NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Medical Technologies Evaluation Programme

Specification for sponsor submission of evidence

AUGUST 2011

Contents

List of tables and figures

Instructions for sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the Medical Technology Evaluation Programme assessment process. It shows sponsors what information NICE requires and the format in which it should be presented.

Those completing the template are asked to pay particular attention to Section 8.2 which describes arrangements for handling of information which NICE may be asked to treat in confidence.

Use of the specification and completion of appendices 1 to 13 (sections 7.1 to 7.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Evaluation Pathway Programme methods guide' (www.nice.org.uk). Users should see NICE's 'Evaluation Pathway Programme process guide' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. Confine yourself to completing the response sections and appendices only. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission.

Appendices are not normally presented to the Medical Technology Advisory Committee. Any additional appendices should be clearly referenced in the body of the submission. **Appendices should not be used for core information that has been requested in the specification.** For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical study reports and protocols should not be submitted, but must be made available on request.

Studies should be identified by the first author or study ID, rather than by relying on numerical referencing alone (for example, ‘Study 123/Jones et al.[126]’ rather than ‘One study[126]’).

For information on submitting economic models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, section 8.

Section A – Decision problem

Section A is to be completed in conjunction with the Scope. Sponsors are requested to submit this section in advance of the full submission (for details on timelines, see the NICE document 'Evaluation Pathway Programme process guide' – www.nice.org.uk).

1 Description of technology under assessment

1.1 Give the brand name, approved name and details of any different versions of the same device.

The PleurX peritoneal catheter drainage system. A different version of the same device is the PleurX pleural catheter drainage system. However, the PleurX pleural catheter drainage system is not being considered as part of this assessment.

1.2 What is the principal mechanism of action of the technology?

The PleurX peritoneal catheter drainage system allows the repeated drainage of ascitic fluid in the community setting. It is intended for use in the palliative management of treatment-resistant, recurrent malignant ascites.

The PleurX peritoneal catheter is made of silicone and is 71cm in length and 5.12mm (15.5 Fr) in diameter. The distal end of the catheter has several side-holes and is placed within the peritoneal cavity. There is a polyester cuff midway along the catheter which is sited 1-2cm within the subcutaneous tunnel and helps to secure the catheter in place by encouraging tissue ingrowth. The initial subcutaneous course of the catheter reduces the risk of subsequent infection and the leakage of peritoneal fluid.

The proximal end of the PleurX catheter has a safety valve that prevents air entering or fluid leaking out of the catheter. A cap protects the valve and prevents debris from accumulating. The drainage system comprises a one litre vacuum bottle with a drainage line that connects to the PleurX catheter for fluid removal. It also includes a procedure pack that contains the supplies needed to perform the drainage procedure, including replacement valve cap and dressing needed to place over the catheter after drainage.

The initial catheter placement procedure can be performed under local anaesthesia in an outpatient setting using ultrasound guidance and follows the same principles as placing a catheter for abdominal paracentesis.
The PleurX peritoneal catheter can remain in place indefinitely and patients and carers are trained to perform fluid drainage themselves as and when

required. When drainage is undertaken, the vacuum bottle is attached to the catheter and a fresh valve cap and dressing are re-applied once the fluid drainage is completed. For the majority of the time, the catheter is coiled up and covered with a gauze pad and waterproof dressing.

1.3 Does the technology have CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes. CE certification for Pleurx (directive 93/42/EEC on medical devices) for the indications detailed in the submission was obtained in July 2010.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the (draft) assessment report (for example, CE marking)). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

N/A

1.5 What is the (anticipated) CE marking, including the indication for use.

EC certificate, Full Quality Assurance System (Annex II, section 3 of the directive 93/42/EEC on Medical Devices.

The PleurX Peritoneal Catheter Mini Kit and PleurX Drainage Kits are indicated for: Intermittent drainage of symptomatic, recurrent, malignant ascites that does not respond to medical management of the underlying disease and palliation of symptoms related to recurrent malignant ascites.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

It is hopeful that the poster presentation highlighted in this submission document (Day 2011) will be published as a complete article in the next 12 months.

A four case study report 'Fibrinolysis in the management of malignant ascites and non-functioning intra-peritoneal tunnelled catheters' has been submitted to CVIR for publication (Dr Damian Mullan, Christie Hospital, UK).

A 50 patient study "Long term follow-up of tunnelled intra-peritoneal catheters in the management of malignant ascites – Complications and cost implications" has been submitted to CVIR for publication. These patients were followed until death (Dr Damian Mullan, Christie Hospital, UK).

Searches were also undertaken in three clinical trials registers (search strategies are presented in the appendices):

- ClinicalTrials.gov (http://clinicaltrials.gov/ct2/results?term=ascites+AND+catheter&show_down=Y#down) on the 29/6/11
- WHO International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) 30/6/11
- European Trials Register https://www.clinicaltrialsregister.eu/ 30/6/11

Nine trials were identified in Clinicaltrials.gov (NCT01077063, NCT01188746, NCT00603200, NCT01030185, NCT00907673, NCT01065246, NCT00822809, NCT00326885, NCT01224327). Of these trials, two are potentially relevant: NCT01077063 and NCT01188746. Both were currently recruiting participants as of 1 July 2011 and both have a completion date in 2012. NCT01077063 is a controlled prospective US trial of the safety and efficacy study of ascites management: standard paracentesis or early intervention with pleurx catheters in patients with malignant ascites. The trial aims to recruit 15 patients in each arm. The second trial, NCT01188746, is exploring the impact of palliative catheter placement on the quality of life of patients with refractory ascites. Quality of life will be measured by the McGill Quality of Life Questionnaire and the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire. The study objective is to assess 50 patients.

The search of the WHO International Clinical Trials Registry Platform (ICTRP) identified three records. One trial had already been retrieved from Clinicaltrials.gov and the other two records were not relevant (ISRCTN58150114 and ISRCTN53863270).

The search of the European Trials Register retrieved six records, but none were about PleurX (EudraCT Number:2009-014076-22, EudraCT Number:2007-003059-36, EudraCT Number:2009-014377-40, EudraCT Number:2009-014378-16, EudraCT Number:2009-017082-39, EudraCT Number:2010-019547-19).

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

N/A. PleurX peritoneal catheter drainage system has already been launched in the UK.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

The PleurX peritoneal catheter drainage system was approved by the Food and Drug Administration (FDA), USA (510k, number K051711) in November 2005 for the intermittent drainage of symptomatic, recurrent, malignant ascites that does not respond to medical management of the underlying disease in order to provide palliation of symptoms related to recurrent malignant ascites.

The PleurX peritoneal catheter drainage system is also approved for use and actively promoted in several other countries including US, Canada, Australia, Germany, France, Spain, Saudi Arabia, Finland and Israel.

1.9 Please complete the table below. If the list price of the technology(s) is not yet known, provide details of the anticipated list price, including the range of possible list prices.

Average cost of treatment related to unit cost and quantity is provided as a guide based on historical sales data from UK Medical Ltd. Some of the consumable items (PleurX Drainage Kit with 1000ml vacuum bottle) drawn from the sales data may have been used to manage patients that do not fall into the scope of the submission e.g. patients with large volume pleural effusion. This means ratio of consumables to catheter and therefore average cost per patient would be less than suggested in table 1.1. Conversely, it may be that consumables not listed in table 1.1 may have been used to manage patients which do fall into the patient population being considered in this report. For this reason please accept the figures as a guide only.

Table 1.2 Unit costs of technology being appraised

List price (excluding VAT)	• PleurX peritoneal catheter mini kit: £245.00 per unit
Average selling price (based on UK unit quantity and cash sales between July 2010 and June 2011)	• PleurX peritoneal catheter mini kit: £234.09 per unit
Range of selling prices	• PleurX peritoneal catheter mini kit: £0.00 – £245.00 per unit
Consumables (average price based on UK unit quantity and cash sales between July 2010 and June 2011)	PleurX Drainage Kit with 1000ml vacuum bottle: • List price:£63.75 per unit • Average price: £57.18 per unit • Range price: £0.00 - £63.75 per unit
Service/maintenance cost	• N/A
Anticipated life span of technology	The PleurX peritoneal catheter can remain in situ indefinitely.
Average length of use per treatment	The drainage procedure takes approximately 10-15 minutes
Average frequency of use	Approximately 3 to 4 times per week
Average cost per treatment (based on UK cash sales between July 2010 and June 2011 of PleurX peritoneal catheter mini kits and PleurX Drainage Kits with 1000ml vacuum bottle (i.e. total cash sales) divided by catheter unit sales within the same time period).	• Average cost would be approximately £2,000 – £2,500 per patient. • PleurX Drainage Kit with 1000ml vacuum bottle unit sales to PleurX peritoneal catheter mini kit unit sales was 36:1 (between July 2010 and June 2011)

1.10 Would this technology require changes to the way current services are organised or delivered?

Formal and clear funding approval in the community would enhance the service e.g. Dedicated PleurX budget for District Nurses / Community.

1.11 Would other facilities or technologies need to be acquired or used alongside the technology being considered, in order for the claimed benefits to be realised?

No

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements or a need for monitoring of patients over and above usual clinical practice for this technology?

No

1.13 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

In some centres prophylactic antibiotics may be prescribed. For example, a single dose of prophylactic intravenous cefuroxime (750mg) and metronidazole (500mg) given 30 minutes to 1 hour before the procedure (Tapping 2011).

1.14 Does the technology require additional infrastructure to be put in place?

N/A. PleurX peritoneal catheters are usually placed within an interventional radiology suite and the drainage procedures are performed at home of the patient.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being considered in the scope.

The PleurX peritoneal catheter drainage system is intended for use in patients with recurrent malignant ascites that is resistant to medical management. Recurrent malignant ascites is an excess accumulation of fluid within the peritoneal cavity. Left untreated vast amounts of fluid can build up leading to a wide range of debilitating symptoms. Examples of such symptoms include dyspnoea, abdominal pain/discomfort, early satiety, oesophageal reflux, reduced mobility and psychological distress related to body image.

In four out of five patients with malignant ascites the disease is caused by ovarian carcinoma or gastrointestinal tumours. It may also occur in patients with breast, pulmonary, uterine and cervical tumours. Patients with malignant ascites have a mean survival of 1 to 4 months, depending on the nature and extent of the underlying tumour. This may be significantly longer in patients undergoing further palliative treatment.

2.2 How many patients are assumed to be eligible for treatment in England and Wales? Present separate results for any groups and subgroups considered in the scope. How are these figures derived? Also present results for the subsequent 5 years.

There are no data available on the prevalence of treatment-resistant, recurrent malignant ascites in the UK. Hospital Episode Statistics (HES) main procedures and interventions data for 2008-9 report approximately 25,000 finished consultant episodes involving abdominal paracentesis for the drainage of ascitic fluid from the peritoneal cavity for both therapeutic and diagnostic indications. Malignant ascites (ascites due to cancer) accounts for approximately 10% of all cases. There is no reason to suspect a significant change in number of patients assumed eligible within the next five years.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

N/A. There is no existing NICE guidance or protocols for the management of treatment-resistant, recurrent malignant ascites.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The present clinical pathway of care for management of treatment resistant, recurrent malignant ascites is often repeated large volume paracentesis (LVP). This involves a patient being admitted to hospital with a possible inpatient stay of five days (Jacob 2009 (4). Patients which experience this pathway of care often loop around the pathway multiple times. In between hospital admission for LVP a patient will accumulate ascites with worsening symptoms.

Pleurx may be able to change this existing pathway by being introduced as an alternative to repeat hospital admissions for LVP. Instead, patients can have a one-off procedure at hospital to implant the PleurX catheter. Subsequent drainage procedures can then be performed intermittently, at home, using a 1 litre PleurX vacuum bottle with drainage kit as and when required.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

The conventional management of patients with treatment-resistant, recurrent malignant ascites involves multiple large volume paracentesis (LVP) procedures that are undertaken in hospital. Paracentesis (abdominal tap) refers to the insertion of a catheter into the peritoneal cavity for the drainage of ascitic fluid. LVP refers to the removal of more than 5 Litres of ascitic fluid in one go. The disadvantages and issues associated with repeated conventional LVP include:

Repeated procedural risks of intestinal injury, peritonitis, fistulae, hypoalbuminaemia, metabolic disturbance and cachexia.

The temporary nature of any palliative benefits, necessitating repeated procedures with progressive symptoms developing as ascites re-accumulates.

The need for repeated hospital visits frequently necessitating overnight stays.

A negative impact on quality of life for patients who are eager to remain in the community and avoid hospital attendance.

2.6 Please identify the main comparator(s) and justify their selection.

The main comparators are inpatient large volume paracentesis and outpatient large volume paracentesis. This is in line with the final scope issued by NICE in the statement of the decision problem.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The manufacturer does not have an approval for intervention. Complications associated with the PleurX peritoneal catheter drainage system will be managed differently depending on individual hospital protocol / discretion of the Clinician. The complications discussed are uncommon but recognised.

In clinical practice, catheter malfunction, due to occlusion through fibrin cast formation and development of loculated ascites has been successfully

managed by catheter exchange and instillation of 250.000 IU streptokinase on six consecutive days through the PleurX drain. This resulted in maintained patency without further intervention (Jacob 2009). In some cases use of fibrinolytics alone may restore catheter patency and avoid the need to replace the catheter. Similarly, in development of loculated ascites (confirmed by US examination) Alteplase was instilled through the catheter, and again at 4 days, to restore catheter function (Courtney 2008).

Peritonitis has been managed through administration of intravenous antibiotics and intraperitoneal streptokinase without the need to remove the PleurX catheter. Intraperitoneal streptokinase as an adjunct to intravenous antibiotics is a recognised therapy in the treatment of peritonitis associated with indwelling catheters for ambulatory dialysis.

Subcutaneous leakage around the exit site of the catheter can be minimized by adopting a medial and superior tunnel direction from where the PleurX catheter enters the peritoneal cavity. Placement of a PleurX catheter before excessive accumulation of fluid has occurred may also reduce the likelihood of this complication. If leakage is persistent regular vacuum drainage to keep the peritoneum relatively free of fluid during the first few days should help to keep the exit site dry.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The drainage procedure would usually be performed in the home setting and in many instances performed by the patient or trained caregiver. A District Nurse would normally attend initial drainage procedures to confirm competence. Courtney 2008 (3) reported 27% of patients elected to have home health or a hospice nurse perform the drainage procedure. In the UK, District Nurse training on how to perform the PleurX drainage procedure is provided by UK Medical Ltd at no charge to the NHS.

2.9 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

National Clinical Classifications Helpdesk have advised that if the PleurX catheter is inserted into the abdomen/peritoneum for drainage, then the most appropriate OPCS-4.6 code is T46.2 Drainage of ascites NEC.

3 Equity and equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to complying fully with legal obligations on equality and human rights.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equality and diversity in NICE guidance, or protocols for the condition for which the technology is being used.

Patients with cancer are protected under the Equality Act 2010.

3.1.2 Are there any equality and diversity issues anticipated for the assessment of this technology (consider issues relating to current legislation and any issues identified in the scope for the assessment)?

Adoption of this product is being assessed in people with treatment-resistant recurrent malignant ascites. As noted in the scope for this assessment, people with cancer are covered by the equalities legislation under the protected characteristic of disability. The PleurX peritoneal drainage system may enable patients to have independent control of their symptoms and fit treatment around their normal lives and so to promote equality and opportunity. It was also mentioned in the scope of this assessment that The Committee considered that the PleurX peritoneal catheter drainage system may have the potential to improve the quality of life for such patients and, therefore, promote equality.

3.1.3 How have the clinical and economic analyses addressed these issues?

Quality of life has been included as an outcome in the sponsor submission.

4 Statement of the decision problem

In this section the decision problem that the submission addresses is specified in the second column, Final scope issued by NICE. This is derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address. The sponsor should specify any additions and/or amendments to the decision problem and rationale in the third and fourth column..

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Patients with treatment-resistant, recurrent malignant ascites		N/A
Intervention	PleurX peritoneal catheter drainage system		N/A
Comparator(s)	Inpatient large volume paracentesis Outpatient large volume paracentesis		N/A
Outcomes	The outcome measures to consider include: • Successful device deployment • Successful drainage of the ascitic fluid • Resolution of symptoms (e.g. bloating, nausea, acid reflux, reduced appetite, perception of body image, psychological well-being and quality of life outcomes • Frequency of drainage • Resource use outcomes e.g. re-admission rates, re-interventions and duration of hospital stay (i.e. total number of hospital bed days related to paracentesis after initial drainage) • Catheter site infections • Peritonitis • Catheter occlusion • Other device related adverse events e.g. haemorrhage, bowel perforation		N/A
Cost analysis	Population: Patients with treatment-resistant, recurrent, malignant ascites Intervention: PleurX peritoneal catheter drainage system Comparator: Inpatient LVP and outpatient LVP Costs will be considered from an NHS and Personal Social Services perspective. The analysis should take into account any resource use associated with hospital and community care and management of the malignant ascites, and training required to use the device. Adverse events and complications relating to the use of the device and treatment required for these complications should also be considered (for example, the costs associated with care if the patient has a peritoneal infection). The time horizon for the economic evaluation should be based on the appropriate time period over which costs and benefits can reasonably be expected to be experienced given the chronic nature of the condition.		N/A
Subgroups to be considered			N/A
Special considerations, including issues related to equity or equality	Patients with cancer are protected under the Equality Act 2010		N/A

Section B – Clinical effectiveness and cost

5 Clinical evidence

Sponsors are requested to present clinical evidence for their technology in the following section. This section should be read in conjunction with NICE's 'Evaluation Pathway Programme methods guide'. The review of the clinical evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA Statement should be used (http://www.prisma-statement.org/statement.htm).

Sponsors are requested to submit the clinical evidence (section 5 and appendices 1-5 (sub-section 7.1-7.5)) in advance of the full submission (for details on timelines, see the NICE document 'Evaluation Pathway Programme process guide' – www.nice.org.uk).

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 7.2, appendix 2.

A range of databases indexing published research was searched for clinical and economic studies on the PleurX peritoneal catheter drainage system for vacuum-assisted drainage of treatment resistant, recurrent malignant ascites. The databases searched included those required by NICE: MEDLINE, MEDLINE In-Process, EMBASE and the Cochrane Library. In addition, searches of regulatory organisation websites, trials registries and conference proceedings were undertaken. The searches were not limited by language or date range. Animal studies were excluded. The strategy employed used the intervention name alone to find relevant studies. This single search strategy is highly sensitive and can identify studies reporting clinical effects, adverse events and economic outcomes. Full details of the search strategies and the databases and resources searched are provided in Appendix 2, Section 7.2.

5.2 Study selection

Two researchers applied the pre-defined inclusion criteria to select studies for inclusion.

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent.

Studies were selected according to the following criteria for the clinical effects and adverse events reviews.

Inclusion Criteria

- Population: Adults (aged 18 and over) with treatment-resistant, recurrent malignant ascites;
- Intervention: PleurX peritoneal catheter drainage system;
- Comparator: inpatient or outpatient large volume paracentesis (abdominal taps);
- Outcomes: successful device deployment; successful drainage of the ascitic fluid; resolution of symptom; frequency of drainage; resource use outcomes; catheter site infections; peritonitis; catheter occlusion; other device-related adverse events;
- Study design: comparative and single-arm studies of any duration and with any number of patients were eligible; technology assessments, including those produced for regulatory agencies were also eligible for inclusion. The inclusion criteria were extended to include case reports following discussion with NICE;
- Language: English language studies were eligible for inclusion;
- Publication status: published, unpublished and grey literature (e.g. conference abstracts) were eligible for inclusion.

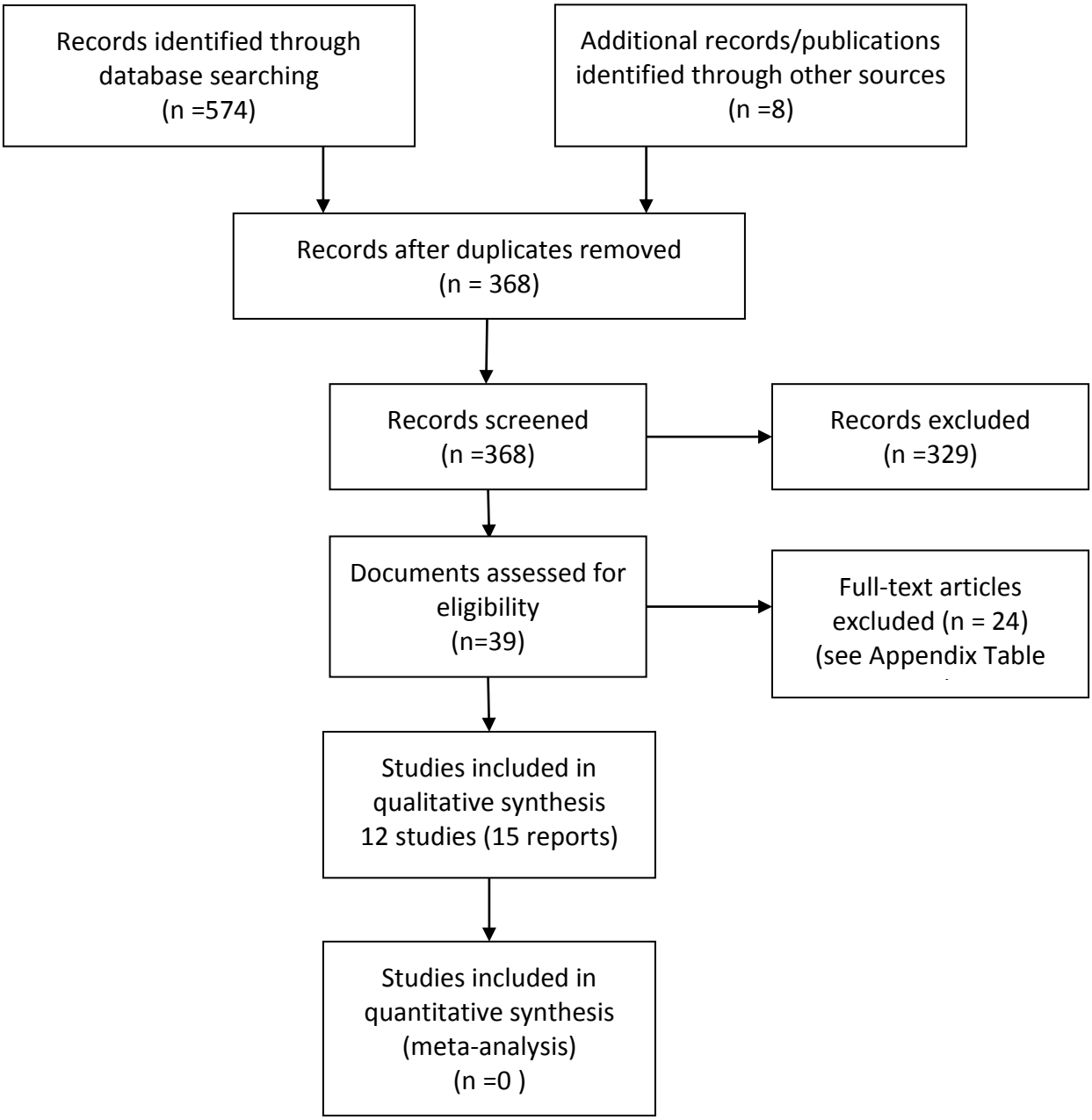
Exclusion Criteria

- Study design: animal studies were not eligible inclusion.

5.2.2 The numbers of studies included and excluded at each stage should be reported

Figure 5.1 presents the number of studies retrieved by the searches and the records selected and rejected following the searches.

Figure 5.1: Study selection diagram showing the selection process for PleurX studies



Complete list of relevant studies (RCTs and non-RCTs)

5.2.3 Provide details of **all** studies that compare the intervention with other therapies in the relevant patient group. Highlight which of these studies compare the intervention directly with the appropriate comparator(s) referred to in the decision problem. If there are none, please state this. The list must be complete and will be validated by independent searches conducted by the External Assessment Group. This should be presented in tabular form. A suggested format is presented below.

No randomised controlled trials studying the PleurX peritoneal catheter drainage system in patients with recurrent malignant ascites were identified. Seven studies (10 reports) of varying design met the criteria for inclusion in the reviews of clinical effects and adverse events. These comprised:

- One retrospective comparative study of large-volume paracentesis versus the PleurX catheter (Rosenberg 2004) (1);
- One qualitative study using semi-structured interviews to elicit patients' views following either paracentesis or PleurX catheter insertion, which was reported both as a prepublication manuscript [redacted]) and as a conference abstract [redacted]
- Four observational/case series studies of PleurX catheters alone (Courtney 2008, Jacob 2009, Richard 2001, Saiz-Mendiguren 2011) (4-7), one of which has since been updated and reported in a prepublication manuscript (Mullan 2011a) (8);
- One retrospective review of patients who had received a PleurX catheter, which was reported both as a journal article (Tapping 2011) (9) and as a conference abstract (Tapping 2011a) (10).

The five case report studies (included following the protocol change) comprised:

- One report of off-label semi-permanent catheter placement in a single case (Brooks 2006) (11);
- One report describing the use of the PleurX catheter in three individual cases (Iyengar 2002) (12);
- One unpublished report on the use of intra-peritoneal fibrinolytics to treat four individual cases of non-functioning catheters (Mullan 2011b) (13). This report contains three patients who also feature in the Mullan case series reported in Mullan 2011a (8).

- Two adverse event reports to the US Department of Health and Human Services, MAUDE database (Denver BioMedical Inc. 2007, Cardinal Health 2008) (14)(15). One of these presented no substantiated information and is recorded here for completeness (Cardinal Health 2008) (15).

The included studies are listed in Table 5.1 and the case reports are listed in Table 5.2. Candidate records, rejected following detailed assessment against the inclusion/exclusion criteria, are listed in the Appendices (7.2.8).

