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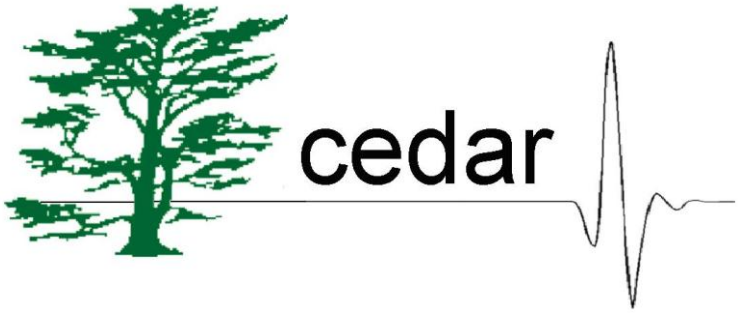

EXTERNAL ASSESSMENT CENTRE REPORT:

PleurX indwelling peritoneal catheter for vacuum assisted drainage of recurrent malignant ascites at home

Produced by: Cedar
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Declared interests of the authors

NICE's code of practice for declaring and dealing with conflicts of interest[1] applies to all work carried out under this contract. Organisations should indicate where they identify areas of conflict applicable to this work package in the context of their existing work base, and how they will handle the issues of conflict of interest so identified.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the National Centre for Health and Clinical Excellence. Any errors are the responsibility of the authors.

[1] http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

Table of Contents

Abbreviations

CF	Contrast Fluoroscopy
CT	Computed Tomography
CVIR	CardioVascular Interventional Radiology
EAC	External Assessment Centre
FDA	UA Food and Drugs Administration
FCE	Finished Consultant Episode
FS	Fluorscopy
HES	Hospital Episodes Statistics
KOL	Key Opinion Leader
LVP	Large Volume Paracentesis
MA	Malignant Ascites
MAUDE	Manufacturer and User Facility Device Experience
MSAS	Memorial Symptom Assessment Scale
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QoL	Quality of Life
RCT	Randomised Controlled Trial
SSQ	Subjective Significance Questionnaire
US	Ultrasound

UK Medical submitted the clinical evidence section of the submission report on the 22nd July 2011 which was critiqued by the EAC. The EAC noted the absence of unpublished material and a non-English study; these observations were shared with the sponsor. On the 19th August, UK Medical submitted the economic evidence. In this second submission the clinical evidence was substantially updated to include additional material identified by the EAC. As a result some information has been duplicated by the EAC in this report.

1 SUMMARY

1.1 Scope of Submission

UK Medical (the sponsor) has presented evidence in their submission in support of the use of the PleurX indwelling catheter (manufactured by CareFusion) for vacuum drainage of malignant ascites (MA) in the community setting. The external assessment centre (EAC), Cedar, identified no inappropriate deviations from the scope outlined by NICE in either the clinical or economic evidence submission.

1.2 Summary of submitted clinical evidence

Nine studies (10 manuscripts) in total were identified which were relevant to the decision problem. All were observational studies, and only one reported comparative outcomes for PleurX and LVP. This low quality of evidence is a potential source of bias and means generalisability of their findings is limited.

Technical success of the initial PleurX placement procedure was 100% in all studies where this outcome was reported. Variation in practice was identified in the use of catheter placement guidance technique, use of anaesthetic, and use of prophylactic antibiotics. Catheter failure rates, including those requiring catheter removal or catheter intervention for restoration of patency, were reported in eight studies. In studies with more than four participants, the number of catheters requiring removal ranged from 0% to 7.5%. Overall complication rates across the studies

ranged from 0% to 59% complications per patient[2]. The only study to compare complication rates for PleurX and LVP reported a rate of 7.5% for both interventions (LVP 95% CI 2.2-15%; PleurX 95% CI 1.6-20%). No device-related deaths were reported in any studies. Device related infections were the most common complication, followed by catheter occlusion, and ascitic leakage. Catheter patency rates ranged from 80% to 96%[3] (from five studies where n>4; Rosenberg (2004) reported 67.5% but in this study 27.5% of patients were lost to follow-up), and mean duration of catheter survival ranged from 52 days to 113 days (weighted mean from five studies was 77.9 days). Individual catheter survival duration ranged from 1 to 365 days in studies where n>4 (a case report described one patient with a PleurX catheter in place for 18 months).

Two studies, one quantitative and one qualitative, reported quality of life (QoL) and symptom relief outcomes. Validated assessment tools showed a significant improvement of some ascites-related symptoms; however an overall improvement in QoL at 12 week follow-up was not clear[4].

[redacted]

1.3 Summary of submitted economic evidence

A robust and well-documented *de novo* cost analysis was presented by UK Medical based on a decision tree model and Markov-style element to account for the weekly changes in life expectancy in patients with MA. Populated with mostly acceptable inputs, the model was used to calculate a 'per patient' cost of PleurX at-home drainage. This included the cost of the initial catheter placement in hospital, ongoing drainage consumables, and ongoing community nurse visits for a proportion of patients who choose not to drain their ascites themselves. The model was populated with some data from published sources, but largely from a prepublication manuscript (Mullan 2011b) and costs from UK Medical. Potential PleurX-related QoL changes were not

[2] This variation is due largely to differences in reporting and definition of complications, e.g. some studies reported only serious complications which resulted in removal of the catheter, others reported minor complications which resolved spontaneously.

[3] Catheter patency defined as the percentage of catheters functioning at death, study end point, or resolution of ascites.

[4] Probably due to a lack of sensitivity of the assessment tool used in detecting device-related improvement in palliative patients.

incorporated into the economic model. Two comparators were investigated: i) inpatient LVP (with hospital stay of 2.8 days); ii) outpatient LVP (single overnight hospital stay).

Results showed that PleurX saves -£679 per patient when compared to inpatient LVP. In this scenario, 7.4 hospital bed days were saved per patient, but required an additional 23.5 community nurse visits to patients' homes. When PleurX was compared to outpatients LVP, there was an additional cost of +£1,010 per patient, as well as 23.5 extra nurse visits. In this scenario, PleurX would save only 1.9 hospital bed days per patient.

1.4 Commentary on the robustness of submitted evidence

Clinical evidence

Upon resubmission of the clinical evidence the sponsor identified 10 full-length manuscripts from 9 studies. Seven papers have been published in peer-reviewed journals and three are in the pre-publication stage. The sponsor also presented two adverse event (AE) reports from the US Food and Drug Administration's (FDA) Manufacturer and User Facility Device Experience (MAUDE) database as case reports but the EAC considered them to be better categorised as AEs as they were not derived from research studies.

All included manuscripts were case series (n=7; of which one was a qualitative study) or case reports (n=3) resulting in a weak quality of evidence. Only one study was prospective (Courtney 2008), and one study was semi-comparative (Rosenberg 2004)[5]. The remaining studies were retrospective case series with no more than 50 patients treated with PleurX in each; most studies showed potential for bias across several areas, and have limited generalisability. Despite this, case series are accepted as appropriate sources of evidence for complications and adverse events.

Economic evidence

The EAC consider the 'per patient' cost and resource-use implications presented in the economic evidence to be realistic. The overall findings of both scenarios (PleurX compared to both inpatient

[5] Outcomes reported for the comparator, large volume paracentesis (LVP), but not compared statistically. No information on treatment allocation was provided.

and outpatient LVP) were robust to changes of ±20% in all inputs. Threshold analysis using a wider range of values for the key drivers of the model showed that overall findings were sensitive to some changes. The EAC considered that most inputs were appropriate and in some cases were conservative (i.e. influenced results against PleurX). It was noted by the EAC that some uncertainty surrounded the frequency and cost of treating complications associated with PleurX. Within the boundaries of the model structure, however, these parameters did not affect the overall outcome. On a population level, the EAC identified two issues: i) an overestimation of the population size; ii) a lack of consideration for the predominance of inpatient versus outpatient LVP procedures within the NHS. These two points have a substantial influence on the NHS-wide cost and resource use savings offered by PleurX. Savings described in the *de novo* cost model were lower than those described in a pre-publication manuscript (Mullan 2011b). This was explained appropriately by the sponsor as being due to omission of costs associated with complications, and omission of costs of providing community nursing visits by the authors of Mullan (2011b).

1.4.1 Strengths

Strengths of clinical evidence

- Well-documented and appropriate literature search
- Comprehensive and accurate data extraction in line with NICE's scope
- Fair and realistic assessment of evidence quality, and explicit reporting of the limitations

Strengths of economic evidence

- Clear and well-structured model
- Sources of model inputs were described
- Assumptions were explicitly reported in most cases
- Sensitivity analysis of all inputs and appropriately extended for key drivers
- Reasonable interpretation of the results with appropriate caveats
- *De novo* economic model outcomes were in line with a cost analysis from a prepublication manuscript (Mullan 2011b; conservative findings of *de novo* model were adequately explained)

1.4.2 Weaknesses

Weaknesses of clinical evidence

- Omission of relevant studies in the initial evidence submission (issue subsequently resolved in updated submission document)
- No randomised control trials were available; all studies identified were observational reports with a substantial risk of bias
- Lack of available comparative studies and therefore limited information for LVP outcomes
- Inconsistent reporting and definitions of certain outcomes such as complication rates in the published evidence

Weaknesses of economic evidence

- Only one economic publication was available, which was from a secondary care perspective and therefore omitted community nursing costs, and did not consider the cost of complications
- Due to a lack of appropriate data, probabilistic sensitivity analysis was not carried out
- The Key Opinion Leaders (KOL) questionnaire had a low response rate; consequently UK Medical did not use the data to inform inputs

1.4.3 Areas of uncertainty

- Size of the population which could potentially be treated using PleurX
- Proportion of patients currently treated using inpatient and outpatient LVP
- Uncertainty surrounding complication rates between the two arms due to limited comparative studies of PleurX versus LVP
- Additional burden imposed on community nursing staff as some patients may receive some level of community health care regardless of whether they have a PleurX drain
- Difficulties in transferring financial budget from secondary care to community setting

1.5 Key Issues

- Clinical evidence in support of the PleurX peritoneal drain is based solely on observational studies, with very limited comparative data. Available evidence suggests PleurX has good technical success, comparable complication rates to LVP, and that PleurX catheters remain *in*

situ for over 10 weeks on average. Patients reported that PleurX was a convenient alternative to LVP and showed improvements in symptom control.

- Economic evidence showed that PleurX was cost-saving when compared to inpatient LVP, but incurred an additional cost when compared to outpatient LVP. The first scenario would also release 7.4 hospital bed days per patient treated using PleurX, but would require an additional 23.5 community nurse visits per patient. The model structure was robust and inputs were derived from mostly appropriate sources.
- There is uncertainty surrounding this number of patients who could be treated using PleurX, and the proportion of patients currently treated using LVP in inpatient and outpatient settings.

2 BACKGROUND

This EAC evaluation report has been prepared to provide an independent critique of the clinical and cost evidence supplied by UK Medical relating to the use of the PleurX to manage malignant ascites at home.

2.1 Critique of manufacturer's description of underlying health problem

In Section 2.1 of the evidence submission, UK Medical provided a definition of ascites and explained the symptoms caused by the condition. They also briefly explained the most common primary malignancies associated with MA. No references were given in this section. Additional background information has been provided by the EAC below.

Malignancy types and life expectancy

A recent Cochrane review (Keen 2010) stated that MA accounts for 10% of all ascites cases. MA is caused most commonly by cancer of the ovary (36.7%) followed by pancreaticobiliary (21%), gastric (18.3%), oesophageal (4.0%), colorectal (3.7%), and breast cancer (3.0%) (Ayantunde 2007; Wilailak 1999). Up to 20% of all MA cases are due to malignancies of unknown origin (Ringenberg 1989). Frequently, ascites is the first physical indication of intraabdominal malignancy (Adam 2004). The onset of MA is associated with a deterioration in quality of life (QoL), poor prognosis, and reduced life expectancy. UK Medical stated that life expectancy after MA diagnosis is 1 to 4 months (no reference); Saiz-Mendiguren (2010) cite 2 to 6 months.

Prevalence of MA

In Section 2.2, UK Medical stated that no data is available on the prevalence of intractable MA in the UK. They go on to cite a value of 25,000 finished consultant episodes (FCEs) for procedures involving abdominal paracentesis for drainage of ascites (Hospital Episodes Statistics (HES) 2008-9), and that 10% of all cases are due to malignant ascites. This value of 2,500 has been used in the economic model as the population who could potentially be treated using PleurX.

The EAC searched extensively for related information but could not identify any reliable population estimates. However, 2,500 is likely to be an overestimate as the number of FCEs cannot be equated to a number of patients with MA. Also a proportion of these abdominal

paracenteses will be diagnostic, and a proportion of MA patients will not have recurrent and untreatable fluid accumulation, and therefore would not benefit from PleurX.

Problems associated with MA are present in 3.6% to 6% of patients admitted to palliative care units (Hanks 2010). Two systematic reviews reported that between 2007 and 2008, MA accounted for over 28,000 bed-days in hospitals in England (Becker 2006;Keen 2010).

2.2 Critique of overview of current service provision

UK Medical reported in Section 2.4 of their evidence submission that repeated large volume paracentesis (LVP) is the most common management option for MA. This technique involves insertion of a drainage tube into the abdomen which is used to drain fluid over the course of hours, and sometimes days. Symptoms of MA were well managed by paracentesis in 90% of patients (Becker 2006); however, it is temporary solution and if ascitic fluid reaccumulates in the peritoneum the symptoms associated with MA may return. Patients will often wait until fluid accumulation is substantial to avoid frequent hospital stays, and to ensure the ascites is amenable to drainage (Keen 2010) resulting in a deterioration on their quality of life. Paracentesis and diuretics are the most commonly used management strategies, followed by peritoneovenous shunts, diet measures, and other modalities like systemic or intraperitoneal chemotherapy (Lee 1998).

Several studies report a lack of national guidelines and variation in treatment approaches for management of MA (Becker 2006;Keen 2010;Stephenson 2002). There is particular variation in respect of radiological investigations used, the length of time drains remain *in situ*, and the use of intravenous fluids. Local variation in treatment practice between hospital wards, and between hospital and hospice practice has been reported. Stephenson and colleagues (2002) reported that in a UK hospice, patients admitted solely for paracentesis may go home the same evening or, more usually, the following day; whereas in hospital patients were often kept in overnight or for several days. Mullan (2011b) reported a mean inpatient stay of 2.8 days (range 1-6) in patients being treated using paracentesis. There is no available information for the proportion of patients treated in inpatient and outpatient settings. One expert commented: “We have day case paracentesis now

established as an alternative, giving the patient the option to some extent". HES data for outpatient procedures has poor coverage and therefore cannot be used as a reliable source.

The sponsor provided a brief overview of the potential application of PleurX in the treatment of MA in the community setting. Certain details surrounding the proposed pathway of care were not explained in sufficient detail in the evidence submission but were addressed in the 'instructions' material available upon request and online at:

http://www.ukmedical.com/images/pdf/Pleural_Catheter_MiniKit.pdf (insertion instructions)

http://www.ukmedical.com/images/pdf/PleurX_Drainage_Instruction.pdf (drainage instructions)

Specifically, the instructions for use state that:

- "the catheter should be placed under image guidance, using precautions normally used for percutaneous placement of indwelling, tunnelled catheters", although the specific guidance technique is not specified, e.g. ultrasound (US), fluoroscopy (FS), or computed tomography (CT);
- "peritoneal placement can be performed using local anaesthetic and sedation. However, depending on patient needs, it may be performed using alternative approaches to anaesthesia or no sedation"
- "catheter placement site selection should be based upon patient anatomy and presentation with consideration given to any possible adhesions or loculated pockets of fluid". Comments by expert advisors suggest that loculations would be assessed on a case-by-case basis to decide whether the ascites is amenable to PleurX placement;
- no more than 2 litres of fluid should be drained from the peritoneal cavity at one time.

3 CRITIQUE OF DEFINITION OF DECISION PROBLEM

The sponsor used the decision problem as specified by NICE with no additions or amendments. The EAC identified some additions as follows:

Population: No amendments

Intervention: No amendments

Comparator: Studies with no comparator will also be included. Paracentesis (drainage of less than 4-6 L of ascitic fluid) is also a comparator

Outcomes: The following additions have been made by the EAC: pain during catheter placement, duration of hospital stay, catheter patency, duration of catheter survival, volume of drainage, location and person providing care, volume drained during each session.

