NCCHTA

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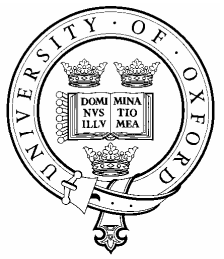

The HOPEFUL Study

Hysterectomy Or Percutaneous Embolisation For Uterine Leiomyomata?

PROTOCOL

Version 2
June 2004

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PROJECT SUMMARY AND RATIONALE:

HOPEFUL is a retrospective cohort study examining the efficacy and safety of two interventions for treating women with symptomatic fibroids. The traditional standard treatment is the surgical removal of the uterus (hysterectomy) and the newer less invasive uterus-conserving treatment is uterine artery embolisation (UAE). The project is a comparative analysis of these two treatments in women treated since the mid 1990s. It is a multi-centre study funded by the HTA and managed by the University of Oxford involving 20 collaborating hospital centres in England and Scotland.

Both the National Institute for Clinical Excellence (NICE)[1] and The Joint Working Party of the Royal College of Obstetricians and Gynaecologists (RCOG)[2] have recognised the lack of medium to long-term data comparing UAE with surgical options for symptomatic fibroids and have emphasised the need for randomised comparisons. Fully informed randomisation between major surgery, which terminates reproductive function, and an intervention which deals with the specific cause of symptoms, is problematic. This project seeks to systematically collate clinical data retrospectively from experience within the UK to provide comparable preliminary data in an observational setting. An attempt will be made to directly compare benefits and costs of the two procedures where possible. Currently UAE is not routinely offered to women within the NHS due to uncertainty about longer term outcomes. However it is available in over 50 centres in the UK with patients consent for audit or research, primarily in London and South East England.

References:

[1.] NICE Interventional Procedures Programme. **Systematic review of the efficacy and safety of uterine artery embolisation in the treatment of fibroids** (www.nice.org.uk)
June 2004: The Interventional Procedures Advisory Committee (IPAC) have reviewed the results of the systematic review and NICE have issued a second consultation document about its safety and efficacy, based on these results. Their provisional recommendations suggest UAE is safe enough for routine use and provides symptomatic benefits in the short term. However evidence of the degree, frequency and durability of the procedures benefits is uncertain. They recommend further research with longer follow-up to reduce this uncertainty.

[2]. Royal College of Radiologists and Royal College of Obstetricians and Gynaecologists. Report of a Joint Working Party. **Clinical Recommendations on the Use of Uterine Artery Embolisation in the Management of Fibroids. (**Royal College Joint Report) November 2000. (www.rcog.org.uk)

BACKGROUND:

What are fibroids?

Uterine fibroids (leiomyomata or myomas) are benign tumours of smooth muscle cells and fibrous connective tissue that develop within the walls of the uterus. Intramural fibroids develop within the uterine walls, subserosal fibroids project into the uterine cavity and submucosal fibroids project from the outer surface of the uterus. They are the most common gynaecological problem in women in the UK, occurring in up to 50% women over 30 years of age. The aetiology of fibroids is not fully understood but their occurrence during the female reproductive lifespan indicates an association with the hormones oestrogen and progesterone. They occur more commonly in overweight women, nulliparous women and in women of Afro-Caribbean ethnic origin.

Asymptomatic fibroids require no treatment other than routine monitoring. Some fibroids however cause symptoms of prolonged and/or heavy menstrual bleeding, painful menstruation, or pelvic pain and pressure resulting from the bulk of fibroids which may also include urinary frequency/urgency or constipation. Fibroids may also be a factor in sub-fertility and pregnancy loss.

Treatments for symptomatic fibroids

The typical treatment for symptomatic fibroids is surgical, either complete removal of the uterus (hysterectomy) or less commonly removal of the fibroids only (myomectomy). Of the 70,000 hysterectomies performed annually in the UK around a third of these are for fibroids.

While hysterectomy eliminates all fibroid symptoms, it is unsuitable for women who have not completed their family or wish to retain their womb. It is a costly major operation with significant morbidity (major morbidity in 3% cases, minor morbidity in 14% cases).[3] There is a mortality rate of 1-2 per 1000 women. Women may require 2-3 months off work following surgery and a further 2-3 months to recover fully. They may subsequently experience urinary incontinence and sexual dysfunction. There may also be psychological side effects including a loss of femininity and depression.

No pharmacological intervention is known to have a long term effect on symptoms. Gonadotrophin inhibits fibroid growth for the duration of therapy only and this effect ceases upon stopping treatment.

