MAPS STUDY

(Men After Prostate Surgery)

(Conservative treatment for men with urinary incontinence after prostate surgery: Multicentre randomised controlled trial of pelvic floor muscle training and biofeedback)

PROTOCOL

A UK Collaborative Study funded by the
NHS R&D HTA Programme

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PROTOCOL SUMMARY

QUESTION ADDRESSED	Does conservative (physical) treatment improve urinary incontinence in men who have had prostate surgery?
CONSIDERED FOR ENTRY	Men who have urinary incontinence after prostate surgery, approached initially when inpatients having surgery.
POPULATIONS	1. Radical Prostatectomy (RP) 2. Transurethral Resection of Prostate (TURP)
STUDY ENTRY	Information about all men having prostate surgery collected by recruitment officers in centres, sent to MAPS Study Office. Screening postal questionnaire sent from MAPS Study Office at 3 weeks after surgery. Consent to RCT obtained from incontinent men after written and oral information, and after completing Baseline Questionnaire and Urinary Diary.
INTERVENTIONS	Active group attend four treatment sessions during 3-month period after randomisation (pelvic floor muscle training with biofeedback, bladder training) Control group do not have active treatment Both groups receive Lifestyles Advice Leaflet
OUTCOME ASSESSMENT	Postal questionnaires at 6 and 12 months after randomisation Urinary diaries (incontinent episodes and pad use) and health care utilisation questions at 3, 6, 9 and 12 months
CO-ORDINATION	**Local**: by local lead Urologist and Recruitment Officer. **Central**: by Study Office in Aberdeen (telephone 01224 551103). **Overall**: by the Project Management Group, and overseen by the Steering Committee and the Data Monitoring Committee.
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MAPS PERSONNEL

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Other Information

International Standard Randomised Controlled Trial Number (ISRCTN)	ISRCTN87696430
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HTA Project Number	03/14/03

Trial Registrations

The NHS HTA Programme website http://www.hta.nhsweb.nhs.uk/projectdata

The CancerHelp UK website: www.cancerhelp.org.uk

INVOLVE www.invo.org.uk

National Cancer Research Network Trials Portfolio: NCRN Trial ID 1459

Current Controlled Trials website: ISRCTN87696430

NIH website: ClinicalTrials.gov Identifier: NCT00237029

CONSERVATIVE TREATMENT FOR URINARY INCONTINENCE IN MEN AFTER PROSTATE SURGERY

Known as MAPS (Men After Prostate Surgery)

Title of trial: Conservative treatment for urinary incontinence in men after prostate surgery (MAPS): multicentre randomised controlled trial of pelvic floor muscle training, biofeedback and bladder training

This protocol describes a major multicentre UK trial to establish whether conservative physical treatment delivered personally by a trained health professional results in better urinary and other outcomes compared with standard management in men who are incontinent after prostate surgery. The study is designed to be as simple as possible both for those participating and for those involved in clinical care.

Recruitment officers in each centre will identify and recruit men undergoing prostate surgery and collect descriptive information. Those who are incontinent will be invited to enter a randomised trial of conservative treatment. They will be followed up at 6 and 12 months.

1. THE REASONS FOR THE TRIAL

1.1 The burden of the problem

Prostate surgery is an iatrogenic cause of male urinary incontinence. Urinary incontinence is defined as the complaint of any involuntary leakage of urine.[1] It is a debilitating condition that has a greater effect on quality of life than erectile dysfunction (which is another consequence of prostate surgery).[2] The economic costs include personal (such as need to use pads or devices, and deleterious effect on quality of life) and societal ones (use of health services and need for residential or nursing home care).

Based on a population audit of over 3000 men, an estimated 11% of men needed to use pads at 3 months after endoscopic resection of prostate.[3] The prevalence of urinary incontinence after radical prostatectomy is more widely reported, ranging from 5% to 45%, albeit at varying times after operation.[4] Estimates of incontinence soon after radical operation are much higher (e.g. 82% in 1013 men[5]). We have used estimates of 5% and 50% respectively in calculation of sample sizes (which may be conservative, based on data from a feasibility study).

1.2 The decision to test conservative treatment

A recent Cochrane review has identified that, although conservative treatment based on pelvic floor muscle training may be offered to men with urinary incontinence after either type of prostate surgery, there is insufficient evidence to evaluate its effectiveness, cost-effectiveness and effect on quality of life.[6] Data from three trials involving 232 men provided estimates of the effects of pelvic floor muscle training on the chance of incontinence after radical prostatectomy at 1 year: relative risk (RR) for incontinence, pelvic floor muscle training plus biofeedback versus control, 0.55, 95% CI 0.24 to 1.23.[7–9] However, not all of the men included in the trials were incontinent at baseline, and the trials were all small. Thus the data suggest (but do not provide conclusive evidence) that conservative treatment may reduce incontinence at 1 year after operation.

Data available from these trials suggest that, amongst men incontinent at around 6 weeks after surgery, about 30% will still be incontinent at 1 year. The Cochrane review therefore suggests that this might be reduced to 15%, and this is the basis for the sample size in the proposed trial (70% ‘dry’ increased to 85% ‘dry’).

In one small trial of pelvic floor muscle training started before surgery amongst men having endoscopic resection of prostate, the RR for incontinence at 4 weeks after surgery was 0.31, 95% CI 0.03 to 2.82[10] although again the trial included some men who were not incontinent at baseline. After the first 4 weeks, there were no trial data about expected incontinence rates or effect sizes amongst men having endoscopic resection of prostate.