Cost analysis: No amendments

Subgroups: none were identified

Special considerations: No amendments (no equality and diversity issues were identified to be addressed in the submission).

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

UK Medical presented a clear and well-documented literature search in their evidence submission. The search strategy was reasonably robust and identified all studies which were relevant to the decision problem. The inclusion and exclusion criteria used for the selection of studies were mostly appropriate (with some exceptions which were dealt with in their resubmission, see below), and the application of these criteria was explained through flow diagrams and a table of exclusion reasons. The sponsor critically appraised all of their included publications, and was realistic about the weaknesses associated with the standard of evidence in support of PleurX. UK Medical accurately extracted relevant outcomes from their selected studies and kept inside the scope set by NICE.

Following the initial submission, issues were identified by the EAC surrounding omission of unpublished material and non-English language publications. After discussions with NICE and the EAC the sponsor included a further four manuscripts (three studies) in a second clinical evidence submission.

4.1.1 Description and critique of the manufacturer's identification and selection of studies.

Search Strategy

The sponsor applied a thorough and well-documented search strategy to retrieve publications on the use of PleurX for drainage of malignant ascites. UK Medical searched a broad range of databases, trials registers, societies, and regulatory bodies. The EAC commissioned the Support Unit for Research Evidence (SURE) at Cardiff University, specialists in literature search design, to identify any potential improvements or modifications. SURE restructured the search strategy to include broader search terms and a more intuitive design (EAC report Appendix 1), which resulted in an increase in retrieved references from 368 to 406 after duplicate removal. Two expert advisors noted that no cancer-specific society sites had been searched by the sponsor. To address this, the EAC searched four further societies (Appendix 1 of EAC report) which captured no further studies.

EAC modifications to study inclusion/exclusion criteria

Following amendments to the evidence submission, the sponsor applied appropriate pre-defined inclusion and exclusion criteria to their retrieved references which were stated in Section 5.2 of the evidence submission. The EAC disagreed with two original exclusion criterion used by the sponsor (these issues were addressed in the second evidence submission):

- **Unpublished material** – UK Medical cited two unpublished reports in Section 1.6 of the evidence submission, but did not use them as evidence sources. The EAC contacted the author, Dr Damian Mullan (Clinical Radiology Consultant, The Christie NHS Foundation Trust), who kindly provided the full-text manuscripts Mullan (2011a; 2011b). One manuscript was the full-length version of the Jacob (2009) poster selected by the sponsor for inclusion. [redacted]
- **Non-English language reports** – non-English language publications were excluded in the sponsor's initial study selection criteria; however, the EAC identified two potentially relevant studies. One was a German publication with an English title available (Semmo 2009), neither an abstract nor a full-text manuscript could be accessed, and therefore it was excluded. The other was a Spanish-language citation which was available as a full manuscript in English (Saiz-Mendiguren 2010) and was pertinent to the decision problem.

4.1.2 Table of identified studies. What studies were included in the submission and what were excluded. Include details of any relevant studies that were not included in the submission.

Seven case-series were included (one of which was a qualitative study; sponsor's Table 5.1) and three case reports (sponsor's Table 5.2). The sponsor also included two adverse event reports from the FDA's MAUDE database in Table 5.2; the EAC recommend that these should be considered separately as adverse event reports only. The EAC has presented the included studies in Table 1 (EAC report). A summary of the details of the 9 studies has been provided in this report by the EAC for ease of reference (EAC report Table 2).

Table 1 References of included studies

EAC reference	Sponsor reference number	Citation
Case Series		
Rosenberg (2004)	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.
Courtney (2008)	4	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
Mullan (2011b)	8	Mullan, D, Laasch, H-U, and Jacob, A Hassan H. Tunneled intra-peritoneal catheters in the management of malignant ascites: Complications and cost implications. Unpublished 2011a.
	5	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.
Richard (2011)	6	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.
Tapping (2011)	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. *British Journal of Radiology.* 2011:doi:10.1259/bjr/24538524.
Saiz-Mendiguran (2010)	7	Saiz-Mendiguren, R., Gomez-Ayechu, M., Noguera, J. J., Garcia-Lallana, A., Marginet, C., Cano, D., and Benito, A. Permanent tunneled drainage for malignant ascites: Initial experience with the PleurX catheter. [Spanish, available in English]. *Radiologia* 52(6), 541-545. 2010.
Qualitative Study		
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
Case Reports (n<4)		
Brooks (2006)	11	Brooks, R. A., Herzog, T. J., Brooks, Rebecca A., and Herzog, Thomas J. Long-term semi-permanent catheter use for the palliation of malignant ascites. *Gynecologic Oncology* 101(2), 360-362. 2006.
Iyengar (2002)	12	Iyengar, T. D., Herzog, T. J., Iyengar, Tara D., and Herzog, Thomas J. Management of symptomatic ascites in recurrent ovarian cancer patients using an intra-abdominal semi-permanent catheter. *American Journal of Hospice & Palliative Medicine* 19(1), 35-38. 2002.
Mullan (2011a)*	13	Mullan, D, Laasch, H-U, and Hassan, H. Fibrinolysis in the management of malignant ascites and non-functioning intra-peritoneal tunnelled catheters. Unpublished 2011b

* The second manuscript provided by Dr Damian Mullan (Mullan 2011a) was a case report of four patients which were a subset of the main case series study of 50 patients (Mullan 2011b). This case report detailed the treatment of four patients with fibrinolysis to restore patency in blocked PleurX catheters. Being a subset of the main study, the details of this smaller report do not add to the evidence for PleurX, and therefore the EAC will not evaluate it as a separate study from Mullan (2001b).

4.1.3 Description and critique of manufacturers approach to validity assessment and details of the quality assessment of studies.

The sponsor critically appraised the seven case series studies using a checklist of 6 questions designed to assess generalisability, risk of bias, reliability of outcome measure, and length of follow-up in observational studies (Table 5.10 and Section 7.3.1). No quality appraisal was performed on the case reports. UK Medical also provided a realistic and fair narrative quality appraisal. In this description the following key points were highlighted:

- Observational studies are low in the hierarchy of evidence
- Poor reporting in studies meant some quality appraisal elements were unclear, e.g.
    - whether study population was representative
    - generalisability of data
    - appropriateness of follow-up duration
    - validity of outcome measures
- Retrospective design of Rosenberg (2004) and Tapping (2011)

The tabulated and narrative quality appraisal technique was adequate to identify the main limitations of the included publications; however, some aspects of critical appraisal of observational studies were not considered (Chan 2011;West 2002;Young 2009). The following items can potentially reduce bias and provide more reliable and useful results:

- consecutive patient enrolment
- prospective outcome data collection
- high follow-up rate
- well-defined study protocol
- specified time interval for patient recruitment
- clinically relevant outcomes
- accurate and appropriate measures (outcome measure were described by the sponsor in Table 5.8 but validity was not adequately assessed)

The EAC constructed a modified version of the sponsor's Table 5.7 in order to encompass these additional quality appraisal points (EAC report Table 3). From this quality appraisal the following trends of poor study design were highlighted:

- **limitations of case series design** – all of the studies were case series (Brooks 2006;Iyengar 2002 were case reports). This study design is low in the hierarchy of evidence due to an absence of randomisation, absence of appropriate controls, often small patient numbers, often retrospective nature, often non-consecutive patient selection; all of these issues subject case series/reports to bias.
- **inadequate use of concurrent controls** – only one study was comparative (Rosenberg 2004), but even this did not report the allocation criteria for treatment with paracentesis versus PleurX (risk of allocation bias). Without adequate controls the reliability of the data is reduced, and the ability to interpret results is compromised.
- **limitations of retrospective study design** – only one study was prospectively designed (Courtney 2008). A retrospectively designed case series is limited by availability and accuracy of medical records, and is subject to selection bias.
- **inadequate reporting of absence of inclusion/exclusion criteria and non-consecutive patient selection** – several studies failed to report adequate criteria for both treatment allocation and study inclusion. Most studies identified here did not provide total numbers of MA patients seen at a treatment centre, and the proportion of those treated with PleurX; this is essential in assessing the generalisability of the results and detecting selection bias. Not all of the studies presented criteria for including patients in the study, or included consecutive PleurX-treated patients. Non-consecutive patient selection is a major source of selection bias.
- **outcome selection –** only Courtney (2008) prospectively assessed outcomes as the remaining studies were retrospectively designed. There was variation across the studies in the choice of outcomes and the reliability of their measures. This was particularly apparent in the reporting of complications and QoL outcomes.
    - ***Complications*** **-** all studies [redacted] explicitly commented on the occurrence of complications related to the PleurX drain, however there appeared to be wide fluctuations in the definition of a complication, and in many cases a definition was not provided at all. For instance Rosenberg (2004) reported only complications where the catheter failed and required removal, whereas Courtney (2008) was much more inclusive in its reporting, e.g. minor complications including those that resolved spontaneously with no treatment such as temporary dizziness.

- ***QoL and resolution of symptoms***

[redacted] Courtney (2008) used two patient-reported outcome tools to measure improvements in QoL and cancer-related symptoms compared to baseline measurements before PleurX drain placement. The absence of a control group in this study means such measures have limited value because of the progressively worsening health status of participants receiving palliative care.

[redacted]

Patients included in studies

A comprehensive description of study inclusion and exclusion criteria and baseline characteristics of included patients was provided in Tables 5.6, 5.7 and 5.11 of the sponsor's submission. The relevant details have been summarised into a single table by the EAC (Table 3). Overall, study participants were similar in age, primary co-morbidity and previous treatment with paracentesis. Three studies (Brooks 2006;Iyengar 2002;Mullan 2011b) were dominated by female participants as ovarian cancer was the most prevalent primary morbidity. All studies which reported previous treatment regimes stated prior treatment with standard paracentesis. Only two studies (Courtney 2008;Mullan 2011b) reported exclusion criteria and therefore differences between patient

populations cannot be adequately assessed. Exclusions which may be important in practice were (Courtney 2008;Mullan 2011b):

- multi-loculated ascites;
- functional limitations which restrict patients from using PleurX;
- current intraperitoneal chemotherapy;
- life-expectancy of patient.

4.1.4 Description and critique of manufacturer's outcome selection

The sponsor presented study outcomes relevant to the original scope set out by NICE from their seven selected studies across five tables (sponsor's submission Tables 5.12 – 5.16); outcomes from case reports were presented in Table 17. UK Medical at times included substantial text in tables which made interpretation difficult; the EAC restructured these tables and reorganised the extracted data for ease of reference and comparison across studies (EAC Tables 5-9).

Technical Success (EAC Table 5)

Technical or procedural success was explicitly reported in four studies (Courtney 2008;Mullan 2011b;Saiz-Mendiguren 2010;Tapping 2011) and was implied from the remaining selected studies [redacted] Generally technical success was defined as successful placement of catheter, withdrawal of ascetic fluid, and no procedural complications. All studies reported 100% technical success. Courtney (2008) reported one minor complication of epigastric vein injury during the tunnelling procedure. Saiz-Mendiguren (2010) reported that 2 of 10 patients reported discomfort during the procedure (VAS score 2 and 3, out of a maximum of 10), the remaining 8 patients reported 0 on the VAS score.

Procedural variations were identified (EAC report Table 5) relating to:

- ***insertion guidance technique*** **–** 7 of 9 studies reported which technique was used to guide insertion of the PleurX catheter. A combination of ultrasonographic (US) and fluoroscopic (FS) guidance was used in a total of 83 procedures. US guidance alone was used in 97 procedures, and a combination of US and computed tomography (CT) was used in 1 procedure. The following comment was provided by an expert advisor: "In our experience we use ultrasound for PleurX placement in malignant ascites without fluoroscopy…";
- ***anaesthetic*** **–** procedures were performed using either local anaesthetic (LA) with or without conscious sedation, or with general anaesthetic (GA). The following comment was provided

by an expert advisor: "We use local anaesthetic in all cases. The use of sedation is then considered on a case by case basis but is always offered".

Drainage Session Details (EAC Table 6)

Three studies reported details of duration of procedure or length of stay. The length of procedure ranged from 30 minutes (Tapping 2011) to 50 minutes (Saiz-Mendiguren 2010) (EAC report Table 5), and the inpatient stay was approximately 24 hours or less (Mullan 2011b;Tapping 2011). The method of measurement for these values was not reported. Only one study reported the mean number of PleurX drainage sessions carried out by the patient or care giver (Courtney 2008), 23.3 (range 5-56). Generally the publications suggested that patients should drain small amounts repeatedly but the actual drainage volume and frequency varied widely between patients. Four studies explicitly stated who carried out the drainage sessions; in the majority of cases this was done by the patient themselves or by a relative/friend. Courtney (2008) reported that 13% of sessions were carried out by a home health nurse.

Catheter Functioning (EAC Table 7)

UK Medical presented results of successful drainage rates and frequency of drainage sessions as set out in NICE's scope (Tables 5.13 and 5.15 in the sponsor's submission document). The EAC agreed with their selected outcomes and found that accurate and relevant information had been extracted (EAC Table 7). The results have been summarised into a number of points:

- ***catheter patency –*** [redacted] Rosenberg (2004) reported the lowest patency (67.5%) but this low number was due to a high loss of patients to follow-up (27.5%). The authors believe these patients had functioning catheters at time of death. The highest catheter patency was 96% (Mullan 2011b), followed by 90% (Saiz-Mendiguren 2010), 86% (Tapping 2011), 85% (Courtney 2008), and 80% (Richard III 2001). Catheter patency values from case reports (n≤4) should not be relied upon.
- ***catheter survival –*** two of the nine studies did not report catheter survival duration. There was a very wide variation in the mean length of catheter survival across the studies, from 52 days (Saiz-Mendiguren 2010) to 113 days (Tapping 2011). The intra-study range was also very high.
- ***catheter failure –*** the EAC split this category into failure requiring removal and failure requiring an intervention other than removal. In studies with >4 patients catheter failure

rates requiring removal of the catheter (with or without replacement) were between 0% (Richard III 2001;Saiz-Mendiguren 2010;Tapping 2011) and 7.5% (Rosenberg 2004). Catheter failure requiring intervention by the medical team and no removal (usually provision of antibiotics or removal of occlusion) ranged from 0% (Rosenberg 2004;Saiz-Mendiguren 2010) to 19% (Tapping 2011). Reporting of failures requiring intervention but no removal of catheter was sporadic and therefore low failure values should be interpreted cautiously.

Complications / Adverse Events (EAC Table 7)

Only catheter failures requiring removal or intervention were reported in Rosenberg (2004) and Richard (2001) suggesting a risk of under-reporting in these studies. In the remaining studies complication rates ranged from 0% (Saiz-Mendiguren 2010) to 59% (Courtney 2008) (weighted mean 26.2%; EAC Table 7).

- ***Device related infections*** **–** infections were the most common complication in patients included in the case series described in this report. Peritonitis rate was 3% (Courtney 2008) and 2% (Mullan 2011b). Lymphangitis rate was 2% (Mullan 2011b) (EAC report Table 7). General or unspecified infections were reported in 3% (Courtney 2008) and 2.5% of patients (Rosenberg 2004), and the rate of minor catheter site infections was 18% (Tapping 2011). Across all studies 2 infections resulted in removal of catheter and the remainder were treated successfully with antibiotics.
- ***Ascitic fluid leakage*** **–** leakage of fluid through the catheter site was reported in 10 patients. Five cases (Courtney 2008) were attributed to being in the early procedural period and caused by ineffective PleurX catheter positioning[6]. Leakage necessitated removal of the catheter in one case (Rosenberg 2004); the remainder resolved spontaneously as ascites dried and the tunnel matured.
- ***Occlusion and loculations*** **–** these terms were combined as they were used synonymously across the selected publications. There were 10 reported cases of catheter occlusion/loculation across all studies; occlusion rates were between 0% (Saiz-Mendiguren 2010;Tapping 2011) and 12% (Courtney 2008). Two catheters were removed, five were

[6] The authors report that after a change across the institutions in catheter positioning during the placement procedure (tunnelling was done medial and cephalad) there were no further leakage episodes, except one patient.

treated with fibrinolytics (1 unsuccessfully), and 3 were treated with physical disruption of occlusion (1 unsuccessfully).

