MRC

Medical Research Council

APPLICATION FOR AN MRC GRANT
Please type throughout and
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1. Applicant(s)	Applicant 1	Applicant 2	Applicant 3
Surname	See following pages		
Forename(s)			
Age			
Title			
Post held			
No. of hours pw on project			

2. Institution

University of Aberdeen
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3. Title of investigation (*not* exceeding *116* characters including spaces)

Pragmatic randomised trial to evaluate laparoscopic surgical repair for inguinal hernia

4. Type of grant sought

New special project grant

5. Abstract of research (*not* exceeding 250 words)

The introduction of laparoscopic surgery has revolutionised the treatment of many common illnesses. It has been very successful in reducing postoperative pain and hospital stay in general. As a result laparoscopic hernia repair is being introduced without due attention to its known disadvantages (increased costs and the need for a general anaesthetic) or its potential effects on complications and recurrence. A rigorous evaluation comparing laparoscopic with open hernia repair is urgently needed to establish the future role of both operations.

We have therefore designed a pragmatic multi-centre randomised trial to compare laparoscopic hernia repair using a transabdominal preperitoneal approach with the open operation preferred by each individual surgeon. We have already recruited the majority of the 25 surgeons who will each be expected to recruit 80 patients over a period of two years, thus yielding a total sample of 2000 patients. We plan to monitor each surgeon's learning curve prospectively and to eliminate the resulting bias by retrospective statistical analysis. We intend to measure a wide range of patient outcomes including analgesia use, pulmonary function, metabolic response, hospital stay, complications, return to normal activity, general health status and hernia recurrence. We propose to estimate the marginal cost of laparoscopic hernia repair within each hospital, and its value both to patients and to the community. In Central Scotland there is still a real opportunity to conduct a trial that is both rigorous and pragmatic, and thus to take a major step towards an evidence-based health service.

6. Proposed starting date October 1993 **Proposed duration (in months)** 42

[redacted]

GREATER GLASGOW HEALTH BOARD
WESTERN INFIRMARY/GARTNAVEL GENERAL HOSPITAL UNIT

Our Ref JKF/CD 92/106

Your Ref .....

If phoning ask for [redacted]

Western Infirmary
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21 April 1993

Mr P J O'Dwyer
Senior Lecturer
Department of Surgery
WESTERN INFIRMARY

Dear Mr O'Dwyer

PROSPECTIVE RANDOMISED TRIAL COMPARING PATIENT OUTCOME FOLLOWING LAPAROSCOPIC AND CONVENTIONAL HERNIA REPAIR

Thank you for your letter of 8 April enclosing a modified patient consent as requested by the West Ethics Committee, back in August, 1992, when the study was conditionally approved.

I am pleased to confirm that the modified consent is entirely in accordance with the Committee's requirements and accordingly the study now has full and unqualified Ethical Committee approval.

Yours sincerely

[redacted]

Secretary
Ethical Committee

PROPOSED INVESTIGATION

1. Title
2. Purpose
3. Background
4. Plan of investigation
5. Detailed justification for support requested

TITLE

Pragmatic randomised trial to evaluate laparoscopic surgical repair for inguinal hernia.

PURPOSE

To conduct a pragmatic randomised trial to inform practical decision-making in the National Health Service between laparoscopic repair and conventional inguinal hernia repair, with particular reference to patient outcomes and costs including:

1 Analgesia use.
2 Pulmonary function.
3 Metabolic response.
4 Hospital stay.
5 Complications.
6 Return to normal activity.
7 General health status.
8 Hernia recurrence.
9 Cost to National Health Service.
10 Value to the community.

BACKGROUND

Surgical issues

Conventional inguinal hernia repair is associated with a hospital stay of two or three days and avoidance of heavy work or physical activity for six weeks. Post-operative morbidity includes urinary retention (20%), epididymitis or orchitis, scrotal haematoma (5%), testicular atrophy, wound infection (5%) and, less frequently, troublesome parasthesia[1,2,3].

