demographic status (baseline only); screening items to confirm eligibility (baseline only); duration of pain condition (baseline only); location of pain; Morisky Medication Adherence Scale 4 (MMAS-4) (2~~5~~66); participant satisfaction (11 statements derived from the feasibility study for the prescribing arm (3 months only) and additional comments by participants. The MMAS-4 provides a score of self-reported adherence to medication regimen. Scores range from 0 (low adherence) to 4 (high adherence).

Follow-up interviews with staff

Post-intervention, all pharmacists and all GPs in participating practices were invited to take part in semi-structured interviews, carried out face-to-face when possible, otherwise by telephone. Interviews were taped, transcribed verbatim and content analysis was carried out.

Sample size

As this was an exploratory trial to estimate the effect size for a larger trial, no formal sample size calculation was possible (27~~267~~). We aimed to recruit 30 participants per practice (n=180) (~~excluding those recruited for training purposes~~with an additional six per practice for training purposes ~~)~~ i.e. ~~180~~ 216 in total. This was deemed sufficient to give reliable effect size estimates for the ~~primary~~ outcome measures of health status or chronic pain grade~~, or health status~~.

Data management and analysis

Data were entered into identical SPSS databases at each site and accuracy checks carried out on 10% before databases were merged. Descriptive statistics included means and standard deviations (SD) for normally distributed continuous data, medians (interquartile range (IQR)) for skewed continuous data and percentages (n) for categorical data. Analysis was conducted on an intention-to-treat basis for participants with complete data on relevant measures using SPSS version 18.

Exploratory analyses ~~-~~for parametric data included the paired t-test for within-arm comparisons of mean difference between baseline and 6 months and one-way ANOVA for between arm comparisons of mean difference. For non-parametric data it included the Wilcoxon Signed Rank test for within-arm comparisons of median difference and the Kruskal Wallis test for between arm comparisons of median difference. Categorical data was analysed using the marginal homogeneity test for within-arm comparisons ~~of~~ (with null hypotheis that the distribution of CPG grade or HADS group does not change between baseline and 6 month follow-up) and the Chi-squared test for between arm comparisons; analyses reported here are based on 6 month follow-up data (other than for participant experiences). Within arm effect sizes, expressed in terms of a Pearson correlation coefficient (r) have been calculated using the formulas from Rosenthal (1991) (287). Effect sizes can be directly compared using Cohen's (1988) (298) criteria of r=0.1 (small effect); r=0.3 (medium effect) and r=0.5 (large effect).

Results

Response rates and demography

Six of the seven practices approached participated. GPs excluded 12% (392/3281) of patients, mostly those with dementia. There was no statistically significant difference between participants and non-participants in terms of age, gender, and index of multiple deprivation.

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Figure 1 shows the flow of participants through the study. Overall, the consent rate was 25% (356/1397) and the recruitment rate was 14% (196/1397).

[INSERT FIGURE 1 HERE]

Eighty six percent of participants (251/289) returned baseline questionnaires, of whom 232 were randomised (36 participants were randomised to one of the two intervention arms for training purposes and were not included in any further analysis and 19 were not included as recruitment target had been met). The overall follow-up rate at 3 months was 86% (161/187)and at 6 months 84% (152/180).

As shown in Table 1, groups were similar at baseline for demographic and socioeconomic variables and pain data. Most participants were married, Caucasian and female, older (mean (SD) age 65 (12.6) years), had an annual income of <£25,000 and had suffered from pain for at least five years. Most (57%;103/181) reported being fully adherent to their medication regimen (MMAS-4, median 4.0 (IQR 3.0- 4.0)) (15 missing MMAS scores).

[INSERT TABLE 1 HERE]

In the prescribing arm, 78% (53/68) attended an initial prescribing consultation, 31 had at least one planned follow-up (of which 34/37 were ~~generally~~ conducted by phone) and 130 recommendations were made for 92% (49/53) of participants seen. Examples are shown in Box 1. The median time taken for the note-based record review was 35 minutes (IQR 20.0, 45.0), the consultation was 30 minutes (IQR 20.0, 40.0), careplan preparation 10 minutes (IQR 10.0, 20.0) and median duration of follow-ups was 10 minutes (IQR 5.0- 15.0).