1.3 The questions which this study will address

The following questions will be addressed, primarily in terms of regaining urinary continence at 12 months after recruitment:

(a) For men with urinary incontinence 6 weeks after radical prostatectomy, what is the clinical and cost-effectiveness of active conservative treatment delivered by a specialist continence physiotherapist or a specialist continence nurse compared with usual management?
(b) For men with urinary incontinence 6 weeks after transurethral resection of prostate, what is the clinical and cost-effectiveness of active conservative treatment delivered by a specialist continence physiotherapist or a specialist continence nurse compared with usual management?

The hypothesis being tested in each group of men (in two parallel but separate trials) is that active conservative management will increase the proportion of continent men by 15% at 1 year after recruitment. The two groups are being considered independently because the rates of incontinence are expected to be different.

2. TRIAL RECRUITMENT AND ALLOCATION

2.1 Men considered for trial entry

The trial will involve men who have urinary incontinence after prostate surgery. Two parallel but separate trials will be conducted, amongst:
(i) men having a radical prostatectomy usually for prostate cancer, and
(ii) men having a transurethral resection of prostate, usually for benign prostatic hypertrophy.

Inclusion criteria:

- Urinary incontinence at 6 weeks after prostate surgery (incontinence defined as a response indicating a loss of urine to either of two questions in the screening questionnaire: 'how often do you leak urine' and 'how much urine do you leak').
- Informed consent.
- Ability to comply with intervention.

Exclusion criteria:

- Referral for formal therapy (teaching of pelvic floor muscle training) because of prostate surgery.
- Radiotherapy planned or given during the first 3 months after surgery for men with prostate cancer.
- Endoscopic resection of prostate carried out as palliation for outflow obstruction in advanced prostate cancer.
- Inability to complete study questionnaires.

Men with prostate cancer diagnosed at TURP:

Around 15% of men may be found to have incidental prostate cancer when the prostatic chips removed at TURP are examined for pathology. If he is not going to have formal treatment (wait and see policy), he will be eligible for the RCT.

If the cancer is identified before he is randomised and either radiotherapy or radical prostatectomy are planned, he will **not** be eligible for the RCT (TURP group). However, if he is subsequently readmitted for radical prostatectomy, he will be

eligible to be recruited as a new participant to the Radical group. He would sign a new consent form and be sent a new screening questionnaire.

If the cancer is only diagnosed once he has been randomised, even if radiotherapy or radical prostatectomy are planned, he will remain in the group to which he was allocated, and be followed up as normal.

The study consists of two stages: Stage 1 (Section 2.2) concerns the screening survey used to identify eligible men, and Stage 2 (Section 2.3) the randomised controlled trial.

2.2 Screening for postoperative urinary incontinence (Stage 1 of study)

Potential participants will be identified by Recruitment Officers in each clinical centre from amongst all men admitted to the urological ward(s) for prostate surgery. A log will be kept of men meeting the inclusion criteria, describing reasons if they do not agree to receive a screening questionnaire (Appendix 1).

Each man will be given the Hospital Patient Information Sheet by the Recruitment Officer. After reading it and having the opportunity to discuss all aspects of the study, each man will be asked for his consent to be sent the Screening Questionnaire at 3 weeks after surgery. The patient information sheet, the consent form and the questionnaire all refer to the possibility of being contacted about further research if the men are willing. If he agrees, his signed contact details (address, phone number, date of birth, Study Number and Hospital Number) will be sent to the Study Office in Aberdeen (Appendix I).

The questionnaire (Appendix VI) will be sent to men from the Study Office in Aberdeen at 3 weeks after the date of operation (together with a covering letter, Appendix II). A reminder letter will be sent after 2 weeks if there is no response (Appendix II). If the returned questionnaire indicates that a man has urinary incontinence, he will be eligible for Stage 2.

2.3 Recruitment to the RCT of conservative treatment (Stage 2, the trial)

Each man with urinary incontinence will be sent a Patient Information Sheet (PIS, Appendix III) by the Study Office in Aberdeen to inform him about the trial.

- *For men who have a phone*
  The Aberdeen Recruitment Co-ordinator will send the man a Patient Information Sheet (Appendix III*)* by post, with a consent form, Baseline Questionnaire and Urinary Diary. About a week after sending the trial information and documents, she will contact the man by telephone using a Standard Instruction Sheet (Appendix III). She will ask if he has received the Patient Information Sheet, answer any questions or concerns, and ask whether he might be interested in entering the trial. She will explain what would happen in the two groups, that allocation would be randomised and what follow-up is involved. If he agrees orally, he will be asked to complete and return: a Consent Form (Appendix III); a Baseline Questionnaire (Appendix VI); and a Urinary Diary (Appendix VI). Optionally, the man may fill in the Baseline Questionnaire over the phone but written consent is still required before randomisation.
- *For men who do not have a phone:*
  All the documents [the Patient Information Sheet (Appendix III), a Consent Form (Appendix III), a Baseline Questionnaire (Appendix VI) and a Urinary Diary (Appendix VI)] will be sent by mail. The man will be able to ring a helpline (to the Aberdeen Recruitment Officer) if he has any queries. If he decides to enter the trial, he will complete and return the last three documents.

The man would keep the Information Sheet and the bottom (fourth) copy of the consent form (returning the top three to the Study Office in Aberdeen).

If the three documents are not returned by 3 weeks after posting (no phone contact), or 2 weeks after oral consent was given over the phone, men will be sent a postal reminder with duplicate documentation. If they are not returned after another 2 weeks, they will be phoned (if possible) or sent a further reminder letter (if no phone).