The recurrence rate is difficult to estimate because of the variety of operations performed[4]. A conservative estimate suggests that at least 10% of all hernias recur following repair in general surgical units within the UK[3]. However recurrence rates of less than 1% have been reported by hernia specialists using the Shouldice operation[5,6,7,8]. Nevertheless the effectiveness of this technique is variable: in one recent trial the recurrence rate at two years was 4% for Shouldice repair and 2% for plication darn repair[3]; in another recent trial, the recurrence rate for the Shouldice repair was 7% after three years, and did not differ significantly from that for the McVay repair[9].

Hernia recurrence is thought to be caused by a combination of poor technique and placing excessive tension on fascia when closing large hernia defects. The concept of a tension-free hernia repair using polypropylene mesh has been practised by a number of authors in the United States with minimal wound infection rates, mesh rejection rates and recurrence rates[10,11,12,13,14,15]. The other major advantage of this method is that the recovery period is short and patients may return to work one or two weeks after the repair.

Recently the feasibility of using a closed laparoscopic method for polypropylene mesh repair has been demonstrated[16,17,18]. However laparoscopic hernia repair may suffer a higher incidence of recurrence than open methods. Nolen et al reported two recurrences within ten months in 70 repairs using a mersilene fan[17], and Hawasli reported two early recurrences in 120 repairs using a polypropylene mesh repair[18]. These recurrences may reflect initial enthusiasm for placing unsecured mesh at the site of the hernia defect. Most authors now secure the polypropiene mesh to transversalis fascia and Cooper's ligament, thereby producing a laparoscopic repair that maintains the surgical principles of the open method. In a report of 360 repairs using this technique the recurrence rate was less than 1% with a follow-up of between one and nine years[19].

The introduction of laparoscopic surgery has revolutionised the treatment of many common surgical illnesses. It has been so successful in reducing post-operative pain and hospital stay that surgeons, once through the learning curve, have judged randomised trials to be unnecessary. Laparoscopic hernia repair is also being introduced in uncritical fashion without due attention to its drawbacks - increased costs (materials, time under anaesthesia and surgical training) and the requirement for a full general anaesthetic. In contrast open hernia repair is relatively simple and can be performed as a day procedure under local anaesthesia (though not routinely undertaken in this manner in the United Kingdom). A pragmatic randomised trial comparing laparoscopic with open hernia repair is therefore required to establish the future role of both procedures in clinical practice.

Methodological issues

Many commentators have written about the problems of evaluating new surgical procedures. In one of the most cogent of these commentaries, Stirrat et al[20] list seven potential obstacles to the use of randomised trials to evaluate these procedures:

a Surgical trials cannot be placebo controlled.
b Surgical trials cannot be double blind.
c Surgical trials usually compare established procedures with new procedures (the problem of the 'learning curve').
d Surgical trials may find recruitment difficult.
e Multi-centre trials may suffer from differences in skills between centres.
f Patients may prefer one procedure to another (an obstacle to randomised trials of laparoscopic hernia repair already considered difficult to surmount in Australia[21,22,23]).
g Appropriate end points may require years of follow-up.

Recent discussions within the MRC Health Services Research Board have reaffirmed that, although a and b represent obstacles to 'explanatory' trials conducted under laboratory conditions to enhance scientific knowledge, they present no obstacle to pragmatic trials designed to assist decision-making in clinical practice[24,25]. Recent experience in the West of Scotland[26,27] has established that obstacles d and f may be overcome by an enthusiastic group of surgeons keen to extend the rigorous evidence available within their discipline, and committed to briefing their patients assiduously about the advantages and disadvantages of alternative surgical procedures; in particular the recruitment of 300 patients into a pragmatic randomised trial of laparoscopic versus minilaparotomy cholecystectomy has been completed four months ahead of schedule. As Stirrat et al[20] themselves point out, obstacle e can be overcome by stratified randomisation. One effective solution to obstacle g is to ensure that the trial coordinating centre is based in a research unit with a rolling contract; the Health Services Research Unit (HSRU) of Aberdeen University has such a contract, which should soon be extended until the end of 1998. Thus we are confident that the proposed trial can overcome six of the seven obstacles without great difficulty.