[INSERT BOX 1 HERE]

In the review arm 97% (60/62) of participants' records were reviewed (note there was one post randomisation exclusion) for whom 197 recommendations were made. Where GP feedback was provided (n=48), they generally agreed with pharmacists' recommendations, which were fully implemented for 20 participants (two by the pharmacist following request by GP), partially for 19 participants and not at all for nine participants. The median time taken for the note-based record review was 30 minutes (IQR24.3, 45.0), and careplan preparation was 10 minutes (IQR 5.0, 20.0).

Clinical outcome measures

Table 2 shows the mean (SD) or median (IQR) of the CPG for each arm at baseline and 6 month follow-up. Table 3 shows the SF-12 scores and Table 4 shows the HADS-A and HADS-D results.

[INSERT TABLE 2,3,4, HERE]

In the prescribing arm, there was a statistically significant within arm improvement for the CPG intensity (p=0.002, effect size (r)=0.45) and disability (p=0.003, effect size (r)=0.43) subscales, and between arms on the intensity sub-scale (p=0.02), but not the disability subscale (p=0.55) (Table 2). There was a significant within-arm improvement in overall CPG grade in the prescribing (p=0.003) and review arm (p=0.001), but not in the TAU arm. The SF-12 Physical Component Score showed a statistically significant within arm improvement in the TAU arm (p=0.02, effect size (r)=0.35) (Table 3), but not between trial arms. The SF-12 Mental Component Score showed a statistically significant deterioration in the TAU arm (p=0.002, effect size (r)=0.45)(Table 3), as did the HADS-D (p=0.03, Table 4). Analysis was also carried out on the non-categorised HADS scores which showed a statistically significant improvement within the prescribing arm for Depression (p=0.022) and Anxiety (p=0.007). These were both significant between groups (p=0.022 and p=0.045 respectively) (Table 5).

Acceptability of the pharmacist prescribing intervention

All six pharmacists and 56% of the GPs (23/41) were interviewed. All pharmacists and most GPs were positive about the intervention, although some GPs suggested that the pharmacists' recommendations had been minor and questioned the cost-effectiveness of the service. Patient participants were generally positive about the pharmacist prescribing service although some concerns were identified, as Illustrated by the quotes shown in Box 2.

[INSERT BOX 2 HERE]

Discussion

Principal findings

This exploratory RCT of pharmacist-led management of patients with chronic pain suggests that pharmacist prescribing (and possibly pharmacist review alone) may be effective in improving pain-related outcomes and be acceptable to both patients and most professionals. There was an indication of a positive effect on emotional health, but no measurable effect on general health.

Strengths and weaknesses

This was the first RCT to assess clinical and humanistic outcomes after pharmacist prescribing for any clinical condition compared to usual GP care, and the first RCT to specifically assess pharmacist-led management of chronic pain, compared with usual GP care. It was based on extensive development and feasibility work (14,15) in line with MRC framework for development and evaluation of complex interventions (~~28~~29~~30~~). A range of validated outcome measures was included, as well as a parallel qualitative process evaluation which ~~demonstrated~~ assessed satisfaction and acceptability. The inclusion of six practices and their associated pharmacists from both Scotland and England increased the generalisability of the findings. Pharmacists received formal training and agreed and used a common treatment algorithm which should have increased standardisation of treatment~~.~~. The preponderance of females (overall 62%) and average age of 65 years reflects the wider chronic pain population (1) as does the distribution of pain site (31,32~~0, 31,29,30~~)

There were, however limitations. Although high follow-up response rates were achieved at both three (86%) and six months (85%) only 25% of eligible patients entered the trial. This low initial consent rate is in line with other studies (33,34~~2, 33~~29,30), but may cause unknown biases including problems of generalisability, as does the solely Caucasian~~.~~ ethnicity. Concerns identified by participants during the formal feedback e.g. having too many people involved in one's care may have contributed to poor response rates and r~~R~~ewording of participant recruitment documentation to reassure participants of the role of the pharmacist could address this. ~~some of the concerns identified by participant feedback e.g. having too many people involved in one's care.~~ More participants withdrew in the prescribing arm compared with the other two arms, which might be attributed to the need for an additional practice visit. The study was an exploratory trial so no formal power calculation was undertaken. ~~.~~**However, because there were no published MIDs available to estimate effect size for the outcomes in this population, it was important to present the actual clinical magnitude of change in outcome at 6 months alongside a statistical assessment of this change (p-value). This allows an assessment of both clinical and statistical significance simultaneously with the caveat that this is an exploratory study. With around 50 patients per arm, this was deemed sufficient numbers to examine the change in outcome measures with appropriate within and between group univariate statistical tests.** ~~**because of no prior** knowledge of effect size.~~ Due to the nature of the intervention, no participants were blind to their group allocation, and so some

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outcomes, especially the qualitative components, may have been affected by social desirability bias.