Table 5.1: Details of studies of PleurX catheters

Study ID	Intervention	Comparator	Population	Primary study reference
Rosenberg 2004 (1)	PleurX catheter	Repeated large volume paracentesis	Patients with recurrent malignant ascites.	Rosenberg S, Courtney A, Nemcek AA Jr., Omary RA. Comparison of percutaneous management techniques for recurrent malignant ascites. Journal of Vascular & Interventional Radiology 2004;15(10):1129-1131.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Courtney 2008 (4)	Modified PleurX tunnelled peritoneal catheter	This was not a comparative study	Patients with recurrent ascites associated with advanced abdominal malignancy.	Courtney A, Nemcek AA, Rosenberg S, Darcy M, Gordon G. Prospective evaluation of the PleurX catheter when used to treat recurrent ascites associated with malignancy. Journal of Vascular & Interventional Radiology 2008;19(12):1723-1731
Mullan 2011a (5, 8)	PleurX tunnelled peritoneal catheter	This was not a comparative study. Costs of PleurX were compared with conventional large-volume paracentesis.	Patients with recurrent ascites and advanced abdominal malignancy.	Mullan D, Laasch HU, Jacob A, Hassan H. Tunnelled intra-peritoneal catheters in the management of malignant ascites: complications and cost implications. [prepublication manuscript] 2011. Academic in confidence.
Richard 2001 (6)	PleurX tunnelled catheter	This was not a comparative study.	Patients with intractable ascites and abdominal carcinomatosis.	Richard HM, Coldwell DM, Boyd-Kranis RL, Murthy R, van Echo DA. PleurX tunneled catheter in the management of malignant ascites. Journal of Vascular & Interventional Radiology 2001;12(3):373-375.
Tapping 2011 (9)(10)	PleurX tunnelled abdominal drain	This was not a comparative study	Patients with refractory malignant ascites.	Tapping CR, Ling L, Razack A. PleurX drain use in the management of malignant ascites: safety, complications, long term patency and factors predictive of success. British Journal of Radiology. Published online before print March 22, 2011. doi: 10.1259/bjr/24538524

Saiz-Mendiguren 2010 (7)	PleurX tunnelled catheter	This was not a comparative study	Patients with peritoneal metastatic disease and recurrent ascites.	Saiz-Mendigurena R, Gómez-Ayechub M, Nogueraa JJ, García-Lallana A,Marginet C, Canoa D, Benito A. Permanent tunneled drainage for malignant ascites: initial experience with the PleurX catheter. Radiologia 2010;52(6):541-545.

Table 5.2: Details of PleurX case reports

Study ID	Intervention	Population	Primary study reference
Brooks 2006 (11)	PleurX intraperitoneal catheter	One patient with rapidly accumulating malignant ascites, in the intensive care unit, requiring twice weekly paracentesis.	Brooks RA, Herzog TJ. Long-term semi-permanent catheter use for the palliation of malignant ascites. Gynecologic Oncology 2006;101(2):360-362.
Iyengar 2002 (12)	PleurX intraperitoneal catheter	Three patients with intractable abdominal ascites and recurrent ovarian cancer.	Iyengar TD, Herzog TJ. Management of symptomatic ascites in recurrent ovarian cancer patients using an intra-abdominal semi-permanent catheter. American Journal of Hospice & Palliative Medicine 2002;19(1): 35-38.
Mullan 2011b (13)	Streptokinase (250 000 IU, once daily for 5 days) administered via the PleurX tunnelled intraperitoneal catheter.	Four patients with a non-functioning, tunnelled intra-peritoneal catheter that had been implanted for the treatment of malignant ascites. Three of the four patients also feature in the Mullan case series (8).	Mullan D, Laasch HU, Jacob A, Hassan H. Fibrinolysis in the management of malignant ascites and non-functioning intra-peritoneal tunnelled catheters [unpublished manuscript] 2011. Academic in confidence.
Denver BioMedical Inc. 2007 (14)	PleurX catheter	One patient with tunneled peritoneal drain placed for malignant ascites.	US Food and Drug Administration. Maude adverse event report: Denver Biomedical Inc, PleurX peritoneal catheter [report number 905214]. Washington, DC, US Food and Drug Administration; 2007.
Cardinal Health 2008 (15)	PleurX catheter	Single case; no details reported.	US Food and Drug Administration. Maude adverse event report: Cardinal Health PleurX peritoneal catheter [report number 1423507-2008-00042]. Washington, DC, US Food and Drug Administration; 2008.

5.2.4 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of study data required, this should be indicated.

With the exception of one case report, no studies initially identified as relevant have been excluded from further discussion in the report. A MAUDE adverse event report presented no substantiated information and has not been considered further in this review (Cardinal Health 2008) (15).

5.3 Summary of methodology of relevant studies

5.3.1 As a minimum, the summary should include information on the study(s) under the subheadings listed in this section. It is expected that all key aspects of methodology will be in the public domain; if a sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE.

Data on study methodology were extracted by one reviewer and checked independently by a second reviewer.

This section provides a summary of the included studies in terms of their methods, participants and outcomes. In the absence of randomized controlled trials comparing the PleurX catheter drainage system versus conventional management by large volume paracentesis, or other fluid drainage systems, evidence from a diverse range of prospective and retrospective study designs was considered. There was wide variation and inconsistencies in the reporting of the included studies, and details were often sparse. Five studies were published as journal articles: Rosenberg 2004 (1), Courtney 2008 (4), Richard 2001 (6), Tapping 2011 (9) and Saiz-Mendiguren 2010 (7). The remaining two studies, [redacted] and Mullan 2011a (8) were unpublished manuscripts. Summaries of study methodology, participant characteristics and outcomes are presented in Tables 5.3-5.8. A critical appraisal of the selected studies is presented in Section 5.4 summary) and Appendix 7.3 (full quality assessment).

Two case report studies were published as journal articles (Brooks 2006, Iyengar 2002) (11) (12), one was an unpublished report (Mullan 2011b) (13) and one was a notification to the US Department of Health and Human Services, MAUDE database, of an adverse event (Denver BioMedical Inc. 2007) (14).

Methods

5.3.2 Describe the study(s) design and interventions. Include details of length of follow-up and timing of assessments.

Table 5.3 summarizes the methodology of the included studies. In brief, the included studies comprised one retrospective comparative study, one qualitative study, four observational (case series) studies and one retrospective review. The studies were small in size, ranging from 10 to 107 patients, with typically fewer than 40 participants and were conducted in Spain, the UK or USA. Only four studies described study duration or the period of follow-up (Rosenberg 2004 (1), Courtney 2008 (4), Tapping 2011 (9), [redacted]. Table 5.4 summarizes the methods of the four case reports describing nine individual cases.

Table 5.3: Comparative summary of methodology of the studies

Study ID	Rosenberg 2004 (1)	[redacted]	Courtney 2008 (4)	Mullan 2011a (8)	Richard 2001 (6)	Tapping 2011 (9)	Saiz-Mendiguren 2010 (7)
Location	Single centre, USA (tertiary care metropolitan medical centre)	[redacted]	Multicentre, USA (four institutions: hospitals, medical college, university school of medicine)	Single centre, UK (hospital radiology department)	Single centre, USA (university medical system)	Single centre, UK (hospital)	Single centre, Spain (university radiology department)
Design	Retrospective comparative study (patients were selected from an interventional radiology database of patients with recurrent malignant ascites).	[redacted]	Prospective, observational (case series) study.	Observational (case series) study. A cost analysis was also described.	Observational (case series) study.	Retrospective review of patient records,	Observational (case series) study
Duration of study or follow-up	41 months.	[redacted]	12 weeks (or until death or catheter removal for safety monitoring beyond 12 weeks).	Patients were followed-up until death.	Not reported.	The records of patient treated within a four year period were reviewed from initial procedure until death. The average length of treatment was	Not reported.

Study ID	Rosenberg 2004 (1)	[redacted]	Courtney 2008 (4)	Mullan 2011a (8)	Richard 2001 (6)	Tapping 2011 (9)	Saiz-Mendiguren 2010 (7)
						not reported.	
Randomisation	Not applicable	[redacted]	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Blinding	Not applicable		Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Intervention	PleurX catheter (n=40). Catheter was placed under ultrasound and fluoroscopic guidance.	[redacted]	Modified PleurX tunnelled peritoneal catheter (n=34). Catheter was placed using combined ultrasonographic (US) and fluoroscopic guidance (n=31), US alone (n=2) or US and computed tomography (n=1). The modified catheter had a longer non-fenestrated portion for placement in the subcutaneous tunnel to prevent ascites leakage into	PleurX tunnelled peritoneal catheter (n=50 patients, 52 catheters). A pre-procedure ultrasound was performed to identify an area suitable for drain insertion. All drains were inserted under local anaesthesia with ultrasound assistance. Accurate home drainage volumes were not available.	PleurX tunnelled catheter (n=10). Catheter was placed using combined ultrasonographic (US) and fluoroscopic guidance (n=8) or US guidance alone (n=2). 1500-3000 mL of ascitic fluid were removed after device insertion. Frequency of fluid drainage ranged from every other day to once per week. Volume of fluid drained was unclear:	PleurX tunnelled abdominal drain (n=28 patients, 32 drains). Catheters were inserted using a combination of fluoroscopy and ultrasound (US) guidance (n=4) or under US guidance alone (n=28). Three patients had their drain inserted under conscious sedation. Hospital inpatient stay was <1 day. Average 5000 mL ascitic fluid per patient (range: 3500-7000) was removed	PleurX tunnelled catheter (n=10). Catheter was placed with ultrasound guidance and local anaesthesia. A mean of 1 litre fluid was drained every 2-10 days.

Study ID	Rosenberg 2004 (1)	[redacted]	Courtney 2008 (4)	Mullan 2011a (8)	Richard 2001 (6)	Tapping 2011 (9)	Saiz-Mendiguren 2010 (7)
			subcutaneous tissue. Mean 3240 mL ascitic fluid per patient (range: 800-7000) was removed following device insertion. 440 drainage sessions were subsequently carried out, mostly every other day. Typical drainage volume ranged from 1200-2000 mL/day.		"Patients initially drained between 0.5 and 1 litre of fluid per day for the first week and the amount of the fluid removed varied according to the management of the patient's oncologist, ranging from 0.5-3 litres per day."	following device insertion. Subsequent drainage sessions removed <=500 mL fluid every 12 hours.	
Comparator	Repeated large-volume paracentesis (n=67). Paracentesis was performed under direct ultrasound	[redacted]	Not applicable	Costs were evaluated in comparison to conventional paracentesis	Not applicable	Not applicable	Not applicable

Study ID	Rosenberg 2004 (1)	[redacted]	Courtney 2008 (4)	Mullan 2011a (8)	Richard 2001 (6)	Tapping 2011 (9)	Saiz-Mendiguren 2010 (7)
	guidance with a 5-F Yueh needle. 392 procedures.						
Apparent primary outcomesa	Specified primary outcomes: Complication rate, defined similarly to Richard 2001, including infection and catheter failure. Infection was defined as subcutaneous infection, bacterial peritonitis or positive blood cultures. Catheter failure was defined as poor patency causing malfunction or inability to provide symptomatic relief.	[redacted]	Safety: Adverse events. Patients were followed up weekly until death, catheter removal, or 12 weeks of catheter use, and every 2 weeks thereafter.	Safety and efficacy: technical success, procedural complications, catheter failure/removal, catheter patency.	Procedural complications (specifically hematoma, bowel damage, and haemorrhage at the catheter insertion site), serum albumin levels, infection, catheter efficacy, and duration of catheter patency. Patients' charts were reviewed for procedural complications. Serum albumin was measured at 0, 3 and 6 weeks. Patients' clinical courses were reviewed for	Success, long-term patency and complications. Patient history, biochemical profiles, pathological and procedural records and clinical follow-up until death were reviewed. Technical success was defined as successful placement of the drain and drainage of ascites at insertion. Complications were classified into three groups:	Safety and efficacy: complications, discomfort, catheter failure/removal, catheter patency.

Study ID	Rosenberg 2004 (1)	[redacted]	Courtney 2008 (4)	Mullan 2011a (8)	Richard 2001 (6)	Tapping 2011 (9)	Saiz-Mendiguren 2010 (7)
	Patients were given standard instructions for follow up and infection/complication surveillance, and were asked to report back with any signs of infection, difficulty draining the catheter, or other problems.				catheter-related infections, catheter efficacy and duration of catheter patency. Catheter patency was calculated from the number of days that patients had functioning catheters free from infection or malfunction.	immediate, <24 hours from the procedure; early, 24 hours to 30 days after the procedure; and late, >30 days after the procedure.	
Secondary outcomes	Other adverse events.	[redacted]	System effectiveness: technical success, catheter failure, functioning, removal, survival. Technical success was defined by intraperitoneal positioning of the device and the ability to	Costs in comparison with conventional paracentesis.		Overall and 30-day mortality. Procedural mortality defined as death attributed directly to the procedure.	

Study ID	Rosenberg 2004 (1)	[redacted]	Courtney 2008 (4)	Mullan 2011a (8)	Richard 2001 (6)	Tapping 2011 (9)	Saiz-Mendiguren 2010 (7)
			withdraw ascitic fluid from the device at completion of the procedure. Patients were followed-up weekly. Quality of life: patients completed the Subjective Significance Questionnaire (SSQ) at 1, 2, 8 and 12 weeks. Symptoms: patient self-assessment using a modified version of the Memorial Symptom Assessment Survey (MSAS) at 0, 2, 8 and 12 weeks. Biochemical				

Study ID	Rosenberg 2004 (1)	[redacted]	Courtney 2008 (4)	Mullan 2011a (8)	Richard 2001 (6)	Tapping 2011 (9)	Saiz-Mendiguren 2010 (7)
			parameters: blood chemistry measurements taken at each routine follow-up visit. Mean survival.				

Table 5.4: Comparative summary of the methodology of the PleurX case report studies

Study ID	Brooks 2006 (11)	Iyengar 2002 (12)	Mullan 2011b (13)	Denver BioMedical Inc. 2007 (14)
Location	Single centre, USA (obstetrics and gynaecology department).	Single centre, USA (obstetrics and gynaecology department).	Single centre, UK (hospital radiology department).	Single centre, USA (hospital).
Design	Case report (1 case)	Case report (3 cases)	Case report (4 cases: three of the four patients also feature in the Mullan case series (8).)	MAUDE adverse event report (1 case)
Duration of study or follow-up	Not specifically reported, but appears to be until patient death.	Not reported; patients were followed-up on a monthly basis.	Not specifically reported; 3 patients were followed until death and one was still alive.	Not applicable.
Intervention	PleurX intraperitoneal catheter, placed under general anaesthesia since the patient was already intubated in the intensive care unit. 7 litres of ascitic fluid were	PleurX intraperitoneal catheter, placed under general anaesthesia with ultrasound guidance. The volume of ascitic fluid removed after device insertion	Streptokinase (250 000 IU, once daily for 5 days) administered via the PleurX tunnelled intraperitoneal catheter.	PleurX peritoneal catheter.

Study ID	Brooks 2006 (11)	Iyengar 2002 (12)	Mullan 2011b (13)	Denver BioMedical Inc. 2007 (14)
	removed after device insertion.	was 2.5 litres for one patient, 5 litres for another patient, and was not reported for the third patient.		
Outcomes reported	Safety and efficacy: procedural complications, catheter functioning, adverse events.	Safety and efficacy: catheter indwelling time, procedural complications, catheter functioning, catheter failure/removal, paracentesis requirements, hospital stay, adverse events.	Safety and efficacy: catheter indwelling time, restoration of catheter function, catheter effectiveness, adverse events.	Device age, adverse events.

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the study. The following table provides a suggested format for the eligibility criteria for when there is more than one study. Highlight any differences between the studies.

The inclusion and exclusion criteria employed by each of the included studies, where reported, are summarised in Table 5.5. The criteria were variably reported within the studies. Only Rosenberg 2004 (1) specifically restricted the study to adult participants.

Table 5.5: Eligibility criteria in the studies

Study ID	Inclusion criteria	Exclusion criteria
Rosenberg 2004 (1)	Adult patients (aged 18 years or older) who had undergone at least two previous paracenteses and presented with either cytologically proven malignant ascites or clinically suspected malignant ascites caused by reaccumulation of fluid and diagnosis of cancer.	Not reported.
[redacted]	[redacted]	[redacted]
Courtney 2008 (4)	Symptomatic ascites associated with malignancy, as defined by proven abdominal malignancy with concurrent ascites; ascites requiring >= 2 therapeutic paracentesis procedures in previous 30 days and reported relief of symptoms after paracentesis.	History of cirrhotic liver disease, end-stage renal disease requiring dialysis, ascites likely to respond to additional treatment of primary disease, known infection of the abdominal cavity, multiloculated ascites, functional limitations too severe to allow successful participation, severe coagulopathy, thrombocytopenia as defined by an International Normalized Ratio >1.5 or platelet count 50,000 microlitres, or current intraperitoneal chemotherapy or immunotherapy.
Mullan 2011a (8)	Not specifically reported: all patients selected for drain placement had documented intra-abdominal tumour spread and radiologically proven symptomatic ascites, and had undergone at least one conventional ascitic drainage in	Not specifically reported. Contraindications to device insertion were multi-loculated ascites not responsive to intra-peritoneal fibrinolysis, current intra-peritoneal infection, or severe coagulopathy not

Study ID	Inclusion criteria	Exclusion criteria
	the preceding 2 weeks, requiring radiological marking, inpatient admission and resulting in symptom relief. All patients were referred by a Consultant Clinical or Medical Oncologist with an expectation of requiring repeated paracentesis.	responsive to reversal.
Richard 2001 (6)	Not specifically reported: patients managed with optimum medical care and repeated large volume paracentesis for malignancy-related ascites were referred for placement of a tunnelled PleurX catheter.	Not reported.
Tapping 2011 (9)	Consecutive patients with malignant refractory ascites who had undergone tunnelled long-term drain (PleurX) insertion. Patients who had >=3 recent standard ascitic drainages with the two most recent drainages <6 weeks apart (i.e. Requiring frequent drainages) were considered suitable for this procedure. All of these patients were receiving palliative/end of life care. Patients receiving chemotherapy for whom ascites was a main problem and for whom a multidisciplinary team review felt the procedure would be of benefit were also eligible.	Multiloculated ascites, noncorrectable coagulopathy or infected peritoneal cavity.
Saiz-Mendiguren 2010 (7)	Not reported	Not reported

The five case report studies described positive and negative experiences observed with the use of the PleurX catheter in individual patients. One study reported specifically on attempts to restore catheter functioning in catheters that had ceased to function (Mullan 2011b) (13).

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups.

Table 5.6 summarises the baseline characteristics of the participants in the included studies, which were reported variably across the included studies. There were similarities in patient populations across the studies in terms of the extent of disease and prior conventional treatment, in addition to demographics. Where reported, the participants were adults aged 21-91 years, typically in the 40-80 age range, and gender composition ranged from 25%-83% male. None of the studies reported ethnicity. Rosenberg 2004 (1) reported that there were no significant differences (p-value not stated) in proportions when comparing the general characteristics of the intervention and control groups in their retrospective comparative study.

Table 5.7 summarises the baseline characteristics of the patients in the case report studies. Details reported were sparse.

Table 5.6: Participant baseline characteristics in the PleurX studies

Study ID	Number of patients (I= PleurX, C=comparator)	Mean age in years (range)	Ethnicity	Gender composition male/female (%)	Extent of ascites	Primary malignancy and comorbidities	Ascitic fluid drainage prior to PleurX insertion
Rosenberg 2004 (1)	N=107 I: 40 C: 67	Mean not reported (21-85) I: (21-81) C: (31-85)	Not reported	40/67 (37.4%/62.6%) I: 17/23 (42.5%/57.5%) C: 23/44 (34.3%/65.7%)	Recurrent malignant	I: Ovarian (8), Breast (7), Colorectal (7), Other (18). C: Ovarian (12), Breast (7), Colorectal (12), Other (36).	Inclusion criteria specified at least 2 prior paracenteses. One patient in the PleurX group also had concomitant percutaneous gastrostomy and nephrostomy drains.
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Courtney 2008 (4)	N=34[a]	64.3 (40-81)	Not reported	13/21 (38%/62%)	Recurrent, nonhepatic, symptomatic abdominal ascites associated with malignancy.	Pancreatic (7), Breast (6), Colon (5), Neuroendocrine (3), Ovary (3), Liver (2), Gastrointestinal stromal tumour (1), Mesothelioma (1), Other site	Enrolled patients had undergone 1-8 paracenteses (mean 2.8) in the 30 days before catheter insertion. Average 3744 mL ascites removed (range

Study ID	Number of patients (I= PleurX, C=comparator)	Mean age in years (range)	Ethnicity	Gender composition male/female (%)	Extent of ascites	Primary malignancy and comorbidities	Ascitic fluid drainage prior to PleurX insertion
						(6). 11 (55%) of 20 patients examined had positive cytologic findings of ascitic fluid prior to catheter placement. 21 patients (62%) were receiving chemotherapy at time of enrolment. 10 patients (30%) were receiving diuretic therapy	70-7500).
Mullan 2011a (8)	N=50	66 (33-82)	Not reported	15/35 (30%/70%)	Recurrent malignant	Ovarian 8; Uterine 3; Breast 9; Colon 1; Pancreatic 13; Cholangiocarcinoma 3; Prostate 1; Primary	Conventional inpatient paracentesis. 225 episodes (mean 4.5 drainage episodes per patient).

Study ID	Number of patients (I= PleurX, C=comparator)	Mean age in years (range)	Ethnicity	Gender composition male/female (%)	Extent of ascites	Primary malignancy and comorbidities	Ascitic fluid drainage prior to PleurX insertion
						Peritoneal 2; Gastric/Oesophagus 2; Sarcoma 1; Melanoma 1; Unknown Primary 1; Renal 1; Neuroendocrine 3; Hepatocellular carcinoma 1.	For patients admitted solely for inpatient paracentesis and with accurately documented drainage details (n=23), average of 5.3 drainage procedures per person (range: 1-30). Average of 9.2 litres of fluid removed (range: 4-17 litres). Average hospital stay 2.8 days (range: 1-6)
Richard 2001 (6)	N=10	61 (43-78)	Not reported	7/3 (70%/30%)	Intractable ascites	Gastrointestinal (7), Breast (1), Lymphoma (1), Mesothelioma (1)	Repeated large-volume paracentesis.
Tapping 2011 (9)	N=28	61 (43-91)	Not reported	7/21 (25%/75%)	Refractory malignant	Gastrointestinal, (7), lung (3), gynaecological (10), pancreatic (5), breast (3).	Inclusion criteria specified patients who had >=3 recent standard ascitic drainages with the two most recent drainages

Study ID	Number of patients (I= PleurX, C=comparator)	Mean age in years (range)	Ethnicity	Gender composition male/female (%)	Extent of ascites	Primary malignancy and comorbidities	Ascitic fluid drainage prior to PleurX insertion
						Co-morbid diagnosis was significant renal disease (GFR <60 mL min 1.73 m-2) (4 patients), hypertension (medically managed currently normotensive) in 7 patients, ischaemic heart disease in 7 patients (three with history of myocardial infarction and four with medically managed angina), Type 2 diabetes medically managed in 7 patients.	<6 weeks apart.
Saiz-Mendiguren 2010 (7)	N=10	58 (40-71)	Not reported	3/7 (30%/70%)	Recurrent malignant	Breast 2; Gastric 2; Pancreatic 2;	Not reported

Study ID	Number of patients (I= PleurX, C=comparator)	Mean age in years (range)	Ethnicity	Gender composition male/female (%)	Extent of ascites	Primary malignancy and comorbidities	Ascitic fluid drainage prior to PleurX insertion
						Cholangiocarcinoma 2; Colon 1; Lung 1.	

[a] In retrospect, the authors considered 5 patients enrolled in the study to be protocol deviations (four had only one paracentesis in the previous 30 days, and one had multiple loculations and poor performance status); all 5 were included in the analysis.

Table 5.7: PleurX case report studies: participant baseline characteristics

Study ID	Number of individual cases	Age (years)	Ethnicity	Gender	Extent of ascites	Primary malignancy	Ascitic fluid drainage prior to PleurX insertion
Brooks 2006 (11)	1	58	Not reported.	Female	Rapidly reaccumulating malignant ascites.	Recurrent progressive stage IV papillary serous adenocarcinoma of the ovary.	Paracentesis twice weekly with each procedure yielding more than 3 litres.
Iyengar 2002 (12)	3	50 76 83	Not reported.	All female	Intractable abdominal ascites.	Recurrent ovarian cancer: stage IIIC, mixed mullerian mesodermal tumour (1); papillary serous adenocarcinoma, originally stage IIC (1); grade 2 papillary serous carcinoma (1).	Repeated paracentesis, ranging from 2-3 litres removed every 1-3 weeks to weekly sessions for 12 weeks.
Mullan 2011b (13)	4 (Three of the four patients also feature in the Mullan case series (8)).	34 55 59 68	Not reported.	2 male/2 female	Recurrent malignant ascites.	Stage IV gastric adenocarcinoma (1), stage IV renal cell carcinoma (1), or stage IV neuroendocrine carcinoma (1); all with peritoneal metastases. Stage IV breast carcinoma with visceral abdominal metastases (1).	Not reported. One patient required “repeated inpatient admission”.
Denver BioMedical Inc. 2007 (14)	1	Not reported.	Not reported.	Not reported.	Malignant ascites.	Not reported.	Not reported.

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the study protocol as primary or secondary, and whether they are relevant with reference to the decision problem. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one study.