The seventh obstacle, that of the 'learning curve', is the most difficult to overcome - in our view and that of many eminent surgeons, notably the members of the Joint Working Group set up by the Department of Health and the Scottish Office Home and Health Department. In their forthcoming report[28] they recommend that 'prospective clinical audit should precede formal clinical trials'. Recognising that this recommendation could occlude 'the window of opportunity to (evaluate) endoscopic operations' they conclude that 'research is urgently needed (to derive) alternative models of prospective clinical evaluation'. We propose to undertake a rigorous evaluation of laparoscopic hernia repair that incorporates prospective monitoring of the learning curve within the framework of a pragmatic randomised trial, notably by:

1 Defining the control operation as the open operation preferred by each individual surgeon.
2 Delaying randomisation for each surgeon until he or she has performed 20 laparoscopic repairs, at least two under the supervision of one of the three surgical applicants or another surgeon experienced in this technique.
3 Analysing the resulting data by treating the current experience of each surgeon as a 'covariate' (in statistical terms, or a 'confounding factor' in epidemiological terms) and thus defining the learning curve of each surgeon in retrospect.

This general approach was endorsed by the MRC Health Services Research Board at its meeting on 11 February 1993.

PLAN OF INVESTIGATION

Laparoscopic hernia repair

Laparoscopic hernia repair will be performed using a transabdominal preperitoneal approach. After the preperitoneal space has been entered by incising the peritoneum transversely at the level of the anterior superior iliac spine, the hernial sac will be reduced, separating it from all cord structures. The inferior epigastric vessels, pubic tubercle, Cooper's ligament, iliopubic tract and iliac vessels will be identified and exposed. A large piece of polypropylene mesh will then be placed over the defect and secured to pubic tubercle, transversalis fascia and Cooper's ligament with titanium staples. Finally the peritoneum will be closed over the mesh with staples.

Conventional hernia repair

As the trial is pragmatic this will be carried out using the preferred method of each individual surgeon. The predominant method of repair will be the plication darn, the method most commonly used by consultant surgeons in the UK[3].

Surgeons
The operations will be carried out by surgeons with previous experience of laparoscopic surgery. Sixteen surgeons from 11 hospitals are already committed to participate in the study. We are confident of recruiting a similar number once funding is assured.

Patients
Initially eligible patients with inguinal hernias will be asked for their informed consent to undergo laparoscopic hernia repair. After each surgeon has completed 20 laparoscopic hernia repairs, his eligible patients will be asked for informed consent to randomisation between laparoscopic and conventional hernia repair. Incisions in both groups will be infiltrated with 0.5% Bupivacaine to prevent wound pain. A structured record of pre-operative characteristics, operative findings (including hernia type and repair performed), and operative and post-operative complications will be kept for all patients, including those excluded from the trial for one or more of the following reasons:

a The surgeon has not completed 20 laparoscopic hernia repairs.
b The patient is medically unfit for general anaesthesia.
c The patient has had a previous lower midline abdominal incision.

The progress of excluded patients will be monitored to ensure that the study describes the care of a defined population of patients with inguinal hernia.

Analgesia use
An accurate record of the analgesia used by both groups will be kept in the three main Glasgow hospitals - Western and Royal Infirmaries and Southern General Hospital. In all hospitals, the type of analgesia will be standardised, both in the ward and on discharge, and the degree of pain will be monitored by patient-completed linear analogue scores.

