**Technology Assessment Report Commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence – Final Protocol**

**19th May 2005**

## 1. Title of the project:

The clinical and cost effectiveness of laparoscopic surgery for colorectal cancer

## 2. Name of TAR team and 'lead'

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## 3. Plain English Summary

Colorectal cancer (CRC), often called bowel cancer, is a common disease in the United Kingdom. In 2002, 35,969 new cases were diagnosed in the UK. Surgical resection of the primary tumour is the only curative treatment in CRC. Open surgical resection is the recommended means, with approximately 80% of patients diagnosed with CRC undergoing surgery. Five-year relative survival after this procedure is high in people with tumours in an early stage. However, morbidity rates associated with open resection are high. Laparoscopic surgery is a less invasive procedure, utilising a number of ports through which the special laparoscopic surgical instruments are inserted. Laparoscopic surgery techniques can be of three types: laparoscopic, laparoscopic assisted and hand-assisted laparoscopic surgery. The first two techniques, hereafter referred to as laparoscopic surgery, involve making the smallest possible incision (minimal access) required to remove the tumour. The latter approach in comparison to open repair is "reduced" access rather than minimal access surgery.

The review will assess the effectiveness and cost-effectiveness of the laparoscopic and hand assisted laparoscopic surgery for the treatment of colorectal cancer and provide guidance to the NHS in England and Wales.

The assessment will focus on both short-term (e.g. patient symptoms, peri-operative outcomes, complications, post-operative complications) and long-term measures (e.g. cancer recurrence, time to further surgery, survival) of the effectiveness of laparoscopic and hand assisted laparoscopic surgery. Costs and cost-effectiveness will be assessed from the perspective of the NHS and personal social services.

Information of the relative effectiveness of the alternative interventions will be derived by systematically reviewing relevant randomised controlled trials (RCTs). Cohort studies with a follow-up of three years or longer will also be systematically reviewed to provide information on long-term outcomes which are unlikely to be available from the RCTs. Information on cost-effectiveness will initially be assessed using a systematic review of economic evaluations comparing laparoscopic or hand assisted laparoscopic surgery with open surgery. Should the systematic review of economic evaluations provide insufficient information on relative cost-effectiveness, an economic model may be developed which would use the findings of the systematic review of effectiveness to help provide estimates of the relative cost-effectiveness of the surgical procedures.

## 4. Decision Problem

Colorectal cancer (CRC) frequently results from a malignant change in adenomas that have developed in the lining of the large intestine (colon and rectum). Colonic cancer consists of all tumours occurring in the area from the large intestine proximal to the rectum. Rectal cancer is defined as a tumour within 15 cm of the anal verge.[1,2]

CRC is a common disorder affecting both sexes, however it is more common in males than in females. In the UK, the male to female ratio for colonic and rectal cancer is 11:10 and 7:4 respectively.[3] CRC is rare in people aged under 40 years. Approximately 41% of patients affected are above 75 years of age, and 52% of deaths occur in this age group.[4]

Overall, 35,969 new cases were diagnosed in the UK in 2002.[5] Moreover, CRC was responsible for 17,190 deaths.[3] It is the second most commonly occurring tumour in the UK in terms of both incidence and mortality.

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[1] Phillips, R, (1998), *Colorectal Surgery*, WB Saunders Company Ltd, London, UK

[2] Smith, J, King, P, Lane, R, Thompson, M, (2003), Evidence of the effect of 'specialization' on the management, surgical outcome and survival from colorectal cancer in Wessex, *British Journal of Surgery*, **90**, 583-592

[3] Card and Logan, (2003), Colorectal cancer: Prevention and Early Diagnosis, *Medicine*, **31**, 60-64

[4] NICE Technology Appraisal Guidance no. 33, March 2002

[5] Globocan (2002), Cancer Incidence, Mortality, and Prevalence Worldwide (2002 estimates) – website accessed on the 5th of April 2005

A small subgroup of CRC is caused by inherited predisposition, however, it is estimated that 75% arises sporadically. Diet is a major risk factor: over-nutrition, high meat and fat consumption, and deficiencies in vegetables, key minerals and vitamins are associated with higher risk[3]. If CRC is left untreated, it is invariably fatal, just like most cancers.