- ***Catheter displacement*** **–** there were 6 reports of catheters being inadvertently dislodged or removed by patients or nurses. Maximum displacement rate was 14% (Tapping 2011). In all cases the catheters were subsequently removed.

Two adverse events related to PleurX peritoneal catheter were reported in the MAUDE database:

- July 2007 (report number: 905214): "Pt had tunnelled peritoneal drain placed for malignant ascites. Due to continued abdominal discomfort, patient requested drain be removed. Radiologist unable to remove catheter, which appears to be trapped in peritoneum, possibly in tumor. Unable to contact product engineer to determine tensile strength; and how aggressively to attempt removal. Catheter is still in patient; is functioning and has not caused injury, but is uncomfortable."
- April 2008 (report number: 1423507-2008-00042): "Hosp has reported that their last two catheters that were placed, the pt reportedly developed an infection after 2-3 months of use"

Quality of life and resolution of symptoms (EAC Table 8)

The sponsor presented accurate and comprehensive results from two studies which reported QoL or resolution of symptoms data in Table 5.14 of the sponsor's evidence submission. Courtney (2008) and [redacted] were the only studies to report QoL outcomes.

- **Quality of Life -** Courtney (2008) assessed changes in symptom severity using a modified Memorial Symptom Assessment Scale (MSAS) at 2, 8 and 12 weeks compared to baseline values at time of PleurX catheter placement (EAC report Table 8). Results suggested an improvement in symptoms across most symptom categories after insertion of a PleurX drain, and significant reduction in severity of abdominal discomfort, bloating, diarrhoea, and nausea. The sponsor appropriately highlighted the absence of an ascites-specific symptom assessment tool; MSAS may lack the sensitivity to accurately examine improvements due to PleurX. The patients' QoL was assessed used the Subjective Significance Questionnaire (SSQ) which is designed to detect a change in QoL in the previous week. The absence of a control group of patients in this study, and the nature of terminal disease progression means that such a tool would understate any QoL improvement due to PleurX. This may be reflected in

the SSQ results where by week 12 only 28% of patient report an overall improvement in QoL (EAC report Table 8).

[redacted]

Comparative Outcomes: paracentesis versus PleurX (EAC Table 9)

Four of the nine studies included some information from patients treated with the comparator (paracentesis; Courtney 2008; [redacted] Mullan 2011b). This information varied greatly in its depth, reliability and usefulness. Only one study (Rosenberg 2004) examined results from patients treated with paracentesis only in parallel with patients treated with paracentesis followed by PleurX. No publications compared paracentesis and PleurX results directly or used comparative statistical analyses.

- ***Complication rates*** - Rosenberg (2004) reported a complication rate for paracentesis-only patients of 7.5% (95% CIs 2.2%-15%) and 7.5% (CIs 1.6%-20%) for PleurX patients (Table9), and the authors suggested that PleurX is as safe as paracentesis for drainage of malignant ascites. These overall complication rates should be interpreted cautiously as the authors reported only failures requiring catheter removal and not those which resulted in an intervention to rescue the catheter, e.g. antibiotic treatment or removal of occlusion. The data in this study was also collected retrospectively and is therefore subject to bias.
- ***Hospital inpatient stay*** – Mullan (2011) collected data retrospectively on patients who had been treated using paracentesis prior to insertion of a PleurX catheter. Of the 50 patients in this study, 23 had accurate clinical information and were admitted for the sole purpose of an inpatient paracentesis. Data from these patients was used to calculate a comparator inpatient length of stay of 2.8 days (range 1-6 days) for paracentesis. The paper suggests that data was not gathered prospectively on length of hospital admission for PleurX

catheter placement, but the Methods section reports that "if complication free, [the patient] is discharged home within 24 hours".

4.1.5 Describe and critique the statistical approach used

UK Medical presented a summary of statistical tests and data management approaches used in their six selected studies (sponsor's submission Table 5.9). The information provided was accurate and thorough. The EAC concur with the assertion made by UK Medical that the design of the selected studies resulted in a paucity of statistic analysis. The absence of appropriately described concurrent controls in all of the studies meant that comparative statistics were not used widely.

4.1.6 Summary statement about the review of clinical effectiveness

UK Medical constructed a thorough and accurate clinical evidence submission in accordance with the decision problem stated in NICE's scope. All relevant studies were identified using a revised search strategy and appropriate data were extracted by the sponsor. Data were presented in a series of tables and in narrative form. Sensible and realistic conclusions were drawn from the presented data, and limitations of the evidence were well reported. The EAC consider the clinical evidence submission to be complete with no important omissions or inaccuracies.

4.2 Summary of submitted evidence

4.2.1 Quality of evidence

Three manuscripts were at the prepublication stage and as such have not been peer reviewed [redacted]Mullan 2011a;Mullan 2011b). All nine studies identified in the clinical evidence submission were observational studies (case series and case reports) resulting in several areas of potential bias in favour of PleurX. The most important issue relates to the absence of appropriate concurrent controls resulting in a paucity of comparative data. Additionally, there were issues surrounding small patient numbers, retrospective design, and non-consecutive patient selection. Particularly problematic in these studies is a lack of reporting of study inclusion/exclusion criteria or, in the case of retrospective studies, an absence of criteria used by clinicians to allocate treatment with PleurX. As a result, external generalisability of the results is limited. However, observational studies are an accepted method for gathering information on complications and adverse events, and as such these six case series provide valuable information on the treatment of

MA using a PleurX drain including procedural success, catheter patency, and complication rates and types.

Three case reports (n≤4) were identified but provide very limited amounts of evidence due to very low patient numbers. Most importantly results cannot be generalised because cases have been selected without criteria. One qualitative study was available which also provides limited generalisable evidence; however there was a paucity of evidence on the effect of PleurX treatment on patients' quality of life and therefore this study provided valuable insight.

4.2.2 Summary of results

- ***Technical success*** – six case series (n>4)[7] reported 100% success during the initial PleurX catheter placement procedure (one minor complication). There was variation across the studies in the choice of insertion guidance technique and in the type of anaesthetic used.
- ***Catheter functioning*** – catheter patency ranged 67.5%[8] to 96% across five studies and mean duration of catheter survival ranged from 52 days to 113 days (weighted mean from five studies was 77.9 days). In studies with >4 patients, catheter failure rates (requiring removal of the catheter) were between 0% and 7.5% (weighted mean 3.4%), and those requiring medical intervention but not removal ranged from 0% to 19% (weighted mean 8.6%).
- ***Complications*** – 24.4% of patients suffered complications (including minor complications such as dizziness) in the 172 patients with PleurX catheters across six studies with >4 participants[9]. The most common PleurX-related complications were infection, occlusion/loculation, ascitic leakage, and inadvertent displacement. Only one study compared PleurX complications and those in LVP-patients, 7.5% complication rate for both interventions.
- ***Resolution of symptoms and quality of life*** – one study used a validated tool to assess changes in symptoms after placement of the PleurX catheter (Courtney 2008). Results showed a significant reduction in abdominal discomfort, bloating, diarrhoea, and nausea,

[7] Rates of technical success, catheter patency, catheter failures and complications from case reports with ≤4 patients should not be relied upon due to small patient numbers and potential sampling bias

[8] 27.5% of patients lost to follow up in this study (Rosenberg 2004)

[9] There large inconsistencies in the definition and reporting of complications across studies.

but did not show an overall improvement in QoL.

[redacted]

4.2.3 Critique of submitted evidence syntheses

No systematic reviews or meta-analyses pertinent to the decision problem were identified by the sponsor or the EAC. Given the nature of these observational studies and particularly issues such as inconsistent reporting of outcomes such as complication rates, and lack of statistical analyses, the EAC felt that meta-analysis would not yield any meaningful results. The EAC has calculated unweighted means for some outcomes which have been presented in summary sections in this report.

Table 2 Overview of study design from publications relevant to the PleurX decision problem

Study	Design	Intervention (I) & Comparator (C)	Outcomes	Reliability / Validity / Generalisibility
Case Series (≥ 4 patients)				
Rosenberg (2004)	• Single centre, USA • Retrospective case series (n=107) • Medical records review (April 1999 – Sept 2002) • Comparative • Follow up not standardised – complication surveillance carried out by patient	• I: PleurX catheter (n=40) • C: paracentesis (n=67)	• Complication rate (incl. catheter failure and infection) • Adverse Events	• Case series design limitations, e.g. no control, risk of selection bias, reporting bias • Retrospective design limitations, e.g. availability and accuracy of medical records, patient selection bias • No treatment allocation criteria – limited generalisability • Issues of reliance on patients to report complications
Courtney (2008)	• 4 centres, USA • Prospective case series (n=34) • Non-comparative • March 2004 – April 2005 • 12-week follow up (beyond for some pts)	• I: PleurX (modified device) (n=34) • C: None	• Catheter survival • Technical success • QoL and symptom relief • Procedural complications and ease of use (patient reported)	• Case series design limitations and non-comparative • No criteria for inclusion in follow-up past 12 wks • QoL measures in non-controlled have limited usefulness • Patient- reported complications.
Mullan (2011b)	• Single NHS hospital, UK • Retrospective case series (n=50) • March 2008 – March 2011 • Non-comparative (but paracentesis outcomes also assessed) • Follow-up until death	• I: PleurX • C: None (but some paracentesis outcomes assessed)	• Procedural success • Procedural complications • Time to discharge post catheter insertion • 30-day mortality • Catheter survival / patency • Adverse events	• Unpublished, full-length draft manuscript • Retrospective case series design limitations • No direct comparator
Richard (2001)	• Single centre, USA • Retrospective case series (n=10) • Non-comparative • Follow-up period not stated • Study period not stated	• I: PleurX (n=10) • C: None	• Complication rate • Catheter patency	• Retrospective case series design limitations • No criteria set for assessment of "catheter efficacy"
Tapping (2011)	• Single NHS hospital, UK • Retrospective case series (n=28) • Non-comparative • July 2005 – July 2009 • Follow-up not standardised – complication surveillance carried out by patient	• I: PleurX (n=28) • C: None	• Procedural success • Complications • 30 day mortality	• Retrospective case series design limitations
Saiz-Mendiguren (2010)	• Single centre, Spain • Retrospective case series (n=10) • Non-comparative • April 2009 – Feb 2010 • Follow-up period not reported	• I: PleurX (n=10) • C: None	• Length of procedure • Pain during procedure • Procedural complications • Catheter patency • Infection rate • Mean volume drained	• Retrospective case series design limitations • Details of pain scoring system (VAS) administering not provided – risk of bias

Study	Design	Intervention (I) & Comparator (C)	Outcomes	Reliability / Validity / Generalisibility
Qualitative Study (n=4)				
[redacted]	• [redacted]	• [redacted]	• [redacted]	• [redacted]
Case Reports (<4 patients)				
Brooks (2006)	• Single centre, USA • Case report (n=1)	• I: paracentesis followed by PleurX (n=1) • C: N/A	• Complications, incl. infections • Catheter patency • Rate of drainage	• Very limited generalisability due to case report design. High risk of bias.
Iyengar (2002)	• Single centre, USA • Case report (n=3) • Monthly follow-up until removal or death	• I: paracentesis and PLD followed by PleurX (n=3) • C: None	• Freq. and vol. of paracentesis prior to PleurX • Freq. and vol. of PleurX drainage • Complications • Catheter survival • Post-op length of stay	• Very limited generalisability due to case report design. High risk of bias.
Mullan (2011a)	• Case report of subset of 4 patients from Mullan (2011b) with catheter occlusion. This case report will not be evaluated separately.			

Table 3 Quality assessment of selected PleurX studies

Study	Use of concurrent controls?	Consecutive patient selection into study?	Prospective outcome data collection?	Well defined study protocol?	Sample representative of relevant population?	Explicit criteria for inclusion in study?	Explicit criteria for treatment allocation?	Entry at standardised disease progression point?	Specified time interval for patient recruitment?	Follow-up long enough to detect adverse events?	Clinically relevant outcomes & assessed using appropriate criteria?
Case Series (≥ 4 patients)											
Rosenberg (2004)	Y	N	N	Y	Unclear	Y	N	N	Y	Unclear	Unclear
Courtney (2008)	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Mullan (2011b)	N	Y	N	Y	Unclear	Y	N	Y	Y	Y	Y
Richard (2001)	N	N	N	N	N	N	N	N	N	Y	N
Tapping (2011)	N	Y	N	Y	Unclear	Y	Y	Y	Y	Y	Y
Saiz-Mendiguren (2010)	N	Y	N	N	Y	N	N	N	Y	Y	Y
Qualitative Study (n=4)											
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Case Reports (n<4)											
Brooks (2006)	N	N	N	N	N	N	N	N	N	Y	N
Iyengar (2002)	N	N	N	N	N	N	N	N	N	Y	N
Mullan (2011a)	This was a case report of a subset of patients from Mullan (2011b) and therefore has not been quality assessed										

[redacted]

Table 4 Baseline characteristics of patients within included studies

Study	MA definition	Mean Age (Range)	Gender composition (male/female)	Primary Co-morbidities	Paracentesis prior to PleurX?	Exclusions?
Case Series (n≥4)						
Rosenberg (2004) (n= 107; PleurX = 40; paracentesis = 67)	Cytologically proven malignant ascites or clinically suspected malignant ascites caused by reaccumulation of fluid and diagnosis of cancer.	Mean not reported PleurX: (21-81) Paracentesis: (31-85)	PleurX: 42.5%/57.5% Paracentesis: 34.3%/65.7%	PleurX: Ovarian (8), Breast (7), Colorectal (7), Other (18). paracentesis: Ovarian (12), Breast (7), Colorectal (12), Other (36).	≥2 previous paracentesis	None reported
Courtney (2008) (n= 34)	Proven abdominal malignancy with concurrent ascites; ascites requiring ≥ 2 therapeutic paracentesis in previous 30 days and reported relief of symptoms after paracentesis.	64.3 (40-81)	38%/62%	Pancreatic (7), Breast (6), Colon (5), Neuroendocrine (3), Ovary (3), Liver (2), Gastrointestinal stromal tumour (1), Mesothelioma (1), Other site (6).	Mean 2.8 (range 1-8) in 30 days prior to PleurX	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, or current intraperitoneal chemotherapy or immunotherapy.
Mullan (2011b) (n=50)	Intra-abdominal tumour spread and radiologically proven symptomatic ascites	66 (33-82)	30%/70%	Ovarian (8), Uterine (3), Breast (9), Colon (1), Pancreatic (13), Cholangiocarcinoma (3), Prostate (1), Primary Peritoneal (2), Gastric/Oesophagus (2), Sarcoma (1), Melanoma (1), Unknown (1), Renal (1), Neuroendocrine (3), Hepatocellular carcinoma (1)	Mean 4.5 paracenteses prior to PleurX placement. Mean duration between 1st paracentesis and PleurX was 106 days (4-952).	Multi-loculated ascites not responsive to intraperitoneal fibrinolysis, current intraperitoneal infection, or severe coagulopathy not responsive to reversal.
Richard (2001) (n=10)	Malignancy related ascites	61 (43-78)	70%/30%	Gastrointestinal (7), Breast (1), Lymphoma (1), Mesothelioma (1)	Previous repeated paracentesis	None reported
Tapping (2011) (n=28)	Malignant refractory ascites	61 (43-91)	25%/75%	Gastrointestinal(7), Lung (3), Gynaecological (10), Pancreatic (5), Breast (3).	≥3 standard paracentesis (2 most recent drainages <6 wks apart)	Multi-loculated ascites, non-correctable coagulapathy, or infected peritoneal cavity
Saiz-Mendiguren	Ascites caused by peritoneal	58.2	30%/70%	Breast (2), Gastric (2), Pancreatic	Not reported	None reported

Study	MA definition	Mean Age (Range)	Gender composition (male/female)	Primary Co-morbidities	Paracentesis prior to PleurX?	Exclusions?
(2010) (n=10)	progression on malignancy (n=9); ascites due to post-sinusodal portal hypertension secondary to suprahepatic veins	(40-72)		(2), Cholangiocarcinoma (2), Colon (1), Lung (1)		
Qualitative Study (n=4)						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Case Reports (n<4)						
Brooks (2006) (n= 1)	Rapidly reaccumulating malignant ascites	58 (N/A))	0%/100%	Ovarian (1)	Twice weekly	None reported
Iyengar (2002) (n=3)	Malignant abdominal ascites in patients with recurrent ovarian cancer	69.7 (50-83)	0%/100%	Ovarian (3)	Weekly (n=2); Every 1 to 3 weeks (n=1)	None reported
Mullan (2011a) (n=4)	Subset of patients from Mullan (2011b)					