Oral Withdrawal Consent will be obtained from men who initially agree to enter the trial but later decide to withdraw to enable us to maintain their existing data and access NHS data.

2.4 Randomisation and allocation to management group

When the baseline documents are received, the Aberdeen MAPS Study Office will randomise the man to active or standard management.

Randomisation will be by computer allocation using the service that already exists at the Health Service Research Unit. Allocation will be stratified by type of operation (radical prostatectomy or transurethral resection of prostate), and minimised using centre, age and pre-existing urinary incontinence.

The Study Office will send out an allocation letter to all men with details of their allocation (Appendix IV) and the Lifestyle Advice Leaflet (Appendix V). If the man is allocated to the Active Group, the Study Office will arrange for the local Therapist (physiotherapist or continence nurse) to send him the necessary appointments (the first, for an hour, as soon as possible, followed by a three-quarter-hour appointment on three occasions at 2, 6 and 12 weeks) (letter to Therapist, Appendix IV).

A letter and GP Information Sheet (Appendix IV) will be sent to the man's GP. A copy of the GP letter and the consent form will be sent to the hospital urological consultant for filing in the man's hospital notes.

3. TRIAL INTERVENTIONS (Appendix V)

3.1 Intervention arm

The men in the intervention group will receive a physiotherapist or continence nurse assessment of their symptoms at about 6 weeks after surgery. They will be taught pelvic floor muscle training, with bladder training for men with urgency or urge incontinence.[11] The men will be taught:

- to carry out three maximum pelvic floor contractions in three positions (standing, sitting and lying down) twice per day;
- to 'lift' their pelvic floors while walking;
- to tighten their pelvic muscles before activities which may cause them to leak, such as coughing;
- and to tighten after urinating to 'squeeze out' any last drops.

Biofeedback involves monitoring the strength of a pelvic floor contraction (by digital anal assessment) and relaying the information back to the men, in order that they know when they are performing contractions correctly and to inform them when they are increasing the strength or duration of their contractions. Therapists may use machine-mediated biofeedback with an anal biofeedback probe at their clinical discretion (if they feel it is clinically indicated) in centres where this is available in addition to digital anal assessment. Bladder training involves gradually delaying urination (by pelvic floor muscle contraction and distracting activities) to teach the bladder to hold increasing volumes of urine.

The men will also receive a booklet describing pelvic floor muscle training (Pelvic Floor Exercise Booklet, Appendix V) in addition to the one giving general lifestyle advice (Lifestyle Advice Booklet, Appendix V). The men will have reinforcement

sessions on three more occasions over 3 months – at around 2 weeks, 6 weeks and 12 weeks after the first appointment.

Ensuring standardisation of intervention
All the staff delivering the intervention will receive training to ensure consistency of their method of teaching and delivery of the pelvic floor muscle training, bladder training and biofeedback. Both specialist continence physiotherapists and continence nurse specialists will be eligible for training, thus extending the generalisability of the trial.

The therapists will record their assessments and treatment programmes on standard study forms (Appendix V). Data from these forms will be collected centrally.

3.2 Control arm
Men in the control group will receive a booklet containing supportive lifestyle advice only (without reference to pelvic floor muscle training) by post after randomisation (Lifestyle Advice Booklet, Appendix V). Men will not receive any formal assessment or treatment but will be able to access usual care and routine NHS services if they feel they need help. This may include written advice if this is part of routine hospital care.

Use of NHS services, use of pads and practice of pelvic floor muscle training will be documented in both groups using information from questionnaires and Urinary Diaries. The lifestyle and pelvic floor muscle training booklets will be customised for each group.

4. SUBSEQUENT ARRANGEMENTS
4.1 Informing key people
Following formal trial entry, the Study Office will contact:
i) The General Practitioner (by letter enclosing an information sheet, with the MAPS phone number in case of queries or notifiable events)
ii) The Hospital Urologist (by copy of letter sent to GP, and copy of consent form for filing in hospital notes)

4.2 Monitoring the men
Men will be contacted by phone, post or email as appropriate. In case of non-return of questionnaires or diaries, or non-attendance at therapy appointments, attempts will be made by staff at the Study Office to trace the men directly using these means or indirectly by contacting the therapist, the GP or the 'Best Contact'.

Notification by GPs
GPs are asked to phone the Study Office if one of the participants moves, becomes too ill to continue or dies, or any other notifiable event or possible adverse effect occurs. Alternatively, staff at the Study Office may contact the GP.

Notification by 'best contact'
If the MAPS Study Office loses touch with a participant (e.g. questionnaires, diaries or phone calls not returned), we will try to establish why via the 'Best Contact'. Men will be asked (in their trial Baseline Questionnaire) to nominate someone, who will be informed (Appendix IV).

Flagging at Office for National Statistics
All men recruited to the RCT will be flagged at the Office for National Statistics for notification of death.

5. DATA COLLECTION AND PROCESSING

Men will be recruited for a median period of 2 years (range 1–3). Follow-up will continue for 15 months from the date of the last operation (allowing 3 months for recruitment and 12 months for follow-up after randomisation). It is not part of this protocol or the current study to follow up the men beyond this time. However, consent will be sought to make this possible in the future.