Table 5.8 summarises details of the predefined outcomes that were investigated in the included studies and the measures employed to assess them. The methods reported in the papers typically did not differentiate between primary and secondary outcomes; only one paper, Rosenberg 2004 (1) specified a primary outcome. Given the variable and inconsistent reporting of the included studies, only those outcomes specified within the Methods section of the paper will be described. Only two of the case report studies had predefined outcomes: Mullan 2011b (13) studied the use of streptokinase to restore catheter function and the MAUDE adverse event notification recorded an adverse event (Denver BioMedical Inc. 2007) (14).

Table 5.8: Primary and secondary outcomes of the studies

Study ID	Outcome	Measure	Reliability/validity /current use in clinical practice
Rosenberg 2004 (1)	Specified primary: Complication rate, including infection and catheter failure.	Complication rate, defined similarly to Richard 2001 (hematoma, bowel damage, and haemorrhage at the catheter insertion site). Infection defined as subcutaneous infection, bacterial peritonitis, or positive blood cultures. Catheter failure defined as poor patency causing malfunction or inability to provide symptomatic relief. Patients were given standard instructions for follow up and infection/complication surveillance, and asked to report back with any signs of infection, difficulty draining the catheter,	These outcomes and catheter-related issues are commonly raised in clinical practice.

Study ID	Outcome	Measure	Reliability/validity /current use in clinical practice
		or other problems.	
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Courtney 2008 (4)	Catheter survival.	Defined as the period of initial function between catheter insertion and loss of catheter function. For patients who did not experience loss of catheter function, survival (time of ascites control) was measured from the date of catheter placement until the earliest of the following: ascites resolution; last known date of contact before death if the catheter was known to be functioning properly at that time and subject withdrew from study at that time; or death.	This outcome is of interest in clinical practice.
	Technical success	Defined by intraperitoneal positioning of the device and the ability to withdraw ascitic fluid from the device at completion of the procedure. Patients were assessed weekly.	This outcome is of interest in clinical practice.
	Quality of life	Patients completed the Subjective Significance Questionnaire (SSQ) at 1, 2, 8 and 12 weeks.	The authors stated that the SSQ is a validated instrument for assessing QoL in cancer patients.
	Symptom relief	Patient self-assessment using a modified version of the Memorial Symptom Assessment Survey (MSAS) at 0, 2, 8 and 12 weeks.	MSAS is stated to be a validated instrument for assessing symptoms in patients with cancer.
	Biochemical parameters	Blood chemistry measurements taken at each routine follow-up visit if patients met any of the designated criteria.	These outcomes are of interest in terms of monitoring protein loss.
	Procedural complications and ease of device use in home care setting.	Not reported.	These outcomes and catheter-related issues are commonly raised in clinical practice.
Mullan	Complications	Patient and procedural data were	These outcomes

Study ID	Outcome	Measure	Reliability/validity /current use in clinical practice
2011a (8)		obtained from the hospital electronic patient data system, the radiology information system, clinical notes, and a prospective database of interventional radiology cases in the department. Patients were instructed to seek the advice of the Radiologist or Oncologist at the institution if any problems were encountered. Complications were defined as: procedural (occurring during or immediately after the placement and attributable directly to drain placement); Delayed (occurring 1-30 days from drain placement); and late (occurring 30 days following drain placement)	and catheter-related issues are commonly raised in clinical practice.
	Technical success	Technical success with respect to tunnelled drain placement was defined as a complication free intra-peritoneal placement, with free drainage of ascites on completion of the procedure.	This outcome is of interest in clinical practice.
	Catheter survival	Survival times were calculated from the date of tunnelled catheter placement.	This outcome is of interest in clinical practice.
Richard 2001 (6)	Complication rate	Specifically hematoma, bowel damage, and haemorrhage at the catheter insertion site. Assessed from review of patients' charts.	These issues are important to clinical practice.
	Serum albumin level	Measured at 0. 3 and 6 weeks.	These outcomes are of interest in terms of monitoring protein loss.
	Catheter-related infections	Specifically tunnel site, catheter tip or positive blood culture. Assessed from review of patients' "clinical courses."	These issues are important to clinical practice.
	Catheter efficacy	Efficacy in providing drainage of ascites and palliation of symptoms. Assessed from review of patients' clinical courses.	These issues are important to clinical practice.
	Catheter patency	Calculated from the number of days that patients had functioning catheters free from infection or malfunction.	These issues are important to clinical practice.

Study ID	Outcome	Measure	Reliability/validity /current use in clinical practice
Tapping 2011 (9)	Technical success	Defined as successful placement of the drain and drainage of ascites at insertion. Outcomes assessed from review of patient history, biochemical profiles, pathological and procedural records and clinical follow-up from initial procedure until death.	These issues are important to clinical practice.
	Complications	Classified as immediate (<24 h), early (24 h to 30 days) or late (>30 days from procedure). Outcomes assessed from patient review (as above).	These outcomes and catheter-related issues are commonly raised in clinical practice
	Overall and 30-day mortality	Defined as death attributed directly to the procedure. Outcomes assessed from patient review (as above).	These are standard outcomes.
Saiz-Mendigure n 2010 (7)	Complications	Complications during and after the procedure appear to have been monitored. Patient discomfort during catheter placement was assessed on a visual analog scale. Outcomes were reported by telephone or during consultation.	These outcomes are of interest in clinical practice.
	Catheter patency	No further details were provided.	This outcome is of interest in clinical practice.
	Catheter efficacy	Efficacy in providing drainage of ascites. Reported by telephone or during consultation.	This outcome is of interest in clinical practice.

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew. The following table provides a suggested format for presenting the

statistical analyses in the studies when there is more than one study.

Table 5.9 provides a summary of any statistical tests or other analyses that were undertaken by the included studies when assessing the outcomes of interest. The nature of the study designs did not lend themselves to thorough statistical analysis and, where reported, details were sparse. Subgroup analyses were not performed. Statistical analyses were not applicable to the case report studies.

Table 5.9: Summary of statistical analyses in studies

Study ID	Statistical or other tests applied	Data management
Rosenberg 2004 (1)	Mean complication rates and differences in proportions were analysed using descriptive statistical measures, including the 95% confidence interval.	Not reported
[redacted]	[redacted]	[redacted]
Courtney 2008 (4)	Median time of ascites control was estimated using the Kaplan-Meier method; 95% CI was constructed according to the Greenwood formula. Catheter survival calculated using product-limit analysis.	Patients were censored for death, ascites resolution, or time point of last known catheter function. Five patients considered retrospectively to be protocol deviations were still included in the analyses.
Mullan 2011a (8)	All data were analysed from the time of initial inpatient admission for conventional paracentesis until death. Survival times were calculated from the date of tunnelled catheter placement.	Not reported.
Richard 2001 (6)	Student t-test was used to compare results at different time periods. Survival analysis was conducted using Kaplan-Meier method.	Patients who died with functioning catheters were censored.
Tapping 2011 (9)	Kaplan–Meier curves and multivariate logistic regression analyses were performed. A p-value of <0.05 was considered to indicate a significant difference.	Not reported
Saiz-Mendiguren 2010 (7)	Not reported.	Not reported.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

No subgroup analyses were undertaken.

Participant flow

Where applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment.

N/A

5.4 Critical appraisal of relevant studies

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should also be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the External Assessment Group.

In the absence of randomised controlled trials, and given the lack of comparative and protocol-driven studies, evidence was sought from studies lower down in the hierarchy of evidence. The included studies employed various research designs but were generally considered observational. A single checklist was, therefore, applied to assess the strength of evidence from observational studies assessing effectiveness.(16) One reviewer quality assessed each of the included studies. Details of the complete critical appraisal are provided in Appendices 7.2.7 (quality assessment/risk of bias questions) and 7.3 (critical appraisal of each of the included studies). A summary of the quality assessment is presented in Table 5.10. The case report studies were not quality assessed as case reports are usually classified as providing the lowest quality evidence.

The diverse study designs and poor reporting of methods made it difficult to ascertain the true nature of the studies and to pass judgement about their reliability and generalisability. However, this is the best evidence available at this time. The quality of the evidence presented is likely to be low given the inherent biases arising from the use of non-randomised study designs. In addition, the Rosenberg 2004 (1) and Tapping 2011 (9) studies offer the potential for selection and information bias given their retrospective nature.

The wide variation and sporadic reporting of the study eligibility criteria and participant baseline characteristics meant that it was often unclear whether the studies could be considered to be based on a representative sample from a relevant

population. This lack of detail also hindered an assessment of whether the participants were at a similar point in terms of disease progression. Given the poor reporting of follow-up and severity of the underlying disease, it was difficult to assess whether the duration of follow-up was long enough for important events to occur: patients with malignant ascites have a mean survival of 1-4 months, depending on the nature of the extent of the underlying tumour.(17) The methods used to assess outcomes in the included studies generally lacked transparency, although some studies did mention patient self-assessment and qualitative approaches (Rosenberg 2004 (1), [redacted], Courtney 2008 (4)). The results of the studies should, therefore, be interpreted with caution.

5.4.2 Please provide as an appendix a complete quality assessment for each study. See section 7.3, appendix 3 for a suggested format. For the quality assessments use an appropriate and validated quality assessment instrument

A complete quality assessment for each study is provided in Section 7.3, appendix 3.

A Summary of the critical appraisal can be found in Table 5.10.

Table 5.10: Summary of critical appraisal of PleurX studies

Study ID	Checklist components for case series (16) (Yes / No / Unclear)					
	Was the study based on a representative sample selected from a relevant population?	**Were the criteria for inclusion explicit?**	**Did all individuals enter the survey at a similar point in their disease progression?**	**Was follow-up long enough for important events to occur?**	**Were outcomes assessed using objective criteria or was blinding used?**	**If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?**
Rosenberg 2004 (1)	Unclear	Yes	Yes	Yes	No	Not applicable
[redacted]						
Courtney 2008 (4)	Unclear	Yes	Yes	Unclear	Unclear	Not applicable
Mullan 2011a (8)	Yes	Yes	Yes	Unclear	Unclear	Not applicable
Richard 2001 (6)	Unclear	No	Yes	Unclear	Unclear	Not applicable
Tapping 2011 (9)	Yes	Yes	Yes	Yes	Unclear	Not applicable
Saiz-Mendiguren 2010 (7)	Unclear	No	Unclear	Unclear	Unclear	Not applicable

5.5 Results of the relevant studies

5.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one study, tabulate the responses.

5.5.2 For each outcome for each included study, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim study data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that study. Analytical adjustments should be described to cater for the interim nature of the data.

Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Results data were extracted by one reviewer and checked independently by another.

Included Participants

Table 5.11 describes the participants selected for inclusion in the individual studies, and whether any patients had been excluded from the analyses.

Table 5.11: Participants included in the studies

Study ID	Definition of included participants	Age range / years	Exclusions from analysis
Rosenberg 2004 (1)	Adult patients (aged 18 years or older) who had undergone at least two previous paracenteses and presented with either cytologically proved malignant ascites or clinically suspected malignant ascites caused by reaccumulation of fluid and diagnosis of cancer.	Overall: 21-85 PleurX drain: 21-81 Paracentesis: 31-85	Not reported
[redacted]	[redacted]	[redacted]	[redacted]
Courtney 2008 (4)	Patients with symptomatic ascites associated with malignancy, as defined by proven abdominal malignancy with concurrent ascites; ascites requiring >= 2 therapeutic paracentesis procedures in previous 30 days and reported relief of symptoms after paracentesis.	40-81	Patients were censored for death, ascites resolution, or time point of last known catheter function. Five patients considered retrospectively to be protocol deviations were still included in the analyses.
Mullan 2011a (8)	Patients with recurrent malignant ascites and evidence of metastatic stage IV disease.	33-82	Not reported
Richard 2001 (6)	Patients managed with optimum medical care and repeated large volume paracentesis for malignancy-related ascites who had been referred for placement of a tunnelled PleurX catheter.	43-78	Patients who died with functioning catheters were censored.
Tapping 2011 (9)	Patients with malignant refractory ascites who had undergone PleurX	43-91	Not reported

Study ID	Definition of included participants	Age range / years	Exclusions from analysis
	long-term drain insertion; who had >=3 recent standard ascitic drainages with the two most recent drainages <6 weeks apart; and who were being treated for palliative/end of life care. Patients receiving chemotherapy for whom ascites was a main problem, and for whom a multidisciplinary team review felt the procedure would benefit them.		
Saiz-Mendiguren 2010 (7)	Saiz-Mendiguren 2010 (7)	40-71	Not reported

Outcomes

There were both wide variations and inconsistencies in the reporting of the outcomes. The authors did not provide definitions of the outcomes assessed, the measurement methods used, or the time period at which assessments were made. Where details were provided they were often unclear; this hinders interpretation of the results. Clinical outcomes, as specified in the NICE final scope, are successful device deployment, successful drainage of the ascitic fluid, resolution of symptoms (e.g. bloating, nausea, reduced appetite, perception of body image, psychological well-being, and quality of life), frequency of drainage, and resource use outcomes (e.g. re-intervention, readmission rates, and duration of hospital stay for paracentesis after initial drainage).(17) Results are summarised in Tables 5.12-5.16 for the included studies and Table 5.17 for case report studies.

Successful device deployment

Successful device deployment has been interpreted as outcomes referring to the initial placement of the device, specifically technical success, and any procedural complications. The catheter placement procedure was typically a combination of ultrasound and fluoroscopic guidance, or one of these techniques alone. The success of the procedure was reported in three studies: Courtney 2008 (4), Mullan 2011a (8) and Tapping 2011 (9). All three studies reported technical success rates of 100% for 32-52 insertion procedures performed.

Richard 2001 (6) did not specifically evaluate the success of catheter insertion, but did report that no periprocedural complications were observed. Similarly, Mullan 2011a (8) reported no procedure-related complications, injuries or deaths and Saiz-Mendiguren 2010 (7) reported no complications during or after the procedure. Courtney 2008 (4) observed a complication during initial device placement which was considered minor, while

[redacted]. Saiz-Mendiguren 2010 (7) also reported that while patients overall tolerated the procedure, two patients experienced some discomfort. Table 5.12 summarises the results for successful catheter placement.

Device deployment was mentioned in three case report studies (Brooks 2006, Iyengar 2002, Mullan 2011b) (11-13); see Table 5.17. In Brooks 2006, the patient had the catheter placed under general anaesthesia, as they were already intubated in the intensive care unit, and was said to have tolerated the procedure well (11). In Iyengar 2002, catheters were placed under general anaesthesia with ultrasound guidance and no complications were reported for one of the three patients treated (Iyengar 2002) (12). In Mullan 2011b, one of the four patients was specifically reported to have had an uncomplicated placement (13) and three patients were part of the Mullan 2011a case series where it was reported that they experienced no procedure-related complications, injuries or deaths (8). Details of the placement experience of the other patients in Iyengar 2002 were not reported

Successful drainage of the ascitic fluid

In the absence of any specific definition of 'successful drainage', this has been interpreted to mean catheter effectiveness or functioning and to include outcomes such as catheter patency, catheter survival, catheter removal and catheter failure. All of the included studies recorded at least one of these outcomes, although the number of patients assessed and the follow-up point were often unclear. Where defined, the studies did not use common definitions for the outcomes or they used terminology inconsistently or interchangeably. Five studies reported catheter patency/survival, which ranged from a mean of 70-100 days in four studies (Courtney 2008 (4), Richard 2001 (6), Tapping 2011(9), Mullan 2011a (8)). The fifth study reported a median patency of 52 days for the nine patients who had died, and 124 days for the patient still alive at the end of the study Saiz-Mendiguren 2010 (7). Catheter functioning ranged from 60% in one study of 10 patients (Richard 2001) (6) to 100% at time of death in a study of 50 patients, two of whom had had catheters replaced (Mullan 2011a (8)). Accurate representations of catheter functioning could not always be established. For example, patients were lost to follow-up or patients died before an up-to-date assessment could be made. Catheter failures and/or removals were typically low, less than 15% in four of the five studies reporting this outcome. However, in the study that reported the high rate of 40% (4/10 catheters affected), two catheters had been removed because they were no longer needed (ascites resolved) and one had been inadvertently pulled out (Richard 2001) (6). Table 5.13 summarises the results for catheter effectiveness in relation to ascitic fluid drainage.

All four case report studies described issues related to 'successful drainage' of ascitic fluid. Brooks 2006 and Iyengar 2002 (11-12) both reported catheters functioning effectively, essentially until death: approximately 18 months (1/1 case) (Brooks 2006) (11) and 7-12 weeks (3/3 cases), although one of these three patients had their catheter removed as a precaution and because of reduced ascites formation (Iyengar 2002) (12).

Mullan 2011b (13) used fibrinolytics to resolve occlusions and loculations that had caused catheters to malfunction 9, 10, 11 and 20-24 weeks following insertion. Of the three catheters that were salvaged, two remained functioning until the patients' death (3 weeks

and 13 months later) and the third was still operative 14 weeks after fibrinolytic therapy had been affected. One catheter was replaced with a second catheter, which remained in place for 7 weeks (until the patient's death) (13). Note that three of the four patients have also featured in the Mullan case series (Mullan 2011a (8)). An adverse event notification to the MAUDE database (Denver BioMedical Inc. 2007) reported a problem when attempting to remove a catheter that had been in place successfully for 2 months (14). Table 5.17 summarises the results for catheter effectiveness in relation to ascitic fluid drainage.

Resolution of symptoms

[redacted] and Courtney 2008 (4), evaluated physical and psychological symptoms and quality of life (QoL). Both recorded some improvements with the PleurX drainage system and some improvements were significant.

[redacted]

In Courtney 2008 (4) the patients completed the Subjective Significance Questionnaire (Subjective and Memorial Symptom Assessment Surveys). The majority of results reported at 12 weeks were for the 7 surviving patients (of the original 34) in the study (others had died from their underlying disease within the 12-week follow-up period); the results of assessments collected at other time points were not presented. As a limitation of their study, Courtney 2008 (4) noted that the lack of a previously validated instrument specific to ascites hindered their ability to document a change in quality of life (QoL) and therefore might have been unable to detect QoL changes directly attributable to the catheter drainage system. Table 5.14 summarises the changes in physical, physiological and QoL outcomes observed.

Issues related to the resolution of symptoms were mentioned in two case report studies (Iyengar 2002, Mullan 2011b) (12-13); see Table 5.17. All three patients in one report expressed satisfaction with the elimination of repeated hospital visits and paracentesis (Iyengar 2002) (12). In the other report, ascites was considered well controlled (1/3 cases) (Iyengar 2002) (12), or completely resolved (1/4 cases) and successfully palliated until death (3/4 cases) (Mullan 2011b) (13).

Frequency of drainage

Four studies recorded details of ascitic fluid drainage, including the number and frequency of drainage sessions and the volume of fluid removed (Courtney 2008 (4), Richard 2001 (6),

Tapping 2011(9), Saiz-Mendiguren 2010 (7)). Details were inconsistently recorded but, overall, volumes of 1500-5000 mL of fluid were removed following device insertion and ranged from ≤500 mL every 12 hours to 3000 mL per day in subsequent sessions, although Courtney 2008 (4) did not advise routine removal of >2000 mL of ascites without further clinical evaluation. The frequency of fluid drainage ranged from every other day to every 2-10 days. Difficulties or complications in conducting the drainage were uncommon. Table 5.15 summarises details of the fluid drainage sessions reported in the studies.

One of case report studies reported that 7 litres of fluid was drained initially after catheter insertion, with approximately 2 litres/day subsequently (1/1 case) (Brooks 2006) (11). Another study of three cases reported initial drainage volumes of 2.5 and 5 litres after device insertion (2/3 cases), with subsequent removal of unspecified amounts of fluid performed once to twice weekly by the patient, a family member, or a home health nurse (Iyengar 2002) (12). See Table Table 5.17 for a summary of case reports of fluid drainage

Resource use outcomes

The need for re-intervention was reported in four studies of 4 to 50 patients (Courtney 2008 (4), [redacted], Mullan 2011a (8), Tapping 2011(9)). Only a small number of patients (between 1 and 4) were affected in each study. In one study of 34 patients, three patients required an aggregate of 13 interventions such as paracentesis and peritoneovenous shunt revisions. (4) Re-admission rates and the duration of hospital stay necessitated by such re-interventions were not reported. Mullan 2011a (8) reported that, although the majority of patients were discharged within 24 hours after the initial catheter insertion, one patient had a 10-day hospital stay because the primary care trust would not provide follow-up at home. Table 5.16 summarises published details of resource use.

Re-admission was reported in two case report studies (Iyengar 2002, Mullan 2011b) (12-13); see Table 5.17. Of the three cases described by Iyengar 2002, one patient needed an overnight stay because of dehydration while another had a urinary tract infection that necessitated a 2-day stay (12). One of the four patients treated with fibrinolysis to resolve non-functioning catheters required the subsequent insertion of another catheter (Mullan 2011b) (13).

Table 5.12: Results of PleurX studies reporting device deployment

Study ID	Measure	Definition	Device and insertion technique	Number of participants	Success rate	Complications on device insertion
Rosenberg 2004 (1)	Not evaluated		PleurX catheter. Ultrasound and fluoroscopic guidance.	N=40		
Day 2011 (2)	Not evaluated		PleurX drain. Insertion technique not reported.	N=4		One patient needed the device re-siting.
Courtney 2008 (4)	Technical success	Intraperitoneal positioning of the device and the ability to withdraw ascitic fluid from the device at completion of the procedure.	Modified PleurX tunnelled peritoneal catheter. Combined ultrasonographic (US) and fluoroscopic guidance (n=31), US alone (n=2), US and computed tomography (n=1).	N=34	100%	One epigastric vein was injured during initial placement. No major complications occurred during placement.
Mullan 2011a (8)	Technical success	Complication-free intra-peritoneal placement, with free drainage of ascites on completion of the procedure.	PleurX tunnelled peritoneal catheter. A pre-procedure ultrasound was performed to identify an area suitable for drain insertion. All drains were inserted under local anaesthesia with ultrasound assistance.	N=50 patients (52 procedures)	100%	No procedure-related complications or deaths occurred. No bowel, solid organ or vessel injuries were observed during or following tunnelled drain insertion.
Richard 2001 (6)	Not specifically evaluated		PleurX tunnelled catheter. Combined ultrasonographic (US) and fluoroscopic guidance (n=8), US guidance alone (n=2).	N=10		No periprocedural complications were identified, specifically, no patients exhibited hypotension.
Tapping 2011 (9)	Technical success	Successful placement of the drain and drainage of ascites at insertion.	PleurX tunnelled abdominal drain. Combination of fluoroscopy and ultrasound (US) guidance (n=4), US guidance alone (n=28). Three patients had their drain inserted under conscious sedation. Hospital inpatient stay was <1 day.	N=28 patients (32 procedures)	100%	No procedural complications: no vessels were injured, there were no bowel perforations, and no procedure-related deaths

Study ID	Measure	Definition	Device and insertion technique	Number of participants	Success rate	Complications on device insertion
Saiz-Mendiguren 2010 (7)	Not specifically evaluated		PleurX tunnelled catheter. Placed under ultrasonographic guidance and local anaesthesia.	N=10		Two patients reported discomfort during catheter placement (3/10 and 2/10 on pain VAS). No complications were reported during or after the procedure.

Table 5.13: Results of PleurX studies reporting drainage of the ascitic fluid

Study ID	Number of participants	Timing of follow-up assessment	Catheter patency or survival Definition / Results	Catheter functioning Definition / Results	Catheter failure/removal Definition / Results	Other measure of catheter effectiveness
Rosenberg 2004 (1)	N=40	Not reported	Not evaluated	Not defined. 26 patients (65%) died with functioning catheters. 11 patients were lost to follow-when they moved into hospice care; unclear whether catheters were still functioning. Author commented that although the oncologists believe the patients died with their catheters functioning, it is possible	Catheter failure defined as poor patency causing malfunction or inability to provide symptomatic relief. 3 (7.5%) catheters affected. One catheter removed because of infection, one because of leakage of ascitic fluid into subcutaneous tissues, and one because the fluid had stopped accumulating.	

Study ID	Number of participants	Timing of follow-up assessment	Catheter patency or survival Definition / Results	Catheter functioning Definition / Results	Catheter failure/removal Definition / Results	Other measure of catheter effectiveness
				that there were problems not reported to the physicians.		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Courtney 2008 (4)	N=34	Weekly up to 12 weeks of catheter use, or until death	Survival (time of ascites control) defined as the period of initial function between catheter insertion and loss of catheter function. 86 days (only lower limit of 95% CI estimable); it exceeded protocol-specified objective performance criterion of 35 days. For patients who did not experience loss	Not specifically defined, but appears to be no requirement for catheter intervention or separate therapeutic paracentesis during 12 weeks' observation or until patient death. 85% (29/34). 15% (5/34) had indeterminate functioning: catheters were functioning at	Not defined. 15% (5/34) catheters failed. Catheters failed because of: decreased output due to loculated ascites and subsequent tumour ingrowth (1); catheter occlusion (2); multiple loculations in the peritoneum and poor performance (1); patient too ill to go to hospital for evaluation (1). A further catheter had a temporary occlusion, which was removed on cleaning, and no further intervention was needed. The ascites did not accumulate and the catheter was removed the following week.	Patients were asked whether they thought the ascites symptoms were being well controlled by home drainage: Each week, 83-100% of patients responded affirmatively. Clinicians were asked to assess ascites control at weeks 2, 8 and 10 (no further details): findings were positive for control of ascites in 80-95% of cases. Periumbilical girth (measured at site of greatest distension):

Study ID	Number of participants	Timing of follow-up assessment	Catheter patency or survival Definition / Results	Catheter functioning Definition / Results	Catheter failure/removal Definition / Results	Other measure of catheter effectiveness
			of catheter function, survival was measured from the date of catheter placement until the earliest of the following: ascites resolution; last known date of contact before death if the catheter was known to be functioning properly at that time and subject withdrew from study at that time; or death.	the last follow-up, but there was no follow-up within 1 week of the patient's death.		significant reduction compared with baseline at 2 weeks (p=0.0002), 8 weeks (p=0.0246) and 12 weeks (p=0.0483).
Mullan 2011a (8)	N=50 patients (52 catheters)	Not specifically reported. Patients were followed-up until death.	Survival times were calculated from the date of tunneled catheter placement. Primary or secondary catheter patency at death was 100%.	Not defined. All patients (100%) had functioning tunneled drains in situ at the time of death.	Not defined. 4% (2/50) catheters were affected. One catheter was displaced after inappropriate removal of the skin suture; the other had ceased to function due to formation of fibrin cast and loculation of ascites. Both needed replacement. A further two patients developed loculated ascites with non	

Study ID	Number of participants	Timing of follow-up assessment	Catheter patency or survival Definition / Results	Catheter functioning Definition / Results	Catheter failure/removal Definition / Results	Other measure of catheter effectiveness
			Time of death not reported.		functioning catheters, but these were only temporary and were resolved with fibrinolysis.	
Richard 2001 (6)	N=10	Not reported	Survival and patency appear to have been used interchangeably. Catheter patency was based on the number of days that patients had functioning catheters that were free from infection or malfunction. Mean survival 70 days (range: 1-100)	Not defined. 6 catheters (60%) remained functional at patient death, 3 were removed for reasons other than failure, and one malfunctioned but was 'mended'.	Not defined. 4 (40%) catheters affected. Two catheters were removed because no longer needed, one was inadvertently pulled out by the patient and not replaced, and one had a temporary malfunction.	
Tapping 2011 (9)	N=28 patients (32 catheters)	Not reported	The time that the catheter was in situ seems to be the measure of catheter patency. Mean patency 113 days (range: 5-365)	Not defined. 86% (24/28) original catheters were functioning until the patient's death.	Not defined. 4/28 (14%) catheters were affected. Drains were dislodged and re-intervention was needed.	The annual event rate (unspecified) was 0.45 events per year. This seems to relate to drains being dislodged and new drains inserted (episodes happened at 23, 29, 40 and 42 days post-insertion).

