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Nursing, Midwifery and Allied Health Professions Research Unit
Improving health through research
CHIEF SCIENTIST OFFICE

Multicentre randomised trial of the effectiveness and cost-effectiveness of basic versus biofeedback-mediated intensive pelvic floor muscle training for female stress or mixed urinary incontinence

PROTOCOL

A UK Collaborative Study funded by the
NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC),
Health Technology Assessment (HTA) Programme

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PROTOCOL SUMMARY

QUESTION ADDRESSED	Is biofeedback-mediated intensive PFMT more effective and cost-effectiveness than basic PFMT for the treatment of female stress or mixed urinary incontinence?
CONSIDERED FOR ENTRY	Women seeking treatment for urinary incontinence
POPULATIONS	1. Stress urinary incontinence 2. Mixed urinary incontinence
TRIAL ENTRY	Consent will be obtained from eligible women after written and oral information has been provided.
INTERVENTIONS	1. Basic PFMT 2. Biofeedback-intensified PFMT
OUTCOME ASSESSMENT	• Postal questionnaires at 6, 12 and 24 months after the date of their randomisation • Pelvic floor muscle assessment at 6 months following randomisation • Bladder diary at 24 months • Health care utilisation questions at 6, 12 and 24 months • Participant time and travel cost questionnaire at 6 months only
CO-ORDINATION	**Local**: by local lead Principal Investigator (Gynaecologist or Continence Lead) and Recruitment Officer. **Central**: by Trial Office in Glasgow. **Overall**: by the Project Management Group and overseen by the Trial Steering Committee and the Data Monitoring and Ethics Committee.
FUNDING	National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre, Health Technology Assessment (NETSCC HTA) Programme
Start date:	September 2013
Planned finish date:	May 2018
Planned reporting date:	May 2018

Glossary of abbreviations

CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
DMEC	Data Monitoring and Ethics Committee
HTA	Health Technology Assessment
ISRCTN	International Standard Randomised Controlled Trial Number
MUI	mixed urinary incontinence
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
OPAL	Optimal Pelvic floor muscle training for Adherence Long-term
PFMT	pelvic floor muscle training
PMG	Project Management Group
REC	Research Ethics Committee
SAE	Serious Adverse Event
SUI	stress urinary incontinence
TSC	Trial Steering Committee
UI	urinary incontinence

Protocol summary in plain English

Accidental urine leakage (incontinence) is a distressing problem that affects about 1 in 3 women, and the NHS spends large amounts of money treating it.

Many women have stress incontinence; that is, accidental urine leakage that happens with coughing, sneezing and physical activity. Based on past research, current UK guidelines recommend that these women are offered at least three months of pelvic floor muscle exercises. The exercises are taught by a specialist physiotherapist or nurse. There is evidence that these exercises can strengthen the muscles and decrease leakage. It is not clear how "intensively" women have to exercise to get a good result that lasts thus improving the woman's quality of life and reducing the likelihood of surgery.

This research aims to find out whether the use of biofeedback can help to improve the results of pelvic floor muscle exercises in the short- and longer-term. Using a probe inserted into the vagina, biofeedback equipment shows women what their pelvic floor muscles do. Because the muscles are "inside" they are "hidden", and biofeedback allows women to "see" the muscles working as they exercise. "Seeing" the muscles working on the biofeedback screen might help with teaching the exercises and encourage women to continue doing their exercises. A graph can be printed out to show changes in the muscle strength over time. The women who receive biofeedback may exercise more because they are more confident about doing the exercises and the changes that the exercises can achieve.

Women who attend or are referred to one of the participating study centres for treatment of incontinence for the first time will be asked to take part. Those who agree to participate will be allocated at random to one of two groups, either the usual exercise programme recommended by the UK guidelines (called basic exercise) or these same exercises with the addition of biofeedback (called intensive exercise). Both groups will visit a specialist nurse or physiotherapist 6 times in 16 weeks who will teach and encourage them in the exercises. The intensive exercise group will also have biofeedback at each appointment. At the 1st appointment women in the intensive exercise group will also be given a simple, portable biofeedback machine so they can monitor the exercises themselves at home.

We will measure the results of treatment after 6 months, 1 and 2 years. We are primarily interested in whether women in the intensive exercise group have had more improvement in their incontinence at 2 years after they start the study than the basic exercise group. We also want to find out how much urine leakage women in both groups have, how much this impacts on their lives, what other bladder problems they have, what other treatments they have had, how much exercise they did, how confident they were about exercising and how much their muscles have strengthened. We will also measure the costs of the treatments and any costs to the woman and her family, and balance these against any benefits of the intensive treatment.

During the trial we will assess how well the exercise programmes were delivered by speaking with physiotherapists and nurses and listening to recordings of some therapy appointments. We will talk with women to find out how they perceive the treatment they received and how they got on with exercising during the treatment period and once treatment finished. We will then explore how the treatment delivery and women's perceptions impact on the women's incontinence.

We have worked out from previous research that if 600 women take part and most complete the trial, we will have enough data to successfully compare the two treatments to find out if one is better than the other. Women's participation will be entirely voluntary and we do not believe there are any risks associated with taking part.

OPAL Personnel

Grant Holders

1	Suzanne Hagen	10	Mary Kilonzo
2	Doreen McClurg	11	Andrew Elders
3	Cathryn Glazener	12	Gladys McPherson
4	Mohamed Abdel-fattah	13	Alison McDonald
5	Wael Agur	14	Joanne Booth
6	Carol Bugge	15	Brian Buckley
7	Sarah Dean	16	Karen Guerrero
8	John Norrie	17	Lyndsay Wilson
9	Jean Hay-Smith		

Project Management Group

This group is comprised of all grant holders along with the OPAL trial researchers.

OPAL trial researchers

1	Susan Stratton	Trial Manager
2	Nicole Sergenson	Data Coordinator
3	Aileen Grant	Qualitative Researcher

Trial Steering Committee

This committee is comprised of independent members along with the Chief Investigator (Suzanne Hagen). Representatives from the other OPAL grant-holders and trial researchers (e.g. the trial manager) may be invited to attend meetings to provide information as appropriate. The funders and the sponsor will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate.

Independent members of TSC

1	Mr Chris Mayne, Chair	3	Mrs Teresa Cook, Women's Health Physiotherapist, Lecturer
2	Dr Thomas Chadwick, Statistician	4	Ms Kirsty Craig, Consumer Representative
3	Ms Veronica Haggar, Continence Nurse Specialist		

Data Monitoring and Ethics Committee members:

1	Dr Steff Lewis Chair	3	Dr Sue Hallam, Physiotherapist
2	Mr Simon Emery, Consultant Urogynaecologist		

OPAL Trial Office Team:
This team is comprised of the Glasgow- and Stirling-based grant holders along with the Glasgow- and Stirling-based trial research team members.

Other Information

International Standard Randomised Controlled Trial Number (ISRCTN)	57746448
REC Reference Number	13/WS/0048
HTA Project Number	11/71/03
The NETSCC, HTA Programme website	http://www.nets.nihr.ac.uk/projects/hta/117103
Trial website:	https://www.opaltrial.co.uk/

1 Reasons for the Trial

1.1 Scale of the problem and use of NHS resources

Urinary incontinence (UI), any involuntary loss of urine [Abrams et al 2002], is a common condition in women. The prevalence of UI depends on the definition: using a broad definition, a range of between 5% and 69% is reported, with most studies in the range 25% to 45% for women over 15 years of age [Abrams et al 2009]. The main types of UI are stress, urgency and mixed, with stress being most prevalent (around half of all women with UI), followed by mixed UI (stress and urgency combined) (~30%), and fewer having urgency UI alone (~10%). The cost to the UK NHS annually of treating clinically significant UI in women was estimated in the Leicestershire MRC Incontinence Study [Perry et al 2000] as £233M, not including the personal costs borne by the women which were estimated to be £178M in the same study [Turner et al 2004]. Literature suggests that UI significantly impacts on daily living for the majority of women, with an associated increased prevalence of major depression [Melville et al 2009]. Among older women, social isolation, psychological distress [Bognor et al 2002) and increased risk of admission to long-term care institutions [Thom et al 1997] feature highly. Thus UI is prevalent and costly to the NHS, and to women both financially and in terms of physical and mental wellbeing.