5.1 Questionnaires (Appendix VI)

Men will be sent questionnaires at baseline, 6 and 12 months (Appendix VI). Content will include:

i) Urinary outcome questions [leakage of urine, amount, effect on QOL (http://www.iciq.net/), pad use, catheter use]
ii) Bowel function outcome questions
iii) Sexual function
iv) Health care utilisation questions
v) Exercise, weight and height, including pelvic floor exercises
vi) EQ-5D[12]
vii) SF-12[13]

and additionally at baseline only:

i) Date of operation, type of operation and reason for operation
ii) GP address and phone number
iii) 'Best Contact' at another address for follow-up (not wife or partner)
iv) Other medical problems

and additionally at 6 months only:

i) Health Care Unit Cost Questionnaire

and additionally at 12 months only:

i) Need for further treatment for incontinence
ii) Further treatment for prostate planned?

5.2 Urinary diaries (Appendix VI)

Men will be asked to keep diaries at 3, 6, 9 and 12 months, kept for 3 days at each time period. Content will include:

i) Frequency of urination (day and night)
ii) Daily episodes of incontinence, quantity of loss
ii) Daily use of pads, need to change clothing or bedding

and additionally at 3 and 9 months only:

iii) Health care utilisation questions (Appendix VI)

5.3 ISD Data (Scotland only)

At 6 months after the last man has been recruited we will run a check for Scottish men only to compare self-reported operations, diagnoses and hospital admissions with centrally collected data to validate a proportion of the data.

5.4 Data processing

Data from the various sources outlined above will be sent to the Study Office in Aberdeen for processing. Staff in the Study Office will work closely with local Recruitment Officers to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

6. ANALYSIS PLANS

6.1 Ground rules for the statistical analysis

The statistical analysis will be based on all men as randomised, irrespective of subsequent compliance with the treatment allocated. The principal comparisons will be:

1. After radical prostatectomy

i) men allocated to active therapy (four visits to therapist plus Lifestyle Advice Leaflet), compared with

ii) men allocated to control group (Lifestyle Advice Leaflet only)

2. After transurethral resection of prostate

i) men allocated to active therapy (four visits to therapist plus Lifestyle Advice Leaflet) , compared with

ii) men allocated to control group (Lifestyle Advice Leaflet only)

6.2 Measures of outcome

The primary clinical outcome is:

- Subjective report of urinary continence at 12 months (http://www.iciq.net/)

The primary measure of cost-effectiveness is:

- Incremental cost per quality-adjusted life-year

Secondary outcome measures include:

Clinical

- Subjective report of continence or improvement of urinary incontinence at 3, 6 and 9 months after randomisation, and improvement at 12 months
- Number of incontinent episodes in previous week (objective, from diary)
- Duration of incontinence (based on time of resolution relative to time of operation and randomisation)*
- Use of absorbent pads, penile collecting sheath, bladder catheter or bed/chair pads
- Number and type of incontinence products used
- Co-existence, cure or development of urgency or urge incontinence
- Urinary frequency
- Nocturia
- Faecal incontinence (passive or urge)
- Other bowel dysfunction (urgency, constipation, other bowel diseases)
- Sexual function at 12 months (including information about erection, ejaculation, retrograde ejaculation, pain, change in sex life and reason for change)

Quality of life

- Incontinence-specific quality of life outcome measure (10-point scale, ICI questionnaire (http://www.iciq.net/)
- General health measures (SF-12,[13] EQ-5D[12])

Use of health services for urinary incontinence

- Need for alternative management for incontinence (e.g. surgery, drugs)
- Use of GP, nurse, consultant urologist, physiotherapist

Other use of health services

- Visits to GP
- Visits to practice nurse

* We will obtain an estimate from the men who become dry of when they became dry – both by asking them to name the month they were last wet, and for how many months after their operation were they wet, as well as by the change in the 3-monthly diaries, from wet to dry.

Effects of interventions

- Use of PFMT
- Lifestyle changes (weight, constipation, lifting, coughing, exercise)

Economic measures

- Patient costs [e.g. self-care (e.g. pads, laundry), travel to health services, sick leave]
- Cost of conservative trial treatment
- Cost of alternative or additional NHS treatments [e.g. pads, catheters, drugs (e.g. adrenergic agonists, anticholinergics, oral medication for erectile dysfunction), hospital admissions or further surgery]
- Other measures of cost-effectiveness (e.g. incremental cost per additional man continent at 12 months)

The ways in which these data will be analysed are set out in Appendix VII (Dummy Tabulations).

It is anticipated that the data generated by the study, along with other focused data collection sets, may be used as a basis for exploratory or epidemiological research, but these will be described in separate protocols.

6.3 Timing and frequency of analyses

A single principal analysis is anticipated at 15 months after the last man is recruited (at month 48). The Data Monitoring Committee will determine the frequency of confidential interim analyses, but at present these are planned on three occasions during the data collection period (at months 16, 28 and 35).

6.4 Planned secondary subgroup analyses

The two populations of men (having radical prostatectomy or transurethral resection) will be analysed as separate trials as shown above in section 6.1.

Subgroup analyses (separately for the two populations) will explore the effect on urinary incontinence at 12 months after randomisation of:

1. pre-existing urinary incontinence (before prostate surgery)
2. age (up to 70, 71 and over)
3. type of incontinence at trial entry (stress, urge, mixed, other)
4. body mass index up to 30, 30–34.9, 35 or greater
5. centres with and without biofeedback machines
6. type of therapist (physiotherapist or nurse)
7. other morbidity/treatment for other morbidity

Stricter levels of statistical significance ($2p<0.01$) will be sought, reflecting the exploratory nature of these analyses.

All study analyses will be according to a statistical analysis plan that will be agreed in advance by the MAPS Steering Committee.

