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Research priorities in mesothelioma: A James Lind Alliance Priority Setting Partnership

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ABSTRACT

Background: In the UK, despite the import and use of all forms of asbestos being banned more than 15 years ago, the incidence of mesothelioma continues to rise. Mesothelioma is almost invariably fatal, and more research is required, not only to find more effective treatments, but also to achieve an earlier diagnosis and improve palliative care. Following a debate in the House of Lords in July 2013, a package of measures was agreed, which included a James Lind Alliance Priority Setting Partnership, funded by the National Institute for Health Research. The partnership brought together patients, carers, health professionals and support organisations to agree the top 10 research priorities relating to the diagnosis, treatment and care of patients with mesothelioma.

Methods: Following the established James Lind Alliance priority setting process, mesothelioma patients, current and bereaved carers, and health professionals were surveyed to elicit their concerns regarding diagnosis, treatment and care. Research questions were generated from the survey responses, and following checks that the questions were currently unanswered, an interim prioritisation survey was conducted to identify a shortlist of questions to take to a final consensus meeting.

Findings: Four hundred and fifty-three initial surveys were returned, which were refined into 52 unique unanswered research questions. The interim prioritisation survey was completed by 202 responders, and the top 30 questions were taken to a final meeting where mesothelioma patients, carers, and health professionals prioritised all the questions, and reached a consensus on the top 10.

Interpretation: The top 10 questions cover a wide portfolio of research (including assessing the value of immunotherapy, individualised chemotherapy, second-line treatment and immediate chemotherapy, monitoring patients with pleural thickening, defining the management of ascites in peritoneal mesothelioma, and optimising follow-up strategy). This list is an invaluable resource, which should be used to inform the prioritisation and funding of future mesothelioma research.

1. Introduction

Mesothelioma is a malignant disease that can develop in the pleural membranes around the lungs, and, less often, in the peritoneum. Virtually all cases of mesothelioma occur as the result of exposure to asbestos, and although, in the UK, the import and use of amosite and crocidolite were banned in 1985 and chrysotile in 1999, the incidence of mesothelioma continues to rise. In 2012 there were 2535 new cases [1], and the peak is now predicted to be reached around the year 2022 [2]. Although the increasing incidence reflects the increasing number of groups at risk [3], the pattern of disease remains similar, with around 85% of patients being male, the majority of cases affecting the pleura, and, typically, symptoms appearing on average 30–40 years after exposure to asbestos. Once diagnosed the median survival is 9–12 months [4], and although the ultimate aim is to find a cure, progress to extend the survival and improve the quality of life of patients has been slow. The use of extrapleural pneumonectomy within a multimodality approach has now been largely abandoned in Europe

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following the results of the Mesothelioma and Radical Surgery (MARS) trial [5]. Radiotherapy is mainly used in a palliative setting and the value of prophylactic radiotherapy, to avoid cancer cell seeding along surgical tracts, is currently being investigated in two randomised trials [6,7]. Although chemotherapy has been shown to give a small survival benefit in patients with a good performance status [8], the disease, in virtually all patients, will progress. Therefore the future is likely to lie in translational research, where there have been some encouraging insights into tumorigenesis, biomarkers, and immune response [9–12]. However in the meantime, patients experience delays in diagnosis, limited treatment options and many debilitating symptoms and side effects [13,14].

The UK Parliament identified mesothelioma research as a priority area for the Department of Health, following a debate in the House of Lords in July 2013 [15]. A package of measures was agreed, which included a James Lind Alliance (JLA) Priority Setting Partnership (PSP), funded by the National Institute for Health Research (NIHR) to identify patients', carers', health professionals' and support organisations' priorities for mesothelioma research. The JLA, which was established in 2004, is a non-profit making initiative, hosted by the NIHR, with the aim of helping to achieve meaningful patient and clinician involvement in research priority setting and to ensure that those who conduct and fund health research are aware of the gaps in knowledge that matter most to patients, caregivers, and clinicians [16,17]. The aim of a JLA PSP is to identify and prioritise 'treatment uncertainties' [18], that are defined as research questions about the effects of a healthcare intervention for which there are no up-to-date, reliable, systematic reviews of research evidence.

2. Aims

The aim of this PSP was to identify the top 10 research priorities relating to mesothelioma (pleural or peritoneal), and specifically to identify those unanswered questions that involved an intervention, in order to aid translation into immediately answerable research questions. Thus detailed, rather than general, questions were required, which specified the intervention(s) to be tested and did not simply identify the need for research into a topic (e.g. breathlessness).

3. Methods

Priority setting methods have been established and used by almost 30 JLA PSPs, including prostate cancer [19], vitiligo [20], palliative and end of life care [21], childhood neurodisability [22], and dystrophic epidermolysis bullosa [23]. Details of the methods agreed and adopted can be found in a number of publications [24–28], and therefore only a brief summary is presented here. Key stages involve:

- Establishing a Steering Group to define the scope of the partnership and develop a protocol detailing the methods to be used.
- Developing an initial survey questionnaire to gather a wide range of experiences from patients, carers, and health professionals about the diagnosis, treatment and care of patients.
- Reviewing the survey responses, identifying unique 'themes' and generating draft research questions.
- Searching national guidelines, systematic reviews and randomised trials to ensure that each research question has not already been reliably answered.
- Undertaking an interim prioritisation survey of patients, carers, health professionals and support organisations to identify objectively a shortlist of priorities.
- Setting up a final priority setting consensus meeting to rank all of the questions on the shortlist, but in particular to agree the top 10 priorities.
- Adding all the identified unanswered questions to the UK Database of Uncertainties about the Effects of Treatment (UK DUETs), a web-based public information repository [29].
- An additional requirement of the mesothelioma PSP was to include only interventional questions (i.e. questions that could be formatted using a 'PICO' (Population-Intervention-Comparison-Outcome) structure [30,31]). Any questions that did not satisfy this criteria were deemed 'out of scope'.