Study ID	Number of participants	Timing of follow-up assessment	Catheter patency or survival Definition / Results	Catheter functioning Definition / Results	Catheter failure/removal Definition / Results	Other measure of catheter effectiveness
Saiz-Mendiguren 2010 (7)	N=10	Not specifically reported. One patient was still alive at 124 days but the other nine patients had died.	Not defined. Median catheter patency was 52 days (range: 13-113) in the nine patients who died (one had their catheter removed whilst still patent). Catheter patency was 124 days in the patient who was still alive.	Not evaluated.	Not defined. 1 (10%) catheters affected. Patient was admitted with generalized sepsis, and although there were no signs of local device-related infection, the catheter was removed.	

Table 5.14: Results of PleurX studies reporting resolution of symptoms

Study ID	No. of participants	Measure	Assessment tool (assessment timing)	Baseline value/comment	Follow-up value/comment
Rosenberg 2004 (1)	N=40	Symptom resolution and QoL were not evaluated.			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study ID	No. of participants	Measure	Assessment tool (assessment timing)	Baseline value/comment	Follow-up value/comment
					[redacted]
Courtney 2008 (4)	N=34 at baseline Unclear how many patients were assessed at each follow-up	Abdominal discomfort	MSAS (0, 2, 8 and 12 weeks)	>=6	Authors state there was a lower score at all three follow-up visits, but this was significant at 2 and 8 weeks (p=0.0059 and p=0.01).
		Feeling bloated		>=6	Authors state there was a lower score at all three follow-up visits, but this was significant at 2 and 8 weeks (p=0.0001 and p<0.0001).
		Lack of appetite, shortness of breath, diarrhoea, self-perception, nausea, pain, difficulty sleeping, worrying		>=6 for each symptom	The authors reported "improvement" in each symptom with a significant difference for diarrhoea (p=0.0123) and nausea (p=0.0013) (timepoint not specified)
		Dry mouth and lack of energy;	MSAS	>=6 for each l symptom	no improvement in either symptom

Study ID	No. of participants	Measure	Assessment tool (assessment timing)	Baseline value/comment	Follow-up value/comment
		Problems with urination	(0, 2, 8 and 12 weeks)	Not reported	no significant change.
		Dizziness		Not reported	Significant increase at 2 weeks (p=0.0407), but not at 8 or 12 weeks.
		Swelling of arms and legs		Not reported	no significant change.
	N=28 patients with results	Overall quality of life	SSQ (1, 2, 8 and 12 weeks)	SSQ not administered at baseline.	1 week: 15/27 patients (56%) stated that their overall QoL had improved. 12 weeks: 5/7 (28%) stated that their overall QoL had improved.
Mullan 2011a (8)	N=50	Symptom resolution and QoL were not evaluated			
Richard 2001 (6)	N=10	Symptom resolution and QoL were not evaluated			
Tapping 2011 (9)	N=28	Symptom resolution and QoL were not evaluated			
Saiz-Mendiguren 2010 (7)	N=10	Symptom resolution and QoL were not evaluated			

Table 5.15: Results of PleurX studies reporting frequency of ascites drainage

Study ID	Number of participants	Drainage at initial catheter placement	Subsequent drainage: number of sessions performed and by whom	Frequency of sessions and volume of fluid drained	Problems experienced
Rosenberg 2004 (1)	N=40	Not reported	Not reported	Not reported	Not reported
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Courtney 2008 (4)	N=34	Mean 3240 mL ascitic fluid per patient (range: 800-7000)	Complete records for 440 sessions (19 patients); mean 23.3 drainage records (range: 5-56; median 17). Time period not specified. 252 sessions were performed by a caregiver, 123 by the patient alone, 58 by a nurse, and 7 were unspecified.	Most patients (not specified) drained their ascites every other day. Typical drainage volume ranged from 1200-2000 mL. Routine removal of >2000 mL ascites per day was not advised.	No problems were reported in 372 sessions (84.5%) with 19 patients. Procedural problems occurred in <1% of sessions. No patients stopped using the catheter because of procedural difficulties.
Mullan 2011a (8)	N=50	Not reported	Not reported	Accurate home drainage volumes were not available. On average, thirty 1- litre bottles were dispensed per PleurX catheter but the number used is not reported.	Not reported
Richard 2001 (6)	N=10	1.500-3000 mL of ascitic fluid were removed after device insertion.	The number of sessions was not reported. Drainage sessions were conducted by patients or caregivers.	Frequency of fluid drainage ranged from every other day to once per week. Volume drained was unclear: "Patients initially drained between 0.5 and 1 litre of fluid per day for the first week and the amount of the fluid removed varied according to the management of the patient's oncologist, ranging from 0.5-3	Not reported

Study ID	Number of participants	Drainage at initial catheter placement	Subsequent drainage: number of sessions performed and by whom	Frequency of sessions and volume of fluid drained	Problems experienced
				litres per day."	
Tapping 2011 (9)	N=28	Average 5000 mL ascitic fluid per patient (range: 3500-7000) were removed following device insertion.	Not reported	Drainage sessions were recommended not to exceed 500 mL fluid every 12 hours.	Not reported
Saiz-Mendiguren 2010 (7)	N=10	Not reported	Not reported	Mean drainage volume was1 litre every 2-10 days.	Not reported

Table 5.16: Results of PleurX studies reporting resource use

Study ID	Number of participants	Re-interventions	Re-admission rates	Duration of hospital stay
Rosenberg 2004 (1)	N=40	Not reported	Not reported	Not reported
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Courtney 2008 (4)	N=34	Three patients required an aggregate of 13 interventions, including paracentesis, alteplase infusions, peritoneovenous shunt revisions, and repeated mechanical disruptions (to remove obstructions).	Not reported	Not reported
Mullan 2011a (8)	N=50	Two PleurX catheters were replaced because of failure/removal of the original device.	Not reported	49 patients left hospital within 24 hours of the initial procedure. One patient stayed in hospital for 10 days in the absence of district nurse follow-up at home.
Richard 2001 (6)	N=10	Not reported	Not reported	Not reported
Tapping 2011 (9)	N=28	Four PleurX drains failed/were removed and four new drains were inserted on the opposite side of the abdominal wall	Not reported	Not reported
Saiz-Mendiguren 2010 (7)	N=10			Not specifically reported. The mean time spent inserting the drain was 50 minutes.

Table 5.17: PleurX case report studies: results for device deployment, fluid drainage, symptom resolution and resource use

Study ID	Cases reported	Successful device deployment	Successful drainage of the ascitic fluid	Resolution of symptoms	Frequency of drainage	Resource use outcomes
Brooks 2006 (11)	1	Patient tolerated placement of PleurX catheter under general anaesthesia well.	The catheter functioned effectively until the patient's death (approximately 18 months).	Not reported.	7 litres of ascitic fluid were removed after device insertion, with subsequent removal of approximately 2 litres fluid/day. Renal function and electrolyte balance were unaffected.	Not reported.
Iyengar 2002 (12)	3	PleurX catheter placed under general anaesthesia with ultrasound guidance. No complications were reported for one patient; no comment was made for the other two patients.	Two patients had their catheter in place until death: 7 and 12 weeks. The third patient had their catheter removed after 12 weeks as a precaution and due to decreased ascites formation, and died 6 weeks later.	All three patients expressed satisfaction with the elimination of repeated visits to the hospital and the pain and anxiety of repeated abdominal taps. Ascites was considered well controlled in one patient.	The volume of ascitic fluid removed after device insertion was 2.5 litres for one patient, 5 litres another patient and was not reported for the third patient. Drainage sessions were performed by the patient (1), family member (1) or home health nurse (1). Drainage sessions were conducted once weekly, one or two times weekly, or twice weekly; the fluid volume removed was not reported. None of the patients required further paracentesis.	Patients were discharged home the day after catheter placement. One patient suffering from dehydration had an overnight stay in the following 6 weeks. One patient had a 2-day admission for pain control and urinary tract infection.
Mullan 2011a (13)	4	PleurX tunnelled intraperitoneal	This was a study of non-functioning catheters.	Three patients had successful palliation	Not reported.	One patient returned to hospital

Study ID	Cases reported	Successful device deployment	Successful drainage of the ascitic fluid	Resolution of symptoms	Frequency of drainage	Resource use outcomes
		catheter. One patient was explicitly reported to have had an uncomplicated placement; nothing was reported for the other three patients.	Successful drainage until catheter malfunction was 9, 10, 11 and 20/24* weeks in the four patients. Fibrinolysis restored catheter function in three patients. Two of the originally placed catheters remained functioning until the patient's death (3 weeks and 13 months later) and the other catheter was still functioning after 14 weeks. Fibrinolysis failed to restore catheter function in the fourth patient and a second catheter was inserted. With fibrinolysis repeated to resolve ascitic loculation, the new catheter remained functioning for about 7 weeks (until the patient's death).	of ascites until death and the fourth achieved complete resolution of ascites.		for insertion of a new catheter (for administration of Streptokinase to reduce loculation).
Denver BioMedical Inc. 2007 (14)	1	Not reported.	Device age (analogous to duration of functioning catheter) was 2 months.	Not reported.	Not reported.	Not reported.

* Reported variously in the results and discussion sections of the article.

5.6 Meta-analysis and evidence synthesis

When considered appropriate, techniques for evidence synthesis such as meta-analysis, and indirect and mixed treatment comparisons can be used.

5.6.1 Describe the technique used for meta-analysis and/or evidence synthesis, the steps undertaken and results of the analysis including methodology. For example, when direct comparative evidence is not available, indirect treatment comparison methods can be used. The following descriptions should be included if indirect or mixed treatment comparisons are undertaken.

- Identification, selection, methodology and quality assessment of relevant studies
- Summary of the studies used to conduct the indirect comparison. For the selected studies, provide a summary of the data used in the analysis.
- Indirect/mixed treatment comparison methodology.
- Results of the analysis.
- The statistical assessment of heterogeneity and any sensitivity analyses

The studies were not suitable for meta-analysis because of their design and inadequacies in the reporting of results.

5.6.2 If evidence synthesis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

There are no randomised controlled trials of PleurX catheter drainage for recurrent malignant ascites. The seven uncontrolled studies identified used various research designs and were not specifically designed to be prospective. They appeared to be non-protocol driven, experimental case series in their intent, and were consequently treated as case series for the purpose of critical appraisal. The study designs included are not ideal sources of data, and the studies themselves had small samples sizes and largely indeterminate duration/follow-up, but they provide the best

available evidence at the current time. The case report studies were not quality assessed as the quality of the evidence they provide is generally accepted to be low.

Given the inconsistencies and poor reporting of the included studies, many of the checklist components of the quality assessment could not be answered directly with a 'Yes' or 'No' and were largely designated 'Unclear'. Only Tapping 2011 (Tapping, 2011 #593} could be considered to have satisfied the majority of the quality questions (4/6 applicable questions). To summarise, where authors reported specific detail:

Two studies were based on a representative sample selected from a relevant population;
Four studies had explicit inclusion criteria;
Five studies involved patients who were at a similar point in their disease progression;
Two studies had follow-up sufficient to capture important events;
None of the studies definitely assessed outcomes using objective criteria.

With an awareness of the shortcomings of the study designs, the quality of the evidence presented is likely to be low. Further detail of the quality assessment is provided in Section 5.4 and Appendix 7.3

5.7 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

5.7.1 If any of the main studies are designed primarily to assess safety outcomes, please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the studies, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each study should be provided in sections 7.4 and 7.5, appendices 4 and 5.

Sections 5.1-5.4 describe the identification of studies, selection of studies, summary of methodology of relevant studies, and critical appraisal of the included studies.

5.7.2 Please provide details of all important adverse events. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Adverse outcomes, as specified in the NICE final scope, are catheter site infections, peritonitis, catheter occlusion, and other device-related adverse events (e.g. haemorrhage, bowel perforation) (17). Table 5.18 summarises the catheter-related

adverse events reported in the included studies and Table 5.19 summarises those reported in the case report studies.

Where reported, the incidence of adverse events was low. One study did not monitor adverse events [redacted], one study only reported the absence of complications during and after the procedure (Saiz-Mendiguren 2010 (7)), and one study recorded the absence of catheter-site infections and hypotension (Richard 2001) (6). The other four studies recorded zero or small numbers of events in small patient populations fitted with a PleurX catheter (N=28 to 50) or undergoing large volume paracentesis (N=67) (Courtney 2008 (4), Rosenberg 2004 (1), Mullan 2011a (8), Tapping 2011(9)). The most common adverse events associated with catheter insertion were ascitic fluid leakage in 10 patients (4 studies, total N=152 patients, representing between 2% and 21% of patients in those 4 studies), erythema/exudative discharge in 5 patients (1 study, N=28), and temporary dizziness or weakness potentially related to catheter occlusion or ascites drainage in 9 patients (1 study, N=34). There was one case of peritonitis reported in patients with a PleurX drain inserted (Courtney 2008 (4)) and three cases of peritonitis (<1% of procedures) in patients undergoing large-volume paracentesis in a different study (Rosenberg 2004 (1)). Catheter occlusion (3/34 patients) was only reported in one study (Courtney 2008 (4)). Rosenberg 2004 (1) reported identical complication rates (7.5%) in patients with PleurX catheters (N=40) and those patients undergoing large-volume paracentesis (N=67). One possibly catheter-related death was reported by Courtney 2008 (4).

The incidence of adverse events recorded in the case report studies was low. One study reported no complications on device insertion in 3/3 patients (Iyengar 2002) (12). Mullan 2011b (three of whose patients were also included in the Mullan case series) did not report any complications on insertion for the four patients presented (13). One study focused on 4 cases treating catheter malfunctions arising from occlusions and ascitic loculations (Mullan 2011b) (13) (three of these patients were also included in the Mullan case series); only catheter occlusion was reported in the other case reports (Brooks 2006) (11). There were single occurrences of other device-related events: peritonitis and hernia around the catheter site (1/1 case) (Brooks 2006) (11), abdominal distension (1/4 cases) (Mullan 2011b) (13) and continued abdominal discomfort (1/1 case) (Denver BioMedical Inc. 2007) (14). Mullan 2011b (13) also reported an absence of haemorrhagic sequelae. Deaths in the case reports were attributed to underlying disease progression and were not considered to be catheter-related.

Table 5.18: Adverse events reported in the Pleurx studies

Study ID	Number of participants	Catheter site infections Number of patients (%)	Peritonitis Number of patients (%)	Catheter occlusion Number of patients (%)	Other device-related events Number of patients (%)	Overall adverse events or complications
Rosenberg 2004 (1)	PleurX N=40	1 (2.5% of patients)			Fluid leakage: 1 (2.5%). Loculations: 1 (2.5%)	7.5% (95% CI: 1.6–20) of patients
	Paracentesis N=67 (392 procedures)		3 cases (<1% of procedures)		Loculations: 2 (3%)	7.5% (95% CI, 2.2–15) of patients
[redacted]	[redacted]	[redacted]				
Courtney 2008 (4)	N=34	1 (3%)	1 (3%)	3 (9%)	Epigastric vein injury during initial catheter placement: 1 (3%). Ascites leakage: 7 (21%). Temporary dizziness or weakness potentially related to ascites drainage or catheter occlusion: 9 (26%). Severe pain during drainage: 1 (3%). Loculations: 1 (3%). Minor discomfort with drainage:	14 patients (41%) had no adverse events; 11 patients (32%) experienced a single event; 9 patients (26%) experienced 2 or more events

Study ID	Number of participants	Catheter site infections Number of patients (%)	Peritonitis Number of patients (%)	Catheter occlusion Number of patients (%)	Other device-related events Number of patients (%)	Overall adverse events or complications
					32/440 sessions (7% of sessions). One death (3%) from a presumed pulmonary embolism 2 days after sudden onset of shortness of breath and coughing that developed several hours after catheter placement.	
Mullan 2011a (8)	N=50				No bowel, solid organ or vessel injuries were observed during or following tunnelled drain insertion. There were no procedure-related complications or deaths. Fluid leakage: 1/50 (2%). Loculations: 3/50 (6%). Pain on drainage: 1/50 (2%).	Overall complication rate 16%. 7 patients experienced 8 adverse events: 4 were classed as early (1-30 days after insertion): 4 classed as late (>30 days after insertion).
Richard 2001 (6)	N=10	0 cases			Hypotension: 0 cases	
Tapping 2011 (9)	N=28	Erythema and discharge: 5 (18%)			Fluid leakage: 1 (4%). Incisional site hernia: 1 (4%). No procedural complications:	Minor complications: Immediate (<24 h): 3 (10%); Early (24 h – 30 days): 3 (10%); Late (>30 days): 2 (7%).

Study ID	Number of participants	Catheter site infections Number of patients (%)	Peritonitis Number of patients (%)	Catheter occlusion Number of patients (%)	Other device-related events Number of patients (%)	Overall adverse events or complications
					0 vessels injured; 0 bowel perforations; 0 procedure-related deaths.	Major complications: 0
Saiz-Mendiguren 2010 (7)	N=10				No complications were reported during or after the procedure.	

Table 5.19: Adverse events reported in the PleurX case report studies

Study ID	Cases reported	Catheter site infections	Peritonitis	Catheter occlusion	Other device-related events
Brooks 2006 (11)	1	Not reported.	1 case.	1 case.	Hernia around catheter site:1/1 No sepsis.
Iyengar 2002 (12)	3	Not reported.	Not reported.	Not reported.	No complications on catheter insertion.
Mullan 2011b (13)	4 (Three of the four patients also feature in the Mullan case series (8)).	Not reported.	Not reported.	2 cases.	Abdominal distension: 1/4. Loculations: 3/4. Haemorrhagic sequelae:0/4. Catheter insertion was specifically reported to be uncomplicated in one patient. No information on catheter insertion experiences was provided for the other three patients.
Denver BioMedical Inc. 2007 (14)	1	Not reported.	Not reported.	Not reported.	Patient experienced continued abdominal discomfort and requested catheter removal. Attempts to remove the functioning catheter were unsuccessful (catheter appeared trapped in peritoneum).

5.7.3 Give a brief overview of the safety of the technology in relation to the decision problem.

The studies and case reports indicate a low incidence of PleurX insertion difficulties and adverse events in routine use. The most frequently reported adverse events associated with catheter insertion were ascitic fluid leakage, erythema/exudative discharge and temporary dizziness or weakness potentially related to catheter occlusion or ascites drainage: but these were few in number. A small number of cases of peritonitis and catheter occlusion were reported during routine use. One possibly catheter-related death was reported in one study.

5.8 Interpretation of clinical evidence

5.8.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Evidence from seven observational studies and four case report studies describing 9 cases suggests that PleurX catheter insertion is a technically feasible approach that can be used by medical providers and patients/carers for the management of malignant recurrent ascites in the home setting. Initial catheter insertion appears to be safe and subsequent catheter failure and adverse event rates are low. Results from subjective measures of physical and psychological well-being indicate a reduction in some symptoms. The procedure reduces the discomfort and potential complications of multiple paracentesis for the patient, and avoids repeat trips to the hospital. In addition, frequent drainage in smaller quantities avoids the build up of a large volume of ascites and thus offers better control of symptoms. The resultant gain in social independence is likely to be extremely important to patients who are terminally ill and may only have a short life expectancy (ranging from a few days to months). One small qualitative study involving 4 patients reported some negative feelings about semi-permanent drains: they are a constant reminder of illness, the timing of drainage may be an issue and the placement of the drain can make it difficult to sleep.

The studies identified some patient/carer educational needs to ensure that any complications and adverse effects are identified before they worsen. Standard guidelines on correct operation of the drainage system and clear instructions for follow-up and infection/complication surveillance should be given to the patients, and the patients should be encouraged to report back

with any signs of infection, difficulty in draining the catheter, or other problems. Care and regular follow-up is still needed, especially for those patients on chemotherapy and those with a pre-procedure diagnosis of renal disease who may be at greater risk of complications and have the drain in situ for a reduced length of time.

Further prospective, controlled studies comparing the PleurX catheter with other types of catheter and other methods of drainage (e.g. large volume paracentesis and peritoneovenous shunting), in order to define the role of the PleurX catheter in the palliation of recurrent malignant ascites, are warranted. The qualitative study, however, indicated that patients have some ambivalence about participation in randomised controlled trials of these interventions.

5.8.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

No controlled trials were identified. The evidence presented was obtained from studies lower down in the hierarchy of evidence, predominantly observational case series. Case reports were subsequently included in this review, following a protocol change request. The included studies used various research designs, none of which are ideal sources of effectiveness data, and the quality of the evidence presented is likely to be low. There was wide variation and inconsistencies in the reporting of the studies, which made it difficult to judge their reliability and generalisability. In addition, differences between the studies precluded meta-analysis and hindered comparisons between studies within the narrative synthesis. The included studies were small in size (4 to 50 patients with PleurX catheters, where reported) and of indeterminate study duration/follow-up; case reports described 1 to 4 patients. The findings of this review are based on the best available evidence and in the knowledge that the studies reviewed are open to a range of biases.

5.8.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical studies to the clinical benefits experienced by patients in practice.

The outcomes assessed in the studies were relevant to clinical practice and the decision problem. There is a clear trend of good performance of the PleurX peritoneal catheter drainage system in avoiding unnecessary repeated

taps (and its potential complications) and repeat hospital visits associated with large volume paracentesis.

The PleurX peritoneal drainage catheter has demonstrated it can provide ongoing relief and control of symptoms associated with treatment resistant, recurrent malignant ascites with minimal complications in an outpatient setting. In contrast, LVP, although effective at providing initial relief of symptoms, is ineffective at maintaining control of symptoms. This is demonstrated by the very nature of the need for repeat hospital admission and inpatient stay. The clinical limitations of LVP are frequently referenced in the studies selected.

5.8.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the study, issues relating to the conduct of the study compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted.

The 6 studies highlighted in this review indicate favourable results and patient benefits in comparison to LVP.

The outcomes reported in the studies were expected and fall in line with what occurs in clinical practice. The studies included patients with treatment resistant, recurrent malignant ascites and are therefore relevant to the decision problem and clinical practice.

PleurX is an outpatient management option and therefore it is fitting that the studies selected report on the benefits and complications that occur in this setting.

The complication rates reported in the studies are recognised as a fair reflection of what can occur in routine clinical practice e.g. loculated ascites, peritonitis. Resolution of such complications in patients with a PleurX catheter

appears to be possible with minimal intervention and avoidance of catheter removal.

The use of a PleurX peritoneal drainage system clearly points towards a reduction in hospital admission rates and length of hospital stay. This was a common theme reported in the studies and should be expected to be replicated in centres that adopt the PleurX peritoneal catheter drainage system to manage treatment resistant, recurrent malignant ascites. Jacob 2009, suggested 10-15 hospital bed days per patient per month may be avoided by adopting use of the PleurX peritoneal catheter drainage system.

The reported outcomes indicate that intermittent vacuum drainage with the PleurX system can be performed successfully at home, offering good palliation of symptoms. The studies reported that vacuum drainage in an outpatient setting can efficiently manage the symptoms associated with recurrent malignant ascites. Therefore palliation of symptoms is expected to be realised in routine clinical practice.

A randomised controlled trial versus LVP may be helpful but due to the patient types and the nature of their disease this may not be practically possible. A key consideration is the decision on when to move from LVP to PleurX catheter placement i.e. after how many taps.

6 Analysis of Cost

6.1 Published cost-effectiveness and cost evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and identify all unpublished data. Health economics studies should include all types of economic evaluation and cost studies, including cost analyses and budget impact analyses. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 7.6, appendix 6.

A range of databases indexing published research was searched for clinical and economic studies on the PleurX peritoneal catheter drainage system for vacuum-assisted drainage of treatment resistant, recurrent malignant ascites. The literature searches were undertaken using methods which conform to requirements for systematic reviews that may be used to support submissions to NICE. The databases searched included those required by NICE: MEDLINE, MEDLINE In-Process, EMBASE and the Cochrane Library. In addition, searches of regulatory organisation websites, trials registries and conference proceedings were undertaken. The searches were not limited by language or date range, and animal studies were excluded. The strategy employed uses the intervention name alone to find relevant studies, which gives the advantage of making a single search strategy sensitive enough, in MEDLINE, EMBASE and the Cochrane Library, to identify studies reporting clinical effects, adverse events and economic outcomes. Full details of the search strategies and the databases and resources searched are provided in Appendix 2, Section 7.2.