Our ~~main~~ outcome measures were self-reported, but this is the norm in pain studies as pain is a subjective experience (18). Furthermore we do not know how important the observed differences were to participants. Following precedents set in previous research (25), and because there is no consensus on an alternative measure (3~~54~~31) we used the HADS as a tool to classify people by severity of depression and anxiety. However it is strictly a screening tool, and the four levels of severity have not been formally validated. We therefore also compared outcomes using it as a continuous scale.

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Relationship with other studies

This study is important because no other RCT has evaluated pharmacist prescribing and few studies, and importantly no RCTs, have evaluated pharmacist interventions for pain. In pharmacist prescribing most research has focussed on reported experiences of professionals and patients, and not used validated outcome measures. Yet pharmacist prescribing is now widely practised. For pain, there have been a few small studies. Briggs et al (2008) (36~~52~~) conducted a small before-and-after evaluation (involving 65 patients) of a nurse and pharmacist-led chronic pain clinic in primary care. Pain intensity Visual Analogue Scale scores reduced significantly over six months. Another evaluation of 26 patients using a medication review service provided jointly by a physiotherapist and pharmacist in the UK~~-~~, reported improvement in pain control for 88% of patients (37~~63~~).

The CPG was found to show a graded effect across the three arms, showing discrimination with both direction and strength of improvement, suggesting maximum benefit for those in the pharmacist prescribing arm. However, the reduction in overall score appears to be mediated by a change in the intensity of pain subscale rather than in pain-related disability. The effect size of 0.45 suggests this could be an important difference. In contrast, the SF-12, a measure of general health and functionality showed no significant difference between intervention arms, reflecting either no effect or or lack of powerto detect an effect.

Whilst most participants in this study were already within the normal range on the HADS scale, and therefore had minimal chance of improvement, there were nonetheless suggestions of better ourcomes in participants in the prescribing arm. Including a range of instruments is in

line with IMMPACT recommendations (3874), which state that focus should be on the whole person, not just about pain. However, this needs to be balanced with minimising participant burden.

Explanations, implications, and future research

The number of pharmacists' recommendations per participant was higher in the review arm than in the prescribing arm. This might seem contradictory to the possible greater benefit found in the prescribing arm. However, in the prescribing arm pharmacists met the participant and may have more readily identified and dismissed suggestions previously tried. The interview feedback highlighted that some recommendations for change, whilst sensible, had been tried already. This might also be the reason why there were only 60% of pharmacist recommendations with which the GP fully agreed. Self-reported adherence to medication at baseline was good. Despite this, the pharmacists still improved pain outcomes in the prescribing arm. This could have been due to changes in medications and/or participant education about optimal timing for administration of analgesic medicines. Further research is needed to confirm the beneficial effect of pharmacist prescribing and its sustainability.

Conclusion

Our results suggest that pharmacist prescribing (and possibly pharmacist review alone) for patients with chronic pain is feasible, acceptable and may lead to improvements~~...acceptable and leads to improvements~~ in pain and other measures. A larger fully-powered trial is now needed to confirm these findings.

Data sharing statement

Consent was not obtained from participants for data sharing; the presented data are anonymised and there is no risk of individual identification. Requests for data should be made to the contact author who will provide this in a format in which risk of patient identification will be minimal.

Conflict of interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3

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years; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

HB and CB drafted the manuscript.

All authors:

1) made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;

2) were involved in drafting the manuscript or revising it critically for important intellectual content; and

3) have given final approval of the version to be published.