6.5 Economic analysis

Both trials (radical prostatectomy or transurethral resection of prostate) will include a formal economic evaluation. Resource use and costs will be estimated for every trial participant. Resource-use data collected will include the intervention and the use of primary and secondary NHS services by the men including referral for specialist management. Personal costs to the men (such as use of pads or work/social restrictions) will also be described. Thus the point of view adopted is that of the NHS and the patient.

6.5.1 Collection of data

At each time point of contact during the study (baseline and 3, 6, 9 and 12 months after randomisation), men will provide information about their use of health services

(via the health care utilisation questions, Appendix VI). At baseline, 6 and 12 months, they will complete the SF-12 and EQ-5D. Midway through the trial (at 6 months after randomisation), a questionnaire survey of all men will be used to ascribe costs to typical episodes of such health service use (the Health Care Unit Cost Questionnaire, Appendix VI). The underlying aim is to keep economic data collection as parsimonious as possible to minimise the burden on the men and the effect on response rates.

6.5.2 Participant costs of urinary incontinence

Participant costs will comprise three main elements: self-purchased health care; travel costs for making return visit(s) to NHS health care; and time costs of travelling and attending NHS health care.

- Self-purchased health care is likely to include items such as pads bought by the participant, prescription costs and over-the-counter medications. Information about these will be collected through the health care utilisation questions (see 6.5.1 above).
- Estimation of travel costs requires information from participants about the number of visits to, for example, their GP or physiotherapist (estimated from the health care utilisation questions) and the unit cost of making a return journey to each type of health care provider (from the Participant Unit Cost Questionnaire, Appendix VI).
- The cost of participant time will be estimated in a similar manner. The participant will be asked, in the Participant Unit Cost Questionnaire, how long they spent travelling to and attending their last visit to each type of health care provider. Participants will also be asked what activity they would have been undertaking (e.g. paid work, leisure, housework) had they not attended the health care provider. These data will be presented in their natural units, e.g. hours, and also costed using standard economic conventions, e.g. the Department of Transport estimates for the value of leisure time. These unit time costs, measured in terms of their natural and monetary terms, will then be combined with estimates of number of health care contacts derived from the health care utilisation questions.

6.5.3 Costs of intervention

Health service costs incurred as the consequence of the intervention will be recorded prospectively for every participant in the study. Main areas of costs will be: staffing (four sessions with the therapist), capital costs (buildings and equipment), and consumables (probes for biofeedback, pads).

6.5.4 NHS costs of other health services used

- Consumables (drugs, pads, etc.)
- Staff time (GP, nurse, consultants)
- Outpatient visits
- Hospital admissions (operations, other)

6.5.5 Cost-effectiveness

Effectiveness within the trials will be measured in terms of quality-adjusted life-years (QALYs) and subjective continence at 12 months (assessed using data from the ICI questionnaire). QALYs will be estimated by combining estimated quantity of life, with quality of life derived from the EQ-5D questionnaire (administered at baseline, 6 and 12 months) and UK tariffs. The estimation of QALYs will take account of the mortality of study participants. Participants who die within the study follow-up will be assigned a zero utility weight from their death until the end of the study follow-up. QALYs before death will be estimated using linear extrapolation between the QALY scores at baseline and all available EQ-5D scores up to death. The method of eliciting QALYs described is one commonly adopted in economic evaluation.

The primary analysis is based on the 1-year follow-up of the trial and two outcomes have been specified. These are incremental cost per additional man continent and incremental cost per QALY. The former outcome has been chosen to facilitate understanding of the findings amongst health care professionals while the second measure, the primary economic outcome, has been chosen to reflect a societal decision-making perspective. The results will be presented as point estimates of mean incremental costs, proportion of men continent, QALYs, and cost per man continent or per QALY. Measures of variance for these outcomes are likely to involve bootstrapping estimates of costs, proportion of men continent, QALYs, and incremental cost per additional man continent and per QALY. Incremental cost-effectiveness data will be presented in terms of cost-effectiveness acceptability curves (CEACs).

Other forms of uncertainty, e.g. concerning the unit cost of a resource, will be addressed using standard deterministic sensitivity analysis. The results of the sensitivity analyses will also be presented as CEACs. Further sensitivity analysis will be conducted to consider the effect of differential timing over which treatments may be given. These data are likely to prove useful for the economic model.

6.5.6 Modelling

While the within study results will prove useful it is important to note that incontinence is a chronic condition and the effects of treatment on costs and outcomes may persist into the future. Therefore, assuming that one intervention is not dominant (less costly but more effective at 12 months), additional useful information for policy makers will be derived from an economic model that considers a longer time horizon. In the model, the findings of the trial will be extrapolated to the patient's lifetime. The model will describe the change in levels of incontinence over the patient's lifetime following the start of treatment. The structure of the model will be developed in collaboration with clinicians and trial collaborators, and parameter estimates for costs and utilities will be derived from the trial data.

In order to extrapolate estimates of cost-effectiveness to a longer time horizon (e.g. the participant's lifetime) than that considered by the trial, a modelling exercise will be developed. The model will be populated using individual patient data from the study as well as both published and unpublished evidence in the field. The methods used to assemble additional data will follow recognised methodology, which will vary according to the type of parameter, extent of uncertainty and role within the model. Therefore, comprehensive systematic searching will be limited to those parameters to which the results of the model are likely to be particularly sensitive. The modelling exercise will comply with recent recommendations on good practice for modelling[14] and the results will be presented in terms of incremental cost per continent man and incremental cost per QALY gained.