1.2 Pelvic floor muscle training

Currently, supervised pelvic floor muscle training of at least 3 months' duration is the first-line treatment for stress and mixed UI [NICE 2006]. Potential annual spend on PFMT is estimated at £38M (0.03% of the NHS budget of £106bn), based on 0.8% of women aged 15 years or above being referred to UI services each year [NICE 2008]. PFMT refers to the regular practice of repetitive pelvic floor muscle contractions in order to produce a training effect on the muscles. The aim of a PFMT programme is to increase the strength of the muscles to build up muscle volume and thus improve structural support; to increase endurance; to improve resting tone; to improve recruitment through improved nerve function and properties of muscle fibres; and improve cognitive awareness of body posture and a relaxed versus an un-relaxed state of the pelvic floor.

To produce improvements in muscle strength and endurance the basic physiological principles must be adhered to [McArdle et al 1994]: overload (muscles need to perform more work than usual resulting in fatigue); specificity (muscles must be trained with physical activity that replicates as closely as possible the functional movement required); maintenance and reversibility (benefits of the exercise are reversible if they are not undertaken on a regular basis). There is evidence to suggest that for effective strength training in skeletal muscles in adults, three to five sets of 8 to 12 slow velocity, close to maximal contractions per day should be performed 2 to 5 days per week for 16 weeks [American College of Sports Medicine 2011].

There is good evidence from a Cochrane review that PFMT is effective for women with UI (particularly stress and mixed) when compared to no treatment [Dumoulin et al 2010], however there is little evidence to guide practice regarding what is the optimal PFMT regimen. The recent HTA review on non-surgical treatments for women with stress UI [Imamura et al 2010] found no evidence that basic PFMT (≤2 supervised sessions per month) was better in terms of cure than no treatment. However, there was evidence that PFMT with extra sessions (>2 supervised sessions per month), and basic PFMT with the addition of biofeedback (either clinic-based, home-based or both), were more effective in terms of cure than no treatment and basic PFMT. Both methods of intensifying PFMT were found to be equally effective. However, limitations of the findings were highlighted relating to the data available from the primary studies reviewed: conclusions were based on data from a limited number of small trials, only 16% of which had a low risk of bias as assessed by adequate random allocation sequence generation and concealment. Thus uncertainty remains and the authors concluded "*More intensive forms of PFMT appear worthwhile but research is required to define an optimal form of more intensive therapy that is feasible and efficient for the NHS to provide*".

1.3 Biofeedback

Biofeedback is commonly used as an adjunct to PFMT, and is less expensive than the addition of extra supervised sessions. Biofeedback is the technique by which information about a normally unconscious physiological process is presented to the patient and/or the therapist as a visual, auditory or tactile signal [Abrams et al 2002]. Electromyography (EMG) is the study of minute electrical potentials produced by depolarisation of muscle membrane [Siroky 1996]. In EMG biofeedback electrical activity arising from muscle activity (during exercise and voluntary effort) is recorded in microvolts and displayed as a visual signal for both patient and therapist to view. Within a PFMT programme, an internal vaginal probe is used to record electrical information from pelvic floor muscles through surface recordings. The probe is connected by cables to a biofeedback unit. Handheld units with a small visual display screen are available for home use. The display provides a visual representation of the muscles contracting and relaxing, allowing monitoring of strength, endurance and repetitions.

The effect of PFMT relies on sufficient exercise being undertaken for long enough to strengthen the muscles, and the continuation of sufficient exercise so that strength is maintained [Bø 2004]. Thus to intensify PFMT, adherence must be maximised. Women may lack self-efficacy for undertaking PFMT [Ashworth and Hagan 1993, Hay-Smith et al 2007] and there is evidence that self-efficacy influences intention to adhere [Alewijnse et al 2001] and actual adherence to PFMT both during [Chen and Tzeng 2009] and one year after supervised treatment [Alewijnse et al 2003]. Biofeedback is thus a means of increasing self-efficacy, which in turn increases adherence and PFMT intensity.

A Cochrane systematic review of biofeedback-assisted PFMT for women with UI [Herderschee et al 2011] found, like the HTA review [Imamura et al 2010], that biofeedback-assisted PFMT appeared to offer benefit over PFMT alone (risk ratio for no improvement in UI 0.75 [95% confidence interval 0.66 to 0.86]). The Cochrane review, with its more restricted scope, conducted a finer grained analysis of the biofeedback trials. While women who received biofeedback-assisted PFMT were more likely to report symptom cure or improvement, a subgroup analysis suggested that this effect might be confounded by the greater amount of health professional contact in the biofeedback groups compared to the groups without biofeedback.

1.4 Implications for the proposed trial

Therefore, based on current evidence, it is not clear if the apparent benefit of biofeedback can be attributed to the biofeedback or to some other variable such as more health professional contact in those women receiving biofeedback. Some of the trials included in the Cochrane review had the same PFMT programme in both arms of the trial, and the same amount of health professional contact. The summary statistics for cure and improvement in these trials still favoured biofeedback, although the difference between groups was not statistically significant. However, a common problem in all these trials was the failure to clearly state the purpose of biofeedback, or to describe the intervention protocol. Thus, it was not clear if the way the biofeedback was used could theoretically or in practice qualitatively change the intensity or effectiveness of the PFMT.

We contend therefore that a robust comparison of basic PFMT versus biofeedback-mediated intensive PFMT, in which both groups have the same basic PFMT programme and same amount of health professional contact, is imperative in order to establish if biofeedback does improve incontinence outcomes.

1.5 Questions which this trial will address

The aim of the OPAL trial is to determine the effectiveness and cost-effectiveness of basic PFMT compared to biofeedback-mediated intensive PFMT for the treatment of stress or mixed (stress and urgency) female UI.

Specific objectives are:

1. To establish if a PFMT regimen intensified via the addition of a theory-based biofeedback protocol, compared to basic PFMT, is more effective and cost-effective in reducing severity of incontinence at 24 months, and providing greater improvement in quality of life, reduced need for surgery and other UI treatment, improved pelvic floor muscle function and increased self-efficacy for, and adherence to, PFMT.
2. To identify and investigate, via a process evaluation, the possible mediating factors that impact upon the effectiveness of the intervention (including intervention fidelity), how these mediating factors influence effectiveness, and whether the factors differ between randomised groups.
3. To investigate women's experiences of the interventions, both basic and intensive PFMT, to identify the barriers and facilitators which impact on adherence in the short- and long-term, to explain the process through which they influence adherence, and to identify whether these differ between randomised groups.

2 Trial Methods

The research comprises:

1. a parallel group multicentre randomised controlled trial to compare effectiveness and cost-effectiveness of basic PFMT versus biofeedback-mediated intensive PFMT for women with stress UI and mixed UI;
2. a mixed-methods, nested process evaluation, and;
3. a longitudinal semi-structured interview study with purposively selected women from both arms to explore experience of, and adherence to the trial interventions.

Recruitment will take place in UK community, outpatient and primary care settings where women are referred for the treatment of UI. The trial intervention will be delivered by either women's health physiotherapists or continence nurse specialists, contributing to the generalisability of the trial findings.

2.1 Planned inclusion/exclusion criteria

Inclusion criteria

- Women 18 years of age or above, presenting with a new episode of stress or mixed UI, who are willing and suitable to be randomised.

Exclusion criteria

- Women who have urgency UI alone;
- Women who have had formal instruction in PFMT in the last year;
- Women who are unable to contract their pelvic floor muscles;
- Women who are pregnant or are less than 6 months postnatal;
- Women who have prolapse greater than stage II (>1cm below the hymen on Valsalva);
- Women who are having active treatment for pelvic cancer;
- Women who have cognitive impairment affecting capacity to give informed consent;
- Women who have neurological disease (Multiple Sclerosis, Parkinson's Disease, Stroke, Motor Neurone Disease, Spinal Injury);
- Women with a known nickel allergy or sensitivity;
- Women who are currently participating in other research relating to their UI.

2.2 Practical arrangements for allocating participants to trial groups

All women due to attend for a first continence service appointment, or for a first outpatient appointment where UI is the presenting complaint, will be identified in advance from clinic lists by a dedicated local Recruitment Officer (member of the healthcare team) in each centre, over the trial recruitment period (see Flow Diagram, Appendix 1). A Screening Log of such women will be kept locally. Each of these women will be given a unique Study Identity Number.

Where possible, their notes will be flagged and a Clinical Assessment Form will be attached to the notes. The Recruitment Officer will request that a Patient Information Leaflet and introduction letter are included with the routine appointment card/ letter that is sent to the identified women.