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All authors had access to all of the study data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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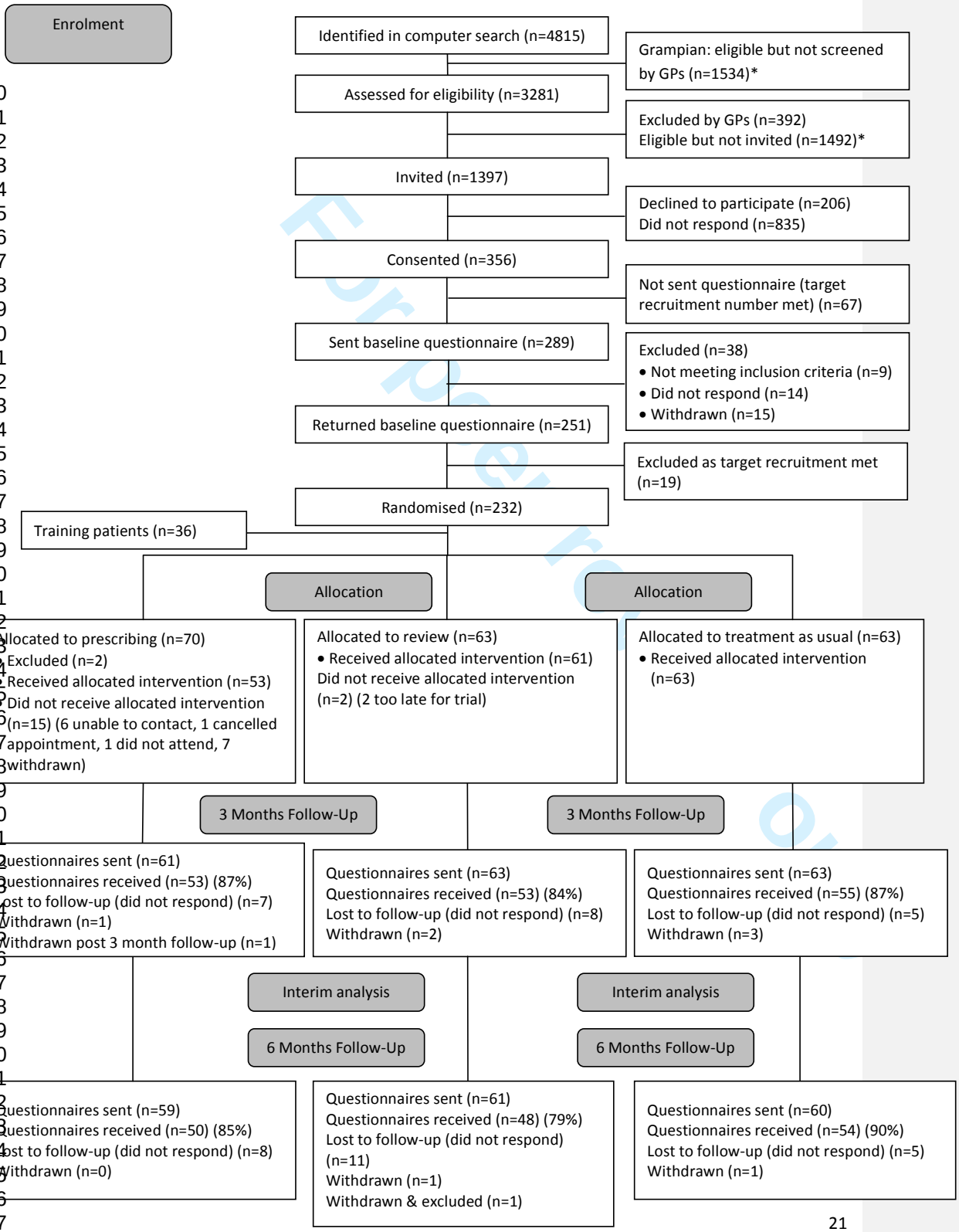
Figure 1: CONSORT Flow Diagram



*In the **Grampian Health Board area**~~Grampian~~, on the basis of response rates in the earlier feasibility study (241 screened patients resulted in 22 recruited) only a random sample of eligible participants were screened (15). In East Anglia all eligible patients were screened.