Uterine artery embolisation (UAE) was first reported as a “stand-alone“ treatment for fibroids in 1995.[4] Prior to this it was performed preparatory to surgical

intervention for fibroids or for the management of other gynaecological conditions such as postpartum haemorrhage. Since the first reports of this alternative uterus-sparing treatment several observational studies of UAE for fibroids report successful levels of fibroid shrinkage (40-75%), symptom improvements and improved quality of life over the short-term (62-95% over 6 months).[1] Pregnancies have been reported following UAE, in three studies totalling 604 women, 24 women (4%) reported pregnancies following UAE. [1]

UAE is performed under conscious sedation by an interventional radiologist using established angiographic techniques. A percutaneous catheter is introduced into a femoral artery and manipulated under fluoroscopic guidance into the uterine arteries. Once in place embolic particles are injected into both uterine arteries to close off the blood supply to the fibroid. The closure of the arteries is considered permanent. As a result of lack of a blood supply the fibroid shrinks. The procedure takes around 1 hour depending on the anatomy of the pelvic arteries. Most patients in the immediate period post-UAE experience a post-embolisation syndrome of pain, nausea and high temperature and remain in hospital overnight. The impact of the procedure on fertility is currently unknown and patients wishing to become pregnant are currently not advised to undergo UAE. Ovarian dysfunction possibly due to non-target embolisation has been reported particularly in older women (rates of reported amenorrhoea in one study of 555 patients ranged from 3% in women younger than 40 yrs to 41% of women aged 50 yrs plus).[1]

There has been a large variation in the reported rates of complications ranging from 5% to 13% in the larger studies.[1] The most frequent major complication is infection and where this cannot be managed effectively emergency hysterectomy may be required. One death has been reported.

References:

[3]. McPherson K, Metcalfe MA, Herbert A, Maresh M, Casbard A, Hargreaves J, Bridgman S, Clarke A. Severe complications of hysterectomy: The Value Study. British Journal of Obstetrics & Gynaecology (accepted for publication).

[4]. Ravina JH, Herbreteau D, Ciraru-Vigneron N et al. Arterial embolisation to treat uterine myomata. Lancet 1995;346:671-2.

STUDY METHODOLOGY:

What are the study questions?

The study will examine the experience of 2 cohorts of women who underwent either hysterectomy or UAE for the purpose of relieving symptomatic fibroids. Differences between the 2 cohorts will be compared where possible.
There are 3 main areas to be addressed:

1. Are the 2 cohorts comparable in confounding factors relevant to outcome measures?

In spite of attempts to ensure comparability, it is quite possible that the patients in the two intervention cohorts will be systematically different in any of a number of ways for example, their demographic characteristics, physical characteristics, clinical indications, treatment preferences and expectations. The following will be considered as possible confounders;
Age, Ethnicity, Educational level
Body Mass Index, Smoking history, Age at menarche, Menstrual status, Parity
Time since index treatment
Family history of fibroids, Family history of breast cancer
Blood pressure, Co-morbidity, Other health problems
Prior surgery, HRT prior to treatment
Previous fibroid treatment, Fibroid symptoms, Fibroid characteristics
Fertility aspirations, Treatment preferences
Treatment variables, Treatment related medication, Length of hospital stay

2. What are the outcome measures? Are there differences between the two treatment cohorts for outcomes that can be assessed in both cohorts?

Clinical outcomes of relevance relate to reduction of fibroid size/uterine size, resolution of fibroid symptoms, avoidance of further treatments, satisfaction with treatment, complications of procedure and associated morbidity/requirement for further treatment and future fertility outcomes. We will attempt to compare the 2 groups on all but fibroid shrinkage and future fertility. For complications we will attempt to categorise into minor/major to enable a comparison by severity as the specific complications differ by the mechanics of each treatment. The following outcome measures will be considered;
Symptom change –general, specific, Satisfaction with treatment
Fibroid/ uterine volume shrinkage, Success of treatment
Gynae/medical conditions-post treatment, Hospital readmissions, Complications
Further treatment for fibroids[†] *,Post-embolisation syndrome*[†] *,Passage of fibroid tissue*[†] *,Transient/permanent amenorrhaea, Subsequent fertility/ pregnancy*[†]
[†] ***NB For UAE only***

3. Can any factors predict variation in outcome measures within the UAE cohort?

We will attempt to examine subgroups/factors within the UAE cohort that may be associated with differences in outcomes if possible. For example, fibroid size, gynaecological comorbidity, embolisation type/particle size.
We will be ascertaining any inclusion/exclusion criteria within each UAE centre regarding patients who receive UAE treatment.