In the UK, open surgical resection of all malignant tissue is the recommended means of primary treatment for CRC.[6] Approximately 80% of patients diagnosed with colorectal cancer at any stage (including some with advanced disease) undergo surgery.[4] According to the 2003/2004 statistics, 31,391 primary excisions were performed in England. Of these, 28% presented as an emergency.[7] After surgical resection, five year relative survival is related to the stage[8] and is approximately 85-95% in Dukes' A cancer (tumour confined to mucosa and sub mucosa of the bowel wall), 60-80% in Dukes' B cancer (tumour penetrating the muscle wall of the bowel) and 30-60% in Dukes' C cancer (metastasis to regional lymph nodes).[9] In the latter, surgery to remove the primary tumour alone is unlikely to be sufficient for cure.

The open surgical procedure involves using a long incision through the abdominal wall, usually from below the breastbone to just above the pubic bone, which allows the surgeon to gain excellent exposure of the colon (laparotomy). The surgical resection of the cancer itself involves not only the removal of the part of the bowel that contains the tumour but also the removal of sufficient margins on either side including any affected organs as well as nearby lymph nodes and vessels with the aim of preventing the possibility of leaving tumour cells behind. For rectal cancer, a total mesorectal excision - the excision of the narrow fold of the peritoneum connecting the upper part of the rectum and the sacrum - is performed to reduce the probability of local recurrence.[6] This is followed by anastomosis - a direct surgical connection formed between two sections of bowel. Shortcomings associated with open surgical resection include: incisional pain, tissue trauma, intraoperative and postoperative metabolic stress, and postoperative ileus from manual intestinal manipulation.[10]

Laparoscopic surgery, however, does not involve a laparotomy incision. Instead, a number of ports are inserted through which the laparoscopic surgical instruments are manipulated. The extent of resection of the cancer should remain the same. The incision through which the cancer is removed is no more than 6 to 15 cm long.[10]

There are three laparoscopic techniques available to the surgeon: laparoscopic, laparoscopic-assisted and hand-assisted laparoscopic resection. The differences influence the size of incisions required to complete the procedure.

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[6] NICE Technology Appraisal Guidance – No 17, December 2005

[7] Department of Health - Hospital Episode Statistics, 2003/2004

[8] Dukes C, (1932), The classification of cancer of the rectum, *Journal of Pathology and Bacteriology*, **35**, 323-332

[9] Cancer research UK, January 2005
http://info.cancerresearchuk.org/cancerstats/bowel/?a=5441 – website assessed on the 11th of April 2005

[10] Australian Safety and Efficacy Register of New Interventional Procedures – Surgical, Consumer Summary laparoscopic assisted resection of colorectal malignancies, June 2000

- In a laparoscopic surgery, the entire procedure is undertaken laparoscopically;
- In a laparoscopically assisted surgery the bowel is manipulated laparoscopically, and then passed through an enlarged laparoscopic port site with excision and/or anastomosis of the bowel being performed externally;
- In a hand-assisted laparoscopic resection, the surgeon's hand is used inside the abdomen along with the laparoscopic equipment.

The majority of laparoscopic procedures will be laparoscopically assisted with a component of the operation performed on the surface making use of the smallest incision possible to remove the resected specimen. In contrast, hand-assisted laparoscopic surgery is technically easier and permits a 'reduced access' rather than 'minimal access' approach. For the purposes of this appraisal, laparoscopic and laparoscopically assisted surgery will be grouped together under the heading laparoscopic surgery.

If the evidence is available, the review will attempt to assess:

- Whether the substitution of laparoscopic or hand-assisted laparoscopic surgery for open surgery is as effective and/ or cost-effective in removing the tumour and preventing recurrence.

- The incidence of complications (including wound infections, anastomotic leakage and abdominal wound breakdown requiring re-operation), number of ports/incisions, operation duration, length of hospital stay, post-operative and long-term pain, and time to return to usual activities, for laparoscopic and hand-assisted laparoscopic surgery in comparison with open surgery.

- Whether the use of laparoscopic or hand-assisted laparoscopic surgery in place of open surgery influences overall survival, disease-free survival, time to tumour recurrence, the incidence of port site and wound metastasis and the risk of incisional hernia.

- The suitability of laparoscopic and hand-assisted laparoscopic surgery applications for individuals of different age groups, described in section 5.2.2 of the protocol.

## 5. Report methods for synthesis of evidence of clinical effectiveness

### 5.1 Search strategy

Extensive electronic searches will be conducted to identify reports of published and ongoing studies on the effectiveness and cost-effectiveness of 'laparoscopic and hand assisted laparoscopic surgery'.

As this review is an update of an earlier review conducted in 2000, searching will be carried out for the time period 2000-2005 for both full papers as well as conference abstracts and there will be no language restrictions. Databases to be searched are listed in Table 1. Preliminary Medline search strategies to be used are given in Appendix 1 and will be adapted for use in the other databases.