Table 5 Technical success of PleurX catheter placement procedure in selected studies

Study	Measure of technical success	Device	Insertion guidance technique (number of procedures)	Anaes-thetic	Pain during placement	Success rate (number of procedures)	Peri-procedural complications
Case Series (n>4)							
Rosenberg (2004)	Peri-procedural complications not defined separately (infection, leakage, loculations)	PleurX	US&FS (40)	Not reported	Not reported	100% (40)	3 overall complications reported, none related to technical success
Courtney (2008)	Technical success: intraperitoneal positioning and ability to withdraw ascetic fluid	PleurX (modified)	US&FS (31) US (2) US&CT (1)	IV Sedation & LA	Not reported	100% (34)	One minor complication: epigastric vein injured during tunnel creation
Mullan (2011b)	Technical success: complication-free intra-peritoneal placement, with free drainage of ascites	PleurX	US (52)	LA	Not reported	100% (52)	None
Richard (2001)	No peri-procedural complications taken as successful device insertion	PleurX	US&FS (8) US (2)	IV Sedation	Not reported	100% (10)	None
Tapping (2011)	Technical success: successful placement of drain and drainage of ascites at insertion	PleurX	US&FS (4) US (28)	LA (29) LA and sedation (3)	Not reported	100% (32)	None
Saiz-Mendiguren (2010)	Defined as no complications during or after the procedure	PleurX	US (10)	LA	Mean 0.5 (range 0-3) Median 0 (VAS score 0-10)	100% (10)	2 pts reported discomfort during catheter placement (3/10 and 2/10 on VAS)
Qualitative Study (n=4)							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Case Reports (n≤4)							
Brooks (2006)	Case report: general reporting of procedure outcome	PleurX	Not reported	GA (patient intubated) & LA	Not reported	100% (1)	None
Iyengar (2002)	Case report: general reporting of procedure outcome	PleurX	US (3)	GA	Not reported	100% (3)	None
Mullan (2011a)	Subset of patients from Mullan (2011b)						

US: Ultrasonographic; FS: Fluoroscopic; US&FS: Ultrasonographic and Fluoroscopic guidance combined; CT: Computed tomography; IV: Intravenous; LA: Local anaesthetic; GA: General anaesthetic; VAS: Visual Analogue Scale

Table 6 PleurX drainage session details

Study	Vol. drained at initial placement	Duration of procedure / hospital stay	Mean no. of subsequent drainage sessions	Frequency and volume of drainage sessions	Location of drainage sessions	Care provider
	Volume drained during PleurX catheter placement procedure	*Length of procedure, or length of time as inpatient*	*Mean number of drainage sessions after initial placement of PleurX catheter*	*Frequency and volume of ascitic fluid drainage after placement of catheter*	*e.g. home, hospital, hospice*	*Person who performed the drainage session, e.g. patient, relative, nurse*
Case Series (n>4)						
Rosenberg (2004)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Courtney (2008)	3,240 ml (range 0.8-7 L)	Not reported	23.3 (Range 5-56; median 17) (n = 440 sessions)	Most pts drained every other day, some drained daily. Typical drainage vol 1.2–2 L	Not reported	58% spouse /friend 28% patient 13% nurse (n = 433 sessions)
Mullan (2011b)	≤ 2 L	Inpatient stay ≤24 h (1 pt stayed for 10 days due to organisational problems)	Not reported	Repeated small volume drainages	Home	Patient or caregiver. District nurse follow-up at home.
Richard (2001)	1.5 – 3 L	Not reported	Not reported	0.5L – 3 L per day. The frequency varied from every other day to once a week	Not reported	Not reported (paper suggests patient or relative)
Tapping (2011)	5 L (range 3.5 – 7 L)	In dept. for 30 min. Inpatient stay 24 h or until ascites has drained	Not reported	Patients advised not to drain more than 500 ml/12 hr	Home	Not reported (paper suggests patient / relative)
Saiz-Mendiguren (2010)	Not reported	Procedure length 50 min	Not reported	Approx 1 L every 2-10 days	Home	Patient or relative
Qualitative Study (n=4)						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Case Reports (n≤4)						
Brooks (2006)	7 L	Not reported	Not reported	2 L per day	Home	Not reported
Iyengar (2002)	5 L (1) 2.5 L (1) Not reported (1)	Not reported	Not reported	Twice weekly (1) 1-2 times weekly (1) Once weekly (1)	Home	Relative (1) Nurse (1) Patient (1)
Mullan (2011a)	Subset of patients from Mullan (2011b)					

Table 7 Catheter survival, function, failure & complications

Study	Number of pts & catheters *No of pts with PleurX drains*	Catheter patency *No. of catheters functioning at death, study end point, or resolution of ascites*	Mean duration of catheter survival *Duration from initial catheter placement to removal, death or study end point*	Catheter failure rate (removal) *No. of catheters which failed & were removed. Failure defined as malfunction or inability to provide symptomatic relief*	Catheter failure rate (intervention) *No. of catheters which failed and required an intervention to rescue (not removed).*	Overall Complication Rate *Rate of AEs or complications per patient*	Complication Type					
							Device related infection	Occlusion or Loculation	Ascitic Leakage	Inadvertently dislodged	Patient felt unwell or in pain	Other
Rosenberg (2004)	40 pts 40 catheters	27/40 (67.5%) 11/40 (27.5%) Lost to follow-up[a]	Not reported	3/40 (7.5%)	0/40 (0%)	3/40 (7.5%)[b]	1/40 (removed)	1/40	1/40	-	-	-
Courtney (2008)	34 pts 34 catheters	29/34 (85%) (5 pts loss to follow-up & censored)	86 days (calculated as lower 95% CI of product-limit analysis)	2/34 (6%) (1 catheter removed but not failure)	3/34 (9%)	20/34 (59%)[c]	1/34 Peritonitis (treated with AB) 1/34 gen. infection (removed)	4/34[d]	7/34[e]		5/34 Dizziness 1/34 Severe Pain	1/34 SoB 1/34 severe anaemia
Mullan (2011b)	50 pts 52 drains	50/52 (96%)	59.4 days (range 4-216 days) This value does not include failed catheters	1/50 (2%) (1 catheter dislodged)	5/50 (10%)	8/50 (16%)	1/50 Peritonitis 1/50 abdominal wall lymphangitis (both treated with AB)	3/50	1/50	1/50	Pain (1)	-
Richard (2001)	10 pts 10 catheters	8/10 (80%)	70 days (range 1 – 100 days)	0/10 (0%) (1 pt inadvertently removed catheter)	1/10 (10%)	2/10 (20%)[b]	-	1/10	-	1/10	-	-
Tapping (2011)	28 pts 32 catheters	24/28 (86%)	113 days (CI 70-157) (range 5-365 days)	0/32 (0%) (4 catheters dislodged and replaced)	6/32 (19%)	12/28 (43%)	5/28 minor catheter site (treated with AB)	-	1/28	4/28	-	1/28 Hernia 1/28 not reported
Saiz-Mendiguren (2010)	10 pts 10 catheters	9/10 (90%)	52 days (range 13-113 days) 1 pt alive at 124 days	0/10 (0%) (1 catheter in septic pt removed as precaution)	0/10 (0%)	0/10 (0%)	-	-	-	-	-	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]						
Brooks (2006)	1 pt 1 catheter	0/1 (0%)	18 months	0/1 (0%)	1/1 (100%)	3 in 1 pt	1/3	1/3	-	-	-	Hernia (1)
Iyengar (2002)	3 pts 3 catheters	2/3 (67%)	6 wks (1) 7 wks (1) 12 wks (1)	0/3 (0%) (1 catheter removed as precaution in sepsis)	0/3 (0%)	1 in 3 pts	-	-	-	-	Dehydration (1)	-
Mullan (2011a)	Subset of patients from Mullan (2011a)											

Grey text indicates studies where patient numbers were too low or outcome was not specifically assessed, and therefore results are not reliable; AE: Adverse Event; SoB: Shortness of breath; AB: Antibiotics; [a] Values in paper do not add up to 40 pts; [b] Only failures reported, no further details of complications and AEs reported; [c] 11 patients experienced a single AE and 11 experienced multiple AEs; [d] 14 occurrences of loculations in 4 patients; [e] After high rate of leakage the centre changed the tunnelling to medial and cephalad. No further leakage AEs

Table 8 Quality of life and resolution of symptoms in patients with a PleurX indwelling catheter

Study	No of pts	Measure	Assessment tool and timing	Baseline values	Follow-up value
Courtney (2008)	n=34 (baseline) n= not reported at each follow-up	Abdominal discomfort	Modified Memorial Symptom Assessment Scale (MSAS)[a] Week 0, 2, 8, 12	≥6 out of 12	Lower score at 3 follow ups (exact score not reported). Significant at 2 & 8 wks (P=0.0059 & P=0.01)
		Feeling bloated		≥6 out of 12	Lower score at 3 follow ups (exact score not reported). Significant at 2 and 8 weeks (P=0.0001 and P<0.0001).
		Lack of appetite, SoB, diarrhoea, self-perception, nausea, pain, difficulty sleeping, worrying		≥6 out of 12 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		≥6 out of 12 for each symptom	No significant change
		Problems with urination		Not reported	No significant change
		Dizziness		Not reported	Significant increase at 2 wks (P=0.0407), but not at 8 or 12 wks.
		Swelling of arms and legs		Not reported	No significant change
	n=27 (week 1) n=7 (week 12)	Overall quality of life	Subjective significance questionnaire (SSQ)[b]	SSQ not administered at week 0	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.
	n= not reported	Control of symptoms	Every week (1-12 wks) Pts asked whether they thought ascites symptoms were being well controlled by home drainage	N/A	83 - 100% responded affirmatively
	n= not reported	Periumbilical girth	Weeks 2,8,10 periumbilical girth was measured	Mean 106 cm	2 wk mean 92.4 cm (P=.0002) 8 wk mean 89.9 cm (P=.0246) 10 wk mean 86.1 (P=0.0483)
	n=not reported	Control of symptoms	Weeks 2,8,10 clinicians assessed whether PleurX was adequately controlling ascites	N/A	80-95% of cases were positive
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]MSAS is a validated patient-reporting tool for assessing symptoms in cancer patients. It consists of 32 physical and psychological symptoms. For each symptom there is an overall score out of 12. The MSAS has been modified in Courtney (2011) to include 2 questions pertinent to ascites, and a question on hair loss was removed.
[b]SSQ is a 4 item survey designed to assess changes in QoL in previous week, there are 7 options for each question with 3 degrees of worsening, 3 degrees of improvement, and no change.

Table 9 Results from studies with relevant comparator (paracentesis/LVP) outcomes

Study	Comparator Type	Complications		Inpatient Stay	
		Comparator (paracentesis)	Intervention (PleurX)	Comparator (paracentesis)	Intervention (PleurX)
Rosenberg (2004)	67 pts treated with paracentesis (no PleurX). Differences in age/malignancy/sex were not significant (PleurX n=40)	5/67 (7.5%)* Peritonitis (3), loculations (2)	3/40 (7.5%)* Leakage (1), infection (1), loculations (1)	Not reported	-
Mullan (2011b)	50 patients treated with LVP prior to PleurX	Not reported	-	Mean 2.8 days (range 1-6 days; n=23)	Pts discharged within 24 hrs (reported in methods)

*No statistical analysis performed

5 ASSESSMENT OF COST ANALYSIS

5.1 Overview of manufacturer's economic assessment

This section of the EAC report assesses the cost analysis and economic model submitted by UK Medical for treatment of malignant ascites (MA) with PleurX. The submission included:

- a systematic literature search, including methods and results;
- description of one study which met the specified selection criteria;
- a comprehensive description of a *de novo* cost analysis undertaken by UK Medical;
- a clear and well-presented model in Microsoft Excel.

Table 10 Reference table for areas of cost analysis in sponsor's evidence

Area of cost analysis evidence	Section in submission document	Tables/Figures in submission document
Review of literature	Section 6.1	Tables 6.1 – 6.3
Model structure	Section 6.2.3	Figure 6.1
Comparator	Section 6.2.2 Section 6.2.4	
Subgroups	Section 6.8	None
Perspective and time horizon	Section 6.2.7	Table 6.4
Resource use and costs	Section 6.3.6 Section 6.4	Tables 6.6 – 6.12
Adverse event costs	Section 6.4.7	Table 6.17
Discount rates	Section 6.2.7	Table 6.4
Sensitivity analysis	Section 6.5	Tables 6.23-6.24 Figures 6.2-6.13
Results	Section 6.6	Table 6.18-6.22
Validation	Section 6.7	None

5.1.1 Methods

UK Medical presented a robust and clear economic model to evaluate the 'per patient' costs and system impact of PleurX for treatment of malignant ascites (MA) compared to LVP (inpatient) and LVP (outpatient). The model also included costs and system impacts at a population level but this information was not available in the evidence submission document.

Identification and Quality Assessment of studies

Using a well-documented and thorough literature search strategy (Appendix 7 of sponsor's evidence submission) UK Medical identified one poster presentation (Jacob 2009) and

accompanying pre-publication full length manuscript (Mullan 2011b). The results from this study were presented and a narrative appraisal discussing the quality of this study was provided by the sponsor.

Model Structure

A *de novo* cost analysis was carried out by York Health Economics Consortium (YHEC) on behalf of the sponsor. The model has a decision-tree structure with a Markov-style time-dependent element based on decreasing survival probabilities of patients with MA. It was appropriately presented from the perspective of the NHS, but did not differentiate between primary and secondary care funding sources. Personal Social Services (PSS) costs were not considered in the analysis, but the submission stated that costs would likely fall on the patient's carer. Inputs were clearly displayed with referenced sources in most cases. The model showed the 'per-patient' and population costs of PleurX and LVP, as well as the incremental cost of PleurX. The model also reported the system costs and benefits given the estimated population.

The cost of PleurX included:

- inpatient stay (1 day);
- procedure consumables and other costs (including staff);
- PleurX at-home drainage kits;
- at-home nurse visits;
- treatment of complications (infection, catheter failure, re-intervention).

The cost of LVP included:

- inpatient stay (2.8 days) or outpatient (1 day);
- procedure consumables;
- treatment of complications.

Assumptions

The sponsor listed assumptions used in the model in Section 6.3.8 of the evidence submission; the EAC noted some missing assumptions (EAC report Section 5.2). Some assumptions were justified using appropriate sources, but not all. Overall, the assumptions used in the model did not bias results in favour of PleurX.

Time Horizon

The time horizon of the model was from the time of initial PleurX insertion until 26 weeks (6 months) later. The Markov-style element was run over 26 weekly cycles to account for the short duration of survival of patients with MA. The cycles used transition probabilities based on 100% survival at week 0 to 4% survival at week 26. The cost of treatment was multiplied by the transition probability at each cycle; half-cycle corrections were used to incorporate changes in survival within a cycle. The time horizon did not take into account the treatment period before PleurX placement which is likely to include several conventional paracenteses.

Data sources

Clinical variables, resource use and costs were displayed in the sponsor's evidence submission (Tables 6.6 – 6.17). The clinical variables, mean patient survival and complication frequency were extracted from Mullan (2011b) and Rosenberg (2004) respectively. Healthcare resource data was taken from a range of studies.

The costs used as inputs in the model were derived mostly from Mullan (2011b) and UK Medical. Mullan (2011b) did not provide a description of the source of most costs and therefore some of this ambiguity was transferred to the sponsor's model. The cost of a bed day was estimated as being £312 (NHS reference costs 2009-10 for an excess bed day). Costs associated with nurse visits were taken from PSSRU 2010 (Curtis 2010) which was a suitable source.

A key opinion leader (KOL) questionnaire was sent to eight clinicians with experience of using PleurX to compensate for a lack of resource use data from published sources; UK Medical received two responses. Data from one KOL questionnaire response was used as an input for the number of nurse visits required to train each patient to use the PleurX catheter.

Discounting

Due to the short time horizon, discounting was appropriately not used.