The two HOPEFUL patient cohorts:

The study sample consists of approximately 2000 women half treated with embolisation and half with hysterectomy. Nine patron radiologists, pioneers of UAE for fibroids, have agreed to provide a complete list of their patients on whom UAE has been performed providing the opportunity to collect clinical data on around 1000 UAE procedures. The control/hysterectomy cohort comes from the VALUE Study [5], which is investigating long-term effects of 37,000 unselected hysterectomies carried out between October 1994 and October 1995 in the UK, except Scotland. This group was initially recruited as a control group for women treated with trans-cervical endometrial ablation for dysfunctional uterine bleeding (DUB). Amongst them, there were about 6000 women with uterine fibroids as the first indication. From this group of 6000, around 1000 patients were treated in 12 VALUE centres that have performed the most hysterectomies for fibroids. These patients are not part of the existing VALUE follow up protocol, which is concerned with patients with menorrhagia as the main indication.

Reference:

[5]. Maresh MJA, Metcalfe MA, McPherson K, Overton C, Hall V, Hargreaves J, Bridgman S, Dobbins J, Casbard A. The VALUE national hysterectomy study: description of the patients and their surgery. *BJOG: an International Journal of Obstetrics and Gynaecology* 2002; 109: 302-12.

Study procedures

All consultants responsible for the patients identified in either the hysterectomy (VALUE study) or UAE cohorts have agreed to a formal collaboration and are the local Principal Investigators (PI) for the study. Temporary research nurses will be employed within each of the collaborating hospitals to collect data according to the study protocol.

Approvals:

Ethical approval has been obtained from a Multi-Centre Research Ethics Committee (MREC) (MREC/03/10/49 approval received on 23rd February 2004

and approval for an amendment to the protocol was subsequently obtained 2nd June 2004.)

Each local centre will obtain their Local Research Ethics Committee (LREC) and local Trust R&D Management approval prior to starting the study.

Eligibility for study:

The eligibility criteria for entry into the HOPEFUL database is that treatment was for fibroids. The research nurses for the hysterectomy cohort will therefore screen VALUE patient notes to select only those that underwent hysterectomy for that indication and that surgery is the index treatment.

All UAE patients in HOPEFUL will have received embolisation for fibroids. The index treatment is their first UAE treatment.

Location of eligible patients:

The research nurse in each centre will inform the Oxford office of all eligible patients and provide their NHS number or contact details at the time of the treatment where there is no NHS number available. Using this information the Oxford office will establish the current status of the eligible patients (deceased or living and if living, locate their current address). The Oxford office will utilise the NHS Tracing Service to establish this information. Permission has been received from the Caldicott Guardian at the Oxford Radcliffe Hospitals NHS Trust for Oxford HOPEFUL project staff to utilise this service for this purpose.

Patient contact, information and consent:

The initial contact with patients for the HOPEFUL study will be a letter from the relevant hospital consultant where the patient received her treatment for fibroids and this will be on local hospital headed paper. The letter will explain the purpose of the study, providing a patient information sheet and seeking written consent from the women to participate in the project.

Data collection:

Following consent, information from patients' hospital notes will be extracted onto clinical data collection forms provided by the Oxford office to the research nurse in each centre for this purpose. The data forms include details confirming the diagnosis, full details of the surgery or embolisation, techniques used and relevant treatment outcomes and complications over a period of several years follow up. The data will be collated in a central anonymised clinical database to be held at the coordinating centre of the study in Oxford.

Following consent, the patients will also receive a simple follow up questionnaire. This questionnaire will include information about their general health, fibroid

symptoms before, treatment choices for fibroids and subsequent health following treatment. Outcomes such as resolved symptoms, specified complications, residual symptoms, subsequent treatments and pregnancies will be recorded. This questionnaire will also ask about satisfaction with the treatment procedure they received. These questionnaires will be anonymised. The patient questionnaires will be sent out by the Oxford office direct to patients with a freephone number for any queries. A freepost envelope will be provided for return of the patient questionnaire to Oxford. Reminder letters and additional questionnaires will be sent to patients who have not responded at 2 weeks and 4 weeks following the first questionnaire being sent.