**Table 1. Databases to be searched**

| Clinical effectiveness | Cost effectiveness |
|---|---|
| Medline | Medline |
| Medline Extra | Medline Extra |
| Embase | Embase |
| Science Citation Index | Science Citation Index |
| Web of Science Proceedings | Web of Science Proceedings |
| Biosis | HMIC |
| Cochrane Controlled Trials Register | CRD NHS EED |
| HTA | HTA |
| Cochrane database of systematic reviews (CDSR) | |
| Database of abstracts of reviews of effectiveness (DARE) | |

Current research registers, including the National Research Register, Current Controlled Trials and Clinical Trials will be searched. Full text searching of key surgical journals (e.g. Surgical Endocopy, Surgical Laparoscopy, British Journal of Surgery, Archives of Surgery, Annals of Surgery) will also be undertaken.

In addition, an Internet search using Copernic Agent will be undertaken and will include key professional organisations, manufacturers, and conference proceedings. Reference lists of all included studies will also be perused. Experts - including the Cochrane Colorectal Cancer Group - will be consulted.

Since the randomised controlled trials that compare the alternative surgical approaches may only have a short follow-up, longer-term follow-up data from non-randomised cohort studies will also be sought. Therefore, cohort studies with a minimum of three year follow-up for the laparoscopic approaches will also be searched for. UK registries such as the Scottish Cancer Registry will be contacted to provide long-term data for open surgery**.**

### 5.2 Inclusion and exclusion criteria

#### 5.2.1 Type of studies

Meta-analyses and systematic reviews of randomised controlled trials and individual randomised controlled trials of laparoscopic and/or hand assisted laparoscopic surgery compared to open surgery for colorectal cancer.

Cohort studies and data from UK registries which provide data for a minimum of three years follow-up for any of the surgical techniques either alone or in comparison with each other.

Potentially relevant non-English language studies will be noted and if time and resources allow, an English translation will be sought.

Studies published only in abstract format will be noted but treated with caution. Assessment of clinical effectiveness will be based mainly on randomised controlled trials published in full in peer-reviewed journals.

Additional data on longer term outcomes will be based on data taken from cohort studies and UK registries.

### 5.2.2 Population

Adult males and females with colorectal cancer who have undergone surgery.

If evidence allows the following subgroups will be considered:

- Location of cancer (colonic, rectal; the appropriateness of further subgroups will be explored but this may be limited by quantity and quality of available data)
- Stage of cancer
- Mean age at diagnosis (15-59, 60-74 and 75+)

### 5.2.3 Types of outcomes to be examined

If evidence permits the main **short-term** outcome measures to be assessed will be:

Primary
- Completeness of resection / margins of tumour clearance
- 30 day mortality

Secondary
- Opposite method initiated
- Number of ports used for laparoscopic repair
- Conversion
- Lymph node retrieval
- Incidence of operative complications (Haematoma, Seroma, Wound/Superficial Infection, Port site hernia, Vascular injury, Visceral injury, anastomotic leakage and abdominal wound breakdown)
- Blood loss and use of blood products
- Operation duration
- Length of hospital stay
- Post operative pain
- Time to return to usual activities

If evidence permits the main **long-term** outcome measures to assess will be:

Primary
- Overall survival

Secondary
- Disease-free survival
- Health-related quality of life
- Incidence of port site metastasis

- Incidence of wound metastasis
- Incidence of incisional hernia
- Long term pain

Studies may use different instruments for assessing health-related quality of life and pooling of data will be attempted only for studies using the same instruments to measure outcomes.

### 5.2.4 Data extraction strategy

All citations identified by the search strategy will be screened on the basis of the title and - where available – of the abstract. Full-text copies of all potentially relevant reports will be obtained. Two reviewers will independently select studies for inclusion and extract data. Information will be recorded on: year of publication, source of funding, study design, methods pre-randomisation (e.g. stratification); method of randomisation; concealment of allocation; blinding procedures; number and characteristics of participants; methods of diagnosis and staging of the tumour; type and duration of interventions; co-interventions (e.g. radiotherapy); choice of outcome measures; length of follow-up. Care will be taken to avoid double counting due to multiple reports of the same data set. The reviewers will not be blinded to authors, institutions, or publications. Any disagreement will be resolved by consensus or referred to a third reviewer. Where there is insufficient information in the published report, attempt will be made to contact the authors for clarification.