Pulmonary function (two samples of 100 patients drawn from, and stratified by, the three main Glasgow hospitals)
Recovery of pulmonary function is influenced by incision size and site. Peripheral oxygen saturation will be measured in both groups by pulse oximetry, pre-operatively and post-operatively for the first 24 hours, or for the entire hospital stay if less than 24 hours. Vital capacity and peak expiratory flow rate will be measured in both groups, pre-operatively and six hours post-operatively.

Metabolic response (two samples of 50 patients drawn from, and stratified by, the three main Glasgow hospitals)
The magnitude of the metabolic response to injury is directly proportional to the degree of surgical trauma[29]. Metabolic variables including cytokine interleukin-6 and acute phase C-reactive protein will be measured in both groups of patients.

Hospital stay
The decision to discharge each patient will be taken by the appropriate consultant. To minimise bias, patients will have to fulfil five criteria before discharge:

1 Be fully mobile around the ward.
2 Be able to perform common 'activities of daily living' such as putting on their clothes.
3 Be able to tolerate a full diet.
4 Require only oral analgesia.
5 Affirm that they could manage at home if discharged.

Participating consultants will be encouraged to discharge within 24 hours of operation patients who fulfil these criteria. Requests for home help and other resources during convalescence will be recorded for all patients.

Complications
The incidence of urinary retention, pulmonary function, scrotal haematoma, wound infection and any other complication will be recorded in both groups. All patients will be independently reviewed at the outpatient clinic one month after surgery, whenever possible by one of the researchers.

Return to normal activity
Patients in both groups (except those whose jobs require heavy physical activity) will be advised that they may return to work as soon as they feel able to do so following their hernia repair. Patients whose jobs require heavy physical activity will be advised that they should not work for two weeks following their repair. All patients will be advised to avoid strenuous exercise for two weeks.

Postal outcome questionnaires

On discharge patients will be given a questionnaire to be completed and returned one week after surgery, together with a business reply envelope addressed to HSRU. A similar questionnaire will be given to patients at the postoperative outpatient clinic after four weeks, and a further similar questionnaire posted to them three months after surgery. The purpose of these questionnaires is to obtain an unbiased assessment of their return to normal activity and improvement in general health status. All three questionnaires will include an anglicised version of the 'Short Form 36' (a health profile developed and validated in the United States[30,31] and increasingly being used in the United Kingdom[32], notably by the HSRU[33]) and the European Quality of Life (EuroQol) instrument[34] (developed by the York Centre for Health Economics with support from the Department of Health). In addition the one-week questionnaire will ask about complications and symptoms, and the three-month questionnaire will estimate the relative value that patients ascribe to the alternative operations by using the Willingness To Pay approach (developed by the Health Economics Research Unit (HERU) with support from the Scottish Office Home and Health Department[35,36]). All three questionnaires will be developed from the corresponding questionnaires developed, tested and implemented within the trial of laparoscopic cholecystectomy conducted by three of the applicants[27].

Hernia recurrence

All patients including those excluded from the trial proper will be recalled to the outpatient clinic at yearly intervals for five years to examine the hernia site for clinical evidence of recurrence or other long-term sequelae. Recurrence will be defined as "a weakness of the operation area necessitating a further operation or provision of a truss"[4]. The HSRU will set up a computerised recall system in Aberdeen and maintain it after any project budget has finished, if necessary from its core budget. Whenever possible patients will be independently reviewed by nurses trained in the diagnosis of hernia recurrence and other relevant long-term complications.

Cost to the National Health Service

The marginal cost of laparoscopic hernia repair will be estimated within each hospital. We shall take account of pre-operative costs (consultation and pre-operative investigation), operative costs (medical and nursing theatre staff, operating time and use of disposable instruments) and post-operative costs (hospital stay and post-operative investigations). Data on these costs will be collected prospectively using the clinical proforma. Resources will be valued according to the marginal cost principle so as to reflect their true opportunity cost. For example, in hospitals with surplus theatre capacity the opportunity cost of theatre time will be less than in hospitals where there is no surplus.