When the woman attends for her appointment, her continence clinician will confirm a clinical diagnosis of SUI or MUI (those with urgency UI alone will be excluded), and assess other trial eligibility criteria via undertaking a vaginal examination. Details will be recorded in the Clinical Assessment Form, which includes the woman's telephone number for further contact. Eligible women who indicate a willingness to hear more about the study will be put in contact with the Recruitment Officer at the conclusion of their clinical appointment.

Potentially, large general practices could participate as recruiting centres and thus a parallel recruiting method which accommodates identification of women at the point of their GP appointment may be developed.

The centre Recruitment Officer will discuss the trial in detail with an eligible woman. The Recruitment Officer will go through the Patient Information Leaflet with the woman and will provide her with a consent form and a baseline questionnaire for completion. After discussion, the Recruitment Officer will ask women who would like to take part to complete the consent form and baseline questionnaire. Women who require additional time to consider participation can take the paperwork home and subsequently, if they decide to take part, return the completed forms to the Trial Office. The Trial Office will contact women by telephone if they have not returned their completed paperwork within two weeks.

Each woman will be required to provide signed informed consent to be randomised and followed up after completion of the intervention by postal questionnaires, a further pelvic floor muscle assessment and use of routine NHS datasets. The Patient Information Leaflet and the consent form will all refer to the possibility of being invited to take part in the interview study, of having a therapy appointment audio-recorded, of longer-term questionnaire follow-up and being contacted about other future incontinence research. Women will have had the opportunity to discuss the trial with their continence clinician, the Recruitment Officer and, if they wish, with the Trial Office research staff and their GP, before deciding to take part. Each participating woman's GP will be informed about her involvement in the trial, pending women's consent.

The Recruitment Officer will provide the Trial Office with the details of eligible women using the Clinical Assessment Form. A limited amount of data from the Screening Log will be provided to the Trial Office on ineligible women and those who decline (age, reason for non-eligibility/non-participation).

Consented women will be given a date for their first therapy appointment (approximately 2 weeks later) and a bladder diary to be completed and brought to her first therapy appointment.

Recruitment Officers will be encouraged to enter data (Screening Log, Clinical Assessment Form) to the trial database and randomise women locally. Alternatively when the Trial Office receives a completed consent form and baseline questionnaire the woman will be randomised, and the Trial Office will notify the woman of her group allocation and the date of her first therapy appointment with an Intervention Therapist at her centre. The Trial Office will also inform the Intervention Therapist of the woman's group allocation.

Some women, who have indicated a willingness on their consent form to hear more about the interview study, will be purposively selected (based on UI type, severity, centre and therapist type), and will be sent an invitation and Patient Information Leaflet for the Interview Study. The Qualitative Research Fellow will telephone these women a few days after they have been sent the information Leaflet to go through the leaflet, discuss the study and answer any

questions. If the woman is then willing to take part, the Qualitative Research Fellow will make an appointment to undertake the woman's first interview. A consent form will be signed at that first interview.

At each therapy appointment, the Intervention Therapist will complete details of the session in a Therapy Assessment Form. Information recorded will include women's reported symptoms, details of the pelvic floor assessment carried out, the PFMT regimen prescribed, lifestyle advice given and adherence to previously prescribed exercise and advice. Therapists will also complete a protocol checklist, indicating the elements of the protocol delivered, which will provide data for the process evaluation.

Approximately 100 women will have one of their therapy appointments audio-recorded for the process evaluation. The Recruitment Officer will take the digital recorder to the Intervention therapist prior to the appointment and remind the Therapist to check consent with the woman prior to switching the recorder on.

All consenting women will receive follow-up questionnaires by post at 6, 12 and 24 months (6 month questionnaire including time and travel questions); will complete a bladder diary at baseline and 24 months; and will attend for blinded assessment of pelvic floor muscles at 6 months. The women recruited into the Interview study will be interviewed at 6 months (face-to-face), 12 months (telephone) and 24 months (telephone).

When a therapist has completed all treatments for all women she is treating in the trial, she will be contacted by the Qualitative Research Fellow and asked to take part in a semi-structured telephone interview.

2.3 Randomisation

Randomisation will utilise the existing proven remote automated computer randomisation application developed at the Centre for Healthcare Randomised Trials (CHaRT, a fully registered UK CRN clinical trials unit) in the Health Services Research Unit, University of Aberdeen. This randomisation application will be accessed by local Recruitment Officers and researchers at the Trial Office (NMAHP Research Unit, Glasgow Caledonian University) as an internet-based service.

Randomisation will be computer-allocated and minimised on:

- Type of UI (SUI or MUI)
- Centre
- Age (<50/≥50 years)
- UI severity (ICIQ-UI SF score <13/≥ 13)

2.4 Methods to protect against other sources of bias

a) Ensuring standardisation of intervention and outcome measurement

Standardisation of intervention delivery will be the responsibility of the co-applicants with clinical expertise in PFMT (DM, JHS, SD, JB). The training required to standardise the use of the intervention protocols will be developed and conducted by these applicants and will be directed towards ensuring standardisation across centres and therapist type, for both basic and intensive PFMT protocols. Intervention therapists from each centre will attend a training day where all aspects of intervention delivery will be explained. Practical sessions will be incorporated and there will be a forum for discussion with opportunities for questions. All centres will use the same clinic and home biofeedback units.

The Recruitment Officers in each centre will ensure completeness and accuracy of local data entry using remote data capture via a trial web-based portal, authored and managed by the UK CRN-registered trials unit in Aberdeen (CHaRT).

Screening Log data and Clinical Assessment Form data (including patient contact details) will be recorded and shared securely with the Trial Office in this way.

b) Loss to follow up

We will take very active measures to minimise loss to follow-up, such as reminder questionnaires, telephoning the women, allowing telephone completion of questionnaires and using shortened versions of questionnaires at reminder stage, using retention incentives and checks with GPs. In addition we will obtain consent from the women to enable us to access routine NHS data for example via the NHS Strategic Tracing Service in England and Wales, and using Community Health Index numbers from the Information Services Division in Scotland. We have extensive experience of using such strategies and measures, resulting in very low attrition. However, a conservative estimate of 20% loss to follow up at 24 months has been used in the power calculations for the current trial.

c) Other sources of bias

Group allocation cannot be concealed from the woman or the therapists delivering the intervention (Intervention Therapists), however outcome assessment is largely by participant self-completed questionnaire, so avoiding assessor bias. The clinician undertaking 6-month pelvic floor muscle assessments will be blinded to women's group allocation. Data entry and statistical analysis will be conducted by research staff blinded to group allocation, using study identity numbers only to identify women and questionnaires. All women will be actively followed up, with analysis based on the intention-to-treat principle, such that women will be analysed in the groups to which they were allocated regardless of the intervention received. All analyses will be clearly predefined, in agreed statistical and economic analysis plans, to avoid bias.

2.5 Proposed sample size

There are no published long-term data on the primary outcome, the ICIQ-UI score, in a similar population to reliably inform sample size calculations. At baseline, studies including women with stress/mixed UI report a mean score of around 10 and standard deviation (SD) around 5 [Hajebrahimi et al 2004, Sherburn et al 2011]. It is likely that the SD at 24 month follow-up will be greater than 5 and perhaps as large as 10. Assuming a clinically meaningful difference of 3 points on the ICIQ-UI score (e.g. change from leaking urine "once a day" to "never"), which is similar to the minimal clinically important difference of 2.5 reported in a study of older women [Sherburn et al 2009], and SD of 10, a sample size of 234 per arm would detect this difference (standardised effect size of 0.3) with 90% power at the 5% level of significance (2-sided alpha). Allowing for 20% drop out, we will randomise 300 women per group. We will check the SD assumption as we accrue data for the first 100 women, and adjust the sample size if required.

With 600 subjects we will also have 90% power to detect important differences in secondary outcomes. For example, a minimum difference in the mean number of leakage episodes of 0.15 per day (1.05 per week) would be detectable based on a 6-month SD of 3.6 for women with SUI treated with PFMT [Castro et al 2008]. We also expect to be adequately powered to detect differences in long-term uptake of surgery. The recent HTA systematic review [Imamura et al 2010] estimated that 59.3% of women who receive basic PFMT will require surgery within 10 years, which means that at a 5% significance level we would have 90% power, assuming loss to follow-up of 25% (routine NHS data will be used to supplement questionnaire data to achieve this), to detect a difference between groups of 15% in the surgery uptake rate.