Sensitivity analysis

UK Medical presented the results of one-way deterministic sensitivity analysis (Tables 6.23-6.24). All variables (except for population size) were tested in this analysis, and were changed by ±20% regardless of the level of confidence in an input or the parameter-specific circumstances. The percentage change in the overall cost saving was presented, enabling the key drivers of the model to be identified. Six key drivers were selected and subjected to deterministic threshold analysis across a wider range of values to identify the point at which PleurX became more costly (compared to inpatient LVP; Figures 6.2-6.7) or cost-saving (compared to outpatient LVP; Figures 6.8-6.13).

5.1.2 Results

The sponsor presented the base-case incremental cost impact on a 'per-patient' basis for two scenarios in line with NICE's scope:

- PleurX compared with inpatient paracentesis (sponsor's submission Table 6.19)
- PleurX compared with outpatient paracentesis (Table 6.21)

This was broken down into costs for drainage, nurse visits, complication, and re-intervention (removal and replacement of PleurX catheter). In addition, the system impact was presented in terms of number of paracentesis sessions, number of litres drained using PleurX, number of bed days, and number of nurse visits, for both of the above scenarios (sponsor's submission Tables 6.20 and 6.22).

- ***Scenario 1*** - according to the sponsor's base-case cost model PleurX would save -£679 per patient compared to inpatient paracentesis (LVP hospital stay of 2.8 days). This scenario would result in a saving of 7.4 bed days per patient and an increase in 23.5 nurse visits.
- ***Scenario 2*** - compared to outpatient paracentesis (with a hospital stay of 1 day) PleurX would incur an additional cost of +£1,010 per patient. PleurX would save 1.9 hospital bed days, and require an additional 23.5 nurse visits per patient.

5.1.3 Model validation

The economic evidence submission states that internal validity checks were undertaken by an independent health economist. The sponsor made no reference to Mullan (2011b) as an external validation measure in Section 6.7, but described the data from this publication elsewhere in the evidence submission (Section 6.9.1). UK Medical explained that the cost savings observed in their

model were consistent with those in Mullan (2011b) and described the differences in approaches which account for the more conservative savings in the sponsor's model, e.g. absence of costs associated with complications and community nurse visits in Mullan (2011b). UK Medical was open about the paucity of published evidence comparing PleurX with paracentesis, and the low response rate to the KOL questionnaire (two responses out of eight).

5.2 Critique of approach used

In this section the EAC has presented a critical appraisal of the sponsor's cost model. A formal checklist (Drummond 1996) was used to assess the quality of the economic model and accompanying narrative (Table 11 EAC report). Overall, the EAC considered the model to be clear and robust. The narrative was direct and thorough in its assessment of uncertainties and limitations, and outcomes and conclusions were stated with suitable caveats. Key areas of the economics evidence have been critiqued by the EAC in the following sections.

Published Evidence

The sponsor performed a robust literature search, and identified a single study relevant to the decision problem (Jacob 2009;Mullan 2011b). The EAC did not modify this search. No formal quality appraisal checklist was presented in the evidence submission and as a result the EAC independently critiqued Mullan (2011b; Appendix 2 EAC report). The EAC agreed with the issues raised by UK Medical in relation to Mullan (2011b) which were:

- no details of how costs were obtained;
- inaccuracy in the calculation of the cost of paracentesis resulting in a substantial overestimate of the incremental saving from PleurX;
- costs associated with complications were omitted;
- costs of community nurse visits for patients treated in their homes were not assessed.

Model Structure

The economic model presented by UK Medical was well-structured and made use of the available evidence. The decision tree combined with a Markov style element was suitable for reflecting the treatment pathway and short life expectancy of patients treated for recurrent malignant ascites.

The EAC noted that the point at which patients entered the decision tree was not described, i.e. the point at which it would be clinically appropriate to treat MA with PleurX. An indwelling catheter such as PleurX would usually only be inserted in patients with intractable and recurrent fluid accumulation, and therefore several paracenteses may be required prior to PleurX placement. Tapping (2011) only included patients with ascites requiring at least three previous conventional paracentesis and Courtney (2008) required two paracenteses in the previous 30 days. The following statements were provided to the EAC by two expert advisors:

"We only carry out PleurX in patients with limited life expectancy and a palliative outlook who have had at least 3 episodes of recurrent and symptomatic ascites following normal paracentesis over a short period of time."

"If the patient has no further chemotherapy options and the ascites recurs within a month a PleurX is considered. We have day case paracentesis now established as an alternative, giving the patient the option to some extent. However if the patient needs 2 or more drainages per month we would definitely recommend a PleurX".

Limitations of the model structure were also recognised by the EAC relating to the potential for complications during PleurX treatment and LVP drainage. Firstly, complications associated with LVP-only patients were not adequately considered. A systematic review by Becker (2006) showed that serious complications have been reported in patients treated using LVP, such as hypotension, pulmonary embolism, and perforation (Appendix 4 EAC report). Secondly, treatment of complications has been assumed to be the same between PleurX and LVP; the EAC believe this may not be the case, not least because LVP patients would already be in a hospital setting and therefore the additional cost of complications would not include an admission cost. Thirdly, the sponsor use "catheter failure" as an aggregate term for complications other than infection, which were treated using streptokinase for occlusion or loculation. However, literature suggests that not all occlusions resolve with streptokinase, and that other complications such as leakage, displacement, and hernia may need to be accounted for (Table 7 EAC report). The model does not consider costs for complications which do not resolve after a single treatment. In addition, the model does not include patients in whom their ascites resolves after placement of the PleurX catheter. Resolution of ascites was reported in the literature: 1/40 (2.5% (Rosenberg 2004)), 2/10 (20% (Richard III 2001)), and 5/34 (14.7% (Courtney 2008)). The directional effect of ignoring

resolved ascites could not be estimated by the EAC as no data was available on resolution rates in LVP patients.

The model does not attempt to capture the impact of PleurX on improvements in quality of life. Due to a paucity of evidence in this area the EAC consider this to be appropriate. Despite the limited data on resolution of symptoms and patient experience (Table 9 EAC report) is would be reasonable to expect that inclusion of QoL data in the model would result in further benefits.

Assumptions

The assumptions listed in Section 6.3.8 by the sponsor were largely sensible and justified; however the EAC noted some further assumptions used in the *de novo* cost model which were not always justifiable:

- the cost of treating complications is the same for both PleurX and LVP;
- all catheter failures are treated using fibrinolytics;
- all infections and catheter failures resolve after treatment;
- no catheters are removed due to resolution of ascites;
- the risk of complication is evenly spread over the time the catheter is *in situ*;
- for 'assisted' PleurX patients, nurse visits would be additional to any routine visits that patients may receive.

Comparators

The economic evidence submission does not discuss the proportion of patients treated using LVP in an inpatient versus outpatient setting. Because PleurX is cost-saving when compared to inpatient paracentesis and incurs a cost when compared to outpatient paracentesis according to the sponsor's base case, understanding how common the two procedure settings are in the NHS is important. The KOL questionnaire asks for the proportion of patients treated in each setting, to which two clinicians responded:

KOL Questionnaire Responses	LVP Setting	
	Inpatient	Outpatient
Clinician 1	64.2%	35.8%
Clinician 2	50%	50%

The sponsor stated that due to a poor response rate that the data from the KOL questionnaire had limited reliability. Uncertainty surrounding the proportion of outpatient and inpatient LVPs means that potential cost savings and system benefits across the NHS are difficult to estimate.

Population

UK Medical used an estimate of 2,500 individuals as the population size that could potentially be treated using PleurX instead of conventional paracentesis. The source of this value was 10% (percentage of total ascites numbers that are due to malignant ascites) of the finished consultant episodes (FCEs) from HES 2008-09. The EAC considers this to be an overestimate for the following reasons:

- it is incorrect to equate FCEs with the number of individuals with ascites. The EAC used a more in depth analysis of HES data (only accessible to NHS staff) and found that in 2009-10 there were 27,461 FCEs but only 16,821 individual patients;
- the HES data includes diagnostic ascites drainage procedures
- many patients will require only one or two drainage procedures, and therefore would not warrant placement of an indwelling PleurX catheter. In a study of 209 patients with MA, 54% were treated using serial paracenteses, with a mean of two (1-7) drainages required (Ayantunde 2007).

The model does not record the proportion of inpatient versus outpatient LVPs undertaken in the NHS. The contrasting cost implications shown in the model between these two comparator settings suggests that this issue would impact heavily on any overall savings.

Costs

In general the sponsor was explicit about the uncertainties surrounding cost inputs to the economic model (Sections 6.4.7 and 6.9.3 of the evidence submission) and stated that sensitivity analysis was used to address this. The EAC has critiqued each individual model input, including whether the sensitivity analysis was adequate to capture real-life variability or to address uncertainty (EAC Table 12). The cost of a hospital bed day (£312), a key driver to the model, was sourced from NHS reference costs for an excess bed day. This was considered to be appropriate as the bed day cost for “General Abdominal – Diagnostic Procedures” includes the procedure costs

and therefore is not suitable. The EAC has highlighted further issues with certain costs used in the model:

- ***Procedure costs/sundries (sourced from Mullan 20110):*** No information on the source of this cost was provided in the manuscript; the EAC contacted the author who stated that this cost included "the nurse, the doctor, the sterile trolley with drapes, antiseptic swabs, scalpel and suture etc".

- ***Complications costs:*** The cost associated with treating complications may have been understated by the sponsor. The EAC requested further information from the authors of Mullan (2011a;2011b) about the care provided to patients who had suffered complications. This was used to compile a treatment cost for each individual (EAC report Appendix 3). The cost of treatment of catheter occlusion using Streptokinase in the four patients in the Mullan (2011a) case report ranged from £582 to £3,036. The economic model used a cost of £395; this disparity was largely due to underestimation of the number of imaging procedures required, costing a single day of Streptokinase treatment instead of five, and omission of inpatient stay for some cases. The treatment for infection ranged from £194 for mild lymphangitis to £2,020 for peritonitis. A cost input of £194 was used in the model which fails to account for more serious infections requiring inpatient stay (EAC report Appendix 3). Despite a substantial underestimation of the cost of complications, this does not impact heavily on the overall model outcome because of approximately equal complication rates and the same cost being applied to each arm. This may not be a reflection of the real cost considerations as patients receiving LVP as an inpatient would not incur an additional admission cost. It is possible that taking this issue into account would result in a smaller cost saving for PleurX.

Inputs

The sponsor used clinical and resource use inputs from a range of suitable sources (EAC Table 12). Several inputs were conservative, particularly the frequency of LVP per month which was the key driver. By changing the value from 1.22 LVPs per month to 2.8 (Courtney 2008), the cost saving associated with PleurX increased to -£3,381 per patient. The number of community nurse visits

per week for assisted PleurX patients was also considered to be conservative because some patients may be receiving a level of community nursing care regardless of ascites drainage technique, and therefore PleurX may not impose as much of a burden. The following comment was provided by an expert advisor: "It is very likely that a district nursing team would be involved in providing care at the patients' home to some extent, whether or not the patient had PleurX". The EAC noted some areas where inputs may be biased in favour of PleurX:

- ***Complication rates:*** UK Medical used rates of infection and catheter failure from a single reference (Rosenberg 2004). This publication was the only one to investigate complications in both PleurX and LVP patients. However, there is a very wide range of complication rates across PleurX-only studies (Table 7 EAC report) which were not adequately tested using one-way sensitivity. Overall complication rates ranged from 0% (Saiz-Mendiguren 2010) to 59% (Courtney 2008). Despite these uncertainties, the low impact of complication rates on the overall model outcome meant that when the EAC doubled the rate and cost of PleurX complications in a two-way sensitivity analysis, this resulted in a minor reduction in saving (PleurX remained cost saving by -£626).
- ***Reintervention rates:*** a 4% reintervention rate (removal and replacement of PleurX) was used in the model (source: Mullan 2011b). Tapping (2011) reported a 12.5% rate from inadvertent displacement of the catheter. The EAC tested change in reintervention rate in the model, and found that PleurX remained cost-saving by -£616.

Sensitivity analysis

The EAC considered the approach of one-deterministic sensitivity analysis using ±20% was insufficient to capture real-life ranges for certain inputs. This was particularly problematic when there was a high degree of uncertainty around the baseline value, e.g. complication rates and cost of treating infection or catheter failure. However, the key drivers were subjected to further sensitivity analysis across a wider range of values and displayed in threshold graphs. This approach was clear and thorough.

Table 11 Quality appraisal of sponsor's cost model

UK Medical Economic Model		
Study question	**Grade**	**EAC Comments**
Study design		
1. Was the research question stated?	Yes	Section A of sponsor's submission was in line with NICE's scope. Decision problem presented in Section 4.
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Table 6.4 sponsor's submission
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	N/A	In line with scope issued by NICE
5. Were the alternatives being compared clearly described?	Yes	Section 2.6
6. Was the form of economic evaluation stated?	Not clear	Section 6.2.8
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	Not explicitly justified
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	Effectiveness of PleurX not included in model
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	As above
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	No meta-analysis
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	N/A	Health states not valued
13. Were the details of the subjects from whom valuations were obtained given?	N/A	As above
14. Were productivity changes (if included) reported separately?	N/A	No productivity changes
15. Was the relevance of productivity changes to the study question discussed?	N/A	As above
16. Were quantities of resources reported separately from their unit cost?	Yes	Tables 6.7 and 6.8, and Excel spreadsheet
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Section 6.3 and Excel spreadsheet
18. Were currency and price data recorded?	N/A	GBP only.
19. Were details of price adjustments for inflation or currency conversion given?	N/A	GBP only. Short time horizon.

UK Medical Economic Model		
Study question	**Grade**	**EAC Comments**
20. Were details of any model used given?	Yes	Section 6.2.3
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Section 6.2.4 – 6.2.7
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Table 6.4
23. Was the discount rate stated?	N/A	Immediate outcomes only
24. Was the choice of rate justified?	N/A	As above
25. Was an explanation given if cost or benefits were not discounted?	Yes	Table 6.4
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	No stochastic data
27. Was the approach to sensitivity analysis described?	Yes	Section 6.5, Tables 6.23-6.24, Figures 6.2-6.13
28. Was the choice of variables for sensitivity analysis justified?	No	±20% used without justification. However, deterministic sensitivity analysis graphs use plausible ranges.
29. Were the ranges over which the parameters were varied stated?	Yes	Shown in Table 6.23-6.24 and Figures 6.2-6.13
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Tables 6.18-6.22, and Excel spreadsheet
31. Was an incremental analysis reported?	Yes	Tables 6.18-6.22, and Excel spreadsheet
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Tables 6.18-6.22. However, aggregating inpatient stay and technology costs into “Draining” resulted in loss of detail
33. Was the answer to the study question given?	Yes	Tables 6.18-6.22, Section 6.9
34. Did conclusions follow from the data reported?	Yes	Section 6.9
35. Were conclusions accompanied by the appropriate caveats?	Yes	Section 6.9.3
36. Were generalisability issues addressed?	No	No information on frequency of inpatient versus outpatient paracentesis in UK hospitals. Overestimate of prevalence of disease.