Estimates of mortality will be based on data from life tables. As the model will be constructed to estimate outcomes both for men with benign disease and for men with prostate cancer, mortality rates will be adjusted, where necessary, using relative risks of mortality for prostate cancer. These data will be obtained from the literature and from an on-going study within the Health Economics Research Unit in Aberdeen that is looking at the cost-effectiveness of screening for prostate cancer.

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 involving 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 though sensitivity analysis. The base-case and sensitivity analyses will be presented as CEACs.

7. SAMPLE SIZE AND FEASIBILITY

7.1 Sample size sought

Based on the aim to detect a difference between intervention and control groups of 15% (70% to 85%) in the number of men no longer incontinent, we will need 174 men per arm of the trial to give 90% power to detect a significant difference at the 5% level. This will allow detection of a difference of 0.30 of a standard deviation at 80% power for continuous measures such as quality of life. Should the proportion of men no longer incontinent be less than 70% we shall still have 80% power to detect a 15% change from 60% to 75%.

Table 1 below is an extrapolation to show the number of men who will need to be approached and hence the number of 'typical sized' clinical centres that will be required. Allowing for a 13% dropout rate after enrolment in the RCT, we plan to recruit 200 men per arm. There will thus be 400 men in each of the two parallel trials who would come from 615 incontinent men assuming that 65% agree to join the trial. Based on conservative assumptions of 50% and 5% incontinent at 6 weeks after radical prostatectomy and endoscopic resection of prostate, respectively, and 80% response rates to the screening questionnaire, 1,540 and 15,400 men will need to be approached. If a typical centre undertakes 30 radical prostatectomies and 300 endoscopic resections of prostate each year, about 26 centres will be required for each trial recruiting over an average of 2 years.

In summary, Table 1 shows that we will need to screen around 17,000 men in Stage 1 of the study, making conservative assumptions about likely response and participation rates. Based on these figures, a 2-year recruitment period in 26 centres will be needed.

Table 1 Recruitment numbers needed

	Radical prostatectomy	Transurethral resection
Men needed per arm (minimum)	174	174
Allowing for 13% dropout	200	200
Total men needed in two arms	400	400
Assuming 65% willing to enter RCT, no. incontinent men needed	615	615
% incontinent at 6 weeks (Stage 2)	50%	5%
No. of men needed to reply to survey	1230	12,300
Assuming 80% response to survey, no. needed for survey (Stage 1)	1540 (approx)	15,400 (approx)
No. of operations per typical centre	30	300
No. of typical centres needed in 2 years	26	26

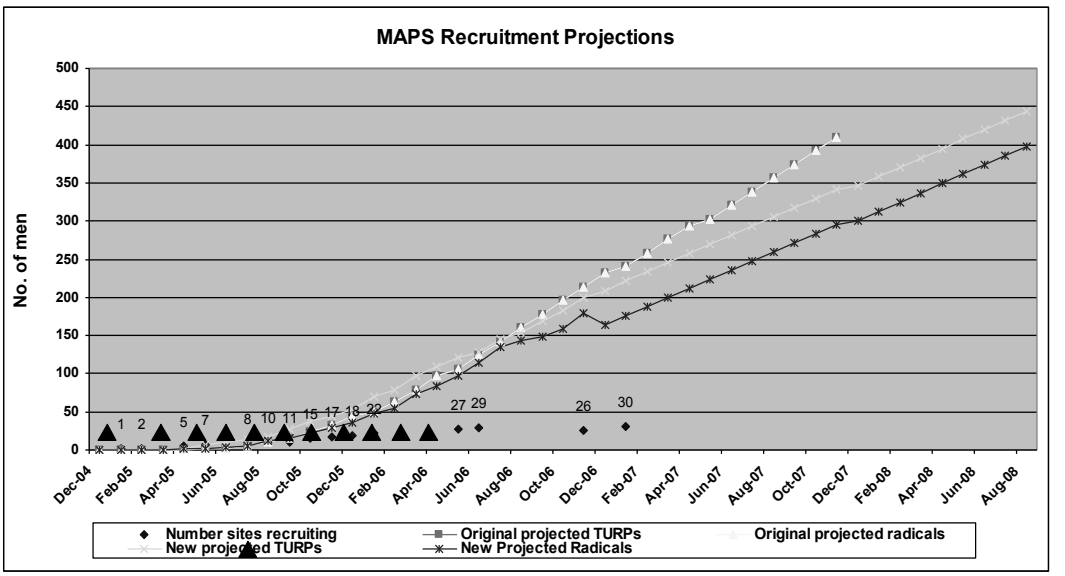
7.2 Recruitment rates

Figure 1 shows the projected recruitment of centres and participants, and projected number of men who would be approached. Three centres will be established relatively early in the project (by 5 months) followed by roll-out to the others over the subsequent 10 months.

The participant recruitment graph in Figure 1 has been modelled to take into account: the phased roll-out to the centres over the first 15 months; that there will be lags between the approach to men when they are in hospital and the despatch of the 'screening' questionnaire and between the despatch of the screening questionnaire and trial recruitment; and that there are likely to be fewer prostatectomies around August and over Christmas (due to holidays). Recruitment continues after the final

screening questionnaires have been sent out because of these 'lags'. The lines for the two trials (radical prostatectomy and endoscopic resection of prostate) are superimposed because their rates of recruitment are expected to be similar.