Assuming, based on recent experience from a multicentre trial of the effectiveness of PFMT for prolapse (POPPY) [Hagen et al 2013], a typical centre can randomise 4 women per month; to randomise 600 women will need 14 centres, recruiting for between 12 and 21 months depending on start date. This is a conservative estimate as UI is more prevalent than prolapse.

Based on the same trial, we assume 70% of eligible women will agree to participate. There are sufficient similarities between OPAL and POPPY in terms of setting, population, intervention and recruitment method to suggest that 70% is an accurate estimate of the uptake rate we can expect in OPAL. Thus we expect to approach 860 women to achieve our sample size of 600. The first three centres to begin recruiting have provided data indicating that approximately 24 eligible women per month will be seen at each of these centres.

We are aware that portable biofeedback units can be purchased in high street shops and online, and that potential participants may view this as an alternative to trial participation. However the recruitment process will emphasise that, within the trial, home biofeedback is an integrated part of a PFMT programme (including specialist teaching of correct pelvic floor muscle contraction, appropriate backup and feedback from a trial therapist, use of clinic and home biofeedback) which has more potential for benefit than self-initiated use of a home unit alone. Therefore we believe that this is unlikely to be a major threat to recruitment, but it is one we will monitor.

2.6 Number of centres involved

We aim to recruit women from 14 centres to achieve the necessary sample size. We have had agreement in principle to participate from 14 centres with which we have previously collaborated. We will continue to gather expressions of interest from additional centres to allow for any drop out or underperformance of centres that may occur. The possibility of involving a large GP practice as a recruiting centre is being pursued.

Trial centres will have staggered start dates. The first three centres have been identified and will start recruiting in month six, providing an internal pilot. Experience of recruitment and data generated from these centres over three months will be used to fine-tune trial processes and protocols if necessary. Between one and two new centres per month will begin recruiting thereafter.

We anticipate that compliance problems at recruiting centres are likely to be few as we will recruit centres that are genuinely motivated to help answer the research question, are known to the research team, and have a track record of successful participation in multicentre research.

2.7 Process evaluation methods

The inclusion of a process evaluation is advised in contemporary trial methodology [MRC 2008] to support the explanation of discrepancies between expected and observed outcome and to assess fidelity to the intervention delivery and uptake. In summary, a concurrent triangulation mixed methods design will be used [Creswell 2009], whereby both quantitative and qualitative data will be gathered simultaneously. Initially data from each source will be analysed separately (to reach separate conclusions) and then there will be cross-method analysis to reveal meta-inferences that will inform conclusions related to fidelity and outcome [Teddlie and Tashakkori 2009]. Data will be gathered from a range of participants and from various sources:

- A protocol checklist will be completed by all Intervention Therapists after each appointment. The checklist will allow assessment of protocol deviations and the reasons they occurred.
- Semi-structured telephone interviews will be undertaken with all consenting Intervention Therapists at the end of their participation in intervention delivery. The interviews will explore the therapist's experiences of delivering the basic and intensive interventions, including their perspectives on adherence to delivering the protocols and women's adherence to intervention.
- Audio-recording of approximately 100 therapy appointments will be undertaken. Appointments will be purposively sampled for variance in: trial arm, centre, woman's type and severity of UI, therapist type and

appointment number (1 to 6). Local Recruitment Officers will provide the Intervention Therapists with a digital recorder to record the selected appointments.

The trial follow-up questionnaires will include questions on women's adherence to PFMT during and after the supervised intervention which will contribute to the process evaluation. In addition, the interview study (described below) will provide data from the women about adherence to treatment to feed into the process evaluation.

2.8 Interview study methods

The interview study examines the perspectives of the women receiving the intervention, in order to identify barriers and facilitators to adherence. The design will be a two-tailed case study [Yin 2003]; the tails are the experimental and comparator arms of the trial. Thirty to 40 randomised women (15 to 20 in each tail) will be purposively sampled for variance in centre [DGH, University, community], woman's type of UI [stress or mixed], severity [less or more severe], therapist type [physiotherapist/ nurse]. If women refuse consent to the interview study on receipt of information, another woman with similar characteristics will be selected and approached. Data on the characteristics of women who refuse will be documented and reported. A sampling table will be populated in order to oversee progress of the recruitment strategy.

Each woman will be asked to undertake a series of interviews at key points that are in line with trial data collection points (baseline, 6, 12 and 24 months post-randomisation). Data will be collected using a series of semi-structured interviews with women which will be piloted in the first three centres. Each interview will have a specific focus:

- Baseline (pre-treatment) interview (face-to-face) will explore the woman's experience of UI, the social contexts within which she experiences UI, and her expectations of treatment.
- 6 month interview (face-to-face) will explore the woman's experience of the intervention, her adherence to therapy appointments and the prescribed programme, and factors that affected that adherence, and her perceptions of treatment outcome.
- 12 month interview (telephone) will explore women's experience of UI post-intervention, of the intervention, of factors that influence ongoing adherence to PFMT and of treatment outcome.
- 24 month interview (telephone) will explore the same issues as at 12 months but with a focus on the longer term.

Interviews will be digitally recorded and transcribed. A case sheet will be completed at the end of the first interview, to note key points relating to the research questions. This will be added to after subsequent interviews [Miles and Huberman 1994].

3 Trial Interventions

3.1 Both trial arms (basic and intensive PFMT)

A basic PFMT protocol will be delivered during six therapy appointments over a 16 week period at around weeks 0, 1, 3, 6, 10 and 15.

At the first therapy appointment, basic demographic and medical history will be recorded. A visual and digital assessment of the vagina and pelvic floor muscles will be carried out to provide the Intervention Therapist with accurate knowledge of the condition of the perineum and vagina (including areas of pain or increased tone), and the woman's capacity for contracting and relaxing her pelvic floor muscles. This information will be recorded using both the Oxford Classification [Laycock 2008] and the International Continence Society method [Messelink et al 2005].

Women will be taught the correct exercise technique and this will be confirmed on digital palpation by the therapist with the women in the supine position. Women will be encouraged to become aware of contracting and holding the muscles, and also of relaxing them. This will be facilitated by the use of different exercise positions (e.g. side lying), counter pressure on their perineum, coordination of contraction/relaxation with breathing. Women will be taught to counterbrace, that is, to pre-contract their pelvic floor muscles prior to an increase in intra-abdominal pressure (e.g. coughing, sneezing, lifting), a technique known as "the knack" [Miller et al 1998].

The initial exercise programme will be identified and agreed between the woman and therapist over the first and second appointment, according to the woman's ability. The exercise programme will be practised during the appointments to allow the therapist to assess progress and adjust the programme as necessary. Home exercise will be prescribed after the first appointment, or as soon as the therapist confirms a correct technique has been achieved.

Home exercise will be tailored to the individual woman, ensuring a training effect on the muscles is achieved, but that the programme is manageable for the woman. Targets of maximum strength, endurance and repetitions will be set, aiming towards a programme of three sets per day of, for example, 8 to 12 maximum strength pelvic floor muscle contractions, holding each contraction for 6 to 10 seconds with a 6 second rest between contractions, followed by up to 10 fast contractions. Exercise position will be varied (lying, sitting, standing, squatting). Potential for progression will be determined during the therapy appointments and will be carried over to home exercise. Progression will be tailored for each woman [American College of Sports Medicine 2009 and 2011, Bø et al 1999, Bø 2003], and will consist of, for example, increased number of contractions, increased length of hold, sub-maximal contractions, decreased rest periods and the introduction of more difficult positions. Functional and core stability exercises will be introduced as appropriate.

Therapists will make use of appropriate motivational techniques and advice detailed within the protocol to encourage correct exercise technique and adherence to the prescribed programme. Women will be given information on good bladder management. They will be taught techniques for dealing with urgency and frequency, and given lifestyle advice, for example on fluid and caffeine intake.

Vaginal examinations will be undertaken following Chartered Society of Physiotherapy and Royal College of Obstetrics and Gynaecology guidelines for performing intimate examinations. Local infection policy will be adhered to and the woman's informed consent will be obtained. A chaperone will be offered. Vaginal assessment of the pelvic floor muscles will be undertaken at the first and last appointments, and during other appointments as clinically indicated and if the woman is agreeable.