Studies were selected according to the following criteria for the economic review.

Inclusion criteria

- Population: Adults (aged 18 and over) with treatment-resistant, recurrent malignant ascites;
- Intervention: PleurX peritoneal catheter drainage system;
- Comparator: inpatient or outpatient large volume paracentesis (abdominal taps);
- Outcomes: total costs, summary health outcomes (quality-adjusted life-years), cost-effectiveness ratios;
- Study design: full economic evaluations; relevant economic data reported in technology assessments, including those produced for regulatory agencies; studies reporting treatment costs;
- Language: English language studies were eligible for inclusion;
- Publication status: published, unpublished and grey literature (e.g. conference abstracts) were eligible for inclusion.

Description of identified studies

6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

The systematic literature search identified one costing study, a conference poster (Jacob 2009 (5)), which has subsequently been reported in an unpublished manuscript (Mullan 2011a (8)). The study primarily assesses the safety and efficacy of PleurX catheters in the management of recurrent ascites in 50 patients (52 catheters) with evidence of metastatic stage IV disease in the Christie NHS Foundation Trust (the poster reports on 14 of the 50 patients). A secondary objective of the study was to determine the cost-benefit of tunnelled catheter placement (PleurX drainage) compared with conventional paracentesis, in particular, to assess whether the cost of the tunnelled catheter and repeated vacuum drainage was offset by a reduced need for repeated inpatient admissions. The patients underwent

insertion of a tunnelled peritoneal catheter between March 2008 and March 2011 and were followed up from their initial inpatient admission for conventional paracentesis until death. The cost-benefit analysis was based on the average volumes of drainage and average inpatient stay for paracentesis. These data were only available for 23 patients in the study. Mullan 2011a (8) reported that the average inpatient stay for a standard non-tunnelled drainage procedure was 2.8 days (range 1-6 days), with an average volume per inpatient drainage of 9.2 litres per person. The paper noted that all but one of the patients admitted for tunnelled catheter placement were discharged within 24 hours. The authors stated that their hospital Finance Department helped in the analysis of the costs. Table 6.1 shows the initial costs of the two procedures (paracentesis and PleurX drainage), reported in the conference poster (5). Table 6.2 compares the costs of continued treatment with the two procedures for patients with low- and high-volume recurrence. Table 6.3 presents the projected cost savings provided by the authors in the unpublished manuscript (8).

Table 6.1: Summary of initial costs (5)

Item	Paracentesis	PleurX drainage
Catheter and pack	£32.00	£245.00
Connector	£6.87	Nil
Drain fix	£4.94	Nil
Drainage bag	£0.64 p/b	Nil
1 litre vacuum bottles x4	Nil	£255.00
Procedural costs	£121.00	£121.00
Inpatient stay	£2040 (average 5 days)*	£1224 (average 3 days)
Total costs to the hospital per procedure	£2205.45	£1845.00

*The poster also reports an average of 5.5 days per hospital stay for paracentesis.

Table 6.2: Cost comparison of continued treatment for patients with low- and high-volume recurrence. (5)

Low-volume recurrence (fluid accumulates at 10 litres/month)		High-volume recurrence (fluid accumulates at 60 litres/month)	
Inpatient paracentesis x2	£4409.62	Inpatient paracentesis x3	£6614.43
PleurX vacuum bottles x10	£637.50	PleurX vacuum bottles x60	£3825.00
Monthly saving using PleurX	£3772.12	Monthly saving using PleurX	£2789.43

In this single hospital setting the initial costs of PleurX drain insertion were less than those for paracentesis. The authors suggested that continued use of the PleurX

catheter can, in the long term, realise follow-on cost-savings of £2700 to £3700 per patient per month, and a reduction in hospital bed use of 10 to 15 inpatient bed days per patient per month.

Table 6.3: Cost comparison of conventional paracentesis and tunnelled paracentesis (8).

Item	Conventional paracentesis (drainage of 9 litres of ascites)	PleurX drain (drainage of 9 litres of ascites)	Cost difference with PleurX drain
Catheter and pack	£32.00	£245.00	+£213.00
Connector	£6.87	(included with catheter and pack)	-£6.87
Drain Fix	£4.94	N/A	-£4.94
2L Drainage Bag/ 1L Bottle	£0.64/Nil	£0.64/ £63.00	+£63.00
Procedure cost/ sundries	£121.00	£121.00	£0.00
Sub-Total	**£165.45**	**£429.64**	**+£264.19**
Inpatient stay(s)	£1244.00 (3 days)	£408.00 (1 day)	-£836.45
Total cost to hospital trust for initial procedure	£2633.45	£837.64	-£1528.81
Total cost to hospital trust for subsequent procedure	£2633.45	£0	-£2633.45
Projected follow-on cost to NHS per 25 days	£2633.45	£567.00 (9 x 1 L bottles)	-£2066.45
Projected follow-on cost to NHS per calendar month (31 days)	£3265.48	£693.00 (11 x 1 L bottles)	-£2572.48

It is unclear how the total cost to the hospital for the initial procedure of conventional paracentesis is estimated. Based on the data presented in Table 6.3, the expected cost is likely to be £1,409.45 and not £2633.45. This would still provide an incremental cost saving to the Trust of £571.81 for the initial procedure when treating patients with tunnelled paracentesis in comparison to conventional paracentesis. Follow-on cost savings are likely, from the perspective of the Trust, but not to the extent presented in the manuscript due to the high level of uncertainty around their estimates.

6.1.3 Please provide a complete quality assessment for each health economics study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 7.7, appendix 7.

Only one costing study was identified, reported in both a conference abstract (Jacob 2009 (5)) and an unpublished manuscript (Mullan 2011a (8)). The authors stated that their aim was to evaluate the cost-effectiveness of PleurX catheters compared with large volume paracentesis, but did not report cost-effectiveness outcomes. The costs were obtained from a single centre and the details of when and how the costs were obtained or estimated are not provided. The quality of the study was therefore not assessed.

The cost saving estimates in the Mullan 2011a (8) manuscript are unclear, as discussed earlier. The cost-benefit analysis only considered the costs of the procedures and did not quantify any potential costing implications resulting from complications. The analysis was limited to only considering the costs that fell in the secondary care setting and did not include or attempt to estimate any other costs to the NHS, such as those resulting from frequent nurse visits in the community once patients were being managed in the home setting following tunnelled catheter placement. The costs of the catheters, consumables and inpatient stay per bed day were identical across the two reports (poster and manuscript). No further details regarding how the costs were obtained or estimated were made explicit in the manuscript. These issues detract from the quality of the study.

6.2 De novo cost analysis

6.2.1 Please provide the rationale for undertaking further cost analysis in relation to the decision-problem.

---

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

There is currently a paucity of published and unpublished economic evidence evaluating the health economic impact of PleurX catheters compared with large volume paracentesis in the management of patients with recurrent malignant ascites.

The two costing studies identified (Jacob 2009 (5), Mullan 2011a (8)) do not capture the potential costs associated with complications, such as infection and catheter failure. The costs presented are those estimated by The Christie NHS Foundation Trust during a single centre study and sufficient details for their costing estimates of hospital stay are not provided. These studies also assumed after the initial procedure (catheter insertion and first drainage) all patients treated with PleurX are self managed and this consequently excludes potential community nurse visits.

There are no studies that estimate the cost effectiveness of the PleurX peritoneal catheter in comparison to large volume paracentesis in patients with recurrent malignant ascites or a costing study that considers the impact of patient survival, care in the home setting and potential complications.

Patients

6.2.2 What patient group(s) is(are) included in the cost analysis?

The population included in the cost analysis are patients aged 18 years and older with treatment-resistant, recurrent malignant ascites. Two comparative treatment strategies are evaluated in the cost analysis in line with the NICE scope.

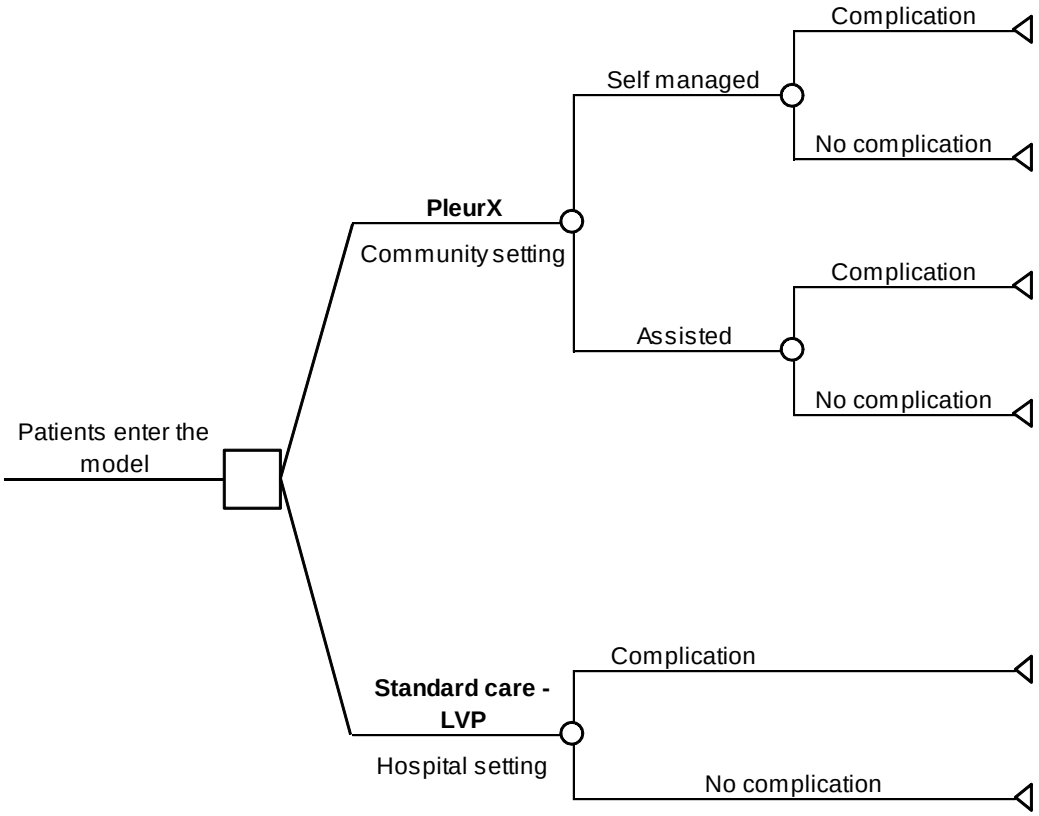
Comparator scenario one: Inpatient large volume paracentesis.

Comparator scenario two: Outpatient large volume paracentesis.

Model structure

6.2.3 Please provide a diagrammatical representation of the model you have chosen.

Figure 6.1: Model schematic of the possible patient pathways



6.2.4 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The diagrammatical representation of the model illustrates the decision point at the beginning of the decision tree, i.e. the choice between the alternative treatment options in the management of recurrent malignant ascites – PleurX or large volume paracentesis (LVP).

The current clinical pathway of care is repeated LVP in the hospital setting. During each hospital visit to drain the ascites, there is a chance the patient may suffer an adverse event, i.e. risk of complication. Patients with recurrent malignant ascites will potentially require admission for drainage multiple times per month when treated with LVP, therefore each patient in the model cohort may follow the pathway on more than one occasion (dependent on the probability of survival). As per the NICE scope, two strategies of LVP will be investigated. The two comparator scenarios investigated will both follow the pathway presented in Section 6.2.4.

As mentioned in Section 2.4, PleurX may be able to change the existing pathway. PleurX involves a one-off hospital procedure to implant the peritoneal catheter and any subsequent drainage procedures can then be managed within the home setting (i.e. in the community). A proportion of patients will require a community nurse to perform the drainage procedure (i.e. assisted). During each drainage procedure, patients are at risk of potential complications. Patients can follow the pathway multiple times during each cycle captured in the model. Ascites is drained more frequently in patients treated with the PleurX catheter in comparison to LVP.

6.2.5 Please define what the health states in the model are meant to capture.

The model structure of the cost analysis takes the form of a decision tree approach. This does not capture patients in various health states but follows the pathways of alternative treatment strategies represented by a series of decision points and 'one-off' events.

However, the decision tree model does contain an additional Markov-style element to capture the (mean) survival of patients with recurrent malignant ascites.

6.2.6 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

Patients with malignant ascites have a mean survival of between 1 to 4 months. The main benefit of the PleurX peritoneal catheter drainage system is its ability to change the existing pathway of care rather than avoiding disease progression. The cost analysis, therefore, captures potential changes to the care pathway in the management of recurrent malignant ascites.

Patients have a one-off procedure at the hospital to implant the PleurX peritoneal catheter and then subsequent drainage procedures are performed in the home

setting avoiding the need for repeat hospital admissions and inpatient stay. The model does not capture any potential impact to the health related quality of life for patients who are eager to remain in the community and avoid hospital attendance.

6.2.7 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 6.4: Key features of analysis

Factor	Chosen values	Justification
Time horizon	6 months	Patients with malignant ascites have a mean survival of 1 to 4 months, depending on the nature and extent of underlying tumor (NICE scope).
Cycle length	Weekly cycles	Patients with recurrent malignant ascites have a very short life expectancy. This analysis estimates the expected costs based on the probability of patient survival.
Half-cycle correction	Only applied to the costs of nurse visits and drainage kits once the patient is managed in the home setting.	Drainage and home visits for patients with the PleurX peritoneal catheter occur at various time points throughout the week, i.e. every other day, rather than at one time point such as the beginning of the cycle (week). One-off costs such as LVP, PleurX peritoneal catheter placement and PleurX catheter use training are assumed to occur at the beginning of the cycles and are not adjusted using the half-cycle correction.
Discount rates	N/A	The model only considers immediate outcomes therefore discounting of costs and benefits is not necessary.
Perspective	NHS	As per NICE reference case. Lack of suitable data available to analyse from a PSS perspective.

Technology

6.2.8 Are the intervention and comparator(s) implemented in the model as per their CE marking as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

The cost analysis considers implementing the PleurX peritoneal catheter in patients with recurrent malignant ascites. This is in accordance with its stated CE mark documented in sections 1.3 and 1.5.

LVP is a procedure which uses a variety of products (catheters) at different NHS sites. Two of the most common products used during LVP are the Bonnano catheter which is unlicensed to drain ascites and the multi-purpose pigtail drainage catheter which is licensed to drain ascites.

6.2.9 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The cost analysis assumes patients are treated with the PleurX peritoneal catheter until death. The cost analysis includes cases of PleurX catheter re-intervention, i.e. patients are admitted to hospital and a new drain is inserted.

Three studies (Courtney 2008 (4), Tapping 2011) (9), Mullan 2011a (8)) reported re-interventions in a total of nine patients out of one hundred and six (8.5%). Jacob 2009 (5) has been excluded in the case of the patients being double counted due to the inclusion of Mullan 2011a (8). Seven of these nine patients had their PleurX peritoneal catheters replaced, one patient had their catheter functioning resolved by intervention removing the obstruction and the remaining patient went on to receive paracentesis twice before death.

Based on these observations in the evidence and the short life expectancy of patients with recurrent malignant ascites it seems reasonable to assume patients with recurrent malignant ascites will be have their condition managed with the PleurX peritoneal catheter until death.

6.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

6.3.1 Please demonstrate how the clinical data were implemented into the model.

The clinical parameters in the model include mean survival and the complications that are consistently reported in the literature.

The patient survival data is taken from Mullan 2011a (8) which reported a mean survival of 59.4 days post tunnelled drain insertion in 50 patients in the UK healthcare setting. Other estimates of survival reported in the literature included a median survival of 30 days in the US healthcare setting (Courtney 2008 (4)). The survival of patients with recurrent malignant ascites may be underestimated in this publication

as the Kaplan-Meier plots only include the patients who died during the follow up period.

The cost analysis applies weekly cycles and the mean survival reported in Mullan 2011a (8) was converted into weeks (i.e. 8.45 weeks). This enabled the probability of survival to be calculated for a given week of the models time horizon (see section 6.3.2 for further details).

Two complications were consistently reported in the literature and are included in the cost analysis; infection and catheter failure. The definitions of these complications are consistent with the definitions reported in Rosenberg 2004 (1). Rosenberg 2004 (1) was the only comparative study available and reported the complication rates in 67 patients who underwent repeated LVP and 40 patients with PleurX. Although the study is based in the US setting, it is identified as the most appropriate in the context of the cost analysis due to its comparative nature, large sample size and the length of the follow up period. Three (4.5%) and two (3.0%) patients who underwent LVP suffered infection and catheter failure respectively over the course of the study follow up. One (3.0%) and two (4.5%) patients who had a PleurX peritoneal catheter inserted suffered infection and catheter failure respectively.

Catheter re-intervention was also included in the model. The rate of re-intervention reported in the Mullan 2011a (8) study is applied in the cost analysis. Two patients out of fifty who were followed up until death in the UK healthcare setting underwent re-insertion of the drains (i.e. 4.0%).

Sensitivity analysis will investigate the estimates for mean survival and the rates of complications.

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The rate of survival was converted to weekly transition probabilities using the formula:

$$PW = 1 / S$$

Where: *PW* = the weekly probability of death;

S = the mean survival of patients with recurrent malignant ascites (weeks).

Table 6.5: Probability of survival for the first ten weeks of the models time horizon

Week	Probability of survival
0	100%
1	88%
2	78%
3	69%
4	60%
5	53%
6	47%
7	41%
8	37%
9	32%
10	28%

The total costs of treating the cohort are multiplied by the probability of survival to estimate the expected costs for each treatment strategy.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

There was no evidence in the literature to suggest the mortality of patients changing over time for recurrent malignant ascites.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

N/A.

6.3.5 If clinical experts assessed the applicability of values available, or estimated or adjusted any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method(s) used to collect and collate the opinions.

The uncertainty around these values should be addressed in the sensitivity analysis.

Due to the paucity of evidence suitable for the costing analysis a KOL Questionnaire was developed to help support the limited evidence and/or populate the model in cases in which no data (including non-UK setting studies) was available.

UK Medical contacted eight clinicians in total. These included three radiologists, three palliative care consultants, one clinical nurse specialist and one advanced nurse practitioner.

UK Medical selected people based on their relationship, known experience with Pleurx and from links to published articles or their plans to do research. Only two participated which included Dr Laasch from the Christie NHS Foundation Trust and Dr Perkins from the Gloucestershire Hospitals NHS Foundation Trust. Their responses are disclosed and attached with this submission.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

The two nurse contacts said they did not feel they had the relevant information or experience to answer the questions properly. One Radiologist and one Palliative care consultant were on annual leave and, therefore did not reply. A palliative care consultant will provide audit results in a few months time but currently does not have the answer to the questions asked. Another radiologist said they would provide details but this never materialised.

One of the palliative care consultants (Dr Perkins) who did provide a completed KOL Questionnaire has received an educational grant of £10,000 from UK Medical (half from CareFusion) to help fund their research into Pleurx and patient experiences.

Due to the low response rate and uncertainty surrounding the estimates in the completed KOL Questionnaires, only in the cases in which the evidence base is not available have the responses from the two completed questionnaires been referenced or applied.

All of the model inputs are investigated through deterministic one-way sensitivity analysis. The results of which are explicitly reported in Section 6.6.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 6.6: The clinical variables

Parameter	Value	Reference to section in submission
Mean survival (weeks)	8.45	Section 6.3.1 and 6.3.2.
Probability of infection (LVP)	4.5%	Section 6.3.1. The complication rate when the patient is used as the outcome measure, i.e. not per procedure.
Probability of catheter failure (LVP)	3.0%	Section 6.3.1. The complication rate when the patient is used as the outcome measure.
Probability of infection (PleurX)	2.5%	Section 6.3.1. The complication rate when the patient is used as the outcome measure.
Probability of catheter failure (PleurX)	5.0%	Section 6.3.1. The complication rate when the patient is used as the outcome measure.

Table 6.7: The healthcare resource use of large volume paracentesis

Parameter	Value	Reference to section in submission
Bed days for LVP per session	2.8	Section 6.4.1.
Frequency of repeated LVP (per month)	1.22	Section 6.4.1.

Table 6.8: The healthcare resource use of PleurX

Parameter	Value	Reference to section in submission
Bed days for catheter placement	1.0	Section 6.4.1.
Probability of re-intervention (PleurX)	4.0%	Section 6.3.1.
Proportion who are self-managed	73.0%	Section 6.4.1.
Length of contact per nurse visit (hours)	0.25	Section 6.4.1. Drainage time varies between 10 and 15 minutes – upper bound applied.
Nurse visits for catheter use training	2.0	Section 6.4.1.
Nurse visits per week	3.5	Section 6.4.1.
Number of 1000ml bottle drainage kits used (per week)	3.5	Section 6.4.5.

Table 6.9: The cost per hospital bed day

Parameter	Value	Reference to section in submission
Hospital bed day	£312.00	Section 6.4.1.

Table 6.10: The costs of consumables associated with large volume paracentesis

Parameter	Value	Reference to section in submission
Catheter and pack	£32.00	Section 6.4.5.
Connector	£6.87	Section 6.4.5.
Drain	£4.94	Section 6.4.5.
2L Drainage Bag	£0.64	Section 6.4.5.
Procedure cost/sundries	£121.00	Section 6.4.5.

Table 6.11: The costs associated with the PleurX peritoneal catheter

Parameter	Value	Reference to section in submission
Catheter	£245.00	Section 6.4.5.
2L Drainage Bag and 1L Drainage kit	£64.39	Section 6.4.5.
Procedure cost/sundries	£121.00	Section 6.4.5.
Drainage kit box	£637.50	Section 6.4.5.
Cost per home visit (assisted/per hour)	£78.00	Section 6.4.1.
Cost of travel per visit (assisted)	£1.50	Section 6.4.1.

Table 6.12: The cost of complications

Parameter	Value	Reference to section in submission
Infection	£265.06	Section 6.4.7.
Catheter failure	£395.91	Section 6.4.7.
Catheter re-intervention	£742.39	Section 6.4.7.

6.3.7 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? What assumptions and/or techniques were used for the extrapolation of longer term differences in clinical outcomes between the intervention and its comparator?

No extrapolations were carried out since the duration of follow up in the published evidence adequately covered the time horizon of the model. This is supported by the short life expectancy of patients with recurrent malignant ascites.

Due to a lack of suitable data the adverse events are not captured within the weekly cycles of the model. Complication rates were not available for both LVP and PleurX per drainage. Therefore the differences in complications between large volume paracentesis and PleurX are captured by adopting the patient as the outcome measure, i.e. 4.5% of the models cohort who undergo repeated LVP will suffer an infection.

The costs of managing ascites with repeated LVP or with PleurX are estimated for each cycle in the model and multiplied by the probability of survival to calculate the expected costs.

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

- The survival of patients with recurrent malignant ascites is equivalent for both treatment strategies. Despite a number of studies demonstrating PleurX has the potential to improve the quality of life of patients, there is not sufficient evidence to suggest this increases survival.
- Patients treated with PleurX who self-manage their condition require two nurse visits to develop the level of expertise required to carry out the technique independently.
- The number of routine checkups is equivalent for PleurX patients who are self managed and for patients who undergo repeated LVP.
- Nurse visits for assisted patients are 15 minutes in length. Draining takes between 10 and 15 minutes with the PleurX drainage kit unit.
- Patients who undergo repeated LVP drain 9.2 or more litres of ascites per session (Mullan 2011a (8)).
- Patients treated with PleurX drain 3.5 litres of ascites per week. This assumption implies patients treated with PleurX will on average, drain a marginally higher volume of ascites per month than patients who undergo repeated LVP.
- For the purpose of the costing analysis assisted patients require one nurse visit per litre of ascites drained. However in reality, it is recognised the management of ascites is unique to individual patient requirements and in some cases, for example, patients may drain two litres of ascites per nurse visit and therefore require fewer nurse visits.
- The cost of the PleurX re-intervention is equal to the cost of PleurX peritoneal placement in the first instance.
- Drainage kits can be purchased separately rather than as part of a kit box (i.e. set of 10 units). UK Medical does occasionally sell the PleurX catheter kits on an individual basis depending on customer requirement.

6.4 Resource identification, measurement and valuation

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

6.4.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

Large volume paracentesis (LVP) in patients with recurrent malignant ascites is currently costed in the NHS Reference Costs (2009/10).

Table 6.13: The PbR tariffs for the "General Abdominal – Diagnostic Procedures" HRG codes

Currency code	Type	Activity	Unit cost	LOS
FZ13Z	Elective	7,329	£1,179	1.11
FZ13Z	Non-elective (long stay)	1,325	£1,965	5.10
FZ13Z	Non-elective (short stay)	5,548	£826	1.0
FZ13Z	Day case	21,541	£917	-

HRGs includes a number of OPCS surgical procedure codes. The OPCS code for draining ascites via paracentesis is T46.1. The NHS Classification Service stated in response to a UK Medical enquiry that the most appropriate OPCS code for the placement of the PleurX catheter procedure is T46.2 (see section 2.9). These two OPCS surgical procedure codes fall into the same HRG code.