Figure 1 Projected recruitment chart



In summary, we originally aimed to recruit an average of 8 men to the randomised trial per week over a 2-year period. We estimated that if we had 26 centres, that would have amounted to 30 men per centre in 2 years, half of whom (around 15 in 2 years, or 8 per year) will be randomised to active therapy. In order to achieve this, we estimated that approximately 7 men per centre will need to be screened each week for 2 years. As the recruitment period was extended by 9 months in May 2007 (by the HTA) recruitment targets have altered since these original projections –the graph above therefore now reflects both the original and the extended recruitment periods.

8 ORGANISATION

A detailed plan and timetable of study organisation is given in the Gantt chart (Appendix VIII). In summary, it is as follows – 1–4 months: set up office, assemble team, and establish first centre; 5–15 months: establish study in all 26 centres; 5–36 months: identify and recruit 800 men with urinary incontinence (average 24 months in each centre); 13–48 months: follow up at 6 and 12 months after randomisation; 49–54 months: complete data collection, analysis and dissemination. In the light of the revised recruitment period (the 9-month extension) the Gantt chart has also been revised (Version 6 protocol).

The Gantt chart also shows when we expect the major study events to occur, including recruitment, study progress and meetings. There will be 3-monthly project management meetings, five meetings of the Steering Committee and four of the Data Monitoring Committee. Two meetings are planned for collaborators (including urologists, therapists, local recruitment officers and consumer participants), the first timed to occur when all the sites have been identified and the second when results are available. Four Training Meetings will be held to train the therapists during the course of the first year. Remote training of any other thepaists unable to attend these days will occur as and when applicable.

Based on this chart, the specific, time-related milestones given in Appendix VII will be used to allow close monitoring of progress.

8.1 Local organisation in centres

i) Lead Urologist (Local Principal Investigator)

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

- establish the study locally [for example by getting agreement from clinical colleagues; facilitate local research ethics committee approval (LREC); liaise with R&D department; identify and appoint a local Recruitment Officer; and inform all relevant local staff about the study (e.g. secretaries, ward staff)]
- take responsibility for clinical aspects of the study locally (for example if any particular concerns occur)
- notify the Study Office of any unexpected clinical events which might be related to study participation
- provide support and supervision for the local Recruitment Officer
- represent the centre at the collaborators' meeting

ii) Local Recruitment Officer

Each collaborating centre will appoint a local Recruitment Officer to organise the day-to-day recruitment of men to Stage 1 of the study (the Screening Survey). The responsibilities of this person will be to:

- keep regular contact with the local Lead Urologist, with notification of any problem or unexpected development
- maintain regular contact with the Study Office
- keep local staff informed of progress in the study
- contact potential participants by: organising mailing out of the Patient Information Sheet to men being admitted electively for prostate surgery; identifying all eligible men on the ward while they are in hospital for their prostate surgery; explaining the screening study and the potential for participation in a trial if they are incontinent after surgery; explaining what is intended by research access to their NHS data; and describing the possibility of long-term follow-up whether or not they are incontinent
- obtain the men's written consent to being sent a screening questionnaire
- keep a log of whether eligible men are recruited or not (with reasons for non-participation) (Appendix I)
- collect baseline data describing the men (Appendix I), and send these to the Study Office along with the signed consent forms (Appendix I)
- organise and supervise alternative recruiters in case of holiday or absence
- represent the centre at the collaborators' meeting

iii) Therapists and training

Each collaborating centre will identify a Lead Therapist who will be responsible for co-ordinating the active intervention at a local level. (S)he will identify the local therapist who will carry out the intervention, or may assume this role personally. The therapist may be a specialist physiotherapist or continence nurse specialist. The therapist will attend a Training Day (led by Professor Grace Dorey) to ensure consistency of training and intervention in each centre. There will be four Training Days at a range of locations throughout the UK during the setting-up phase of the study.

The therapist will use standard study instruction materials and documentation, which will be provided by the Study Office. The Study Office will also be the first point of contact for the therapist in case of problems, concerns, adverse effects or need for advice.

The responsibilities of the therapist will be to:

- attend a training day to become familiar with the standard method of teaching the men and the standard study documentation
- contact men allocated to the active arm by sending them an initial appointment (for one hour), and repeat three-quarter-hour appointments at 2, 6 and 12 weeks thereafter
- notify the Study Office if men fail to attend: a phone number will be provided for this purpose
- notify the Study Office of any unexpected clinical events which might be related to study participation
- teach all the men pelvic floor muscle training, using digital anal biofeedback to reinforce correct contractions
- use machine biofeedback with an anal probe if, in their opinion, it is clinically indicated (and a machine is available)
- teach bladder training to men who have urge incontinence
- provide other lifestyle advice as appropriate
- record the details of the treatment and response to treatment at each visit using standard study documentation (assessment and treatment forms, Appendix V)
- return the assessment and treatment forms to the Study Office at the end of each man's 3-month treatment period
- support the men in adhering to treatment
- represent the centre at the collaborators' meeting

iv) Other training materials

We hope also to provide an interactive CD-rom instruction and reminder package both to supplement the main Training Day teaching, and in case some therapists cannot attend or if staff changes result in new therapists being appointed.

It may be possible to amend this material for use in training other NHS staff after the trial is finished if the intervention is effective.

8.2 Study co-ordination in Aberdeen

i) The Study Office Team

The Study Office is in the Health Services Research Unit in Aberdeen and provides day-to-day support for the clinical centres. It is responsible for all data collection (such as mailing questionnaires), follow-up, data processing and analysis. It is also responsible for randomisation, despatch of Lifestyle Booklets and communicating with the therapists about men allocated to active treatment. Finally, we intend to produce a yearly MAPS Newsletter for participants and collaborators to inform everyone of progress and maintain enthusiasm.