Adapted from 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. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD’s guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Table 12 Critique of PleurX economic model inputs

Item	Value	Source	Sensitivity analysis	EAC Comment	Impact
Inputs which apply to PleurX and LVP arms					
Population	2,500	HES 2008-09	None	Population estimate too high. HES data relates to finished consultant episodes, not number of patients. Also this number would include diagnostic ascites drainage procedures and there would be a subpopulation of MA patients whose fluid accumulation would not warrant an indwelling catheter (see Section 5.2 of EAC report for more information)	**Impacts heavily on population-level incremental cost and system impact**
Mean survival	1.95 months	Mullan (2011b)	Y (±20%)	Appropriate. Time horizon 6 months.	**LOW** PleurX is cost saving across week 1 to week 26
Cost of hospital bed day	£312	NHS Reference costs 2009-10	Y (±20%)	This cost is for an excess bed day. Appropriate as procedural costs have been added in model. No specific excess bed cost for paracentesis procedure.	**HIGH** Sensitivity analysis was appropriate
Procedure costs/sundries	£121	Mullan (2011b)	Y (±20%)	No further details of source in Mullan (2011b). EAC contacted author who stated that this cost included "the nurse, the doctor, the sterile trolley with drapes, antiseptic swabs, scalpel and suture etc".	**MODERATE** Increasing this cost results in an increased saving in favour of PleurX.
Cost of treating infection	£194.06[a]	Assumption	Y (±20%)	EAC consider this to be an underestimate, as some infections require admission to hospital, diagnostics and IV antibiotics. Baseline cost of £194.06 used in model is the very cheapest the cost of treatment could be (EAC report Appendix 3). Baseline needs to be higher, and sensitivity analysis needs to be increased to 200%.	**LOW** If assumed that complication rates are similar between PleurX and LVP, increasing cost of treating the complication does not impact heavily on saving. However, LVP patients will already be in the hospital setting, and therefore cost of inpatient stay will be reduced. Model does not allow this calculation.
Cost of treating catheter failure	£395.91[b]	Assumption		EAC consider this to be an underestimate as Mullan recommends 5 day course of Streptokinase. Also, patients treated with Streptokinase in Mullan (2011a) had 2-5 US imaging procedures, multiple CT scans, and episodes of wire brush manipulation and flushing.	**LOW** (as above)
Inputs which apply to PleurX arm only					
Complication rate	2.5% Infection 5.0%	Rosenberg (2004)	Y (±20%)	Wide variation in complication rates associated with PleurX (between 0% and 59%) was observed, partially due to inconsistent reporting between publications (Table 6 EAC	**LOW** EAC doubled the cost of treating infection and catheter failure and doubled the rate of both

Item	Value	Source	Sensitivity analysis	EAC Comment	Impact
	Catheter failure			report). Sensitivity analysis does not extend far enough. Rosenberg (2004) is the only paper to report complication rates for PleurX and LVP.	complications in the PleurX arm (two-way sensitivity analysis). The result remained cost saving by -£626 in favour of PleurX.
Re-intervention rate	4.0%	Mullan (2011b)	Y (±20%)	Tapping (2011) reported that 4 patients (12.5%) inadvertently displaced their catheter requiring reintervention.	**LOW** EAC increased reintervention rate from 4% to 12.5% (+312.5%). PleurX remained cost saving by -£616.
Bed days for PleurX insertion	1.0	Mullan (2011b)	Y (±20%)	Tapping (2011) also reported 24 h inpatient stay, suggesting that this input is appropriate.	**HIGH** Sensitivity analysis was appropriate
Proportion of self managed patients	73.0%	Courtney (2008)	Y (±20%)	Iyengar (2002; case report of 3) was the only publication other than Courtney (2008) to report proportion of self-managed patients (66.6%).	**LOW** Sensitivity analysis was appropriate
Length of contact per nurse	0.25 hours	Assumption	Y (±20%)	No further information available	**LOW** EAC doubled this value to 0.5 hours which resulted in saving of -£556 in favour of PleurX.
Nurse visits for catheter training	2	KOL	Y (±20%)	EAC expert advisor agreed with this estimate	**LOW** Sensitivity analysis was appropriate
Nurse visits per week for assisted patients	3.5	Courtney (2008) and Richard (2001)	Y (±20%)	Appropriate input based on available evidence	**LOW** Sensitivity analysis was appropriate
Number of 1 litre drainage kits used per week	3.5	Assumption based on above	Y (±20%)	Appropriate input based on available evidence	**HIGH** Sensitivity analysis was appropriate
Cost of PleurX placement consumables	£64.39	Mullan (2011b)	Y (±20%)	Agreement between Mullan (2011b) and UK Medical costs	**MODERATE** Sensitivity analysis was appropriate
Cost of Catheter	£245	UK Medical	Y (±20%)	Based on sponsor costs	**MODERATE** (as above)
Cost of drainage Kit	£63.75	UK Medical	Y (±20%)	Pack of 10 for £637.50. Cost assumes that packs can be divided up.	**HIGH** Sensitivity analysis was appropriate
Cost of re-intervention	£742.39	Based on cost of initial procedure	Y (±20%)	Appropriate assumption	**LOW** Sensitivity analysis was appropriate

Item	Value	Source	Sensitivity analysis	EAC Comment	Impact
Cost of home nurse visit	£78 / hour	PSSRU 2010	Y (±20%)	Reliable and appropriate cost source	**LOW**
Inputs which apply to LVP arm only					
Bed days per LVP	2.8	Mullan (2011b)	Y (±20%)	Mullan (2011b) was the only study to report mean bed days for LVP (mean 2.8 days, range 1-6 days). This value is a key driver of the model, and there is uncertainty surrounding it.	**HIGH** The EAC found that below 2.1 bed days for LVP, PleurX was no longer cost-saving. Using the range in Mullan (1 to 6 days) the cost implications of PleurX ranged from -£3,682 to +£1,010 per patient.
Frequency of LVP per month	1.22	Mullan (2011b)	Y (±20%)	This parameter is a key driver of the model. Results from Courtney (2008), Tapping (2011), Brooks (2006) and Iyengar (2002) suggest that the value used in the model is conservative (Table 3 EAC report)	**HIGH** The EAC found that with 2.8 LVP procedures a month (value from Courtney 2011), the cost saving associated with PleurX would be -£3,381.
Complications	4.5% Infection 3.0% Catheter failure	Rosenberg (2004)	Y (±20%)	Uncertainty surrounding complication rates for LVP. Range from 0% to 28% (see EAC report Appendix 5). However, only Rosenberg (2004) compared LVP and PleurX in same study.	**LOW** (see comment for PleurX complications)
Cost of LVP consumables	£44.45	Mullan (2011b)	Y (±20%)	Appropriate	**MODERATE** Sensitivity analysis was appropriate
LVP procedure costs/sundries	£121	Mullan (2011b)	Y (±20%)	No further details of source in Mullan (2011b). EAC contacted author who stated that this cost included "the nurse, the doctor, the sterile trolley with drapes, antiseptic swabs, scalpel and suture etc".	**MODERATE** Sensitivity analysis was appropriate

US: ultrasound; CT: computed tomography; LVP: large volume paracentesis; KOL: key opinion leader; CF: contrast fluoroscopy

[a] includes medical oncology consultant led attendance & 7 days of Abs

[b] includes medical oncology consultant led attendance, 1 vial Streptokinase, US session (<20 min), CF session (<20 min)

5.3 Results included in manufacturer's submission

The results of the economic model were presented in the form of an incremental cost (saving or otherwise) for PleurX compared to conventional paracentesis. Results for inpatient and outpatient paracentesis as comparators are presented separately. The incremental system impact was also demonstrated in terms of parameters such as number of hospital bed days and nurse visits. It would have been useful to see the cost information presented in parallel with anticipated health benefits to patients, e.g. improved QoL, improved symptom control, increased convenience

5.3.1 Base case

Scenario 1: PleurX versus LVP (inpatient)

Results are shown in Tables 6.19 and 6.20 of the sponsor's submission. When compared to inpatient LVP with a hospital stay of 2.8 days, PleurX was less expensive by -£679 per patient (EAC Table 13). This saving was almost entirely driven by the cost of additional bed days in the comparator arm. This scenario would result in an average saving of 7.4 hospital days per patient, and would require an additional 23.5 nursing visits per patient.

Table 13 Incremental cost impact of PleurX compared to inpatient LVP per patient (taken from sponsor's submission)

	PleurX	Inpatient LVP	Incremental cost
Draining (including bed days, technology, consumables, procedure)	£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**

Scenario 2: PleurX versus LVP (outpatient)

Results are shown in Tables 6.21 and 6.22 of the sponsor's submission. PleurX incurs an additional cost of +£1,010 per patient when compared to outpatient LVP with a hospital stay of 1 day (EAC Table 14). The increased cost of the PleurX catheter and drainage equipment, as well as nurse visits and the cost of reintervention were responsible for this additional cost. A saving of 1.9 bed days and 23.5 additional nursing visits per patient would result from PleurX treatment.

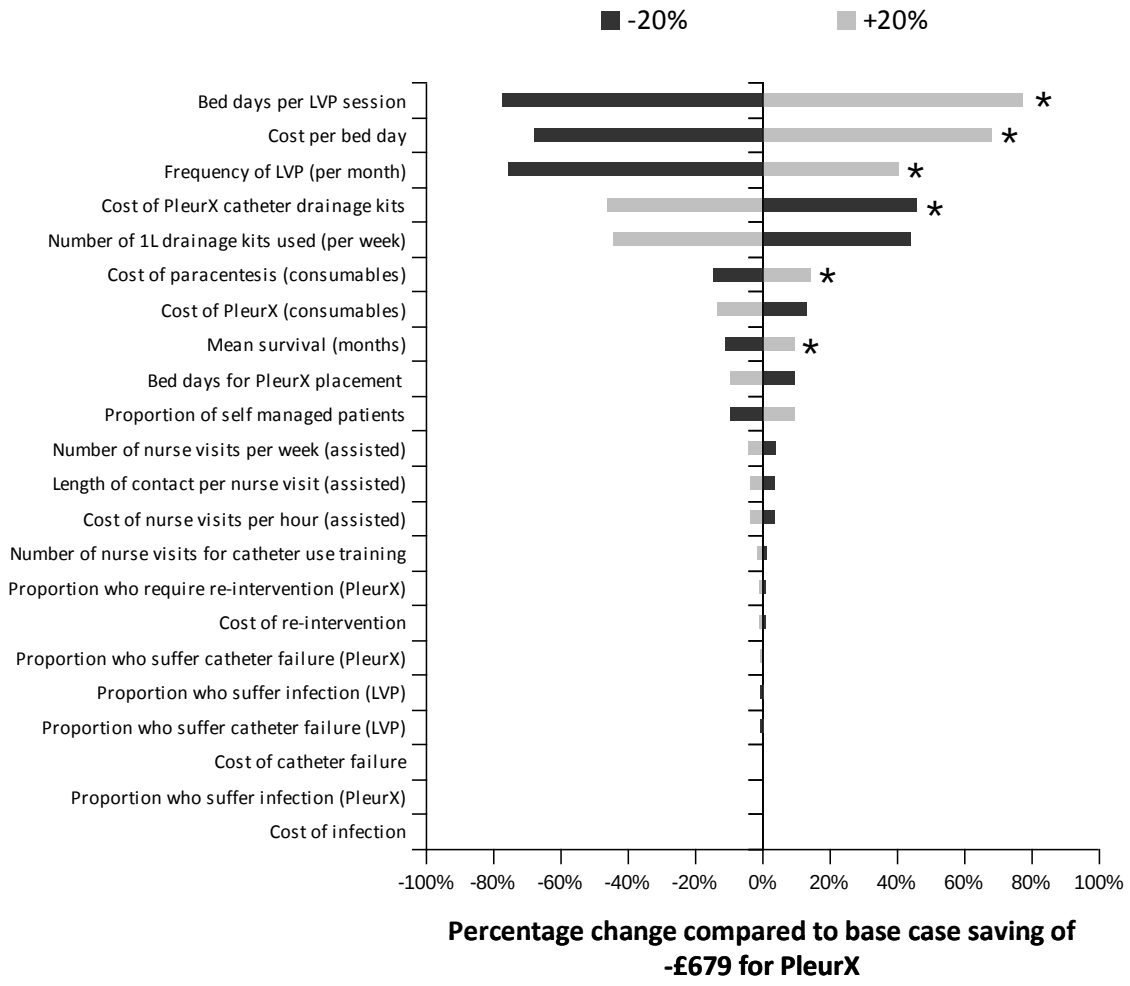
Table 14 Incremental cost impact of PleurX compared to outpatient LVP per patient (taken from sponsor's submission)

	PleurX	Outpatient LVP	Incremental cost
Draining (including bed days, technology, consumables, procedure)	£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**

5.3.2 Sensitivity analysis

All model parameters were subjected to sensitivity analysis (±20%; Table 6.23 sponsor's submission) for both scenarios (EAC Figures 1 and 2) which enabled identification of the key drivers of the model. Key drivers were subjected to further univariate sensitivity analysis across a wider range of values, and displayed as threshold analysis graphs (using an incremental cost impact of £0 as the threshold; Figures 6.2-6.12 of the sponsor's submission). The EAC has presented a summary of this information (Tables 15-16) and noted the threshold input for the key drivers at which the incremental cost impact of PleurX incurs a cost (in the case of inpatient LVP as a comparator; Table 15), or becomes cost saving (in the case of outpatient LVP as a comparator; Table 16). UK Medical provided a helpful narrative overview of the key results from the sensitivity analysis. Probabilistic sensitivity analysis was not conducted; the sponsor state that this was due to a lack of appropriate data. The EAC consider this to be appropriate as confidence intervals were not available for the inputs in any of the publications.

Figure 1 Sensitivity analysis (±20%) of each variable in the cost model where PleurX is compared with inpatient LVP (base case incremental cost impact per patient for PleurX was -£679).



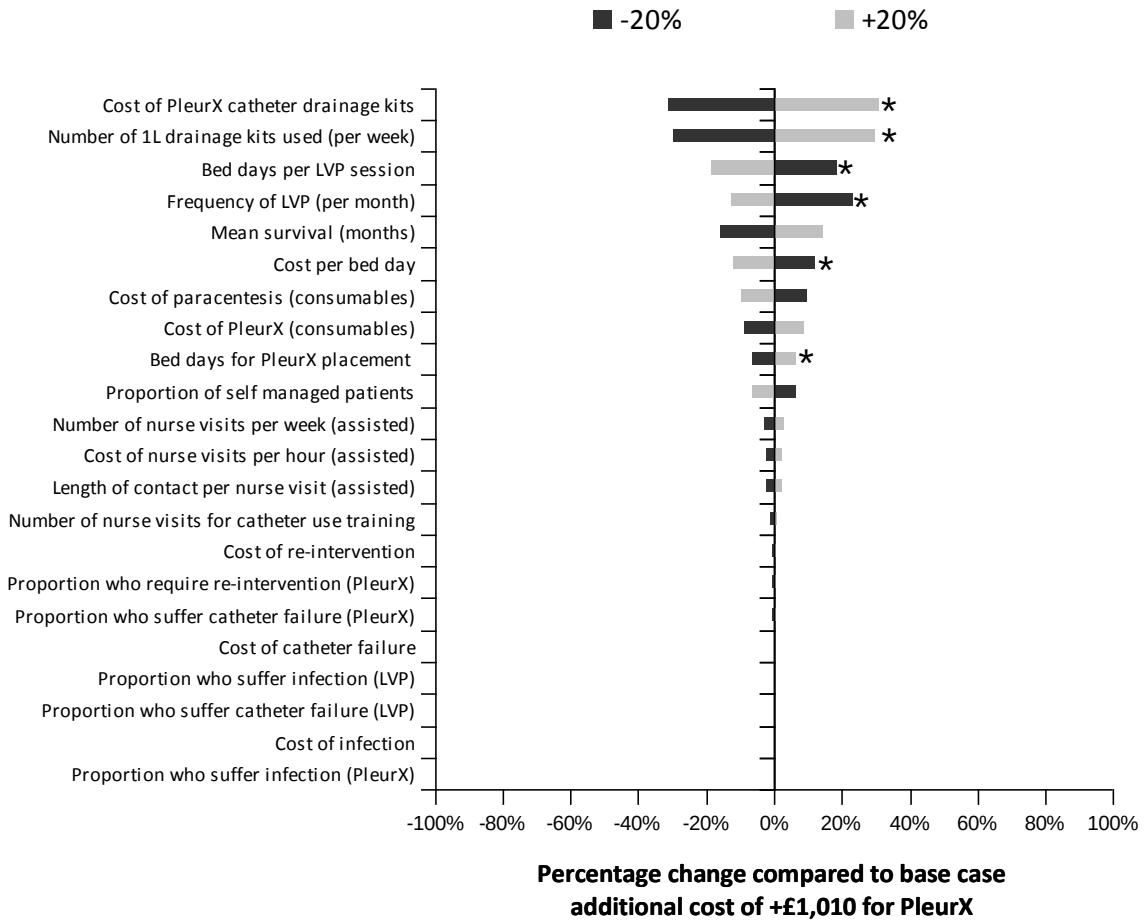
* Parameters which were subjected to enhanced sensitivity analysis using a wider range of input values. Results of extended sensitivity analysis shown in Table 15 below.