List of all OPCS codes that fall under the FZ13Z HRG code:

T43.3: Diagnostic endoscopic ultrasound examination of peritoneum

T43.4: Diagnostic endoscopic ultrasound examination of peritoneum and biopsy of intraabdominal organ

T46.1: Paracentesis abdominis for ascites

T46.2: Drainage of ascites NEC

T46.3: Irrigation of peritoneal cavity

T46.8: Other specified other drainage of peritoneal cavity

T46.9: Unspecified other drainage of peritoneal cavity

T48.2: Introduction of cytotoxic substance into peritoneal cavity

T48.3: Introduction of therapeutic substance into peritoneal cavity

T48.4: Introduction of substance into peritoneal cavity NEC

T48.8: Other specified other operations on peritoneum

The costing analysis does not include the HRGs from the NHS Reference Costs for either of the LVP or PleurX catheter placement procedures. Clinical opinion and the unpublished literature from Jacob 2009 (5) and Mullan 2011a (8) emphasise that there are differences in the length of hospital admission for LVP and the PleurX catheter placement procedure. This cannot be captured if the model applied the same HRG for both procedures. An approach that includes the cost per hospital bed day and the cost of consumables for each procedure is more appropriate in this case and provides greater flexibility in the interpretation of the results. Sensitivity analysis will explore how the incremental cost to the NHS changes when the model base case estimates for cost per bed day and the length of stay for each procedure are varied.

The cost of a hospital bed day in the cost analysis has been taken from the NHS Reference Costs 2009/10. The cost per excess elective bed day is estimated to be £312. This is assumed to be the cost of a bed day for the management of patients with recurrent malignant ascites.

The length of stay per LVP session is taken from Mullan 2011a (8). The average length of inpatient admission for conventional paracentesis was estimated to be 2.8 days per episode (range 1 to 6 days) during March 2008 and March 2011. The Jacob 2009 (5) poster reports an average length of stay of between 5.0 and 5.5 days per episode. The estimate of 2.8 bed days will be applied for the inpatient LVP comparator scenario and an estimate of 1.0 bed day will be applied for the outpatient LVP scenario.

The frequency of repeated LVP is taken from the Mullan 2011a (8) which suggests a typical patient with recurrent malignant ascites require admission every 25 days and drain, on average, a volume of 9.2 litres (i.e. 1.22 LVP per patient per month). Other evidence collected relating to the frequency of LVP was the two completed KOL

Questionnaires. Gloucestershire Hospitals NHS Foundation Trust and The Christie NHS Foundation Trust reported the frequency of LVP to be 1.0 and 1.3 per patient per month respectively (i.e. 1.15 large volume paracentesis per patient per month). However, due to the limitations of the completed KOL questionnaires as noted in Section 6.3.5, the frequency reported in the Mullan 2011a (8) was applied in the base case.

PleurX peritoneal catheter

The length of hospital stay in the cost analysis for PleurX catheter placement is assumed to be one day. Mullan 2011a (8) reported all but one of 50 patients who had the PleurX peritoneal catheter inserted between March 2008 and March 2011 were discharged within 24 hours. Previously, Jacob 2009 (5) reported the mean length of stay to be three days with the intention to become a daycase procedure.

Subsequent management of ascites with PleurX is carried out in the home setting.

A proportion of patients who have the PleurX peritoneal catheter inserted will elect to self manage their condition on their own or with the assistance of a carer. Courtney 2008 (4) reported that 27% of patients in the study requested drainage was performed by a home nurse rather than undertaking the catheter use training or having their carer trained, i.e. 73% of patients are self managed. Of the patients who elect to self manage their condition, two nurse visits are required for either the patient or their carer to become familiar with the draining technique. This was based on the only completed KOL Questionnaire for this specific data point received from the Gloucestershire Hospitals NHS Foundation. Each nurse visit for catheter use training is assumed to last for a typical contact time of 20 minutes and is costed at £27 per home visit, as reported in the PSSRU Unit Costs of Health & Social Care 2010.

It is assumed assisted patients require one nurse visit per litre of ascites drained. Patients treated with PleurX drain their ascites every other day which translates to 3.5 nurse home visit per week. The frequency of drainage is consistently reported in the literature (Courtney 2008 (4), Richard 2001 (6)). Nurse visits for assisted patients are assumed to last 15 minutes, which is the upper bound of the length of time required for draining per session as reported in the Table 1.1. The hourly rate of a community nurse is estimated to be £78 (PSSRU Units Costs of Health & Social Care 2010) and a travel cost of £1.50 is also included for each nurse visit.

In the model patients treated with LVP and PleurX will on average drain 11.2 litres and 15.2 litres per month respectively, if the volume of ascites drained per paracentesis session is consistent with the Mullan 2011a (8) study (i.e. 9.2 litres). This may imply the base case analysis adopts a conservative approach because the placement of the PleurX peritoneal catheter does not lead to the patient accumulating more ascites, therefore a scenario in which the volume of ascites drained per month that is equivalent across both treatment arms would also be a fair reflection. This is explored in the sensitivity analysis (see Section 6).

6.4.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

NHS Reference Costs are appropriate for the PleurX peritoneal catheter placement. The NHS Classification Service (query reference number: 508547) indicated that the most appropriate OPCS-4.6 code to assign for the PleurX catheter placement into the abdomen/peritoneum for drainage is T46.2 (Drainage of ascites NEC).

NHS reference costs are not appropriate for the follow up costs of the PleurX peritoneal catheter in patients with recurrent malignant ascites. Subsequent drainage of ascites after the initial procedure takes place in the home setting.

Resource identification, measurement and valuation studies

6.4.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 7.9, appendix 9. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study

- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

We conducted two sets of searches for resource data and these are described in detail in Section 7.9 appendix 9.

The Pleurx resource data was identified during the searches for Pleurx efficacy, safety and cost-effectiveness. Four studies on resource use were identified and contribute to this section.

Resource data for paracentesis was sought via a second specific search. The paracentesis searches identified 958 records. These were downloaded and after deduplication 709 records remained for assessment for relevance. The vast majority of these records were not relevant to malignant ascites or did not report resource use. 44 records were assessed in detail and none of these were included in this section or found to detail any resource use that has not been previously identified during the Pleurx resource data searches. KOL Questionnaires were also developed alongside these two sets of searches to compensate for a paucity of published evidence relating to resource use. The frequency of paracentesis was taken from the Mullan 2011a (8) paper as previously described. The study and patient characteristics of this study are reported in section 5.

No studies in the searches for PleurX resource data detailed the frequency of nurse visits or the number of nurse visits required for PleurX catheter use training so implied assumptions to estimate these variables were based on the reported frequencies of drainage in the published literature (Courtney 2008 (4), Richard 2001 (6), Tapping 2011) (9)) . The study designs, patient characteristics and reported frequency of draining for each of these studies is detailed in Section 5. The implications for nurse resource use in the management of patients in the home setting are detailed in section 6.4.1.

Only one study (Courtney 2008 (4)) reported the proportion of PleurX patients who are self managed and do not require a nurse for each session, i.e. 73% (see section

6.4.1). This obviously has significant resource implications but it is not sufficiently reported in the literature, especially in the UK setting and therefore explored in the sensitivity analysis.

6.4.4 If clinical experts assessed the applicability of values available, or estimated or adjusted any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method(s) used to collect and collate the opinions.

Please see section 6.3.5.

Intervention and comparators' costs

6.4.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, technology costs should be cross-referenced to sections 1.9. Provide a rationale for the choice of values used in the cost model discussed in section 6.2.3. Uncertainty around prices in sensitivity analysis.

The technology costs of the PleurX peritoneal catheter comprise of two major elements; the catheter and the drainage kits, as reported in section 1.9.

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table 6.14: The technology costs associated with the PleurX peritoneal catheter

Device	Source	Value	Notes
Catheter (50-9050)	UK Medical	£245.00 per unit	List price (excluding VAT), July 2011. Patients are assumed to have the catheter placed indefinitely. This is a 'one-off' cost and is additional to the inpatient procedure cost of catheter placement.
Drainage kit (50-7510)	UK Medical	£63.75 per unit	List price (excluding VAT), July 2011. Drainage kits include 10 units per box at a total cost of £637.50 (1000ml per unit).

During the insertion of the PleurX peritoneal catheter a number of consumables are also required.

Table 6.15: The cost of consumables associated with the PleurX peritoneal catheter

Consumable	Source	Value	Notes
2L drainage bag and 1 litre PleurX kit	Mullan 2011a (8)	£0.63/£63.75	One PleurX drainage kit is assumed cost a tenth of the list price for a box (i.e. 10 units).
Procedure costs/sundries	Mullan 2011a (8)	£121.00	N/A

The paracentesis procedure also requires the 2 litre drainage bag and the procedure costs reported in Table 6.15 as well as a number of other consumables listed in Table 6.16.

Table 6.16: The cost of consumables associated with the PleurX peritoneal catheter

Consumable	Source	Value	Notes
Catheter and pack	Mullan 2011a (8)	£32.00	N/A
Connector	Mullan 2011a (8)	£6.87	N/A
Drain fix	Mullan 2011a (8)	£4.94	N/A

Health-state costs

6.4.6 Please summarise, if appropriate, the costs included in each health state (Explanation of definition of health-state). Cross-reference to

other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost model. The health states should refer to the states in section 6.2.5.

N/A.

Adverse-event costs

6.4.7 Please summarise the costs for each adverse event listed in section 5.7 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost model discussed in section 6.2.3. Adverse event and complications episodes. Include all adverse events and complications costs, both during and longer term post-treatment cost.

The costs of the complications captured in the model are reported in the Table 6.17. Due to a lack of data the probabilities of inpatient and outpatient management of these adverse events could not be explored. The cost analysis is, therefore, restricted to assuming that subsequent treatment for infection and catheter failure is identical in all patient cases when, in reality, this is not likely to be the case.

Table 6.17: The adverse events costs associated with the management of ascites

Adverse event	Source	Value	Notes
Infection	Assumption.	£194.06	The cost of infection is assumed to be the cost of a medical oncology consultant led first attendance visit and a 7 day course of antibiotics. This is consistent with the management of infections reported in the literature (Mullan 2011a (8), Tapping 2011) (9), Courtney 2008 (4)).
Catheter failure	Assumption.	£395.91	The cost of catheter failure includes a medical oncology consultant led first attendance visit, 250,000 unit vial of Streptokinase, an ultrasound lasting less than 20 minutes (Diagnostic

			Imaging Outpatient: RA23Z) and a contrast fluoroscopy lasting less than 20 minutes (Diagnostic Imaging Outpatient: RA16Z). These healthcare resources and therapies are consistent with patients who suffer catheter failure as reported in the Mullan 2011a (8) study.
Catheter re-intervention	Assumption.	£742.39	This is assumed to be the cost of the first PleurX peritoneal catheter placement procedure.

Miscellaneous costs

6.4.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

PSS costs have not been considered within the analysis but would likely fall on the carer of the patient with recurrent malignant ascites. Patients managed with the PleurX peritoneal catheter drain their ascites more frequently and may require assistance more regularly. However, it is not known what proportion of self managed patients undertake the drainage sessions independently and those who rely on a carer, such as a family member, and as such these costs are not known.

6.4.9 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Due the paucity of evidence (non-UK setting included) surrounding the length of stay for each procedure, sensitivity analysis will enable a number of scenarios to be explored. The estimates used in the base case analysis are believed to be the most conservative of those available.

The travel costs of nurse visits are included for the management of the assisted PleurX patients, however, the model does not include any potential ambulance costs that maybe incurred by patients who undergo repeated paracentesis and require travel to the acute trust for treatment. There is a lack of evidence documenting the

proportion of patients who require this service and consequently this variable has not been included to help reduce the level of uncertainty in the models estimates.

6.5 Sensitivity analysis

This section should be read in conjunction with NICE's 'Evaluation Pathway Programme methods guide',

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses.

All inputs used in the analysis will be estimated with a degree of imprecision.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.5.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

No uncertainty around the structural assumptions has been investigated. The model diagram presented in section 6.2.3 appropriately captures the clinical pathway of recurrent malignant ascites given the level of evidence available. Finer details such as whether a complication was an inpatient or outpatient episode could not be explored in a robust manner and would only increase the level of uncertainty involved in the cost analysis estimations.

The two comparator scenarios (inpatient and outpatient paracentesis) do not impact the patient pathways presented in the model diagram, but only the model parameters

for the length of hospital stay for the procedure. This is explored in the deterministic sensitivity analysis (section 6.6.4).

6.5.2 Was deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How variables were varied and what was the rationale for this? Where relevant, the distributions and their sources should be clearly stated. If any parameters or variables listed in section 6.2.7 were omitted from sensitivity analysis, please provide the rationale.

The cost analysis explores deterministic one-way sensitivity analysis but does not evaluate the uncertainty of the data estimates with probabilistic methods. Probabilistic sensitivity analysis was not undertaken due to a lack of appropriate data.

6.6 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Costs.
- Disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A tabulation of the mean cost results.
- Results of the sensitivity analysis

Clinical outcomes from the model

6.6.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical studies. Discuss reasons for any differences between modelled and observed results (for example,

adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

The model includes two complications (catheter failure and infection) and catheter re-intervention. The rates of complication were taken from the only comparative study available (Rosenberg 2004 (1)). The cost impact was estimated at an overall patient level because the evidence did not allow the cost impact to be estimated for each procedure and therefore to be captured within the weekly cycles of the model. The overall complication rates for PleurX and paracentesis were approximately the same; however, the costing model estimated different costs for the management of complications. This was a consequence of the model introducing the extra flexibility of exploring the costs associated with individual complications (e.g. infection, catheter failure) rather than applying an 'overall' complication cost.
The model also included a cost for catheter re-intervention for PleurX.

Table 6.18: The cost impact per patient with malignant recurrent ascites associated with complications

Complication	PleurX	Paracentesis	Incremental cost
Catheter failure	£4.85	£8.73	-£3.88
Infection	£19.80	£11.88	£7.92
Re-intervention	£29.70	£0.00	£29.70
Total	£54.35	£20.61	**£33.74**

6.6.2 Please provide details of the disaggregated costs by health state, and costs by category of cost. Suggested formats are presented below.

N/A.

Base-case analysis

6.6.3 Please present your results in the following table. List interventions and comparator(s) from least to most expensive.

Two base case comparator scenarios are evaluated:

- Scenario one: Inpatient large volume paracentesis (length of stay per session = 2.8 days).
- Scenario two: Outpatient large volume paracentesis (length of stay per session = 1.0 day).
- All other model inputs are identical – as reported in sections 6.3 and 6.4.

Table 6.19 demonstrates that in the base case scenario for LVP in the inpatient setting there is potential for cost savings in the NHS and Table 6.20 estimates that PleurX would be cost increasing to the NHS when LVP is managed on an outpatient basis.

Table 6.19: The incremental cost impact per patient (inpatient paracentesis)

	PleurX	Paracentesis	Incremental cost
Draining*	£2,239.21	£3,124.92	-£885.71
Nurse visits	£172.55	£0.00	£172.55
Complications	£24.65	£20.61	£4.04
Re-intervention	£29.70	£0.00	£29.70
Total	£2,466.11	£3,145.53	**-£679.42**

*including costs of the technology and consumables.

Table 6.20: The incremental system impact per patient (inpatient paracentesis)

Resource	PleurX	Paracentesis	Incremental
Paracentesis sessions	*	3.0	-3.0
PleurX (litres drained)	26.4	*	26.5
Hospital bed days	1.0	8.4	-7.4
Nurse visits (assisted)	23.5	0.0	23.5

Table 6.21: The incremental cost impact per patient (outpatient paracentesis)

	PleurX	Paracentesis	Incremental cost
Draining*	£2,239.21	£1,435.92	£803.29
Nurse visits	£172.55	£0.00	£172.55
Complications	£24.65	£20.61	£4.04
Re-intervention	£29.70	£0.00	£29.70
Total	£2,466.11	£1,456.53	**£1,009.58**

*including costs of the technology and consumables.

Table 6.22: The incremental system impact per patient (outpatient paracentesis)

Resource	PleurX	Paracentesis	Incremental
Paracentesis sessions	*	2.9	-2.9
PleurX (litres drained)	26.4	*	26.5
Hospital bed days	1.0	2.9	-1.9
Nurse visits (assisted)	23.5	0.0	23.5

Sensitivity analyses

6.6.4 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Comparator scenario one

Deterministic sensitivity analysis for the base case incremental cost per patient result is presented in Table 6.23 for inpatient paracentesis. Each of the data inputs are varied by +/- 20% and the percentage change to the base case result is reported.

Table 6.23: Deterministic one-way sensitivity analysis of the incremental cost impact (inpatient paracentesis)

	-20%		+20%	
Unit costs	Cost impact	% change	Cost impact	% change
Cost per bed day	-£218.85	67.8%	-£1,139.99	67.8%
Cost of paracentesis (consumables)	-£579.90	14.6%	-£778.94	14.6%
Cost of PleurX (consumables)	-£768.94	13.2%	-£589.90	13.2%
Cost of PleurX catheter drainage kits	-£992.04	46.0%	-£366.79	46.0%
Cost of infection	-£678.64	0.1%	-£680.20	0.1%
Cost of catheter failure	-£681.00	0.2%	-£677.84	0.2%
Cost of re-intervention	-£685.36	0.9%	-£673.48	0.9%
Cost of nurse visits per hour (assisted)	-£704.14	3.6%	-£654.70	3.6%
Mean survival (months)	-£605.39	10.9%	-£744.05	9.5%
Bed days per LVP session	-£153.95	77.3%	-£1,204.89	77.3%
Bed days for PleurX placement	-£744.32	9.6%	-£614.52	9.6%
Frequency of LVP (per month)	-£166.50	75.5%	-£952.98	40.3%
Proportion who suffer infection (LVP)	-£677.67	0.3%	-£681.17	0.3%
Proportion who suffer catheter failure (LVP)	-£677.04	0.3%	-£681.79	0.3%
Proportion who suffer infection (PleurX)	-£680.39	0.1%	-£678.45	0.1%
Proportion who suffer catheter failure (PleurX)	-£683.38	0.6%	-£675.46	0.6%
Proportion who require re-intervention (PleurX)	-£685.36	0.9%	-£673.48	0.9%
Proportion of self managed patients	-£615.32	9.4%	-£743.52	9.4%
Length of contact per nurse visit	-£704.14	3.6%	-£654.70	3.6%

Unit costs	-20%		+20%	
	Cost impact	% change	Cost impact	% change
(assisted)				
Number of nurse visits for catheter use training	-£687.30	1.2%	-£671.54	1.2%
Number of nurse visits per week (assisted)	-£706.05	3.9%	-£652.79	3.9%
Number of 1L drainage kits used (per week)	-£978.78	44.1%	-£380.05	44.1%

A number of deterministic sensitivity analysis graphs are presented for the most sensitive data inputs shown in Table 6.23, across plausible ranges for each of the model inputs under investigation. For example, the ranges for the length of hospital stay for each procedure are those reported in the literature.

Figure 6.2: Sensitivity analysis exploring the cost per hospital bed day

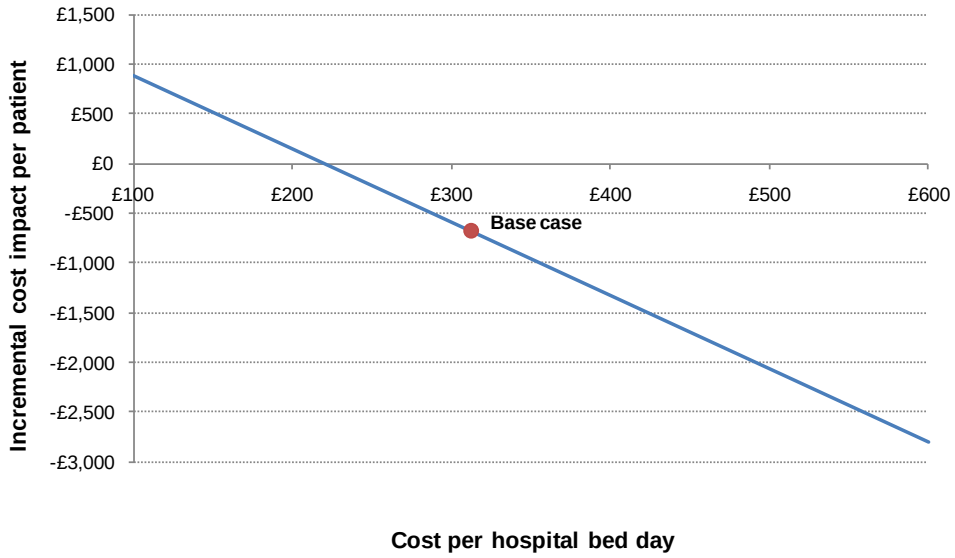


Figure 6.3: Sensitivity analysis exploring the length of stay for paracentesis

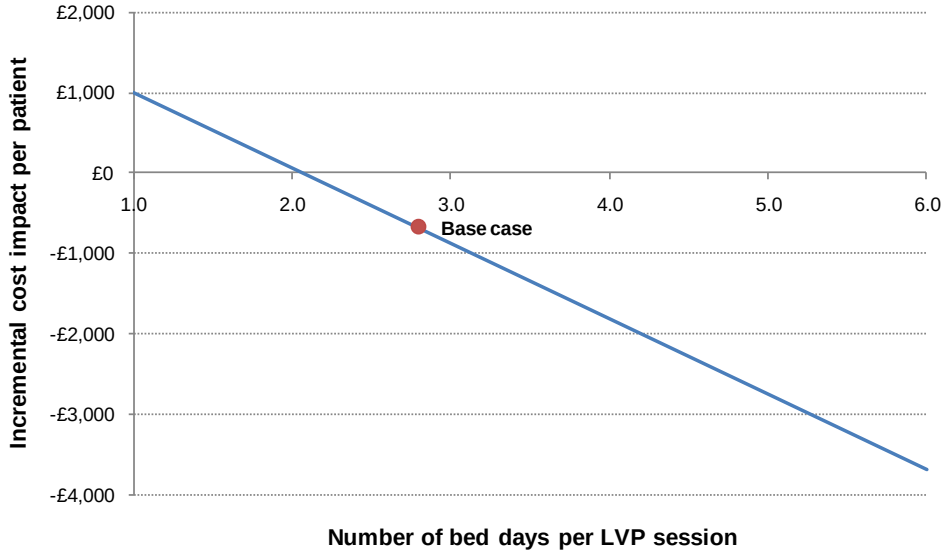


Figure 6.4: Sensitivity analysis exploring the frequency of paracentesis

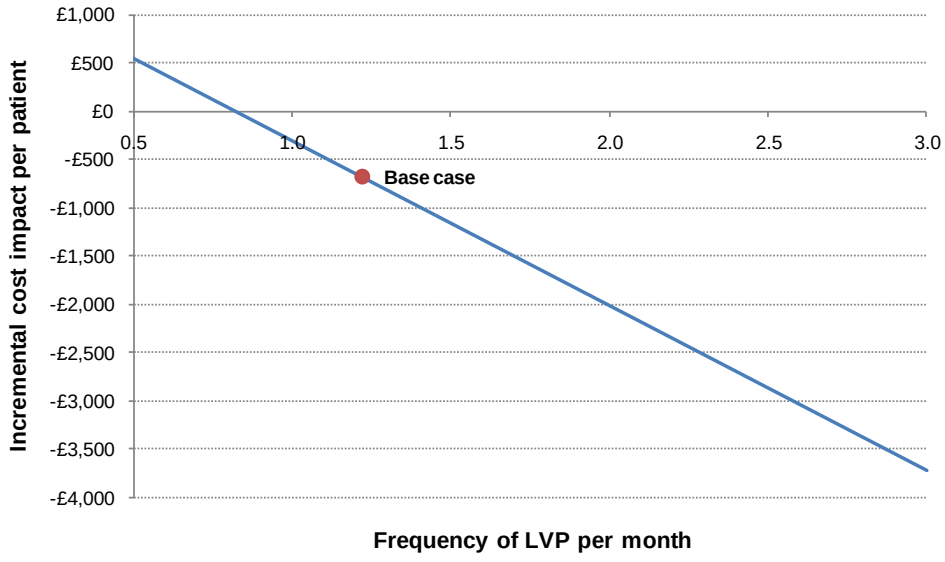


Figure 6.5: Sensitivity analysis exploring the length of stay for PleurX catheter placement

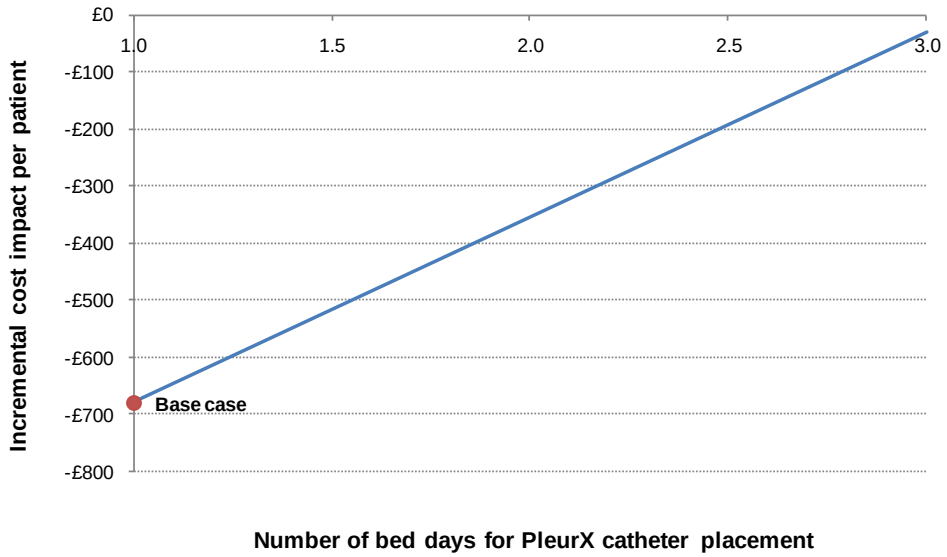


Figure 6.6: Sensitivity analysis exploring the cost of the PleurX drainage kit box

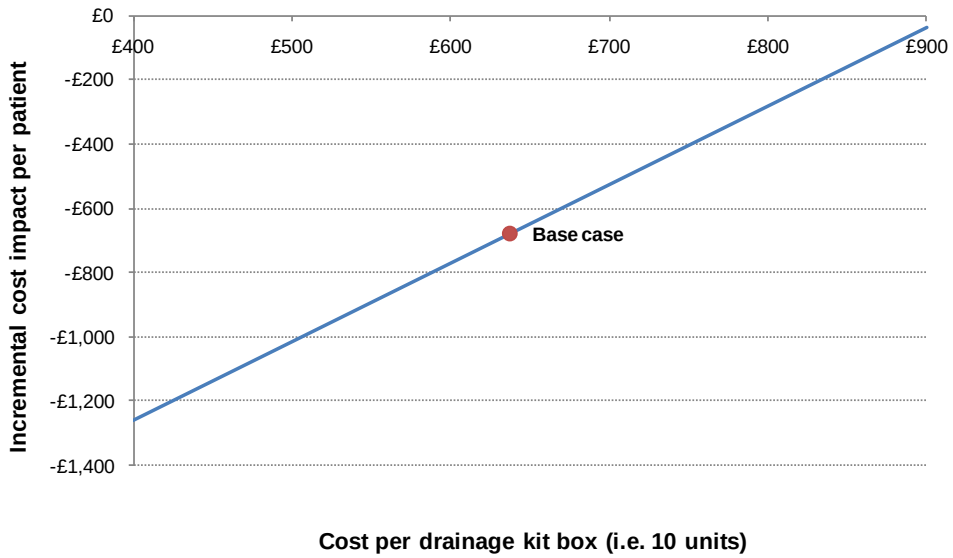
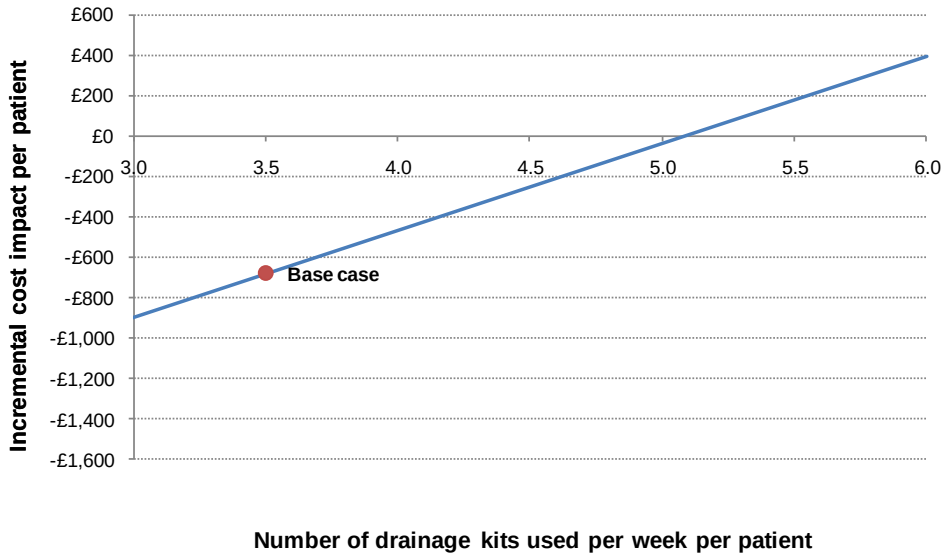


Figure 6.7: Sensitivity analysis exploring the number of drainage kit unit used per week per patient



Comparator scenario two

Deterministic sensitivity analysis for the base case incremental cost per patient result is presented in Table 6.24 for outpatient paracentesis. Each of the data inputs are varied by +/- 20% and the percentage change to the base case result is reported.