Table 1: Baseline demographic, socio-economic and pain data of patients by study arm, prescribing, review and treatment as usual (TAU)

	Prescribing* (n = 68)	**Review*** (n = 62)	**TAU*** (n = 63)
Age: mean (SD)	66.1 (12.1)	65.7 (14.2)	64.9 (11.6)
Missing	1	1	0
Gender (% female)	54.4 (37)	74.2 (46)	58.7 (37)
Marital status			
Married	43	30	41
Single	6	6	3
Divorced/widow	10	21	13
Other	6	4	6
Missing	3	1	0
Highest educational level achieved			
No qualifications	30	27	21
O grade or equivalent	12	6	14
Higher/A-level/NVQ3/SVQ3	6	8	7
Tertiary education/NVQ4/NVQ5	18	17	14
Other	2	1	4
Missing	0	3	3
Employment status			
Employed	16	14	9
Unemployed	3	5	1
Retired	38	35	34
Long term sick/disabled	7	5	9
Other	3	2	7
Missing	1	1	3
Household annual income before tax			
Less than £9,999	13	15	10
£10,000 - £14,999	14	18	22
£15,000 - £24,999	14	12	12
£25,000 – or more	22	11	8
Missing	5	6	11
Ethnic group			
Caucasian	67	62	61
Other	1		
Missing	0	0	2
Pain duration			
< 1 year	3	2	4
1 – 3 years	12	12	7
3 – 5 years	10	13	9
5 – 10 years	17	13	15
> 10 years	26	22	28
Pain localisation (%, n)			
Back	27.9 (19)	32.3 (20)	20.6 (13)
Neck, shoulders	7.4 (5)	9.7 (6)	9.5 (6)
Limbs or hips	42.6 (29)	30.6 (19)	50.8 (32)
Other	8.8 (6)	4.8 (3)	7.9 (5)
Missing	9	14	7

*Denominator based on numbers allocated to the specific arms, minus any exclusions due to protocol violations.

Table 2: Mean (standard deviation, SD) CPG intensity , median (interquartile range, IQR) CPG disability, and count CPG grade at baseline, 6 months follow-up and difference between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). P-values for within and between arm differences are also reported.

	Prescribing		Review		TAU		P (between groups***)
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	
Baseline CPG intensity	47	66.1 (16.0)	45	68.4 (17.6)	54	65.4 (18.0)	
6 month follow-up CPG intensity		58.1 (19.5)		67.4 (21.7)		65.6 (19.6)	
Difference CPG intensity		-8.0 (16.3)		-1.0 (16.0)		0.2 (14.9)	0.02
P (within groups**)		0.002		0.67		0.93	0.02
Effect size (r)		0.45		0.07		0.01	
		Median [IQR]		Median [IQR]		Median [IQR]	
Baseline CPG disability	48	60.0 [30.0; 75.8]	46	66.7 [45.0; 80.0]	53	56.7 [36.7; 80.0]	
6 Month follow-up CPG disability		40.0 [20.0; 60.0]		53.3 [29.2; 73.3]		50.0 [25.0; 80.0]	
Difference CPG disability		-8.3 [-23.3; 0.0]		-3.3 [-16.7; 10.0]		-3.3 [-21.7; 5.0]	0.55
P (within groups**)		0.003		0.15		0.05	0.55
Effect size (r)		0.43		0.20		0.26	
Baseline CPG grade	44	Count (%)	44	Count (%)	48	Count (%)	
I		5 (11.4)		3 (6.8)		5 (10.4)	
II		16 (36.4)		9 (20.5)		13 (27.1)	
III		7 (15.9)		10 (22.7)		13 (27.1)	
VI		16 (36.4)		22 (50.0)		17 (35.4)	
6 month follow-up CPG grade							
I		13 (29.5)		8 (18.2)		6 (12.5)	
II		13 (29.5)		15 (34.1)		17 (35.4)	
III		8 (18.2)		8 (18.2)		11 (22.9)	
IV		10 (22.7)		13 (29.5)		14 (29.2)	
Difference CPG grade							
≤-1		21 (47.7)		17 (38.6)		15 (31.2)	
0		17 (38.6)		25 (56.8)		25 (52.1)	
≥1		6 (13.6)		2 (4.5)		8 (2.1)	0.16
P (within groups***)		0.003		0.001		0.17	

*Number of participants in each group who completed the appropriate part of the CPG at both baseline and follow-up.