Table 15 Summary of extended sensitivity analysis by the EAC for key drivers of the economic model for PleurX versus inpatient LVP (scenario 1)

Parameter	Base case value	Sensitivity Analysis		Threshold at which PleurX incurs a cost (approx)
		Lower limit	Upper limit	
Cost of a hospital bed day	£312	£100	£600	< £220
Number of bed days per LVP session	2.8	1	6	< 2.1
Frequency of LVP per month	1.22	0.5	3.0	< 0.82
Number of bed days for PleurX catheter placement	1.0	1.0	3.0	> 3.1*
Cost per drainage kit box (10 units)	£637.50	£400	£900	> £915*
Number of drainage kits used per week per patient	3.5	3.0	6.0	> 5.1

*sensitivity analysis range did not encompass the threshold value

Figure 2 Sensitivity analysis (±20%) of each variable in the cost model where PleurX is compared with outpatient LVP (base case incremental cost impact per patient for PleurX was +£1,010).



* Parameters which were subjected to enhanced sensitivity analysis using a wider range of input values. Results of extended sensitivity analysis shown in Table 16 below.

Table 16 Summary of extended sensitivity analysis by the EAC for key drivers of the economic model for PleurX versus outpatient LVP (scenario 2)

Parameter	Base case value	Sensitivity Analysis		Threshold at which PleurX is cost saving (approx)
		Lower limit	Upper limit	
Cost of a hospital bed day	£312	£100	£600	> £825*
Number of bed days per LVP session	1.0	1.0	6.0	> 2.1
Frequency of LVP per month	1.22	0.5	3.0	> 2.51
Number of bed days for PleurX placement	1.0	1.0	3.0	PleurX incurs a cost across range
Cost per drainage kit box	£637.50	£400	£900	< £225*
Number of drainage kits used per week per patient	3.5	3.0	6.0	<1.14*

* sensitivity analysis range did not encompass the threshold value

5.3.3 System and population level cost impact

The sponsor presented an incremental system impact for both scenarios on a "per patient" basis in the evidence submission (Tables 6.20 and 6.12). No data was offered for the total cost or system impact on a population level; however this data was available within the Excel spreadsheet and has been presented in EAC Tables 17 and 18. The sponsor used a population size estimate of 2,500 to calculate the incremental cost and system impact for PleurX compared to inpatient and outpatient LVP. For the reasons provided in Section 5.2, the EAC consider this to be a substantial overestimate, and therefore the population-wide cost and system impact should be viewed with caution. One-way sensitivity analysis (-50%) for the population size was conducted by the EAC (EAC Tables 17 and 18). There were no efficiencies of scale and therefore a reduction in population size by 50% reduced the incremental impact by 50% also.

Table 17 Population-level incremental cost and system impact of PleurX compared to inpatient LVP

	Population of 2,500			Population of 1,250		
Cost or resource area	**PleurX**	**LVP**	**Incremental**	**PleurX**	**LVP**	**Incremental**
Incremental cost (population)	£6,165,265	£7,863,814	**-£1,698,549**	£3,082,633	£3,931,907	**-£849,274**
Total number of bed days	2,600.0	21,052.3	**-18,452.3**	1,300	10,526	**-9,226**
Total number of infections	62.5	112.5	**-50.0**	31	56	**-25**
Total number of catheter failures	125.0	75.0	**50.0**	63	38	**25**
Total number of re-intervention	100	0	**100**	50	0	**50**
Total number of nurse visits (self-managed)	5,000	0	**5,000**	2,500	0	**2,500**
Total number of nurse visits (assisted)	58,699	0	**58,699**	29,349	0	**29,349**

Table 18 Population-level incremental cost and system impact of PleurX compared to outpatient LVP

	Population of 2,500			Population of 1,250		
Cost or resource area	**PleurX**	**LVP**	**Incremental**	**PleurX**	**LVP**	**Incremental**
Incremental cost (population)	£6,165,265	£3,641,321	**+£2,523,944**	£3,082,633	£1,820,660	**+£1,261,972**
Total number of bed days	2,600	7,519	**-4,919**	1,300	3,759	**-2,459**
Total number of infections	63	113	**-50**	31	56	**-25**
Total number of catheter failures	125	75	**50**	63	38	**25**
Total number of re-intervention	100	0	**100**	50	0	**50**
Total number of nurse visits (self-managed)	5,000	0	**5,000**	2,500	0	**2,500**
Total number of nurse visits (assisted)	58,699	0	**58,699**	29,349	0	**29,349**

5.4 Comment on validity of results presented with reference to methodology used

The results reported in the economic evidence submission indicate that PleurX is cost saving compared to inpatient paracentesis, and that PleurX incurs a cost compared to outpatient paracentesis. These findings were shown to be resistant to changes of ±20% in all parameters within the boundaries of the model structure. A more robust sensitivity analysis of key drivers of the model using wider yet plausible input ranges was used. Results demonstrated that the overall findings were sensitive to changes within these ranges for some parameters, particularly the cost per hospital bed day, the number of bed days per LVP session, the frequency of LVPs per month, and the number of PleurX drainage kits used per week by each patient. Uncertainties surrounding the conclusions made in the economic evidence submission have been summarised in Section 5.5 below.

5.5 Summary of uncertainties and issues

Population size

There was a high level of uncertainty surrounding the size of the population that could potentially be treated using PleurX. Specifically the EAC considered 2,500 to be an overestimate as:

- it was based on the number of finished consultant episodes rather than the number of patients;
- the number includes diagnostic procedures;
- many patients will require only a small number of paracenteses and therefore not require PleurX placement.

The EAC did not find a more reliable source of population size and as this remains an uncertainty, the EAC presented results based on -50% population size (1,250 patients).

Proportion of inpatient and outpatient procedures

The sponsor's evidence submission did not assess the proportion of patients who receive LVP in an inpatient versus an outpatient setting. Two clinicians provided opinions through a KOL questionnaire (inpatient treated estimated at 50% and 64.2%) but these values were not built into the sponsor's model. As such, there remains substantial uncertainty around this issue which could impact heavily on:

- the expected savings associated with PleurX treatment;
- the indications for use of PleurX, i.e. criteria to diagnose recurrent intractable malignant ascites.

Complications

There was a high degree of uncertainty around the rate, type and cost of complications in both the PleurX and LVP arms. However, within the boundaries of the model structure, the impact of changing these inputs was low.

Transfer of financial burden

The economic evidence submission did not consider the potential barrier to implementation of PleurX from transfer of financial burden. Presently, secondary care budgets bear this

responsibility, but the cost of drainage bottles, and the cost of providing nurse visits would be borne by community health budgets. This may prove to be a difficult barrier to overcome.

6 Additional work undertaken by the External Assessment Centre

- The EAC commissioned the Support Unit for Research Evidence (SURE) to amend and re-run the sponsor's literature search strategy. The EAC subsequently carried out a systematic study selection process and independent quality assessment (Appendix 1).
- Where available full-length pre-publication manuscripts were obtained from study authors [redacted]Mullan 2011a;Mullan 2011b). Relevant clinical data was extracted and presented in table format.
- A single economic study (Mullan 2011b) was subjected to a formal quality assessment (Appendix 2 EAC report).
- The economic evidence submission was also subjected to formal quality assessment (EAC Table 11).
- Further sensitivity analysis was undertaken by the EAC to explore variables beyond the range used by the sponsor, e.g. population size, cost of complications, frequency of complications.
- Cost of complications from Mullan (2011b;2011b) were calculated for each individual patient (EAC report Appendix 3)
- Population-level cost and system impacts were presented by the EAC (Tables 17 and 18)

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

UK Medical has presented evidence in their submission which indicates that PleurX is as safe as LVP and offers benefits to patients, such as avoiding repeated hospital admissions and improved control of symptoms. These assertions are based on a total of nine observational studies (10 manuscripts) of limited quality. The key issue surrounding the clinical evidence is a lack of comparative data; only a single study (Rosenberg 2004) evaluated complication rates in both PleurX and LVP patients; which were shown to be the same (7.5%) for both interventions. Other non-comparative studies reported a wide range of complication rates (0-59%) for PleurX. A systematic review by Becker and colleagues (2006) reported complication rates from five LVP-only studies as being between 0% and 28% (EAC report Appendix 4)[10].

QoL and symptom control outcomes were reported in one non-comparative study (Courtney 2008) which demonstrated that PleurX improved some ascites-related outcomes, but not overall QoL at 12 weeks. Concerns relating the validity of the measures, particularly the lack of a control group, mean these results may be conservative. [redacted]

7.2 Summary of cost issues

The sponsor's economic model strongly suggests that when compared to LVPs carried out in an inpatient setting, that PleurX can save money and release hospital bed days, but would require increased nurse visits to patients' homes in the community. The cost-savings were heavily dependent on a reduction in inpatient stay in the PleurX arm. Conversely, when PleurX was compared to outpatient LVP it incurred an additional cost, and required an increased number of home nurse visits, with only a small saving in hospital bed days. These findings were robust to

[10] In the five studies which reported LVP complication rates (Appelqvist 1982;Fischer 1979;Gotlieb 1998;McNamara 2000;Ross 1989) inconsistent reporting was a factor. Two of the five studies in this review (both >20 years old) reported procedural-related deaths as major adverse events (Appendix 4 EAC report).

changes in most parameters within plausible ranges, and mostly reliable sources were used to populate the model. Despite a possible underestimation of the cost of treating complications, there were no major structural or input-based inaccuracies that would change the overall findings of the cost analysis.

Taking all of the clinical and cost evidence together we can propose that, based on limited evidence, PleurX is a safe and effective alternative to LVP, which when compared to inpatient LVP is cost saving and releases hospital bed days. A small number of studies support the claim of improved quality of life for patients with malignant ascites. This is chiefly due to avoidance of hospital inpatient stays for conventional paracenteses, and improved control of the symptoms of ascites by regularly removing small volumes of fluid, and thus avoiding the problems associated with massive fluid accumulation. The proportion of patients who could potentially benefit from PleurX drain placement is inconclusive and there is substantial uncertainty surrounding the proportion of inpatient versus outpatient LVP procedures undertaken currently in the UK. Finally, introduction of PleurX drainage of MA in the community would require a transfer of financial burden between different budgets which may be a barrier to implementation.

7.3 Implications for guidance and research

This EAC report has highlighted some areas of weakness within the evidence for using PleurX to treat MA in palliative care patients. There are currently two trials underway (Appendix 5 EAC report) in the US, whose outcomes would address many of the uncertainties surrounding the evidence for PleurX. One of these trials aims to assess the safety of the PleurX catheter compared to paracentesis, as well as overall complications, quality of life, overall survival, and symptom control (NCT01077063). The second trial will determine if there is change in the QoL or symptom control in MA patients after the placement of a palliative catheter, including PleurX (NCT01188746; Appendix 5 EAC report). Despite both trials being set in the US, it is likely that both will add relevant information to the decision problem on PleurX.

The following areas of research would provide further data:

- Comparative complication rates for PleurX versus LVP
- Comparative QoL information for PleurX versus LVP using validated measures
- Number of patients in the UK that could potentially be treated using PleurX

- Proportions of patients currently treated using inpatient and outpatient LVP

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Appendix 1 SURE literature search strategy

Introduction

The EAC commissioned the Support Unit for Research Evidence (SURE), Cardiff University, to amend the sponsor's search strategy where improvements could be made, and rerun the revised search. Terms were kept broad as research suggested that the number of retrieved references would be manageable (<1000). The search strategy aimed to capture a wide range of citations relating to the use of PleurX or indwelling catheters for treatment of malignant ascites.

Methods

Where required SURE modified the sponsor's search strategy for the following databases:

- Medline (including Medline 1996-Present and Medline In-Process and other non-indexed citations)
- Cochrane Library (CENTRAL, CDSR, DARE, HTA, EED)
- EMBASE
- Web of Science

The EAC ran simple searches in the following society websites:

- British Gynaecological Cancer Society
- National Forum for Gynaecological Oncology Nurses
- UK Oncology Nursing Society
- Cancer Research UK

The following terms were used to search databases:

Medline/Medline in Process

1 Ascites/ (11703)
2 ascites.ti,ab. (29837)
3 Ascitic Fluid/ or (peritoneal adj3 fluid).ti,ab. (14607)
4 hydroperitoneum.mp. (24)
5 or/1-4 (45983)
6 exp Catheters/ (14924)
7 catheter*.ti,ab. (134933)
8 permcath.ti,ab. (66)
9 exp Drainage/ (40539)
10 drain*.ti,ab. (79630)

11 Paracentesis/ or paracentesis.ti,ab. (2902)
12 or/6-11 (236412)
13 (continuous or permanent or indwelling or tunnel$).ti,ab. (324822)
14 12 and 13 (22755)
15 5 and 14 (254)
16 (pleurx or pleur x).mp. (26)
17 15 or 16 (276)
18 animals/ not (humans/ and animals/) (3535358)
19 17 not 18 (257)
20 limit 19 to english language (220)
21 remove duplicates from 20 (217)

Cochrane Library

#1	MeSH descriptor Ascites, this term only	244
#2	Ascitic Fluid/	178
#3	ascites:ti,ab	675
#4	(peritoneal NEAR/3 fluid):ti,ab	165
#5	hydroperitoneum:ti,ab	0
#6	(#1 OR #2 OR #3 OR #4 OR #5)	935
#7	exp Catheters/	198
#8	catheter*:ti,ab	8421
#9	permcath:ti,ab	5
#10	exp Drainage/	173
#11	drain*:ti,ab	3359
#12	Paracentesis/	271
#13	paracentesis:ti,ab	213
#14	(#6 OR #7 OR #8 OR #9 OR #10 OR #11)	12620
#15	(continuous or permanent or indwelling or tunnel*):ti,ab	20513
#16	(#14 AND #15)	1751
#17	(#6 AND #16)	58
#18	(pleurx or pleur x):ti,ab,kw	4
#19	(#17 OR #18)	62

Embase

1 Ascites/ (29641)
2 ascites.ti,ab. (42876)
3 Ascites Fluid/ or (peritoneal adj3 fluid).ti,ab. (13030)
4 hydroperitoneum.mp. (32)
5 or/1-4 (62089)
6 exp Catheter/ (70362)
7 catheter*.ti,ab. (180468)
8 permcath.ti,ab. (82)
9 abdominal drainage/ (1287)
10 drain*.ti,ab. (112129)
11 Paracentesis/ or paracentesis.ti,ab. (4932)
12 or/6-11 (303832)
13 (continuous or permanent or indwelling or tunnel$).ti,ab. (415054)
14 12 and 13 (30265)

15 5 and 14 (329)
16 (pleurx or pleur x).mp. (38)
17 15 or 16 (360)
18 animals/ not (humans/ and animals/) (1241363)
19 17 not 18 (357)
20 limit 19 to english language (290)

Web of Science

Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=1899-2011

(updated 2011-07-21)

5 140 #4 OR #3

4 31 (TS=(pleurx OR "pleur X")) AND Language=(English)

3 70 #2 AND #1

2 19,088 (TS=(continuous SAME catheter*) OR TS=(permanent SAME catheter*) OR TS=(indwelling SAME catheter*) OR TS=(tunnel* SAME catheter*) OR TS=(continuous SAME drain*) OR TS=(permanent SAME drain*) OR TS=(indwelling SAME drain*) OR TS=(tunnel* SAME drain*)) AND Language=(English)

1 29,327 (TS=(ascites) OR TS=("Ascitic Fluid") OR TS=("peritoneal fluid") OR TS=(hydroperitoneum)) AND Language=(English)

Societies – BGCS, NFGON, UKONS, and Cancer Research UK

"PleurX" or "ascites"

Selection criteria

The following inclusion/exclusion criteria modifications by the EAC relate to the first clinical evidence submission by UK Medical on 22nd July; these issues were addressed by the sponsor in their updated submission:

Study design - two reviewers independently assessed each title and abstract with reference to the study inclusion criteria. The EAC used the same inclusion criteria as the sponsor, but did not exclude any references based on study design. Therefore two case reports which were excluded by the sponsor were included by the EAC (Brooks 2006;Iyengar 2002). Twenty-six references were assessed further (full-text where available). Six studies met the inclusion criteria, and a further two studies were included which had been identified by the sponsor but not by the EAC search strategy (Day 2011a;Jacob 2009).