Table 6.24: Deterministic one-way sensitivity analysis of the incremental cost impact (outpatient paracentesis)

	-20%		+20%	
Parameter	**Cost impact**	**% change**	**Cost impact**	**% change**
Cost per bed day	£1,132.35	12.2%	£886.81	12.2%
Cost of paracentesis (consumables)	£1,109.10	9.9%	£910.06	9.9%
Cost of PleurX (consumables)	£920.06	8.9%	£1,099.10	8.9%
Cost of PleurX catheter drainage kits	£696.95	31.0%	£1,322.20	31.0%
Cost of infection	£1,010.35	0.1%	£1,008.80	0.1%
Cost of catheter failure	£1,007.99	0.2%	£1,011.16	0.2%
Cost of re-intervention	£1,003.64	0.6%	£1,015.52	0.6%
Cost of nurse visits per hour (assisted)	£984.85	2.4%	£1,034.30	2.4%
Mean survival (months)	£850.29	15.8%	£1,154.89	14.4%
Bed days per LVP session	£1,197.24	18.6%	£821.91	18.6%
Bed days for PleurX placement	£944.68	6.4%	£1,074.47	6.4%
Frequency of LVP (per month)	£1,245.27	23.3%	£883.88	12.5%
Proportion who suffer infection (LVP)	£1,011.32	0.2%	£1,007.83	0.2%
Proportion who suffer catheter failure (LVP)	£1,011.95	0.2%	£1,007.20	0.2%
Proportion who suffer infection (PleurX)	£1,008.61	0.1%	£1,010.55	0.1%

Parameter	-20%		+20%	
	Cost impact	% change	Cost impact	% change
Proportion who suffer catheter failure (PleurX)	£1,005.62	0.4%	£1,013.54	0.4%
Proportion who require re-intervention (PleurX)	£1,003.64	0.6%	£1,015.52	0.6%
Proportion of self managed patients	£1,073.68	6.3%	£945.47	6.3%
Length of contact per nurse visit (assisted)	£984.85	2.4%	£1,034.30	2.4%
Number of nurse visits for catheter use training	£1,001.69	0.8%	£1,017.46	0.8%
Number of nurse visits per week (assisted)	£982.95	2.6%	£1,036.20	2.6%
Number of 1L drainage kits used (per week)	£710.21	29.7%	£1,308.94	29.7%

Figure 6.8: Sensitivity analysis exploring the cost per hospital bed day

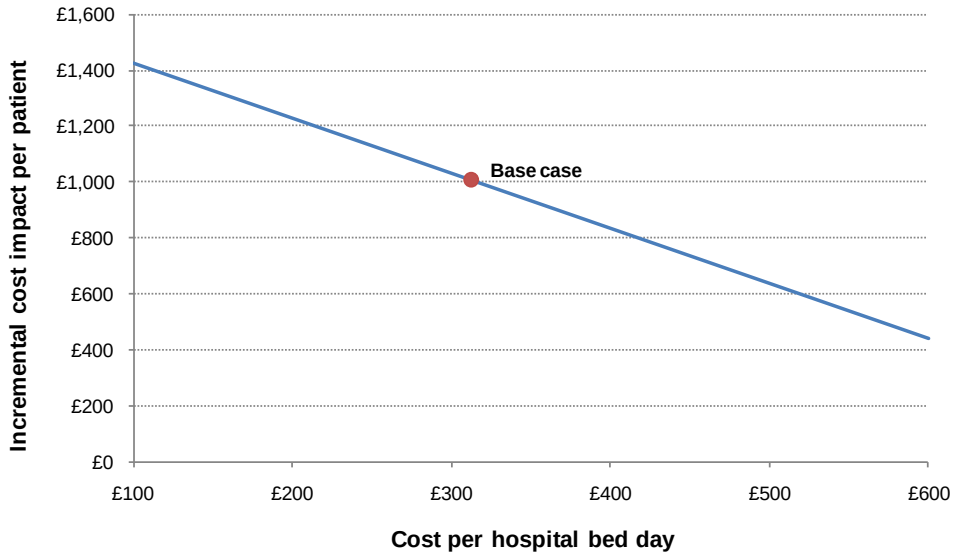


Figure 6.9: Sensitivity analysis exploring the length of stay for paracentesis

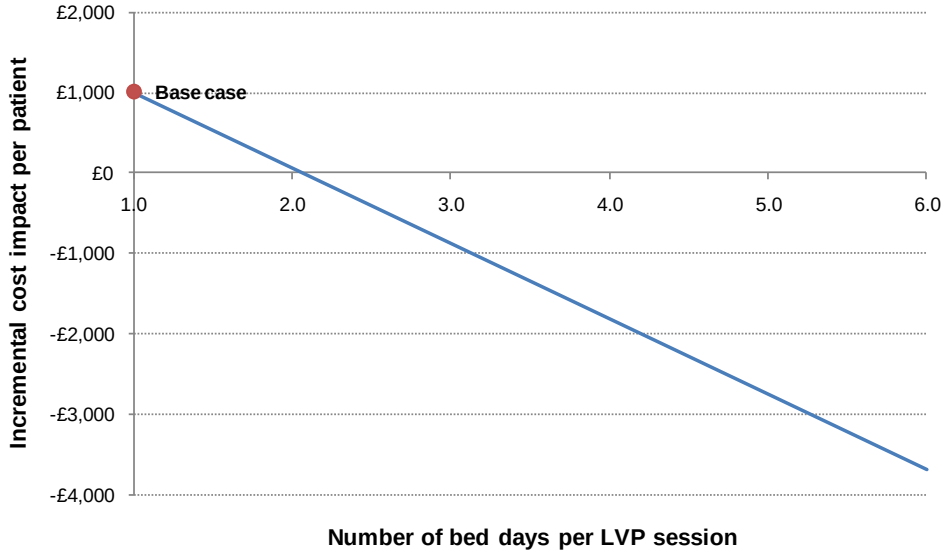


Figure 6.10: Sensitivity analysis exploring the frequency of paracentesis

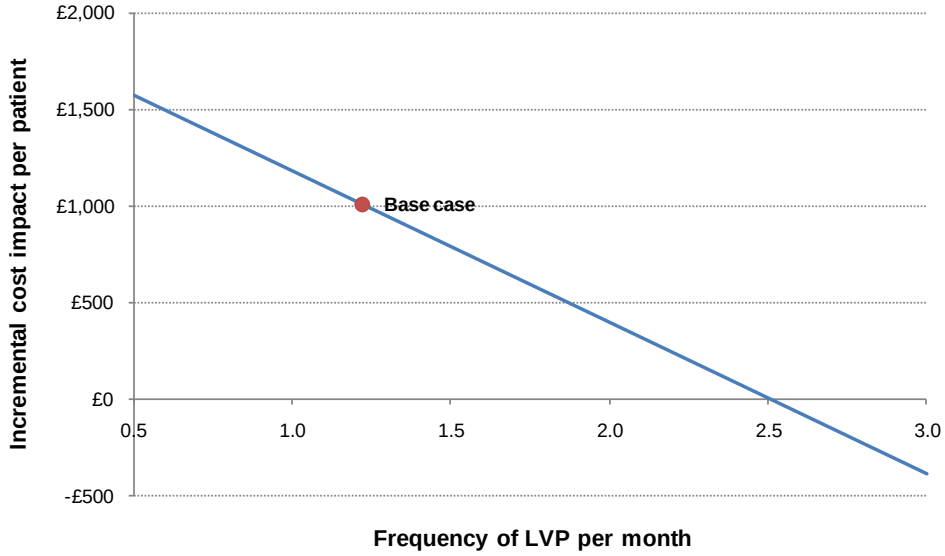


Figure 6.11: Sensitivity analysis exploring the length of stay for PleurX catheter placement

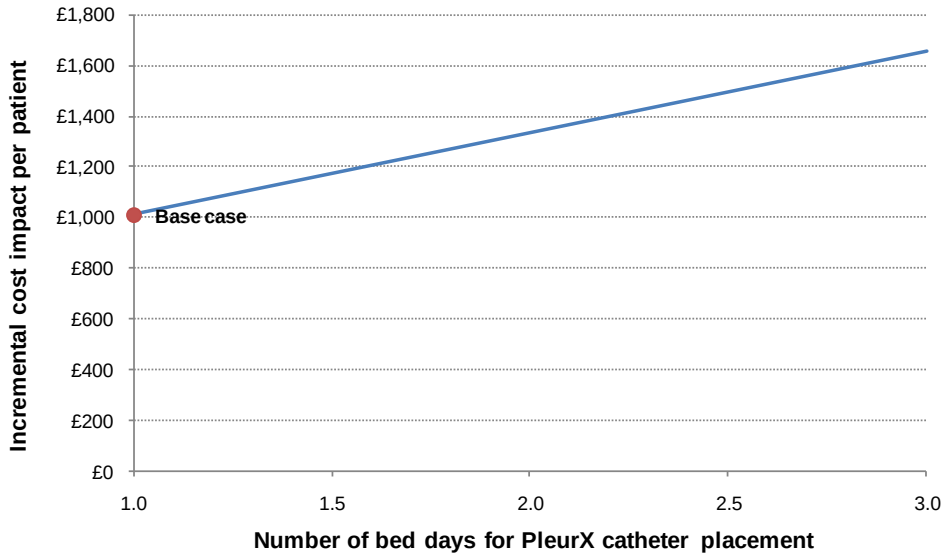


Figure 6.12: Sensitivity analysis exploring the cost of the PleurX drainage kit box

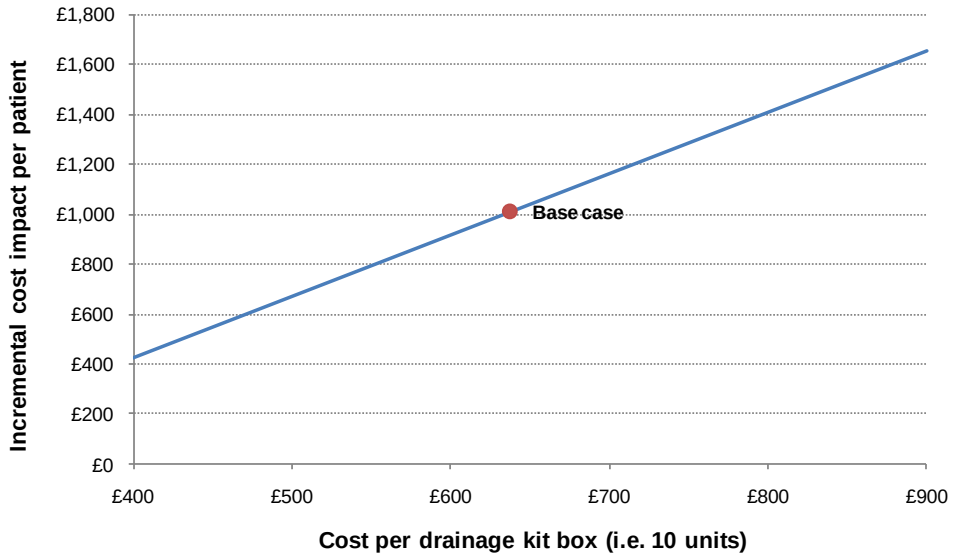
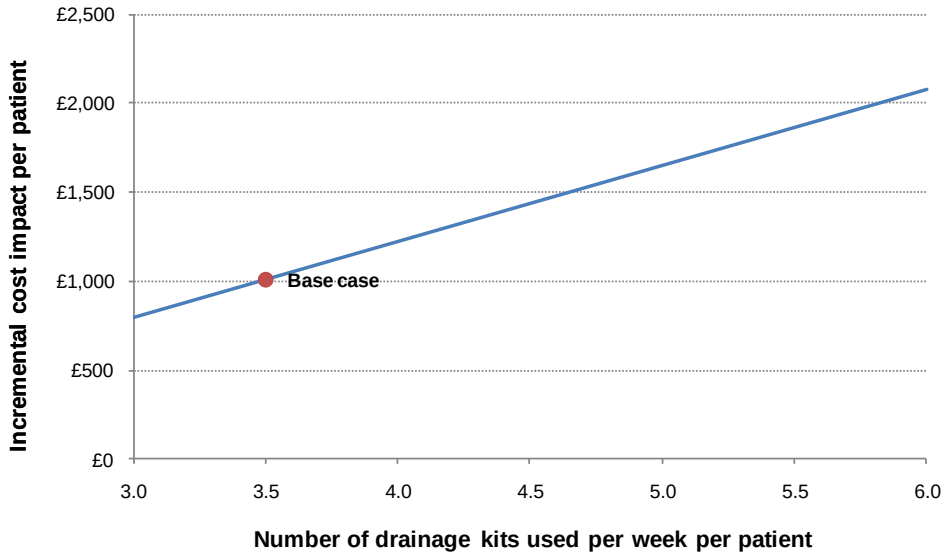


Figure 6.13: Sensitivity analysis exploring the number of drainage kit unit used per week per patient



6.6.5 Please present the results of PSA.

N/A.

6.6.6 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

N/A.

6.6.7 What were the main findings of each of the sensitivity analyses?

The sensitivity analysis demonstrates that the survival of patients with recurrent malignant ascites, complications and nurse visits do not substantially influence the incremental cost per patient treating with PleurX. The key drivers are listed in section 6.6.8 however additional deterministic sensitivity analysis was carried out for each of the key drivers and the implications are discussed below.

Comparator scenario one (inpatient paracentesis)

In the base case scenario the cost per hospital bed day was estimated to be £312, in line with the cost of an elective excess bed day as reported in the NHS Reference Costs 2009/10. Figure 6.2 demonstrates that PleurX is cost neutral in comparison to large volume paracentesis when the cost per bed day is approximately £215. Jacob 2009 (5) and Mullan 2011a (8) report the cost per bed day for the management of patients with recurrent malignant ascites is £400 at the Christie NHS Foundation Trust and this would result in cost savings of approximately £1,400 per patient over the models time horizon of six months.

Figure 6.3 demonstrates that PleurX is cost neutral when large volume paracentesis requires approximately 2.0 bed days. Jacob 2009 (5) reports the average number of bed days per session of paracentesis to be 5.0 days and this would achieve approximately £2,800 of cost savings per patient.

Figure 6.4 shows that PleurX is still cost savings when the frequency of large volume paracentesis is less than once per month. Clinical opinion and the literature suggest the frequency would always be equal to or higher than once per month.

The number of bed days for PleurX catheter placement require upwards of approximately 3.0 days before the intervention becomes cost increasing to the NHS as presented in Figure 6.5. It is anticipated PleurX catheter placement will result in patients being discharge within 24 hours in the majority of cases.

Figure 6.6 and 6.7 demonstrate that by significantly increasing the cost of the drainage kit box or the number of kits used by each ascites patient per week the NHS can still achieve cost savings from adopting PleurX. The analysis already assumes PleurX patients are draining approximately 4 more litres of ascites per month in comparison to paracentesis patients. This may imply a scenario in which a higher volume of ascites is drained in the PleurX treatment arm would be unfair if all the other model inputs remained the same.

Sensitivity analysis demonstrated that PleurX in comparison to large volume paracentesis has substantial scope for cost savings in the NHS.

Comparator scenario two (outpatient paracentesis)

Figures 6.8 to 6.13 show that the scope for cost savings when PleurX is compared to outpatient paracentesis is limited. However, the Mullan 2011a (8) study strongly suggests that the majority of patients require longer inpatient stay for drainage based on the reported average of 2.8 days (range 1 to 6 days) for 50 patients in the UK setting so the outpatient paracentesis comparator may not provide a fair reflection of clinical practice.

6.6.8 What are the key drivers of the cost results?

The key drivers of the cost results are the cost per hospital bed day, the length of hospital stay for paracentesis, frequency of paracentesis, the cost of the PleurX drainage kits and the number of 1L PleurX drainage kits used per week.

6.7 Validation

6.7.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The clinical and economic evidence was systematically identified and reviewed. It has been recognised that there is a paucity of evidence that compares PleurX to paracentesis in the management of recurrent malignant ascites which led to the development of the KOL Questionnaire to help populate the economic model. Unfortunately as documented in section 6.3.5 the number of responses was too low to provide reliable and robust data inputs. However, extensive sensitivity analysis was explored (see section 6), the assumptions (section 6.3.8) and limitations (section 6.9.3) of the model have been made explicit and given the evidence base and volumes of ascites drained per patient per month it is believed the model provides a fair reflection of clinical practice and reality. The model structure and calculations have been quality assured by another health economic modeller who did not contribute to the development of the original model.

6.8 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

6.8.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical effectiveness or cost due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

No additional analyses of subgroups were undertaken (in line with the NICE scope).

6.8.2 Please clearly define the characteristics of patients in the subgroup.

N/A

6.8.3 Please describe how the statistical analysis was undertaken.

N/A

6.8.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.6.3 (Base-case analysis).

N/A

6.8.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

N/A

6.9 Interpretation of economic evidence

6.9.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results from this cost analysis are consistent with Jacob 2009 (5) and Mullan 2011a (8) in that cost savings are achieved in the NHS when comparing PleurX to inpatient large volume paracentesis (LVP). The cost savings presented in Section 6 are not as substantial as those reported in literature, as anticipated. This is due to the introduction of other factors in the model such as patient survival, complications, catheter re-intervention, catheter use training and nurse visits. However, the incremental cost per patient result presented in the base case scenario in Section 6 is still a very positive result for supporting the adoption of PleurX in the NHS considering the assumptions of the model and the current evidence base. The cost per hospital bed day was also extracted from a national NHS database rather than from the daily rate reported in the studies.

Jacob 2009 (5) and Mullan 2011a (8) did not compare PleurX to outpatient LVP. Mullan 2011a (8) presented their savings based on the average length of stay for all admissions recorded during a three year follow period between March 2008 and March 2011, i.e. 2.8 days (range 1.0 – 6.0 bed days). However, if the analysis did consider a outpatient comparator scenario, an estimate of the incremental costs would demonstrate the procedure to be slightly cost increasing to the NHS. This emphasises that the length of stay for LVP is a key driver of the incremental cost.

6.9.2 Is the cost analysis relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

The incremental cost estimates presented in Section 6 are relevant to the patient population identified in the NICE scope (see Section 4). The results are presented at a per patient level and the potential size of the relevant ascites population in the UK is reported in Section 2.2.

6.9.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

One of the key strengths of the model is that it captures the patient and clinical pathway of the condition despite the paucity of evidence. A number of parameters (data inputs) have been introduced such as patient survival, complications, and care in the home setting which have previously not been evaluated. The model includes weekly cycles which help capture the short term outcomes and costs associated with the nature of the disease. The model structure allows the length of hospital stay for each procedure to be evaluated and this provides a high level of flexibility in the interpretation of the results. This has enabled the key drivers of incremental cost to be investigated over their plausible ranges.

The key weakness of the model is the level of uncertainty associated with the model data inputs. However, a number of methods have been applied to help compensate for this weakness and reduce the risk of incorrectly interpreting the results, in the form of extensive sensitivity analysis. Other costs to the NHS such as differentiating between inpatient and outpatient complications, and ambulance journeys to the hospital for patients who undergo LVP could not be included due to a lack of available data.

6.9.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further analyses could include clinical studies monitoring the average length of stay for conventional paracentesis in the UK NHS setting to support the limited evidence

base and findings presented in Section 6. However, Mullan 2011a (8) does follow a high number of patients from initial their paracentesis procedure until death over a three year period in the UK setting and this may adequately reflect current practice. Clinical opinion and inference from the sensitivity analysis may reduce the need for further research in making a sound judgement.

References

Please use a recognised referencing style, such as Harvard or Vancouver.

1. Rosenberg S, Courtney A, Nemcek AA, Omary RA. Comparison of percutaneous management techniques for recurrent malignant ascites. Journal of Vascular & Interventional Radiology. 2004;15:1129-31.

2. [redacted]

3. Courtney A, Nemcek AA, Rosenberg S, Tutton S, Darcy M, Gordon G. Prospective evaluation of the PleurX catheter when used to treat recurrent ascites associated with malignancy. Journal of Vascular & Interventional Radiology. 2008;19:1723-31

4. Jacob AD, Hassan H, Puro P, Laasch H-U. Long-term tunnelled PleurX (c) peritoneal catheters in the management of recurrent malignant ascites: inital experience and cost effectiveness (poster). In: Society of Gastrointestinal Intervention; 2009.

5. Richard HM, Coldwell DM, Boyd-Kranis RL, Murthy R, Van Echo DA. Pleurx tunneled catheter in the management of malignant ascites. Journal of Vascular & Interventional Radiology. 2001;12:373-5.

6. Saiz-Mendiguren R, Gomez-Ayechu M, Noguera JJ, Garcia-Lallana A, Marginet C, Cano D, et al. Permanent tunneled drainage for malignant ascites: initial experience with the PleurX catheter. Radiologia. 2010;52:541-45.

7. Mullan D, Laasch H-U, Jacob A, Hassan H. Tunnelled intra-peritoneal catheters in the management of malignant ascites: Complications and cost implications [manuscript provided by authors]. 2011a.

8. Tapping CR, Ling L, Razack A. PleurX drain use in the management of malignant ascites: safety, complications, long-term patency and factors predictive of success. British Journal of Radiology. 2011:doi:10.1259/bjr/24538524.

9. Tapping CR, Ling L, Razack A. PleurX drain use in the management of malignant ascites-safety, complications, long term patency and factors predictive of success. CardioVascular and Interventional Radiology. 2011;34:S4.

10. Brooks RA, Herzog TJ. Long-term semi-permanent catheter use for the palliation of malignant ascites. Gynecologic Oncology. 2006;101:360-2.

11. Iyengar TD, Herzog TJ. Management of symptomatic ascites in recurrent ovarian cancer patients using an intra-abdominal semi-permanent catheter. American Journal of Hospice & Palliative Medicine. 2002;19:35-8.

12. Mullan D, Laasch H-U, Jacob A, Hassan H. Fibrinolysis in the management of malignant ascites and non-functioning intra-peritoneal tunnelled catheters [manuscript provided by authors]. 2011b.

13. US Food and Drug Administration. Maude adverse event report: Denver Biomedical Inc, Pleurx peritoneal catheter [report number 905214]. Washington, DC: US Food and Drug Administration; 2007. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=905214

14. US Food and Drug Administration. Maude adverse event report: Cardinal Health Pleurx peritoneal catheter [report number 1423507-2008-00042]. Washington, DC: US Food and Drug Administration; 2008. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=1040411

15. NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness. CRD's guidance for those carrying out or commissioning reviews. 2nd ed. York: NHS Centre for Reviews and Dissemination, University of York; 2001.