** From paired t-test, Wilcoxon signed rank test or marginal homogeneity test as appropriate

*** From ANOVA on mean difference, Kruskall-Wallis on median difference or chi-squared test on difference in CPG grade as appropriate

Table 3: Mean (standard deviation, SD) SF12 Physical Component Score (PCS) and median (interquartile range, IQR) Mental Component Score (MCS) at baseline and 6 month follow-up and difference between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.

	Prescribing		Review		TAU		
	n*	Mean (SD)	n*	Mean (SD)	n*	Mean (SD)	P (between groups***)
Baseline SF12 PCS	41	33.5 (10.8)	43	32.59(11.38)	45	29.60 (9.71)	
6 month follow-up SF12 PCS		35.3 (10.8)		34.62 (11.26)		32.59 (9.14)	
Difference SF12 PCS		1.8 (7.5)		2.02 (7.56)		2.99 (8.11)	~~0.75~~
P (within groups**)		0.12		0.09		0.02	0.75
Effect size (r)		0.24~~x~~		0.26~~x~~		0.35~~x~~	
		Median [IQR]		Median (IQR)	45	Median (IQR)	
Baseline SF12 MCS	42	52.4 [42.0; 58.8]	43	47.9 [38.5; 59.9]		51.5 [41.3; 60.7]	
6 month follow-up SF12 MCS		49.6 [42.8; 58.1]		47.9 [38.9; 56.2]		44.7 [37.6; 55.8]	
Difference SF12 MCS		-0.4 [-3.7; 6.0]		-1.2 [-6.6; 4.2]		-3.0 [-10.0; 1.3]	~~0.04~~
P (within groups**)		0.64		0.37		0.002	0.04
Effect size (r)		0.07~~x~~		0.14~~x~~		0.46~~x~~	

* Number of participants in each group who completed the appropriate part of the SF-12 at both baseline and follow-up.

** From paired t-test or Wilcoxon signed rank test as appropriate

*** From ANOVA on mean difference or Kruskall-Wallis test on median difference as appropriate

Table 4: The HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) count of patients according to severity (normal, mild, moderate or severe) and the difference in severity category between the two assessment points for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.*

	n	**Prescribing**	n	**Review**	n	**TAU**	
Baseline HADS-D	44	Count (%)	45	Count (%)	53	Count (%)	P (between groups***)
Normal		32 (72.7)		31 (68.9)		38 (71.7)	
Mild		8 (18.2)		11 (24.4)		7 (13.2)	
Moderate		3 (6.8)		3 (6.7)		8 (15.1)	
Severe		1 (2.3)		0		0	
6 month follow-up HADS-D							
Normal		32 (72.7)		32 (71.1)		32 (60.4)	
Mild		7 (15.9)		6 (13.3)		10 (18.9)	
Moderate		5 (11.4)		6 (13.3)		8 (15.1)	
Severe		0		1 (2.2)		3 (5.7)	
Difference HADS-D							
≤-1		5 (11.4)		4 (8.9)		2 (3.8)	
0		34 (77.3)		37 (82.0)		40 (75.5)	
≥1		5 (11.4)		4 (8.9)		11 (20.8)	0.32~~Not valid**~~
P (within groups**)		1.0		0.71		0.03	
Baseline HADS-A	44	Count (%)	43	Count (%)	48	Count (%)	
Normal		25 (56.8)		30 (69.8)		29 (60.4)	
Mild		8 (18.2)		7 (16.3)		9 (18.8)	
Moderate		8 (18.2)		5 (11.6)		8 (16.7)	
Severe		3 (6.8)		1 (2.3)		2 (4.2)	
6 month follow-up HADS-A							
Normal		27 (61.4)		29 (67.4)		32 (66.7)	
Mild		7 (15.9)		6 (14.0)		5 (10.4)	
Moderate		8 (18.2)		6 (14.0)		10 (20.8)	
Severe		2 (4.5)		2 (4.7)		1 (2.1)	
Difference HADS-A							
≤-1		6 (13.6)		3 (7.0)		10 (20.8)	
0		35 (79.5)		33 (76.7)		29 (60.4)	
≥1		3 (6.8)		7 (16.3)		9 (18.8)	0.14
P (within groups**)		0.25		0.21		0.55	

* Number of participants in each group who completed the appropriate part of the HADS at both baseline and follow-up.