### 5.2.5 Quality assessment strategy

The methodological quality of both meta-analyses and systematic reviews and primary randomised controlled trials will be assessed independently by at least two reviewers using currently available checklists (i.e. the Oxman checklist for review articles[3] and the Delphi criteria list for quality assessment of randomised controlled trials[4]).

### 5.2.6 Methods of analysis/synthesis

If the same outcomes are assessed by more than one primary study the use of a quantitative synthesis of results will be considered. The results of each individual study will be plotted as point estimates with corresponding 95% confidence intervals. For each outcome a test of homogeneity will be carried out using a Mantel-Haenszel chi-square test. If there is no evidence of heterogeneity a fixed-effect meta-analysis will be undertaken. In contrast, if significant heterogeneity ($p<0.10$) is found amongst included studies the following options will be considered: potential reasons for the heterogeneity will be sought, for example by checking the appropriateness of the choice of effect measures and/or using subgroup exploratory analyses, if heterogeneity persists, either synthesis will be avoided or a random effects model will be used in addition to a fixed effects model.

Where possible, subgroup analyses will be conducted to assess:

- differences in site of the cancer (colonic, or rectal; the appropriateness of further subgroups will be explored but this may be limited by quantity and quality of available data)

- differences in stage of cancer
- differences in mean age at diagnosis (15-59, 60-74 and 75+)
- the addition of adjuvant therapy (chemotherapy and radiotherapy)

In order to assess robustness of conclusions, sensitivity analyses will be undertaken to assess the effects of:

- alternative outcome for those converted to the opposite procedure
- excluding low-quality studies;
- excluding studies with high imbalance in terms of conversion rates.

If a quantitative synthesis proves to be inappropriate or unfeasible, a narrative synthesis of the findings of the included primary studies will be undertaken.

### 5.2.7 Methods for estimating quality of life, costs and cost-effectiveness and/or cost per QALY

**Systematic review of existing economic evaluations**

A systematic review will be conducted of the available economic evaluations comparing laparoscopic and/or hand assisted laparoscopic techniques with open surgery for colorectal cancer. The search strategy for economic evaluations will be adapted from that used to identify studies eligible for inclusion into the review of effectiveness.

Studies will not be excluded on the basis of language (although the quality assessment and data extraction may be limited for non-English language reports).

An economist will assess the abstracts of all reports identified by the search for economic evaluations. The full-published papers will be obtained for those studies that appear to be potentially relevant and will be formally assessed for their relevance.

The following data will be extracted for each included study:

1. The study characteristics (the research question; the study design; the comparison; the setting; the basis of costing)
2. Characteristics of the study population (numbers receiving or randomised to each intervention; other systematic differences in clinical management; inclusion/exclusion criteria; dates to which data on effectiveness and costs are related)
3. Duration of follow-up for both effectiveness and costs
4. Results (summary of effectiveness and costs [point estimate and if reported range or standard deviation (sd)]; summary of cost-effectiveness/utility [point estimate and if reported range or standard deviation (sd)]; sensitivity analysis[11])
5. Conclusions as reported by the authors of the study

[11] Including changes to single variable (univariant), two or more variables (multivariate) and stochastic (e.g. bootstrapping). In the first two cases this also includes when one or more variables are altered in order to identify when costs or benefits are equivalent (threshold analysis).

Included studies will be assessed against the BMJ checklist for referees of economic analyses[12] and, where appropriate, the criteria for the review of economic models set out by Phillips and colleagues.[13] Where possible, costs and cost-effectiveness will be assessed from the perspective of the NHS and personal social services.

No attempt will be made to synthesise quantitatively the studies that are identified. Data from the included studies will be summarised in order to identify common results and variations between studies. These data will then be interpreted alongside the results of the systematic review of effectiveness to aid assessment of the relative efficiency of laparoscopic and hand assisted laparoscopic approaches compared with open surgery for colorectal cancer.

**Economic modelling**

A model may be developed to estimate the relative cost-effectiveness of the laparoscopic and hand assisted laparoscopic techniques compared with open surgery for colorectal cancer. This model will combine data on clinical effectiveness with cost data relevant to the UK NHS. Further details of the modelling and data requirements are summarised below.

***Cost data***

The primary perspective for the costing will be the NHS and Personal Social Services. Cost data, therefore, will include the direct health service costs associated with each surgical treatment option and subsequent patient management.