3.2 Experimental trial arm (intensive PFMT)

As above, a PFMT protocol will be delivered to women in the experimental arm during six therapy appointments over a 16 week period at around weeks 0, 1, 3, 6, 10 and 15. In addition, a biofeedback protocol will be incorporated at all of these therapy appointments, and during home exercise sessions between appointments. The content of the biofeedback protocol is underpinned by the Information-Motivation-Behavioral Skills (IMB) model of behaviour change [Fisher and Fisher 2002], incorporating Social Cognitive Theory [Bandura 1977], an evidence-based theory relating to self-efficacy and perseverance. Briefly, self-efficacy for PFMT is enhanced because biofeedback offers *information* to women about a normally 'hidden' muscle activity, supports *motivation* through tracking changes in muscle strength and performance, and enhances *behavioural skills* through improving performance of a muscle contraction during strength training and timing a contraction to reduce leakage with increases in intra-abdominal pressure (e.g. during cough, sneeze, lift).

At each therapy appointment biofeedback equipment will be used to produce information for the woman and

therapist, both graphical representation and numerical readings, relating to the resting state of the muscles, responsiveness during initiation of contraction, endurance, co-ordination, release of muscle activity (onset of relaxation), and the number of repetitions achieved. Women can observe whether they are maintaining a maximal contraction for the required length of time, and whether correct relaxation of the muscles is taking place. A print out of the graphical biofeedback output will be provided for the woman at each appointment.

The biofeedback software to be used produces comprehensive patient progress reports for the Intervention Therapist of contraction onset and release times, average and peak values for periods of contraction and relaxation. This information will: assist in confirming the woman has the correct contraction technique (teaching); inform adjustments to the prescribed number of contractions, duration of hold and rest periods (modulating); be used to highlight improvements in the muscle function to the woman, and hence to improve exercise adherence (encouraging) [Herderschee et al 2011].

The table below gives examples of the ways in which biofeedback will be used at each appointment to intensify treatment:

Appointment/ timing	Theoretical foundation and use of biofeedback to intensify therapy
Appointment 1/ week 0	• Information: visual depiction of correct contraction and baseline muscle performance. Visual depiction of 'the knack' (fast contraction before and held during rise in intra-abdominal pressure) • Motivation: self-efficacy for correct contraction and 'the knack' and set goal for next assessment of muscle performance • Behaviour: begin individualised strength training programme and use of 'the knack'
Appointment 2/ week 1	• Information: visual depiction of held contractions and 'the knack'. Instruction on how to use intravaginal probe and home biofeedback unit. • Motivation: self-efficacy for training through comparison with print out of baseline muscle performance. and set goal for next assessment of muscle performance • Behaviour: add regular home biofeedback to training
Appointment 3/ week 3	• Information: reinforcement of how to use home biofeedback unit with visual depiction of muscle contractions and 'the knack' • Motivation: self-efficacy for use of home biofeedback unit, self-efficacy for training through comparison with previous biofeedback print out, and set goal for next assessment of muscle performance • Behaviour: regular home biofeedback continued, with a focus selected on the basis of what the woman finds most difficult (e.g. holding a contraction with a cough)
Appointment 4/ week 6	• Information: visual depiction of variations in muscle performance with changes in posture. • Motivation: self-efficacy for muscle contraction in range of body postures, self-efficacy for training through comparison with previous

	biofeedback print out, and set goal for next assessment of muscle performance • Behaviour: use home biofeedback to monitor muscle performance in range of training positions (e.g. sitting, standing, lying)
Appointment 5/ week 10	• Information: ways to use home biofeedback as antidote to exercise 'boredom' • Motivation: using range of pre-programmed biofeedback traces to add training variation, self-efficacy for training through comparison with previous biofeedback print out, and set goal for next assessment of muscle performance • Behaviour: add biofeedback programme variations to home training
Appointment 6/ week 15	• Information: discuss downloads from biofeedback unit to relate exercise dose to symptom improvements, and alternatives to biofeedback for monitoring performance • Motivation: self-efficacy for training through comparison with previous biofeedback print out, and set goal for maintenance training • Behaviour: transition to maintenance programme and use of alternatives to biofeedback (e.g. self-digital palpation) as appropriate

Subject to the correct basic techniques being established, at the first therapy appointment women will be provided with a biofeedback unit for use during home exercise. They will be instructed how to insert, use and clean the biofeedback probe, how to operate the unit and interpret the information on the display in relation to biofeedback output seen in the clinic. The parameters of the home unit will be set appropriately for the woman at each appointment in line with the latest assessment. Women will be instructed to use the biofeedback unit at agreed times when exercising at home between therapy appointments. The unit will be activated to record data on its usage between appointments, providing research data on adherence to the use of biofeedback between appointments. This data will also be available for the Intervention Therapist to download and view at appointments. Home use will also be recorded by women in a diary. Therefore if women are unable or unwilling to use the biofeedback unit at home this information will be available. Such women will still have the potential benefit of clinic biofeedback.

4 Data Collection

Data will be collected via participant-completed questionnaires at baseline, 6, 12 and 24 months. In addition at baseline and 24 months: recording of leakage episodes by women in a 3-day diary. At 6 months: blinded assessment of pelvic floor muscle function to quantify muscle change.

Outcome measures on which data will be collected are as follows:

4.1 Primary outcome

UI severity at 24 months (ICIQ-UI score, encompassing urinary leakage frequency, amount and interference with everyday life, scored 0-21) using the ICIQ-UI Short Form questionnaire [Avery et al 2004] The primary economic outcome measure of cost effectiveness is incremental cost per quality-adjusted life-year (QALY) at 24 months based on responses to the EQ-5D (EuroQol Group, 1990).

4.2 Secondary outcomes

Urinary outcomes

- number of episodes of UI per day, recorded by women in a bladder diary [Locher et al 2001]
- impression of global improvement in UI (PGI-I) [Yalcin and Bump 2003]
- number of women with UI cured and number with UI improved, derived from the ICIQ-UI Short Form (cured is a negative response to both "how often do you leak urine?" and "how much urine do you usually leak (whether you wear protection or not)?"
- uptake of surgery for UI
- uptake of other treatment for UI
- other urinary symptoms (ICIQ-FLUTS) [Brookes et al 2004]

Quality of life outcomes

- UI-specific quality of life (ICIQ-LUTSqol)
- General health (EQ-5D-3L) [EuroQol Group]

Pelvic floor related outcomes

- Prolapse symptoms (POP-SS – Hagen et al 2009)
- Bowel symptoms (early version of ICIQ Bowel Short Form)
- Pelvic floor muscle function (Oxford scale – Laycock 2008, ICS method – Messelink et al 2005)
- self-efficacy for PFMT (PFME self-efficacy scale) [Chen 2004]
- adherence to PFMT (exercise diary/follow-up questionnaire)

Economic outcomes

- cost and use of NHS services
- cost to the women and their families/carers
- the incremental costs, QALYs and incremental cost per QALY derived by the economic model.

5 Data analysis

5.1 Main effectiveness analysis

All analyses will be based on the intention-to-treat principle. All outcomes will be described with the appropriate descriptive statistics where relevant: mean and SD for continuous and count outcomes, or medians and inter-quartile range if required for skewed data, numbers and percentages for dichotomous and categorical outcomes.

The analysis of the primary outcome (ICIQ-UI score) will estimate the mean difference (and 95% confidence intervals) between the experimental and comparator arms at 24 months using a general linear model adjusting for minimisation covariates and other important prognostic covariates, including the baseline score. If appropriate, missing outcome data will be estimated using a multiple imputation approach to make use of partial ICIQ-UI Short Form questionnaire responses. A similar analysis will be used for the ICIQ-UI score at 6 and 12 months.

All secondary outcomes will be analysed in a similar manner using an appropriate generalised linear model (for example binary logistic regression for dichotomous outcomes such as uptake of surgery, cure and improvement, and ordinal logistic regression for ordered categorical outcomes such as pelvic floor muscle strength and impression of global improvement). We will explore the analysis of outcomes at all time-points simultaneously using, for example, Generalised Estimating Equations or Generalised Linear Latent and Mixed Models, with relevant link functions, to explore changes in outcome over time.

A single main analysis will be performed at the end of the trial when 24-month follow up has been completed. An independent Data Monitoring and Ethics Committee will review confidential interim analyses of accumulating data at its discretion but at least annually.

5.2 Planned subgroup analyses

Subgroup analyses will be carried out within the following groups:

- Type of incontinence (SUI or MUI)
- Type of therapist (physiotherapist or nurse)
- Age (<50/≥50 years)
- UI severity (ICIQ-UI SF score <13/≥ 13)

Stricter levels of statistical significance (2P<0.01) will be sought, reflecting the exploratory nature of these analyses. Heterogeneity of treatment effects amongst subgroups will be tested for using the appropriate subgroup by treatment group interactions [Wang et al 2007].