~~**Between arms p-value not valid due to low numbers in multiple cells, even after collapsing to th~~

** From marginal homogeneity test

*** From chi-squared test on difference in HADS

~~ree categories.~~

Table 5: Median HADS-Depression (HADS-D) and HADS-Anxiety (HADS-A) scores (interquartile range, IQR) at baseline and 6 month follow-up and difference between the two assessment point for each arm, prescribing, review and treatment as usual (TAU). Within and between arm p-values are also reported.

	Prescribing		Review		TAU		
	n	Median [IQR]	n	Median [IQR]	n	Median [IQR]	P (between groups)
Baseline HADS-D	42	5.0 [3.0;8.0]	44	4.5 [2.3; 8.0]	51	5.0 [3.0; 8.0]	
6 month follow-up HADS-D		4.0 [2.0; 8.0]		5.0 [2.0; 8.8]		5.0 [2.0; 10.0]	
Difference HADS-D		-1.0 [-2.0; 0.0]		0.0 [-1.0; 1.8]		0.0 [-1.0; 2.0]	0.02
P (within groups)		0.02		0.33		0.22	
Baseline HADS-A	44	7.0 [3.3; 10.8]	43	5.0 [3.0; 10.0]	48	6.0[4.0; 10.0]	
6 month follow-up HADS-A		5.0 [2.3; 9.8]		6.0 [3.0; 9.0]		7.0 [4.0; 10.0]	
Difference HADS-A		-1.0 [-2.0; 0.0]		0.0 [-2.0; 2.0]		0.5 [-3.0; 2.0]	0.05
P (within groups)		0.01		0.45		0.81	

* Number of participants in each group who completed the appropriate part of the HADS at both baseline and follow-up.

Box 1 Examples of pharmacist interventions in the prescribing arm

Changes to pain management: 'use paracetamol regularly', 'take tramadol if needed' 'add piroxicam gel PRN', 'given web links to self help groups'

Compliance aid: ' gave written times that this drug could be taken'

Addressing side effects/safety: 'take paracetamol after initial NSAID', 'take senna', 'ordered blood monitoring', 'stop use of two NSAIDS'

General health: 'discussed weight loss', 'invited to practice nurse for BP', 'glucose, lipids and lifestyle update',

Cost minimisation: 'change aspirin EC to plain',

BOX 2 Examples of quotes from Pharmacists (n=6), GPs (n=23) and patient participants (n=40) on the prescribing intervention

Pharmacists (from interviews):

Satisfying (n=6):'contact with patients', 'being able to help patients', 'being able to make a difference to long-standing pain'...'even in small ways'

Interesting (n=6):'learning about pain'

Challenging (n=6):'complex, chronically ill patients'

GPs (from interviews)*:*

Support for the service (n=17): it's been a very positive thing'

Agreement with pharmacists' recommendations (n=23): 'oh very reasonable suggestions', 'tinkering round the edges', 'had been tried already'.

Trust in the practice pharmacist (n=23):'I respect his professional judgement'

Cost effectiveness (n=6): 'if there's limited resources do we want to spend the money on a pharmacist'.

Patients (from 3 month questionnaire):

Closed questions:

Proportion agreeing that:
The pharmacist was interested in them (89%; 39/44)
They were totally satisfied (85%; 39/46)
They were told about their treatment (82%; 38/46)
Their consultation was thorough (79%; 34/44)
They would have liked more time (9%;4/44)
They would have preferred to see their GP (9%; 4/44)
Too many people were now involved in their treatment (11%; 5/44).

Open text questions:

Positive (n=39): 'She was professional, relaxed, pleasant and interested. Excellent!'

Negative (n=1): 'A waste of time, altered my tablets which made my pain worse'.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5-6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	N/A

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	N/A
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10, figure 1(p.18)
	13b	For each group, losses and exclusions after randomisation, together with reasons	10, figure 1(p.18)
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7-8
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	10, Table 1 (p20)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	See Tables 2,3,4,5 and page 9 (ITT)
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	See pages 10/11, and Tables 2,3,4,5. P values reported
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13
Other information			
Registration	23	Registration number and name of trial registry	4

Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	14

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.