16. National Institute for Health and Clinical Excellence. The PleurX peritoneal catheter drainage system for vacuum assisted drainage of treatment-resistant, recurrent malignant ascites: final scope. London: National Institute for Health and Clinical Excellence; 2011.

7 Appendices

7.1 Appendix 1

7.1.1 IFU, scientific discussion or drafts.

7.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

7.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Table 7.2.1 provides information on the specific databases and resources searched, the service provider, and the date on which the search was conducted. Following the extension of the inclusion criteria to include case reports a further search of the FDA website was undertaken to search the Maude database.

Table 7.2.1: Resources searched to identify relevant studies

Resource	Interface/platform/URL	Date searched
MEDLINE and MEDLINE In process	Ovid	29/6/11
EMBASE	Ovid	29/6/11
INSPEC	Ovid	29/6/11
Science Citation Index (Web of Science) and Conference Proceedings Citation Index	Web of Science	29/6/11
CENTRAL (Cochrane Library)	Cochrane Library	29/6/11
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library	29/6/11
Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library	29/6/11
Health Technology Assessment database (HTA)	Cochrane Library	29/6/11
ClinicalTrials.gov	http://clinicaltrials.gov/ct2/results?term=ascites+AND+catheter&show_down=Y#down	29/6/11
WHO International Clinical	http://apps.who.int/trialsearch/	30/6/11

Resource	Interface/platform/URL	Date searched
Trials Registry Platform (ICTRP)		
European Trials Register	https://www.clinicaltrialsregister.eu/	30/6/11
BSIR (British Society for Interventional Radiologists) annual meeting conference	http://www.bsir.org/content/AnnualMeetingHome.aspx	30/6/11
EAPC conference (European Association for Palliative Care)	EAPC 2009 http://www.eapcnet.eu/LinkClick.aspx?fileticket=ZF1mKoUgDf8%3d&tabid=606 EAPC 2010 http://www.eapcnet.eu/LinkClick.aspx?fileticket=tJBqxBVO7Ew%3d&tabid=746 EAPC 2011 – abstracts not yet available	1/7/11
SGI (Society of gastrointestinal Intervention)	SGI 2010 e-abstract book http://www.sgiw.org/upload/elibrary/SGI%20abstract_2010.pdf SGI 2009 e-abstract book http://www.sgiw.org/upload/elibrary/SGI%20abstract_2009.pdf	1/7/11
British Society of Gastrointestinal and Abdominal Radiology (BSGAR)	Abstracts of conferences do not seem to be available on the web	1/7/11
British Society of Gastroenterology (BSG)	BSG Annual meeting 2011 http://gut.bmj.com/content/60/Suppl_1.toc BSG Annual Meeting 2010 http://gut.bmj.com/content/vol59/1_MeetingAbstracts/ BSG Annual meeting 2009 http://gut.bmj.com/content/58/Suppl_1.toc	30/6/11
FDA reports	http://www.fda.gov/	30/6/11 and 1/8/11
NICE appraisals	http://www.nice.org.uk/	30/6/11
NHS EED	Cochrane Library	29/6/11
HEED	Wiley Interscience	4/7/11
CEA Registry	https://research.tufts-nemc.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx	29/6/11
Econlit	Ovid interface	30/6/11

7.2.2 The date on which the search was conducted.

See table 7.2.1 for relevant information.

7.2.3 The date span of the search.

The resources were searched over the following time periods or for all records available to be searched on the day the search was conducted:

- MEDLINE and MEDLINE In-Process (1948 to June 28, 2011);
- EMBASE (1980 to 2011 week 25);
- INSPEC (1987 to 2011 week 25);
- Science Citation Index (Web of Science) (1899 to present);
- Conference Proceedings Citation Index - Science (1990 to present);
- Cochrane Library (CENTRAL, CDSR, DARE, NHS EED, HTA) (29 June 2011);
- ClinicalTrials.gov (29 June 2011);
- ICTRP (30 June 2011);
- European Trials Register (30 June 2011);
- BSIR abstracts (30 June 2011);
- EAPC abstracts (1 July 2011);
- SGI abstracts (1 July 2011)
- BSGAR abstracts (1 July 2011)
- BSG abstracts (30 June 2011);
- FDA website (30 June 2011 and 1 Aug 2011);
- NICE website (30 June 2011);
- CEA Registry (29 June 2011);
- Econlit (30 June 2011);
- HEED (4 July 2011).

7.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete strategies used, including all search terms, are presented below.

MEDLINE and MEDLINE In process

1. (PleurX or pleur x).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (26)
2. ((continuous or permanent or indwelling or tunnel$) adj10 ascites).ti,ab. (138)
3. Ascites/ and catheters, indwelling/ (42)
4. or/1-3 (192)

5. animals/ not (humans/ and animals/) (3520949)
6. 4 not 5 (169)
7. limit 6 to english language (136)

EMBASE

2 (PleurX or pleur x).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (63)
3 ((continuous or permanent or indwelling or tunnel$) adj10 ascites).ti,ab. (151)
4 indwelling catheter/ and ascites/ (27)
5 or/1-3 (228)
6 limit 4 to english language (190)

INSPEC

1 (PleurX or pleur x).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
2 ((continuous or permanent or indwelling or tunnel$) adj10 ascites).ti,ab. (1)
3 or/1-2 (1)
4 limit 3 to english language (1)

The record retrieved was an animal study and was not downloaded.

Science Citation Index (Web of Science) and Conference Proceedings Citation Index – Science

#1 32 TS=(PleurX OR "pleur X") Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=All Years
#2 93 TS=(continuous or permanent or indwelling or tunneled or tunnelled or tunneling or tunnelling) SAME TS=ascites AND Language=(English) Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All Years
#3 123 #1 OR #2 AND Language=(English) Databases=SCI-EXPANDED, SSCI, CPCI-S, CPCI-SSH Timespan=All Years

CENTRAL, CDSR, DARE, HTA, NHS EED were all searched on the Cochrane Library.

#1 (PleurX) (6)
#2 "pleur x" (0)
#3 (continuous or permanent or indwelling or tunnel*) and ascites (100)

#4 (#1 OR #2 OR #3) (105)
#5 MeSH descriptor Ascites explode all trees (246)
#6 MeSH descriptor Catheters, Indwelling explode all trees (860)
#7 (#5 AND #6) (2)
#8 (#4 OR #7) (105)

The following numbers of records were retrieved from the Cochrane Library:

CENTRAL 24 records
HTA 1
NHSEED 4 records
DARE 2 records
COCHRANE reviews 72 (but only 1 was relevant)

Clinicaltrials.gov

Search strategy:
(ascites AND catheter) OR (ascites AND PleurX) OR (ascites AND pleur)

Nine trial records were retrieved: NCT01077063, NCT01188746, NCT00603200, NCT01030185, NCT00907673, NCT01065246, NCT00822809, NCT00326885, NCT01224327.

Of these trials, two trials are potentially relevant: NCT01077063 and NCT01188746. Both were currently recruiting participants as of 1 July 2011 and both have a completion date in 2012.

WHO International Clinical Trials Registry Platform (ICTRP)

Search strategy:
pleur AND ascites OR PleurX AND ascites OR pleur-x AND ascites (1)

The identified record had already been retrieved from Clinicaltrials.gov.

Search strategy:
indwelling AND ascites OR permanent AND ascites OR continuous AND ascites OR tunnel* AND ascites (2)

Neither of the 2 identified records was relevant:

- ISRCTN58150114 A controlled multicentre study comparing early treatment with polytetrafluoroethylene (PTFE) covered stents (Viator) versus optimised medical treatment in patients with cirrhosis and a high risk variceal bleeding episode;
- ISRCTN53863270. A Randomised Study to Evaluate the Impact of Malignant Ascites on Well-Being and the Role of Breathing Exercises in Delaying the Reaccumulation of Recurrent Ascites.

European Trials Register

Search terms:
Pleur
PleurX
Pleur-x

Ascites AND catheter* retrieved 6 documents but none were about PleurX and were not downloaded (EudraCT Number:2009-014076-22, EudraCT Number:2007-003059-36, EudraCT Number:2009-014377-40, EudraCT Number:2009-014378-16, EudraCT Number:2009-017082-39, EudraCT Number:2010-019547-19)

FDA website

Search terms: PleurX
4 records, 2 downloaded.

The search was repeated on 1 Aug 2011 searching the Maude database with the search term PleurX. This yielded 54 records. Of these, two records were for peritoneal drainage. One had been previously downloaded, so one further record was downloaded for assessment.

NICE website

Search terms:
PleurX

The PleurX page was returned: http://guidance.nice.org.uk/index.jsp?action=byId&o=13473

Econlit

1 (pleur or PleurX or pleur-x).mp. [mp=heading words, abstract, title, country as subject] (0)
2 ascites.mp. [mp=heading words, abstract, title, country as subject] (0)
3 or/1-2 (0)

Conference websites

BSG Annual meeting 2011 http://gut.bmj.com/content/60/Suppl_1.toc
BSG Annual Meeting 2010 http://gut.bmj.com/content/vol59/1_MeetingAbstracts/
BSG Annual meeting 2009 http://gut.bmj.com/content/58/Suppl_1.toc

All sites were searched on 30/6/11 using the following terms:

Search terms: PleurX
Pleur
Pleur-x

HEED

Search terms:
PleurX
Pleur x

1 record was identified but this had already been identified in other searches.

CEA registry

Search term:
Ascites

0 results

7.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

UKMedical provided posters presented at conferences held in 2011 and manuscripts of three unpublished papers by [redacted] and Mullan (2).

7.2.6 The inclusion and exclusion criteria.

The clinical evidence review employed the following inclusion and exclusion criteria.

Participants

Eligible participants were adults (aged 18 and over) with treatment-resistant, recurrent malignant ascites.

Interventions

The intervention was the PleurX peritoneal catheter drainage system.

Comparators

The comparators were inpatient or outpatient large volume paracentesis (abdominal taps). No subgroups were specified in the NICE scope.[5]

Outcomes

The outcomes of interest were:

- Successful device deployment;
- Successful drainage of the ascitic fluid;
- Resolution of symptoms (i.e. bloating, nausea, acid reflux, reduced appetite, perception of body image, psychological well-being and quality of life outcomes);
- Frequency of drainage;
- Resource use outcomes such as re-admission rates, reinterventions and duration of hospital stay (i.e. total number of hospital bed days related to paracentesis after initial drainage);
- Catheter site infections;
- Peritonitis;
- Catheter occlusion;
- Other device-related adverse events, e.g. haemorrhage, bowel perforation.

Study Types

Comparative and single-arm trials of any duration were eligible for inclusion in the reviews of clinical effectiveness and adverse events. Studies published as abstracts

---

[5] National Institute for Health and Clinical Excellence. The PleurX peritoneal catheter drainage system for vacuum assisted drainage of treatment-resistant, recurrent malignant ascites: final scope. London: National Institute for Health and Clinical Excellence; 2011.

or conference presentations were to be included in the primary analysis if an associated full published paper could not be found. Unpublished data were eligible for inclusion, as were relevant data reported in technology assessments including those produced for NICE, FDA reports and other regulatory agencies.

Studies of any length and with any number of patients were eligible for inclusion.

Animal studies were excluded. Single case reports were initially excluded but, following discussions with NICE, the inclusion criteria were extended to include case reports.

7.2.7 The data abstraction strategy.

The following data were extracted for this review.

Trial details

- Trial acronym, name or number (if available);
- Intervention;
- Comparator;
- Population.

Methodology

- Location;
- Design;
- Duration of study or follow-up;
- Recruitment procedure ;
- Intervention and comparator details (e.g. dose, administration, etc.);
- Primary outcomes;
- Secondary outcomes;
- Eligibility criteria (inclusion and exclusion).

Patient Characteristics

- Age;
- Gender composition;
- Ethnicity;
- Extent of ascites;
- Primary malignancy and comorbidities;
- Ascitic fluid drainage prior to PleurX intervention.

Outcome Measures for:

- Successful device deployment;
- Successful drainage of the ascitic fluid;
- Resolution of symptoms;
- Frequency of drainage;
- Resource use outcomes;
- Catheter site infections;
- Peritonitis;
- Catheter occlusion;
- Other device-related adverse events.

Details of Statistical Analysis:

- Statistical analysis used;
- Confidence interval;
- Significance level.

Quality Assessment

- Was the study a randomised controlled trial?
- Was the study based on a representative sample selected from a relevant population?
- Were the criteria for inclusion explicit?
- Did all individuals enter the survey at a similar point in their disease progression?
- Was follow-up long enough for important events to occur?
- Were outcomes assessed using objective criteria or was blinding used?
- If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?

Treatment Details

- Number of patients who received treatment;
- Ascitic fluid drainage at initial catheter placement;
- Subsequent ascitic fluid drainage (number of sessions performed and by whom);
- Frequency of drainage sessions;
- Volume of fluid drained in each session;

Economic Evaluations

- Costs of the treatment;
- Resource use;
- Costs of adverse events and complications.

7.3 Appendix 3: Quality assessment of RCT(s) and non-RCT(s) (section 5.4)

7.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Separate critical appraisals for each of the individual included studies are presented below. A summary table is provided in the main text of the report (Section 5.4).

Study ID	**Rosenberg 2004 (1)**	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/ N/A)**
Was the study based on a representative sample selected from a relevant population?	Authors conducted a retrospective search of their interventional database for patients with recurrent malignant ascites from April 1999 to September 2002. Authors acknowledged the potential for selection and information bias.	Unclear
Were the criteria for inclusion explicit?	Eligibility criteria were pre-specified.	Yes
Did all individuals enter the survey at a similar point in their disease progression?	Patients had undergone at least two previous paracenteses and presented with either cytologically proved malignant ascites or clinically suspected malignant ascites caused by reaccumulation of fluid and diagnosis of cancer.	Yes
Was follow-up long enough for important events to occur?	Study period was 41 months	Yes
Were outcomes assessed using objective criteria or was blinding used?	Patients were given standard instructions for follow-up and infection/complication surveillance, and were asked to report back if they had any signs of infection, difficulties draining the catheter, or other problems.	No
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	N/A	N/A

Study ID	[redacted]	
Study question	[redacted]	[redacted]
Was the study based on a representative sample selected from a relevant population?	[redacted]	[redacted]
Were the criteria for inclusion explicit?	[redacted]	[redacted]
Did all individuals enter the survey at a similar point in their disease progression?	[redacted]	[redacted]
Was follow-up long enough for important events to occur?	[redacted]	[redacted]
Were outcomes assessed using objective criteria or was blinding used?	[redacted]	[redacted]
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	[redacted]	[redacted]

Study ID	**Courtney 2008 (4)**	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/ N/A)**
Was the study based on a representative sample selected from a relevant population?	Eligible patients at four institutions were asked to participate, but the numbers and details of those who declined to participate were not recorded.	Unclear
Were the criteria for inclusion explicit?	Eligibility criteria were pre-specified.	Yes
Did all individuals enter the survey at a similar point in their disease progression?	Patients had ascites requiring at least two therapeutic paracentesis procedures in previous 30 days.	Yes
Was follow-up long enough for important events to occur?	Patients who continued using the drainage system were monitored for safety issues until death or catheter removal.	Unclear
Were outcomes assessed using objective criteria or was blinding used?	Some outcomes were defined but there were no details of how they were actually measured. Patient self-assessment of symptoms and quality of life outcomes was conducted using validated instruments/questionnaires.	Unclear
If sub-series compared, was there sufficient description of	N/A	N/A

the series and distribution of prognostic factors?		

Study ID	**Mullan 2011a (8)**	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/ N/A)**
Was the study based on a representative sample selected from a relevant population?	All patients who underwent tunnelled long-term drain insertion in the authors' department between March 2008 and March 2011 were eligible.	Yes
Were the criteria for inclusion explicit?	Eligibility criteria were pre-specified.	Yes
Did all individuals enter the survey at a similar point in their disease progression?	All patients selected for drain placement had documented intra-abdominal tumour spread and radiologically proven symptomatic ascites, and had undergone at least one conventional paracentesis in the preceding 2 weeks.	Yes
Was follow-up long enough for important events to occur?	Follow-up was until the death of the patient, and was therefore dependent on the patient's condition.	Unclear
Were outcomes assessed using objective criteria or was blinding used?	All patients were specifically instructed to seek the advice of the Radiologist or Oncologist at this institution if any problems were encountered; specific details of assessment methods were not reported.	Unclear
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	N/A	N/A

Study ID	**Richard 2001 (6)**	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/ N/A)**
Was the study based on a representative sample selected from a relevant population?	Study considered a small number of patients who were referred for treatment.	Unclear
Were the criteria for inclusion explicit?	Eligibility criteria were not pre-specified.	No
Did all individuals enter the survey at a similar point in their disease progression?	Patients referred for catheter placement were all managed with optimum medical care and repeated large volume paracentesis for malignancy-related ascites.	Yes
Was follow-up long enough for important events to occur?	Duration of follow-up was not reported.	Unclear
Were outcomes assessed using objective criteria or was blinding used?	Some outcomes were defined but there were no details of how they were actually measured. Reviews of patient charts and patients' "clinical courses".	Unclear
If sub-series compared, was there sufficient description of the series and distribution of	N/A	N/A

prognostic factors?		

Study ID	**Tapping 2011 (9)**	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/ N/A)**
Was the study based on a representative sample selected from a relevant population?	Patients were selected from a prospective database of all cases of tunnelled long-term drain (PleurX) insertion and according to specific criteria.	Yes
Were the criteria for inclusion explicit?	Eligibility criteria were pre-specified.	Yes
Did all individuals enter the survey at a similar point in their disease progression?	Patients who required frequent drainage (defined) were considered suitable for the procedure.	Yes
Was follow-up long enough for important events to occur?	Patients were being treated for palliative/end of life care and were followed-up from initiation of PleurX until death.	Yes
Were outcomes assessed using objective criteria or was blinding used?	Some outcomes were defined but there were no details of how they were actually measured.	Unclear
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	N/A	N/A

Study ID	**Saiz-Mendiguren (7)**	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/ N/A)**
Was the study based on a representative sample selected from a relevant population?	This was an observational study of all 10 patients referred for permanent tunneled catheter placement in the authors' Department between 15 April 2009 and 5 Feb 2010.	Unclear
Were the criteria for inclusion explicit?	Eligibility criteria were not pre-specified.	No
Did all individuals enter the survey at a similar point in their disease progression?	Insufficient information on the patients' characteristics was reported.	Unclear
Was follow-up long enough for important events to occur?	Duration of follow-up was not specifically reported, but patients generally appear to have been followed until death.	Unclear
Were outcomes assessed using objective criteria or was blinding used?	Insufficient information was provided on the methods used to assess the outcomes.	Unclear
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	N/A	N/A

7.4 Appendix 4: Search strategy for section 5.9 (Adverse events)

The following information should be provided.

7.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Section 7.2 provides full details of the databases searched, the search provider used, the dates on which the search was conducted, the date span of the search, the complete strategies used, any additional searches, and the inclusion and exclusion criteria (Sections 7.2.1-7.2.6).

7.5 Appendix 5: Quality assessment of adverse event data in section 5.9 (Adverse events)

7.5.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Section 7.3 provides critical appraisal information and Section 5.4 provides a tabulated summary.

7.6 Appendix 6: Search strategy for cost-effectiveness and cost studies (section 6.1)

The following information should be provided.

7.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process

- EconLIT
- NHS EED.

Section 7.2 provides full details of the databases searched, the search provider used, the dates on which the search was conducted, the date span of the search, the complete strategies used, any additional searches, and the inclusion and exclusion criteria (Sections 7.2.1-7.2.6).

The poster and unpublished manuscript relating to the only cost-effectiveness study identified was obtained by UKMedical from the study authors.

7.7 Appendix 7: Quality assessment of cost-effectiveness and cost studies (section 6.1)

One costing study was identified (Jacob 2009 (5) and Mulllan 2011a (8). The authors stated that their aim was to evaluate the cost-effectiveness of PleurX catheters compared with large volume paracentesis, but did not report cost-effectiveness outcomes. The costs were obtained from a single centre and the details of when and how the costs were obtained or estimated are not provided. The cost saving estimates are unclear. The cost-benefit analysis only considered the costs of the procedures and did not quantify any potential costing implications resulting from complications. The analysis was limited to only considering the costs that fell in the secondary care setting and did not include or attempt to estimate any other costs to the NHS, such as those resulting from frequent nurse visits in the community once patients were being managed in the home setting following tunnelled catheter placement. The costs of the catheters, consumables and inpatient stay per bed day were identical across the two reports (poster and manuscript). No further details regarding how the costs were obtained or estimated were made explicit in the manuscript. These issues detract from the quality of the study.

7.8 Appendix 8: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

7.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase

- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

N/A

7.8.2 The date on which the search was conducted.

N/A

7.8.3 The date span of the search.

N/A

7.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

N/A

7.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

N/A

7.8.6 The inclusion and exclusion criteria.

N/A

7.8.7 The data abstraction strategy.

N/A

7.9 Appendix 9: Resource identification, measurement and valuation (section 6.4)

The following information should be provided.

7.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The searches for Pleurx resource use are described in Appendix 2.

In addition to searches for Pleurx reports, searches for resource use for paracentesis for malignant ascites were conducted in the following databases and additional resources which provide access to grey literature:

- Medline and MEDLINE In Process via the Ovid interface;
- EMBASE via the Ovid interface;
- NHS EED via the Cochrane Library;
- HEED via Wiley-Interscience;
- EconLit via the Ovid interface;
- Opengrey http://www.opengrey.eu/;
- Repec IDEAS http://ideas.repec.org/;
- Google http://www.google.co.uk/.

7.9.2 The date on which the search was conducted.

The Pleurx resource use searches are reported in Appendix 2 section 7.2.2.
The paracentesis resource use searches were conducted on 11 August 2011.

7.9.3 The date span of the search.

The Pleurx resource use searches are reported in Appendix 2 section 7.2.3.
The paracentesis resource use searches span the following dates:

- Medline and MEDLINE In Process: 1948 TO August Week 1 2011

- EMBASE: 1980 to 2011 Week 31
- NHS EED via the Cochrane Library: all records current at 11/8/11
- HEED: all records current at 11/8/11
- EconLit: 1961 to July 2011
- Opengrey: all records available at 11/8/11
- Repec IDEAS: all records available at 11/8/11
- Google: all records available at 11/8/11.

7.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The Pleurx resource use searches are reported in section 7.2.4.
The paracentesis resource use search strategies are listed below.

MEDLINE and MEDLINE IN Process

1 ascites.ti,ab. (30074)
2 ascites/ (11787)
3 or/1-2 (34102)
4 Paracentesis/ (1200)
5 (lvp or paracentesis or paracenteses).ti,ab. (3369)
6 ((abdomen or abdominal) adj3 (tap or taps)).ti,ab. (36)
7 (peritoneal adj (tap or taps)).ti,ab. (45)
8 (intraperitoneal adj (tap or taps)).ti,ab. (0)
9 or/4-8 (4245)
10 3 and 9 (1140)
11 ec.fs. (289218)
12 (cost or costs).ti,ab,hw. (322894)
13 (frequency or hospitali$ or stay or stays or day or days).ti,ab. (1763870)
14 (month or months).ti,ab. (898674)
15 or/11-14 (2840214)
16 10 and 15 (422)
17 limit 16 to english language (373)

EMBASE

1 ascites/ or ascites fluid/ (27024)
2 ascites.ti,ab. (30118)
3 or/1-2 (42822)
4 paracentesis/ (3080)

5 (lvp or paracentesis or paracenteses).ti,ab. (3692)
6 ((abdomen or abdominal) adj3 (tap or taps)).ti,ab. (44)
7 (peritoneal adj (tap or taps)).ti,ab. (38)
8 (intraperitoneal adj (tap or taps)).ti,ab. (0)
9 or/4-8 (5457)
10 3 and 9 (2089)
11 (cost or costs).ti,ab,hw. (460272)
12 (frequency or hospitali$ or stay or stays or day or days).ti,ab. (1948283)
13 "length of stay"/ (53234)
14 (month or months).ti,ab. (1038831)
15 or/11-14 (3099204)
16 10 and 15 (652)
17 limit 16 to english language (578)

NHS EED

#1	(ascites)	865
#2	paracentes*	273
#3	tap or taps or lvp	1280
#4	(#1 AND (#2 OR #3))	154

HEED

AX=ascites (30)
AX=(paracentesis OR paracenteses OR tap OR taps OR lvp) (23)
CS=1 AND 2 (3)

Econlit

(ascites and paracentesis).mp. [mp=heading words, abstract, title, country as subject]
0 records

Opengrey

Ascites

Repec IDEAS

Ascites

Google

Two searches were undertaken restricting the searches to UK sites.

+ascites + paracentesis + cost -cirrhosis site:nhs.uk

+ascites + paracentesis + cost -cirrhosis site:gov.uk

7.9.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

7.9.6 The inclusion and exclusion criteria.

Records were included if they reported data on costs or other resource use for paracentesis for malignant ascites.

Records were excluded if they reported on ascites for conditions other than ascites resulting from cancer. Case reports were excluded. Records which did not indicate resource use were excluded. Searches were restricted to publications in English.

7.9.7 The data abstraction strategy.

There was no strategy for data extraction in the cases in which cost data was available (Jacob 2009 (5), Mullan 2011a (8)). All of the cost estimates presented in the studies are in section 6.1.

8 Related procedures for the submission of evidence

8.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the EAC, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the EAC with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. **Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.**

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the MTCD.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information (provided by NICE) has been completed and submitted.

8.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the MTCD and MTG.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the EAC and the MTAC. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

8.3 Equity and equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to complying fully with legal obligations on equality and human rights.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including

when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).