All analyses will be according to a statistical analysis plan that will be agreed in advance.

5.3 Process evaluation analysis

Each data source will be analysed individually in the first instance to reach separate conclusions.

- Data from the protocol checklists completed by the Intervention Therapists will be analysed descriptively to report the extent to which there were deviations from protocol. Free text comments from the therapists relating to any barriers and facilitators to delivering the protocol they experienced during appointments will be coded using a coding framework developed using content analysis with a 10% representative sample of appointments.
- Data from interviews with therapists will be analysed using the Framework Approach [Ritchie and Spencer 1994]. Following familiarisation with the data, a thematic framework will be developed and applied across the data set. Data will then be tabulated and conceptual maps used to make links between themes.
- A framework will be developed for analysis of the appointment audio-recordings. The framework will be developed using the intervention protocols and the theory underlying the protocols, and data generated from recordings in the first three centres (internal pilot). The framework will contain explicit guidance as to what codes have to be applied in what circumstances. Coded data will then be subject to descriptive and interpretive analysis.

Data synthesis will be undertaken whereby the findings from individual data sources (including the participant outcome measures and data from the participant interview study) will be presented in matrices that bring together key issues from the different analyses, to facilitate drawing overall conclusions about why the interventions may or may not be effective, and which components are most important.

5.4 Interview study analysis

Interview data will be transcribed and entered into QSR NVivo software to support analysis. Analysis will be on four interacting levels:

- *At the level of the individual interview.* An initial *a priori* coding scheme will be applied that focuses on core areas of interest: specifically, women's experiences of UI; experience of PFMT +/- biofeedback; factors that influence adherence to supervised treatment and home exercise; and perceptions of treatment outcome. Grant holder discussions and constant iterative coding will further develop the coding scheme. The combination of the *a priori* scheme and iterative codes will aim, at this stage, to identify barriers and facilitators that influence adherence.

- *At the level of the case (woman)*. Case summaries will be written with a focus on creating an understanding of women's experience in our areas of interest: the problem, the treatment, adherence to supervised treatment and home exercise; perceptions of treatment outcome and how these factors interact. Analysis at this stage will focus on identifying issues relating to changes over time and in developing theoretical propositions to guide subsequent analysis [Yin 2003].
- *At the level of the trial arm*. All the cases for one trial arm will be collected together and consistencies/ inconsistencies searched for. The aim of analysis at this stage is to identify the core barrier and facilitators within the trial arm, the detailed explanations for them and interactions between them.
- *At the cross case level.* The experimental and comparator tails will be compared to one another using the theoretical propositions. The aim of the analysis at this point is to identify similarities and differences in barriers and facilitators between the trial arms.

These last two levels will be used to enhance our understanding of the findings from the main trial by exposing similarities and differences between the experimental and comparator arms. The interview study will cross reference with the process evaluation, hence the final level of analysis will synthesise the case study findings with the process evaluation findings.

For all qualitative datasets, 10% of transcripts will be coded independently by two analysts to assess for inter-rater reliability.

5.5 Economic analysis

The trial will include a formal economic evaluation assessing the costs and cost-effectiveness of the interventions from the perspective of the NHS and the women and their families. Resource-use data collected will include the intervention and primary and secondary NHS services used by the women. Health service resources refer to those provided directly by the NHS due to PFMT and biofeedback for UI and subsequent appointments and procedures. Personal resource utilisation to the women (such as use of containment products, travelling to appointments and work/social restrictions) will also be investigated.

Resource use will be recorded prospectively for every woman within the study. For the PFMT intervention, cost details will be gathered from the Intervention Therapists, recorded at the time of intervention (e.g. length of appointments, materials used). Costs to the women will be collected using questions based on those developed by the UK working party on patient costs, which will be included in follow-up questionnaires. We will collect data on the mode of travel, cost of travel if applicable, amount of time the women take out of their usual activities such as work, to go to the appointments and similar data from family members that either accompany them or look after their children. Data on the use of primary and secondary care services by the women, including medications, GP visits and uptake of surgery, will also be collected within the follow-up questionnaires. Unit costs/prices will be obtained using published estimates for health care services and/or interventions.

The EQ-5D-3L generic instrument [EuroQol Group 1990] and a condition-specific instrument [ICIQ-LUTSqol] will be used to measure health outcomes. Trial participants will complete the EQ-5D-3L and the ICIQ-LUTSqol within the questionnaires at baseline and at 6, 12 and 24 months after randomisation. These instruments will provide the quality of life weights to compute the quality adjusted life years (QALYs).

Incremental cost-effectiveness ratios (ICERs) will be computed comparing the cost of the experimental and comparator interventions. The difference in effectiveness will be expressed in terms of the number of women cured and number of women improved. These data will be retrieved from the women's questionnaire responses to the ICIQ-UI Short Form. The difference in utility will be expressed in terms of QALYs. Where appropriate the analysis of

incremental costs, effectiveness and cost-effectiveness will be based on similar statistical models as those outlined in the statistical analysis section above. This 'within' trial analysis will include both deterministic and stochastic sensitivity analyses to explore statistical and other forms (e.g. around unit costs or the source of utility estimates) of uncertainty.

If relevant, an economic model which considers a longer time horizon will also be developed to provide additional information for policy makers. In the model, the findings of the trial will be extrapolated to the woman's life time. The model will describe care pathways that women may follow and will include the initial intervention and any subsequent treatments. The structure of the model will be developed in collaboration with clinicians and trial collaborators. Parameter estimates for relative effectiveness up to 24 months, costs and utilities will be derived from the trial data. Data from the trial will be supplemented with data from other sources (e.g. Cochrane reviews). These data will be assembled systematically and will follow guidelines for good practice [Phillips et al 2004].

Outcomes in the model will be expressed in terms of an incremental cost per QALY. Parameter uncertainty will be integrated by the incorporation of probability distributions into the model and involve Monte Carlo simulation. Other forms of uncertainty such as that associated with choices made about the structure of the model, discount rate, etc. will be addressed through sensitivity analysis. The base case and sensitivity analyses will be presented as cost-effectiveness acceptability curves. The model will also be used to identify priorities for further research by investigating the expected value of information.

Although costs from both the patient and NHS perspectives will be reported the main cost effectiveness and cost utility analysis will be performed from the perspective of the health care provider. Anecdotal evidence suggests that patients incur expenses in the purchase of containment products. Data collected from the patients will provide information on how great this burden is. Similar methods and assumptions used to estimate NHS costs will be applied to non-health costs if considered to be informative.

All analyses will be according to an economic analysis plan that will be agreed in advance. Similar subgroup analysis will be performed in the economic analysis as defined in the statistical analysis if deemed relevant.

6 Milestones and Recruitment Rate

6.1 Trial timetable and milestones

Year one (Sept 13-Aug 14)		
By month 3	Nov 13	• Set up office and administrative base • Construct database, web-based data entry system, randomisation program Establish first three centres (R&D negotiations, appoint local Recruitment Officers) • First joint Trial Steering Committee & Data Monitoring
By month 6	Feb 14	• Finalise study documentation, therapist training and teaching materials, questionnaires • Start recruitment at first three centres
By month 10	June 14	• Roll out to further 2 centres (R&D, appoint local Recruitment Officers)
By month	Aug 14	• First annual report to funders
Year Two (Sept 14 – Aug 15)		
By month	Nov 14	• 12 centres fully active, 175 women recruited
By month 16	Dec 14	• Second Data Monitoring and Ethics Committee meeting • Second Trial Steering Committee meeting • Establish last 2 original centres (R&D, appoint local Recruitment Officers)
By month 24	Aug 15	• Additional 5 sites opened. 19 sites active. • Second annual report to funders
Year Three (Sept 15 – Aug 16)		
By month 25	Sept 15	• Additional 4 sites opened to recruitment • Second annual report to funders
By month	Oct 15	• 426 women randomised
By month 29	Jan 16	• Third Trial Steering Committee and Data Monitoring and Ethics Committee meetings • Baseline interviews completed
By month 32	Apr 16	• Recruitment complete in centres • Audio-recordings of consultations completed
By month 35	July 16	• Interview follow up at 6 months after randomisation completed
Year Four (Sept 16 – Aug 17)		
By month 38	Oct 16	• Questionnaire follow up at 6 months after randomisation completed. Interviews with therapists completed