The quantity of resources utilised will be identified from consultation with experts, primary data from relevant sources and the reviewed literature. We anticipate that unit cost data will be extracted from the literature or obtained from other relevant sources (e.g. manufacturer price lists, NHS reference costs). All cost data will be converted to a single year (2004) in pounds sterling.

The following data will be required to estimate costs incurred by the NHS for each surgical procedure under consideration:

- Staff time costs, consumables, overheads and capital charges associated with each operative procedure
- Length of stay in hospital
- Post operative secondary care treatment during the period of hospitalisation and convalescence
- Staff time costs, consumables, overheads and capital charges associated with any subsequent patient management

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[12] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;313:275–83.

[13] Phillips Z, Ginelly L, Sculpher MJ, Claxton.K., Golder S, Riemsma R et al. A review of guidelines for good practice in modeling in economic evaluation. Health Technol Assess 2004;8(36):1-172.

Where appropriate, costs will be discounted at 6%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions.

The model will also require data on the following:

- Annual probability of death
- Annual probability of recurrence
- Annual probability of metastasis
- Incidence of complications
- Length of operation
- Time to return to usual activities following an operation

***Assessment of benefits***

Should a model be constructed, benefits of the alternative surgeries for colorectal cancer will be presented in terms of a balance sheet. It is anticipated that the main measures of benefit will be: survival; health related quality of life; and recurrence (defined as recurrence of the colorectal cancer or metastasis). If sufficient data are available from the literature, different outcomes will be ascribed utility values and QALYs will be estimated. Where appropriate benefits will be discounted at 1.5%, the rate recommended in the NICE guidance to manufacturers and sponsors of submissions.

***Modelling***

If there is sufficient evidence, a Markov model will be utilised to estimate the cost–effectiveness of laparoscopic compared with hand assisted laparoscopic and open surgery for colorectal cancer. The precise nature of the model will be constrained by the data available. Where additional searches are needed for specific model parameters, patient preferences and other topics not adequately covered within the clinical effectiveness and cost-effectiveness reviews, these will be based as far as research resources permit on the methodological discussion paper produced by InterTASC (January 2005).

The model will follow a cohort of patients from their initial operation through their convalescence to their return to usual activities. The patients remain in this state until they die or they may suffer a recurrence or metastasis and therefore have a re-operation or some other form of patient management. The cohort of patients could continue to move within the model until they all eventually die. For the purposes of the analysis, the cohort of patients will be modelled for a maximum of 25 years (which would represent the maximum survival for many of the patients) following the initial operation. The type of economic evaluation will be dependant upon the findings of the review of effectiveness and may be restricted to a cost-consequence analysis which would be presented in the form of a balance sheet.

***Sensitivity analysis***

Sensitivity analysis will be applied to the model in order to assess the robustness of the results to realistic variations in the levels of the underlying data. Where the

overall results are sensitive to a particular variable, the sensitivity analysis will be reported.

Finally, the results of the evaluation will be used to estimate the cost implications to the NHS of increasing the number of surgeries for colorectal cancer performed using the intervention which the review of effectiveness finds to be the optimal intervention.

## 6. Handling the company submission(s)

All data submitted by the manufacturers/sponsors will be considered if received by the TAR team no later than 27th July 2005. Data arriving after this date will not be considered. If the data from unpublished studies meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submission, provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model, again using the methods outlined in this protocol. Strengths and weaknesses in terms of methodology adopted, reporting of results and conclusions will be described. If the TAR team judge that the existing economic evidence is not robust then further work will be undertaken, either by adapting what already exists or developing de-novo modelling. The conclusions derived from the company submission may then be compared with that provided by any model we develop so that differences in results can be highlighted. If the model we may develop differs substantively from that put forward by any company, we shall justify any assumptions made.

Any 'commercial in confidence' data taken from a company submission will be underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets).

## 7. Competing interests of authors

Professor Krukowski advised that he has no stocks or shares in any of the companies, and does not currently receive funding. He had received a travel grant from Autosuture (Tyco Healthcare) & the Royal College of Surgeons approximately 10 years ago. In the last two years he has advised Ethicon Endosurgery, Tyco Healthcare and Karl Storz Endoscopy (UK) Ltd on the development of new laparoscopic equipment. Professor Krukowski is also the chair of the data monitoring committee of the MRC CLASICC trial of conventional versus laparoscopic assisted surgery in patients with colorectal cancer.

Ms (Dr) Aileen McKinley likewise stated that she has no stocks or shares in any of the companies but was awarded a training fellowship from Ethicon Endosurgery last year. The fellowship covered travel and accommodation expenses for two trips to Hamburg. One trip was for a two day international laparoscopic colorectal meeting. The other was for a short visit (2 ½ days) to operate in the wet laboratory there (on anaesthetised pigs) – a facility not available in the UK.