The MAPS Study Office Team will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting.

ii) The Project Management Group

The study is supervised by its Project Management Group. This consists of the grant holders and representatives from the Study Office. Observers may be invited to attend at the discretion of the Project Management Group. We plan to meet every 3 months on average.

iii) The Steering Committee

The study is overseen by an independent Steering Committee. The Chairman is Professor Paul Abrams, with Mrs Jane Dixon and Professor David Torgerson as other independent members appointed by the HTA. The other members are the grant holders. Observers or members of the host university (Aberdeen) and the funders (the HTA) may also attend, as may other members of the Project

Management Group or members of other professional bodies at the invitation of the Chair.

8.3 Research Governance, EU Directives, Data Protection and Sponsorship

i) Research Governance, EU Directive

The trial will be conducted in compliance with the EU Clinical Trials Directive (EU-CTD, 1 May 2004) although it does not come within the scope of the Directive. Other studies associated with the trial will either be conducted in compliance with the EU Clinical Trials Directive (1 May 2004) or in line with local implementation of Research Governance to at least the standard of the Aberdeen University policy on Research Governance (http://www.abdn.ac.uk/iahs/research-governance/index.shtml).

ii) Sponsorship

Before April 2007 the sponsorship for these studies (RCT and observational) was the Department of Health, UK. Their duties as sponsors were co-ordinated through the National Coordinating Centre for Health Technology Assessment (NCCHTA) in Southampton. In April 2007 sponsorship responsibility was transferred from the NCCHTA to the host institution, the University of Aberdeen.

Responsibility for transacting Part 3 of the EU-CTD (study initiation and finance), Part IV (Compliance with Good Clinical Practice) and Part V (Pharmacovigilance) will be delegated to the Chief Investigators, Dr James N'Dow and Dr Cathryn Glazener at Aberdeen University. They will ensure, through the Steering Committee, that adequate systems are in place for monitoring the quality of the study (compliance with GCP) and appropriate expedited and routine reports of adverse effects, to a level appropriate to the risk–benefit assessment of the trials.

iii) Data Protection

All data collected and stored within the study will comply with the Data Protection Act.

8.4 Data and safety monitoring

i) Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established. This will be independent of the study organisers. During the period of recruitment to the study, interim analyses will be supplied, in strict confidence, to the Data Monitoring Committee, 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 Data Monitoring Committee will advise the Steering Committee if, in its view:

a) the active intervention has been proved, beyond reasonable doubt,[*] to be different from the control (standard management) for all or some types of men, and
b) the evidence on the economic outcomes is sufficient to guide a decision from health care providers regarding recommendation of this service development.

The Steering Committee can then decide whether or not to modify intake to the trial. Unless this happens, however, the Steering Committee, Project Management Group, clinical collaborators and study 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 Chairman of the Committee, in consultation with the Steering Committee. However, we anticipate that there might be three interim analyses and one final analysis.

[*] Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least three standard deviations in the interim analysis of a major end point may be needed to justify halting, or modifying, such a study prematurely (Peto R et al., *Br J Cancer* 1976;34:548–612).

The Chairman is Professor Peter Langhorne, with Mrs Julia Brown, Mr Thomas McNicholas and Professor Christine Norton as other independent members, to be appointed after confirmation by the HTA.

ii) Safety concerns

The MAPS trial involves conservative interventions which are well established in clinical practice, although unproven regarding effectiveness for men after prostatectomy. We do not anticipate any adverse effects, but would respond appropriately to any notification.

Collaborators and participants may contact the chairman of the Steering Committee through the Study Office about any concerns they may have about the study. If concerns arise about procedures, participants or clinical or research staff (including risks to staff) these will be relayed to the Chairman of the Data Monitoring Committee.

As the trial arm to which men are allocated cannot be blind after randomisation has occurred, unblinding is not an issue in this trial.

The Multicentre Research Ethics Committee for Scotland has approved the study for the UK (ref MREC/04/10/01). The study will be conducted according to the principles of good practice provided by Research Governance Guidelines.

9. FINANCE

The study is supported by a grant from the NHS R&D National Coordinating Centre for Health Technology Assessment (NCCHTA) (ref 03/14/03).

10. EXPLANATORY STUDIES

The funds provided by the NCCHTA are to conduct the screening survey (Stage 1) and the randomised controlled trial (Stage 2) as described in this protocol. It is recognised, however, that the value of the study will be enhanced by smaller ancillary studies of specific aspects. Plans for some of these are being submitted to other grant funding bodies. Further suggestions would be welcome and should be discussed in advance with the Project Management Group and agreed with the NCCHTA. MREC approval will be sought for any new proposals.

11. INDEMNITY

The Patient Information Sheet provides the following statement regarding indemnity for negligent and non-negligent harm:

> 'We do not expect any harm to come to you by taking part in this study. However, if you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms (which includes professional indemnity insurance) would be available to you.'

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

12. PUBLICATION

The success of the study depends entirely on the wholehearted collaboration of a large number of men undergoing prostate surgery, as well as therapists, nurses and doctors. For this reason, chief credit for the study will be given, not to the committees or central organisers, but to all those who have collaborated in the study. The study's publication policy is described in detail in Appendix IX. The results of the study will be reported first to study collaborators. The main report will be drafted by the Project Management Group and circulated to all clinical co-ordinators for comment. The final version will be agreed by the Steering Committee before submission for publication, on behalf of all the MAPS collaborators.

To safeguard the integrity of the main trial, reports of 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 study by publication of MAPS 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 MAPS Newsletter to all involved in the trial.

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