Non-English Language Citations - the sponsor and EAC search strategies imposed a non-English language exclusion criterion. To ensure that no non-English language studies relevant to the decision problem were excluded inappropriately, the EAC retrieved citations excluded based on language from Medline (37 citations) and EMBASE (55 citations) and reviewed titles and abstract where available. Two studies were identified which required further investigation. One study was available as a full-text manuscript in English and met the remaining inclusion criteria (Saiz-Mendiguren 2010). The other citation did not contain an abstract, and no further English-language information could be found (Semmo 2009).

Results

The numbers of retrieved references are shown in Table A. These were imported into Reference Manager and duplicate records were removed.

Table A - References retrieved by EAC

Database	Citations retrieved
Medline and Medline In-process	217
Cochrane Library (CENTRAL, CDSR, DARE, HTA, EED)	62
Embase	290
Web of Science	140
PsychINFO	1
BGCS, NFGON, UKONS, Cancer Research UK	0
Total Before Duplicate Removal	710
Total After Duplicate Removal	406
References selected for full-text assessment	26
Studies selected for inclusion	6
Non-English language studies included*	1
Additional studies identified by sponsor	2 (Day 2011; Jacob 2009)
Total number of studies for data extraction	**9**

*Relevant to decision problem and available in English

Appendix 2 Quality appraisal of Mullan (2011) cost analysis

Mullan (2011) cost analysis		
Study question	**Grade**	**EAC Comments**
Study design		
1. Was the research question stated?	Yes	Aims study describes "to assess whether the short and long term cost of the tunneled catheter and repeated vacuum drainage was offset by reducing the need for repeated inpatient admissions"
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	Assumed from perspective of one hospital. No justification for ignoring transfer of costs to primary care.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	LVP assumed to be standard care but no explicit comment
5. Were the alternatives being compared clearly described?	No	No description of setting, anaesthetic, radiological investigation.
6. Was the form of economic evaluation stated?	No	Cost analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	No justification explicitly stated
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	Study doesn't attempt to show effectiveness of PleurX – only safety. Based on current study. Complication rate not included in model.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	N/A	
13. Were the details of the subjects from whom valuations were obtained given?	N/A	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	No	Table 2 does not provide enough detail to check.
17. Were the methods for the estimation of quantities and unit costs described?	No	No details of sources of costs used.
18. Were currency and price data recorded?	N/A	

Mullan (2011) cost analysis

Study question	Grade	EAC Comments
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	N/A	No model used
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	25 days, 31 days, and 1 year
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No stochastic data
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	N/A	
29. Were the ranges over which the parameters were varied stated?	N/A	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	but minimal – only cost difference stated
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	But some were not appropriate
35. Were conclusions accompanied by the appropriate caveats?	No	No discussion of complications being omitted from analysis and transfer of costs to primary care.
36. Were generalisability issues addressed?	No	

Adapted from 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. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Appendix 3 EAC additional work on cost of complications

	Procedure	Cost per procedure	No. of procedures	Total cost of procedure type
Four patients treated with Fibrinolytics in Mullan (2011b) Case Report	**Patient 1**			
	Ultrasound Scan less than 20 minutes	£52.32	5	£261.62
	Contrast Fluoroscopy Procedures less than 20 mins	£105.51	1	£105.51
	Streptokinase	£15.91	5	£79.55
	Consultant led first attendance (Medical Oncology)	£193	1	£193.00
	Elective Inpatient Excess Bed Day HRG Data	£312	0	£0.00
	TOTAL			**£639.67**
	Patient 2			
	Ultrasound Scan less than 20 minutes	£52.32	3	£156.97
	Computerised Tomography Scan, one area, no contrast	£99.44	2	£198.88
	Contrast Fluoroscopy Procedures less than 20 mins	£105.51	1	£105.51
	Wire brush/flushing	No value	1	
	Catheter replacement (from Model)	£742.39	1	£742.39
	Streptokinase	£15.91	5	£79.55
	Elective Inpatient Excess Bed Day HRG Data	£312	5	£1,560.00
	Consultant led first attendance (Medical Oncology)	£193	1	£193.00
	TOTAL			**£3,036.30**
	Patient 3			
	Ultrasound Scan less than 20 minutes	£52.32	3	£156.97
	Computerised Tomography Scan, one area, no contrast	£99.44	1	£99.44
	Contrast Fluoroscopy Procedures less than 20 mins	£105.51	1	£105.51
	Streptokinase	£15.91	5	£79.55
	Consultant led first attendance (Medical Oncology)	£193	1	£193.00
	TOTAL			**£634.47**
	Patient 4			
	Ultrasound Scan less than 20 minutes	£52.32	2	£104.65
	Computerised Tomography Scan, one area, no contrast	£99.44	1	£99.44
	Wire brush/flushing	No value	2	
	Contrast Fluoroscopy Procedures less than 20 mins	£105.51	1	£105.51
	Streptokinase	£15.91	5	£79.55
	Consultant led first attendance (Medical Oncology)	£193	1	£193.00
	Elective Inpatient Excess Bed Day HRG Data	£312	0	£0.00
	TOTAL			**£582.14**
Five patients from Mullan (2011a) treated for complications other than catheter occlusion	**Patient 1 - Ascitic Leakage (Resolved without treatment)**			
	Consultant led first attendance (Medical Oncology)	£193.00	1	£193.00
	TOTAL			**£193.00**
	Patient 2 - Displacement			
	Removed and replaced (as costed inb model)	£742.39	1	£742.39
	TOTAL			**£742.39**
	Patient 3 - Pain (resolved after advice)			
	Ultrasound Scan less than 20 minutes	£52.32	1	£52.32
	Contrast Fluoroscopy Procedures less than 20 mins	£105.51	1	£105.51
	Consultant led first attendance (Medical Oncology)	£193.00	1	£193.00
	TOTAL			**£350.83**
	Patient 4 - Peritonitis			
	Consultant led first attendance (Medical Oncology)	£193.00	1	£193.00
	Elective Inpatient Excess Bed Day HRG Data	£312.00	5	£1,560.00
	IV Gentamicin (4 mg/kg) approx. 240 mg * 5 days	£5.95	5	£29.75
	Ultrasound Scan less than 20 minutes	£52.32	1	£52.32
	Contrast Fluoroscopy Procedures less than 20 mins	£105.51	1	£105.51
	Streptokinase	£15.91	5	£79.55
	TOTAL			**£2,020.13**
	Patient 7 - Mild Lymphangitis			
	Consultant led first attendance (Medical Oncology)	£193.00	1	£193.00
	Ciprofloxacin (500 mg, 10 pack)	£1.06	1	£1.06
	TOTAL			**£194.06**

Appendix 4 Complication rates from LVP-only studies

Reference	Study Design	Number of patients	Number of procedures	Overall complication rate (per pt)	Overall complication rate (per proc)	Notes
Rosenberg (2004)	Comparative case series	67	392	5/67 (7.5%)	5/392 (1.3%)	3 peritonitis 2 development of multiple loculations
McNamara (2000)	Prospective uncontrolled trial	44	48	0% major 12/44 (28%) minor	0% major 12/48 (25%) minor	11 pts experienced pain (7 required analgesia) 1 pt vomited after drain insertion
Gotleib 1998)	Prospective uncontrolled trial	15	35	0%	0%	No hypotension, no perforation, no peritonitis
Ross (1989)	Case series	43	109	3/43 (7%) major	3/109 (3%) major	2 fatal hypotension 1 non fatal hypotension
Appelqvist (1982)	Case series	100	127	4/100 (4%) major	4/127 (3%) major	2 fatal pulmonary embolism, 1 fatal perforation, 1 fatal peritonitis
Fischer (1979)	Case series	300	-	-	-	No severe hypotension under concurrent infusion with 5% dextrose

Appendix 5 Ongoing trials relevant to the decision problem on PleurX

The following information was taken from http://clinicaltrials.gov/ (accessed on 12th September 2011):

An Early Safety and Efficacy Study of Ascites Management: Standard Paracentesis or Early Intervention With Pleurx Catheters in Patients With Malignant Ascites

This study is currently recruiting participants.
Verified on September 2010 by Sidney Kimmel Comprehensive Cancer Center
First Received on February 25, 2010. Last Updated on July 19, 2011
History of Changes

Sponsor:	Sidney Kimmel Comprehensive Cancer Center
Information provided by:	Sidney Kimmel Comprehensive Cancer Center
ClinicalTrials.gov Identifier:	**NCT01077063**

Purpose
The purpose of this study is to assess in a controlled prospective setting, the safety of the use of Pleurx catheters and standard therapeutic paracentesis in patients with malignant ascites.

Condition:	Malignant Ascites
Intervention:	Procedure: paracentesis
Device:	Pleurx catheter

Study Type:	Interventional
Study Design:	Allocation: Randomized
Intervention Model:	Parallel Assignment
Masking:	Open Label
Primary Purpose:	Treatment
Official Title:	An Early Safety and Efficacy Study of Ascites Management: Standard Paracentesis or Early Intervention With Pleurx Catheters in Patients With Malignant Ascites

Further study details as provided by Sidney Kimmel Comprehensive Cancer Center:

Primary Outcome Measures:
- Safety of Pleurx catheter or paracentesis [Time Frame: 3 years] [Designated as safety issue: Yes]

Primary Outcome: Safety of the Pleurx catheter procedure or paracentesis
Secondary Outcome Measures:
- Overall complications, quality of life, overall survival, and symptom control [Time Frame: 3 years] [Designated as safety issue: Yes]

Secondary outcomes: Overall complications, quality of life, overall survival, and symptom control

Estimated Enrollment:	30
Study Start Date:	February 2010
Estimated Primary Completion Date:	February 2012 (Final data collection date for primary outcome measure)

Arms
Assigned Interventions

paracentesis: Active Comparator
cutting and draining procedure for malignant ascites
Intervention: Procedure: paracentesis Procedure: paracentesis
surgical drainage of malignant ascites
Pleurx catheter: Active Comparator

a catheter drainage system the subject uses himself/herself.
Intervention: Device: Pleurx catheter Device: Pleurx catheter
take home catheter drainage system that the subject uses himself/herself as needed.

Detailed Description:
Study Design: Single institution, open-label, randomized study
Study Device: Pleurx Catheter
Treatment Plan: Cohort A: 15 patients treated with standard therapy (therapeutic paracentesis +/- diuretics)
Cohort B: 15 patients treated with peritoneal Pleurx catheter
Duration of Participation: Patients will be followed for one year, or until death, whichever comes first.
Primary Outcome: Safety of the Pleurx catheter procedure or paracentesis
Secondary outcomes: Overall complications, quality of life, overall survival, and symptom control
Eligibility
Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria
Inclusion Criteria:
(Patients can receive chemotherapy at the discretion of treating oncologist)
1. Patients with recurrent malignant ascites
2. Patients with refractory malignant ascites
3. Proven malignancy
4. Age >= 18 years old
5. Eastern Cooperative Oncology Group (ECOG) performance scale =< 2
6. Ability to understand and willingness to sign a written informed consent
Definitions:
Malignant ascites: One of the following criteria
1. Positive ascitic fluid cytology
2. Histology proven malignancy with imaging studies with evidence of liver metastasis and ascites
3. Malignant Budd Chiari Syndrome with associated ascites
4. Hepatocellular carcinoma and ascites
5. Chylous ascites due to lymphoma
6. Peritoneal carcinomatosis and concurrent ascites
7. Proven abdominal malignancy with concurrent ascites
Refractory / Recurrent ascites: One of the following criteria
1. Symptomatic ascites that recurred after one paracentesis in a patient with known malignant ascites.
2. Symptomatic ascites that did not respond clinically to at least two weeks of diuretics. Use of diuretics at the discretion of the treating physician.
3. Intolerance or relative contraindications to diuretics: (serum sodium (Na) concentration of <125 mmol per liter or serum creatinine >1.5 mg/dl, hyperkalemia (potassium >5.2 mEq/L or azotemia Bun/Creatinine ratio > 20).
4. Removal of at least 5 L in the preceding two months for symptoms relief
Exclusion criteria:
1. Life expectancy less than one month
2. Coagulopathy (international normalized ratio [INR] > 2 that does not correct with fresh frozen plasma)
3. Hepatorenal syndrome
4. Active skin infections at abdomen before procedures
5. Inability to provide inform consent
6. Platelet counts < 50,000/mcL
7. Uncontrolled illness including, but not limited to, ongoing or active infection requiring intravenous (IV) antibiotics, that the physician feels would increase the risk of infection with the procedures or white blood cell (WBC) count > 20,000/mcL
8. Absolute neutrophil count <1000 / cu mm
9. Pregnant women
10. Multiloculated ascites

Impact of Palliative Catheter Placement on the Quality of Life of Patients With Refractory Ascites

This study is ongoing, but not recruiting participants.

First Received on August 24, 2010. Last Updated on August 22, 2011 History of Changes

Sponsor:	Memorial Sloan-Kettering Cancer Center
Information provided by (Responsible Party):	Memorial Sloan-Kettering Cancer Center
ClinicalTrials.gov Identifier:	**NCT01188746**

Purpose
The purpose of this study is look at how treatments for ascites affect quality of life. Your quality of life is the ability for you to enjoy the normal things you do. Ascites (pronounced as-ī-tees) is the presence of extra fluid in the abdomen. Sometimes ascites is caused by cancer, also called malignancy. All people who participate in this study have ascites associated with cancer. Ascites can cause symptoms that make it difficult for the patient to do simple things. Patients with ascites often report: Abdominal swelling Difficulty walking. Difficulty breathing. Feeling full when eating. Clothes not fitting due to a swollen abdomen. Swelling in the legs. It is hoped that this catheter will relieve the symptoms of the ascites. The goal of the investigators study is to understand the quality of life before the procedure and after the procedure. Since the patient is having this procedure to make their symptoms better, the investigators want to hear from the patient of how the procedure has affected their quality of life.

Condition: Ascites
Intervention: Behavioral: McGill Quality of Life Questionnaire and the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Supportive Care
Official Title: Impact of Palliative Catheter Placement on the Quality of Life of Patients With Refractory Ascites

Further study details as provided by Memorial Sloan-Kettering Cancer Center:

Primary Outcome Measures:
- Determine if there is change in the QoL [Time Frame: 2 years] [Designated as safety issue: No]
of patients who have refractory ascites after the placement of a palliative catheter in Interventional Radiology.
- Determine if there is change in symptoms [Time Frame: 2 years] [Designated as safety issue: No]
of patients who have refractory ascites after the placement of a palliative catheter in Interventional Radiology.

Secondary Outcome Measures:
- Determine the impact ascites has on quality of life [Time Frame: 2 years] [Designated as safety issue: No]
via patient interviews and how this is affected by catheter placement.
- Monitor and describe post-catheter placement morbidity and mortality. [Time Frame: 2 years] [Designated as safety issue: No]

Estimated Enrollment:	50
Study Start Date:	August 2010
Estimated Study Completion Date:	August 2012
Estimated Primary Completion Date:	August 2012 (Final data collection date for primary outcome measure)

Arms
Assigned Interventions

Questionnaire or interview: Experimental
A pre-experimental design was chosen to examine changes in QoL following a palliative intervention.

Intervention: Behavioral: McGill Quality of Life Questionnaire and the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire Behavioral: McGill Quality of Life Questionnaire and the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire
Participants will be interviewed twice (if they chose to participate in the qualitative portion) and complete instruments at three time points: 1) immediately prior to the procedure, 2)within seven days after the procedure, preferably prior to discharge, and 3) three weeks after their catheter placement.

Eligibility
Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No
Criteria
Inclusion Criteria:
- Patients diagnosed with a stage IV malignancy or end-stage disease documented in patient's chart.
- Patients referred to interventional radiology for treatment of refractory ascites with the placement of a permanent catheter including, but not limited to, a Tenckhoff catheter, a PleurX catheter, or a Denver Shunt.
- Fluency in English to enable instrument and interview completion.
- Patients must be at least 18 years of age.
- Patients must be physically capable of completing instruments and/or interview.
- Patients must be able to comprehend and execute informed consent.

Exclusion Criteria:
- Unable to complete questionnaire due to a significant physical or mental deficits as assessed by the consenting professional.
- Proxy completion is not accepted
- Medical or psychiatric condition that, in the judgment of the investigator, prevents appropriate comprehension and execution of either the informed consent or the study instrument