By month 41	Jan 17	• Fourth Data Monitoring and Ethics Committee meeting Fourth Trial Steering Committee meeting • Interview follow up at 12 months after randomisation completed
By month	Apr 17	• Questionnaire follow up at 12 months after randomisation completed
By month	Aug 17	• Third annual report to funders
Year Five (Sept 17 – Aug 18)		
By month	Jan 18	• Interview follow up at 24 months after randomisation completed
By month	Apr 18	• Questionnaire follow up at 24 months after randomisation completed
By month 59	Jul 18	• Data entry and cleaning completed • Final Trial Steering Committee meeting
By month 60	Aug 18	• Analysis complete for interview study, therapist interviews and audio recording of consultations
Year Six (Sept 18 – Aug 19)		
By month	Oct 18	• Analysis completed across main trial
By month 63	Nov 18	• Data archiving, arrangements for long-term follow up • Final Collaborators' Meeting • Submit Final Report and dissemination via main papers describing the

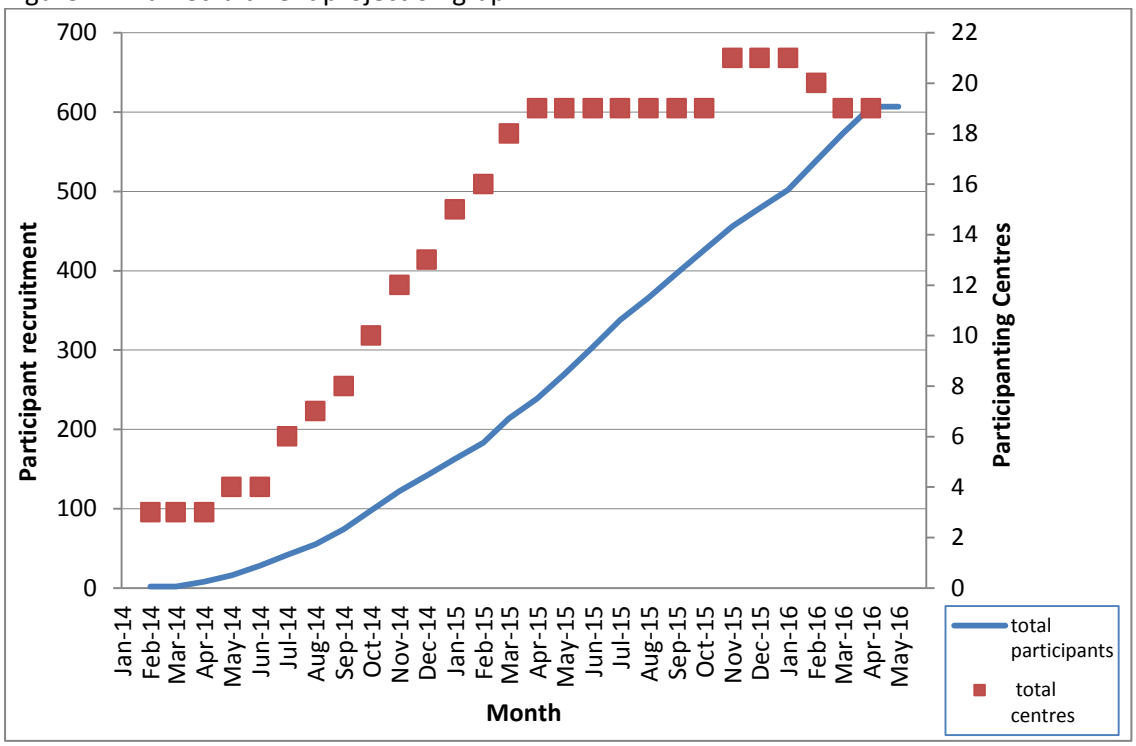
6.2 Recruitment rate

The projected start date for the trial is 1 September 2013, with the trial continuing until the 30th November 2018 (63 months). This includes an additional 6 month extension period to the trial granted by the funder. The recruitment projection is shown in Figure 1.

Three centres will be established relatively early in the project (by six months) followed by roll out to the others over the subsequent 15 months.

The participant recruitment graph in Figure 1 has been modelled to take into account: the phased rollout to the centres over the first 16 months; and that there are likely to be fewer presenting around August and over Christmas (due to holidays).

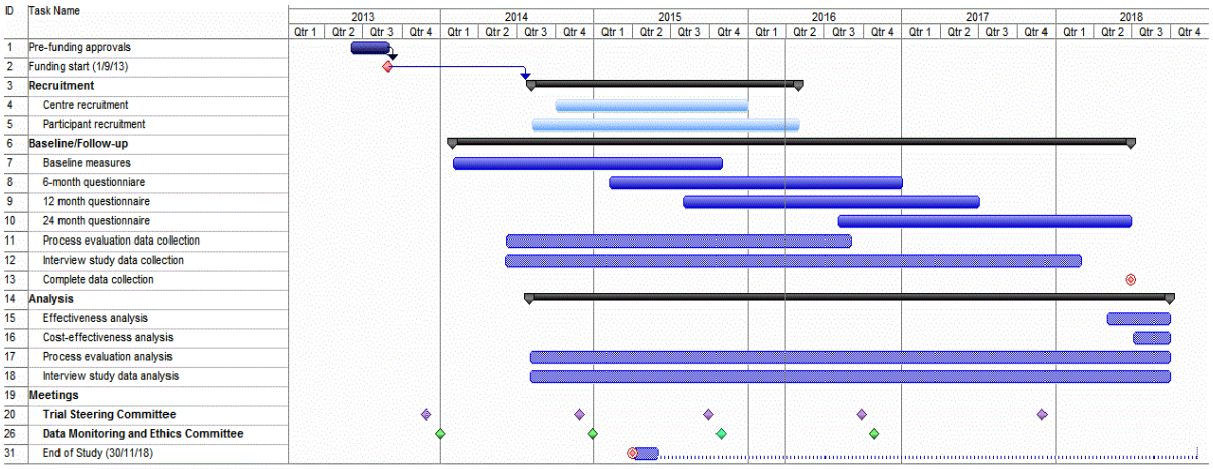
Figure 1. Trial recruitment projection graph



7 Organisation

The Gantt chart (Figure 2) indicates when it is anticipated that the major trial events will occur, including recruitment, analysis and meetings. These time-related milestones will be used to enable close monitoring of progress.

Figure 2. Trial Gantt chart



7.1 Trial coordination

The Trial Office team

The Trial Coordinator and Data Coordinator will be based in the Trial Office at the NMAHP Research Unit, and will be supervised on a day-to-day basis by the Chief Investigator. The Trial Coordinator will be responsible for day-to-day trial management, working to a specific project management plan with set milestones and goals. The qualitative researcher will be based at the School of Nursing, Midwifery and Health, University of Stirling, supervised by CB. SD, University of Exeter Medical School, will provide additional supervision, working closely with CB.

SH, the trial coordinator, data coordinator, qualitative researcher and CB will meet weekly to progress all aspects of the trial. All applicants and trial researchers will form a wider Project Management Group which will meet or teleconference on a monthly basis to review progress and provide regular input. The applicants make up a multidisciplinary team including experts in the clinical management of incontinence and its research, consumer representation, experienced trialists, statisticians, health economists, programmers and trial managers.

The Centre team

Local Principal Investigator

Each collaborating centre will identify a lead clinician who will be the point of contact for that centre. The responsibilities of this person will be to:

- establish the trial locally (for example, by getting agreement from clinical colleagues; facilitate local regulatory approvals; identify, appoint, train and supervise a local Recruitment Officer; and inform all relevant local staff about the trial)
- take responsibility for clinical aspects of the study locally (for example if any particular concerns occur)
- notify the Trial Office of any unexpected clinical events which might be related to trial participation
- provide support, training and supervision for the local Recruitment Officer
- represent the centre at any collaborators' meetings.