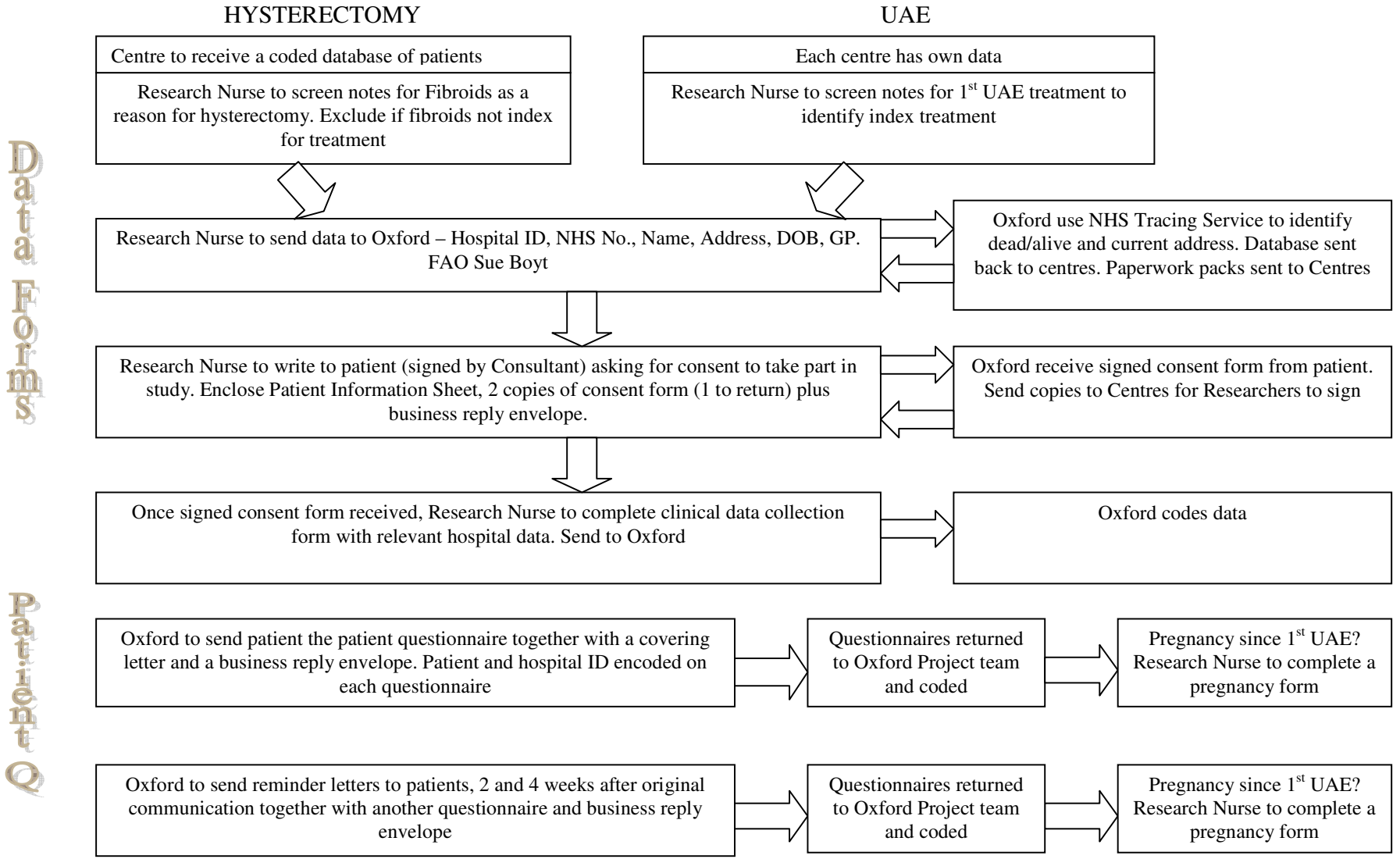
Data analysis:

Analysis will be by using multiple logistic regressions on the risks of complications, with fibroid size and other predisposing determinants of risk (location, number of fibroids, patient's age, previous illness, ethnic origin and obstetric history) as possible confounders. This method will investigate the adjusted and unadjusted relative risk of various important possible complications (for example, death, haemorrhage, septicaemia, visceral damage, further (emergency) surgery, impact on fertility). The role of confounders in determining risk will be explored in detail, and the possibility of important selection of patients tested. The attributable risks for each possible complication will be examined as an extra risk per 1000 women years. Any time dependency will be examined using Cox's proportional hazards methodology.

Publication Policy

The primary publication will be the HTA monograph in accordance with the funder's regulations. Other publications will be submitted to appropriate medical journals with the approval of the HTA. Similarly, presentations at scientific meetings will be made as appropriate with the approval of the HTA.