Value to the community

After the trial data have been analysed, we shall interview a random sample, drawn from Community Health Indexes, of 100 members of the general public within the geographical areas covered by patients recruited into the trial. After presenting them with a simple description of inguinal hernia and the alternative methods of repair, together with a brief summary of our findings, we shall ask them how much the community should be 'willing to pay' out of taxation for each operation[35,36].

Sample size

We plan to recruit 2000 patients into the trial over two years. Using a significance level of 5%, the resulting trial will have 80% power to detect:

a A difference between groups greater than one eighth of the standard deviation of outcomes like reported pain, health status and duration of convalescence (after statistical transformation to yield a normal distribution, when necessary)[37].

b A difference in the five-year recurrence rate between (say) 10% for conventional repair and either 6.5% or 14.1% (since all tests will be two-sided) for laparoscopic repair[38].

The substudies of pulmonary function (200 patients) and metabolic response (100 patients) will have the same 80% power of detecting differences between groups that are smaller than the corresponding differences detected or suggested by the completed trial of laparoscopic cholecystectomy[27].

Timetable

October - December 1993	Final preparation including staff training
1994 and 1995	Recruitment of 2000 patients (40 a year by each of 25 surgeons)
January - March 1996	Completion of short-term data
April - December 1996	(1) Completion of data on recurrence after one year
	(2) Collection of first half of data on recurrence after two years
	(3) Statistical analysis
January - March 1997	Preparation of publications and report

DETAILED JUSTIFICATION FOR SUPPORT REQUESTED

Existing facilities

1 Facilities exist in all hospitals participating in the study to perform both laparoscopic and conventional hernia repair.

2 The three main Glasgow hospitals are equipped with pulse oximeters and spirometers for pulmonary function assessment. (However, the budget includes provision for two additional sets of equipment for times when the existing equipment is in use.)

3 Facilities exist at Glasgow Royal Infirmary to analyse the metabolic response samples.

4 Three of the applicants are currently analysing a very similar trial of laparoscopic cholecystectomy funded by the Scottish Health Services Research Committee[27]; many of the research documents and questionnaires for the proposed trial of laparoscopic hernia repair will be derived from those already developed, tested and implemented.

5 HSRU will train and supervise the proposed staff in the fields in which it has expertise and experience, namely trial design and management, outcome measurement, data management and statistical analysis.

6 HERU will train and supervise the proposed staff in the fields in which it has expertise and experience, namely the valuation of benefits and costs to patients, the National Health Service and the community as a whole.

Justification of requirements

A Clinical Research Fellow based in Glasgow is needed to:

a Coordinate a complex study across at least 11 hospitals.

b Ensure that patients are assiduously recruited in all hospitals.

c Take responsibility for the recruitment of patients, the collection of data, the delivery of analgesia and the independent assessment of complications and recurrence in the three main Glasgow hospitals.

d Measure peripheral oxygen saturation, pulmonary function and metabolic response of patients in the three main Glasgow hospitals.

e Supervise the two research nurses and liaise closely with the Data Manager based in Aberdeen.

We judge that Senior Registrar status is essential to ensure that all these tasks are undertaken effectively.

Two research nurses, one based in Glasgow and the other in Edinburgh, are needed to:

f Ensure assiduous recruitment and accurate data collection in the hospitals for which they are responsible.

g Provide independent assessment of complications and recurrence in these hospitals.

A half-time Data Manager based in Aberdeen is needed to:

h Monitor the quality of data from all hospitals.

i Manage and analyse the data from all hospitals.

j Send postal questionnaires to patients three months after surgery, in particular to assess their return to normal activity.

k Establish and operate a computerised recall system and database to monitor recurrence and other long-term sequelae of (laparoscopic) hernia repair.

l Liaise closely with the research staff based in Glasgow and Edinburgh.

We judge that a Research Fellow with a PhD or equivalent experience is essential to ensure that all these tasks are undertaken effectively.

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