The clinical department of both Professor Krukowski and Ms (Dr) Alieen McKinley use, amongst others, Ethicon Endosurgery, Tyco Healthcare, KeyMed (Medical & Industrial Equipment) Ltd and Richard Wolf UK Ltd equipment for both open and laparoscopic procedures.

Professor Grant attended a single meeting organised by Ethicon Endosurgery in 2003 to discuss possibilities for meta-analysis of trials of laparoscopic surgery for colorectal cancer.

None of the other members of the review team have any stocks or shares in any of the companies, nor do receive any funding.

The Health Services Research Unit and the Health Economics Research Unit are both receiving funding from Grampian University Hospitals NHS Trust (GUHT) to provide economics and statistical support for a randomised control trial of stapled haemorrhoidplexy compared with rubber band ligation for grade II haemorrhoids. GUHT is receiving funding for this trial from Ethicon Endosurgery.

## 8. Appendices

### Draft search strategy

Medline strategy to identify studies assessing clinical effectiveness

1 exp colorectal neoplasms/su
2 exp colectomy/
3 (colectom$ or hemicolect$ or colotom$).tw.
4 or/1-3
5 exp colorectal neoplasms/
6 (cancer adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw. (
7 (carcinoma adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
8 (neoplas$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
9 (adenocarcinoma$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
10 or/5-9
11 colorectal surgery/
12 Surgical procedures,operative/
13 (surgery or surgical or surgeon$).tw.
14 resect$.tw.
15 operation$.tw.
16 or/11-15
17 10 and 16
18 4 or 17
19 laparoscopy/
20 Surgical procedures,minimally invasive/
21 Robotics/
22 minimal$ invasiv$.tw.
23 laparoscop$.tw.
24 (key hole or keyhole).tw.
25 hand assist$.tw.
26 robotic$.tw.
27 or/19-26
28 18 and 27
29 limit 28 to yr=2000-2005
30 animal/
31 human/
32 30 not 31
33 29 not 32

Medline strategy to identify studies assessing cost effectiveness and quality of life

1 exp colorectal neoplasms/su
2 exp colectomy/
3 (colectom$ or hemicolect$ or colotom$).tw.
4 or/1-3
5 exp colorectal neoplasms/
6 (cancer adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
7 (carcinoma adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
8 (neoplas$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
9 (adenocarcinoma$ adj3 (colorectal or colon$ or rectal or rectum or intestin$ or bowel)).tw.
10 or/5-9
11 colorectal surgery/
12 Surgical procedures,operative/
13 (surgery or surgical or surgeon$).tw.
14 resect$.tw.
15 operation$.tw.
16 or/11-15
17 10 and 16
18 4 or 17
19 laparoscopy/
20 Surgical procedures,minimally invasive/
21 minimal$ invasiv$.tw.
22 laparoscop$.tw.
23 (key hole or keyhole).tw.
24 hand assist$.tw.
25 robotic$.tw.
26 robotics/
27 or/19-26
28 exp "costs and cost analysis"/
29 economics/
30 exp economics,hospital/
31 exp economics,medical/
32 economics,pharmaceutical/
33 exp budgets/
34 exp models, economic/
35 exp decision theory/
36 ec.fs.
37 monte carlo method/
38 markov chains/
39 exp quality of life/
40 "Value of Life"/
41 cost of illness/
42 exp health status indicators/
43 cost$.ti.
44 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
45 economics model$.tw.
46 (economics$ or pharmacoeconomic$ or pharmo-economic$).ti.

47 (price$ or pricing$).tw.
48 (financial or finance or finances or financed).tw.
49 (value adj2 (money or monetary)).tw.
50 quality adjusted life.tw.
51 disability adjusted life.tw.
52 (qaly? or qald? or qale? or qtime? or daly?).tw.
53 (euroqol or euro qol or eq5d or eq 5d).tw.
54 (hql or hqol or h qol or hrqol or hr qol).tw.
55 (hye or hyes).tw.
56 (health adj3 (indicator? or status or utilit?)).tw.
57 markov$.tw.
58 monte carlo.tw.
59 (decision$ adj2 (tree? or analy$ or model$)).tw.
60 or/34-65
61 18 and 60
62 4 and 27 and 60
63 10 and 27 and 60
64 or/61-63
65 limit 64 to yr=2000-2005