PROCESS FLOWCHART (Hysterectomy/ UAE)



PROJECT MANAGEMENT AND SUPERVISION:

Oxford Project Coordinating Team

The project is coordinated from a central office in Oxford and is made up of the team below;

Address: Nuffield Dept of Obstetrics & Gynaecology
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Direct office: 01865 225209

Project Statistician:
Sue Dutton
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Direct office: 01865 225830

The responsibilities of the Oxford team include;

- Recruitment of participating local centres.
- Development and supply of project documentation including data collection forms and patient questionnaires.
- Data collection and management including liaison with research nurses in each local centre and adherence to ethical/data protection regulations.
- Construction of the project clinical database.
- Data entry and validation.

- Data analysis.
- Reporting and publishing results of project in accordance with the funder's regulations.

In addition to the Oxford project staff, two other grant-holders function as representatives for the two cohorts of women.

The hysterectomy cohort (VALUE group) are coordinated by Mike Maresh, Consultant in Obstetrics and Gynaecology, St Mary's Hospital for Women and Children, Whitworth Park, Manchester, M13 0JH
michael@maresh.co.uk

The UAE cohort are coordinated by Tony Nicholson
Consultant Vascular Radiologist, Radiology Dept, Jubilee Building, Leeds General Infirmary, Leeds, LS1 3EX
tonynick@tonynick.demon.co.uk

Trial Steering Committee

The running of the project is under the supervision of a Trial Steering Committee which has been constructed for that purpose and will meet twice a year for the duration of the project.

The TSC comprises in addition to the project management team above;

- Dr Nick Chalmers (Chair) (Radiologist, Manchester Royal Infirmary)
- Dr Mary Ann Lumsden (Divison of Developmental Medicine, Reproductive and Maternal Medicine, Glasgow Royal Infirmary)
- Mr Enda McVeigh (Nuffield Dept of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford)
- Dr David Shepherd (Radiologist,The Royal Bournemouth Hospital)
- Professor Doug Altman (Methodologist/Statistician, Centre for Statistics in Medicine, Institute of Health Sciences, Oxford)

Local collaborating centres

The participating centres (for final confirmation) are as below;

Collaborating Hospital	*Consultant(Local PI)*	*Cohort*
Blackpool Victoria Hospital	Mr Frank Wilcox	Hysterectomy
Bradford Royal Infirmary	Ms Sian Jones	Hysterectomy
Countess of Chester Hospital	Mr John Williams	Hysterectomy
Derby City Hospital	Mr Howard Jenkins	Hysterectomy
Gloucestershire Royal Hospital	Mr Mike Read	Hysterectomy
King George Hospital (Ilford)	Ms June Swinhoe	Hysterectomy
Leicester General Hospital	Mr Philip Kirwan	Hysterectomy
Norfolk and Norwich Hospital	Ms Katherine Stanley	Hysterectomy
North Staffordshire Hospital (Stoke)	Mr Duncan Gough	Hysterectomy
Royal Hospital (Chesterfield)	Mr Philip Tromans	Hysterectomy
Royal Victoria Infirmary (Newcastle)	Mr Paul Hilton	Hysterectomy
Solihull Hospital	Mr Ralph Settatree	Hysterectomy
Gartnavel Royal Hospital (Glasgow)	Dr John Moss	UAE
Guy's and St Thomas' Hospital (London)	Dr John Reidy	UAE
Hull Royal Infirmary	Dr Steve Killick	UAE
Royal Berkshire Hospital (Reading)	Dr Peter Torrie	UAE
Royal Free Hospital (London)	Dr Neil Davies	UAE
Royal Surrey Hospital (Guildford)	Dr Woodruff Walker	UAE
St George's Hospital (London)	Dr Anna Belli	UAE
Southampton General Hospital	Dr Nigel Hacking	UAE
The Churchill Hospital (Oxford)	Dr Nigel Cowan	UAE

The Principal Investigator (PI) in each local centre will identify a research nurse for an equivalent period of 6 months half time for the project. The responsibility of the local PI and research nurse will be to:

- Be familiar with the project protocol and aims.
- Liaise with the Project Coordinating Office in Oxford and attend at least one HOPEFUL Collaborators meeting in Oxford during the project's duration if possible.
- Obtain local ethical and Trust R&D Management approval.
- Be responsible for screening patient notes for inclusion eligibility for the project.
- Be responsible for sending the first letter of contact to patients eligible for the study including patient information sheet and consent form.
- To hold patient signed consent forms for the duration of the study.
- Ensure that the clinical data collection forms are completed satisfactorily and returned promptly to the Oxford office.
- To ensure that the confidentiality of all information about patients in the study is respected.