Local Recruitment Officer

Each collaborating centre will appoint a local Recruitment Officer to organise the day to day recruitment of women to the trial. The responsibilities of this person will be to:

- keep regular contact with the local lead clinician, with notification of any problem or unexpected development
- maintain regular contact with the Trial Office
- keep local staff informed of progress in the trial
- contact potential participants by: mailing out the Patient Information Leaflet to women who are potentially eligible based on referral letters; explain the trial and the potential for participation in the trial if they are eligible; explain what is intended by research access to their NHS data; discuss the possibility of being invited to take part in the interview study; and describe the possibility of long-term follow up and participation in other research
- facilitate obtaining the woman's written consent to participation and randomisation
- keep a screening log of whether eligible women are recruited or not (with reasons for non-participation and non-randomisation)
- ensure baseline data describing the women is collected and complete on the Clinical Assessment Form, log this information in the web-based OPAL database and send paper copies to the Trial Office (along with the original signed consent form and baseline questionnaire if completed face to face)
- ensure therapy data are collected, and send paper copies to the Trial Office
- ensure audio recording of any appointments selected by the Trial Office as part of the Process Evaluation
- arrange (and undertake if appropriate) a blinded 6 month pelvic floor muscle assessment for each woman
- file relevant study documentation (e.g. consent forms) in the woman's medical records
- organise and supervise alternative recruiters in case of holiday or absence
- represent the centre at the collaborators' meetings.

7.2 Research Governance, data protection and sponsorship

The trial has the support of the Centre for Healthcare Randomised Trials (CHaRT) based at the Health Services Research Unit, University of Aberdeen. This will ensure compliance with Research Governance, and provide centralised trial administration, database support and economic and statistical analyses.

The trial will comply with the Data Protection Act 1998 and regular checks and monitoring will be in place to ensure compliance. Data will be stored securely in accordance with the Act and archived to a secure data storage facility. The Senior IT Manager (in collaboration with the trial statistician) will manage access rights to the data set. Prospective new users must demonstrate compliance with

legal, data protection and ethical guidelines before any data are released. We anticipate that anonymised trial data will be shared with other researchers to enable international prospective meta-analyses.

The trial is sponsored by Glasgow Caledonian University. It will be overseen by a Trial Steering Committee (TSC) which will include an independent Chairperson and other independent members including a consumer representative. We anticipate that the TSC will meet on five occasions. A separate and independent Data Monitoring and Ethics Committee (DMEC) will be convened. The members will meet once to agree terms of reference and on at least three further occasions to monitor accumulating data and oversee any safety issues.

7.3 Data and safety monitoring

7.3.1 Data Monitoring and Ethics Committee

A separate and independent Data Monitoring and Ethics Committee (DMEC) will be convened. It is anticipated the members will meet once to agree terms of reference and on at least two further occasions to monitor accumulating data and oversee safety issues. This Committee will be independent of the trial organisers and the TSC. During the period of recruitment to the trial, interim analyses will be supplied, in strict confidence, to the DMEC, together with any other analyses that the committee may request. This may include analyses of data from other comparable trials. In the light of these interim analyses, the DMEC will advise the Trial Steering Committee if, in its view intensive PFMT has been proved, beyond reasonable doubt, to be different from the control (basic PFMT) for all or some types of women (in respect of either effectiveness or unacceptable safety concerns).

The TSC can then decide whether or not to modify intake to the trial. Unless this happens, however, the TSC, PMG, clinical collaborators and trial office staff (except those who supply the confidential analyses) will remain ignorant of the interim results.

The frequency of interim analyses will depend on the judgement of the DMEC. However, we anticipate that there might be two interim analyses and one final analysis.

The Chairman and the other independent members are to be appointed after confirmation by the HTA.

7.3.2 Safety concerns

The OPAL trial involves treatments for urinary incontinence which are well established in clinical practice, therefore adverse effects (although these are unlikely) will be those observed in everyday practice associated with the use of PFMT and biofeedback. Expected adverse events arising from the treatments are:

- Pelvic floor muscle soreness
- Low back pain
- Vaginal irritation/discomfort
- Thrush
- Urinary tract infection
- Non menstrual spotting/staining (may be caused by insertion of the Periform)
- Vaginal itchiness and discomfort (Periform may cause if there is Nickel sensitivity/allergy)
- Psychological distress due to vaginal assessment and/or use of Periform (e.g. as a result of previous abuse or distressing labour)

7.3.3 Procedure for reporting untoward and related SAEs in this trial

ICH GCP defines a Serious Adverse Event (SAE) as any untoward medical occurrence in a research participant that;

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the investigator.

In the OPAL trial all SAEs occurring to a research participant will be recorded on the serious adverse event form and reported to the main REC if they occur within 30 days of the participant's last therapy visit and where in the opinion of the Chief Investigator and the Chair of the DMEC the event was:

- Related – that is, it resulted from administration of any of the research procedures, and
- Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence.

In addition, SAE forms will record all deaths for any cause during the course of the trial.

7.3.4 Reporting responsibilities of the CI

The CI will be automatically notified of any potential related and unexpected SAEs. If, in the opinion of the local PI and the CI, the event is confirmed as being related and unexpected, the CI will submit a report to the main REC, the trial sponsor and the DMEC within 15 days of the CI becoming aware of it.

Collaborators and participants may contact the chairman of the TSC through the Trial Office about any concerns they may have about the trial. If concerns arise about procedures, participants or clinical or research staff (including risks to staff) these will be relayed to the Chairman of the DMEC.

As the trial arm to which women are allocated cannot be masked from the women or the therapist after randomisation has occurred, unblinding is not an issue in this trial.

7.4 Ethical issues and arrangements

We will submit our research proposal for review and approval to the National Research Ethics Service (NRES) via the West of Scotland (4) Research Ethics Committee.

We believe that the trial does not pose any specific risks to individual participants nor does it raise any particular ethical issues. PFMT is a low-risk intervention and the addition of biofeedback is unlikely to present any additional risks.

Trial participants in the experimental arm will benefit from exposure to a highly specified and evidence-based clinic and home biofeedback protocol which is unlikely to be available outside the trial. The wider benefit of the trial for society will be the generation of evidence regarding an intervention which may provide significant benefit for women with UI, reducing symptoms that are

bothersome and improving quality of life, and reducing costs, both personal and to the NHS, of products and other treatment.

Women will be informed of possible benefits and known risks of participation in the trial by means of a Patient Information Leaflet, discussion with the local Recruitment Officers, the NHS healthcare professional responsible for their continence care (dependent on their recruitment location e.g. consultant gynaecologist, continence specialist, GP) and the Trial Office researchers. Women will sign a consent form approved by the ethics committee. They will be consented to participating in the trial, being randomised and followed up, including electronic tracing using NHS data, and data linkage with computerised NHS data sources, for audio-recording of consultations and being contacted in the future about this and other research. Women who are not able or not willing to be randomised will not be recruited. Women will be sent an additional Patient Information Leaflet relating to the interview study, with separate consent subsequently sought.

It is intended to follow up the whole cohort of women for at least 10 years, and data will be retained as long as necessary for this purpose. Permissions will be sought from the relevant Research Governance bodies and the Ethics Committee. Attention has recently been drawn to the importance of long-term follow up, especially in the study of pelvic floor dysfunction [Hilton 2008].

8 Finance

The trial is supported by a grant from the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), Health Technology Assessment (HTA) Programme (11/71/03).

9 Indemnity

The Patient Information Leaflet provides a statement regarding indemnity for negligent and non-negligent harm.

We do not expect any harm to come to women by taking part in the study. All the materials and techniques are already being used in the NHS for conservative management of urinary incontinence. Participation in the study is therefore only to help evaluate the procedures and should not involve any additional. Taking part in this study does not affect normal legal rights. Whether or not women take part, the same legal rights apply as any other patient in the NHS (which include professional indemnity insurance for negligence). If a participant wishes to complain about their health care or any aspects of this study, the normal NHS mechanisms will be available.

In addition, the universities involved with the trial hold and maintain a ‘no fault’ insurance policy. This policy covers all employees of the universities and those working under their direction.

10 Publication

The success of the trial depends entirely on the wholehearted collaboration of a large number of women undergoing urinary incontinence treatment, as well as their physiotherapists, nurses and doctors. For this reason, chief credit for the trial will be given, not to the committees or central organisers, but to all those who have collaborated in the trial. A trial publication policy will be developed. The results of the trial will be reported first to study collaborators. The main report will be drafted by the Project Management Group and circulated to all collaborators for comment. The final version will be agreed by the Trial Steering Committee before submission for publication, on behalf of all the OPAL collaborators.

To safeguard the integrity of the main trial, reports of any explanatory or satellite studies will not be submitted for publication without prior agreement from the Project Management Group.

We intend to maintain interest in the trial by publication of OPAL newsletters at intervals for participants, staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final OPAL Newsletter to all involved in the trial.

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Appendix 1 Flow Diagram