4. Results

The JLA Mesothelioma PSP Steering Group comprised two patients, one bereaved carer, nine health professionals (including nurses, surgeons, oncologists, chest physicians and palliative care experts), and four representatives of patient and family support groups (one of the representatives was also a bereaved carer). The Steering Group was chaired by a JLA facilitator, coordinated and supported by the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), and also included representatives from 3 UK-based charities (the British Lung Foundation, Mesothelioma UK, and the June Hancock Mesothelioma Research Fund), and an information specialist. A launch meeting was held in December 2013.

Between February and April 2014, the initial survey, asking whether responders "had ever had a question about the diagnosis, treatment or care of mesothelioma, and not been able to find the answer" was circulated to known support organisations and health professionals with a request that it be passed on to as many interested parties as possible, as well as being made available on various relevant websites. A total of 453 responses were returned (including 103 from patients, 242 from carers, partners or relatives of mesothelioma patients, 82 from health professionals, and the remaining 26 from support organisations, and those who either did not indicate a category, or indicated they belonged to more than one category). There was an excellent responder representation according to age, gender, location and health professional specialty, with the majority (79%) of the patients who responded being male, the majority (86%) of the carers being female, and only 5% of the patients (as identified by the patient themselves or their carer) having peritoneal mesothelioma.

Although the survey asked for suggestions for research questions, most of the responses were written as personal stories, and thus this subjective narrative text had to be transformed into objective questions. To do this, the 453 responses were all reviewed, and 'themes' (e.g. breathlessness, role of immunotherapy, GP awareness, etc.) were listed. After merging similar themes, 98 separate themes remained, and draft research questions were generated. The draft questions were then reviewed to see whether they involved an intervention, and were able to be written in a PICO format. A total of 52 questions fitted these criteria, whereas the remaining 46 questions were considered 'out of scope' and will be reported elsewhere.

In order to check that the draft research questions had not already been reliably answered, a search was made in May 2014 for relevant systematic reviews, (searching for 'mesothelioma' in the Reviews section of the Cochrane Library, and for papers with 'mesothelioma' and 'systematic review' in their title in Pubmed). A total of 30 were found, but only one [32] made a clear recommendation ('that the addition of pemetrexed to cisplatin may improve survival') whilst most of the rest called for more trials to provide reliable evidence. Therefore none of the 52 questions were removed.

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Between August and September 2014, the interim prioritisation survey was circulated to 397 people who had previously indicated their interest in the project, asking them to rank the importance of each of the 52 questions on a scale of one to five. There were 202 respondents and their responses were allocated to four subgroups depending on the type of responder: 38 patients, 98 carers, 50 health professionals and 16 support organisations. Within each subgroup the scores for each of the 52 questions were added, thus creating a ranked list. The rank positions of each question in the 4 subgroups were then added together, and the questions were put into interim order of priority. As is clear from online Table A this interim prioritisation exercise reflected the differences in knowledge, experience and concerns of patients, carers, and health professionals. The Steering Group proposed that the top 30 ranked questions from the interim prioritisation survey be taken to the workshop for final prioritisation, and these 30 questions were given identifiers A–Z and then AA–DD.

Thirty people (six mesothelioma patients, four carers, 16 health professionals [including surgeons, medical oncologists, clinical oncologists, palliative care and respiratory physicians, and specialist nurses], and four representatives of patient support organisations) attended a final consensus meeting on 10th November 2014. Participants initially worked in three mixed groups, each led by an independent JLA facilitator, to rank all 30 questions, and the combined scores and ranks are displayed in online Table B. There was a high level of agreement between the three groups. The participants were then re-configured into three new groups and asked to review the combined rankings, but made only minor changes. However, at the final plenary session there was much discussion around:

- the generality of many of the questions and the relationship with questions that had a more specific focus,
- questions that were not mesothelioma specific,
- symptoms and side effects that had multiple causes and multiple treatments,
- questions that were dependent on other unanswered questions (i.e. the value of chemotherapy before surgery, without knowing the value of surgery),
- whether a question should be de-prioritised if the intervention to be studied was only appropriate for a small number of patients,
- whether peritoneal mesothelioma should be a separate category,
- whether the top 10 should aim to cover a portfolio of topics, and
- whether questions that were being addressed by ongoing trials should be included.

However, despite these discussions, the ranking of only four questions was changed, and the meeting closed with a unanimous

Table 1
Mesothelioma top 10 research priority list (plus 3 highly recommend questions).

Rank	Research question	Comments
1	Does boosting the immune system (using new agents such as PD-1 or PD-L1) improve response and survival rates for mesothelioma patients?	The relative lack of success of chemotherapy, and the positive signs from recent phase I trials, have shifted interest towards immunotherapy.
2	Can individualised chemotherapy be given to mesothelioma patients based on predictive factors (e.g. the subtype of mesothelioma (epithelioid, sarcomatoid, or mixed), or thymidylate synthase inhibitor status (the protein that drugs like pemetrexed act against), etc.)?	Recent predictive factor analyses have revealed different responses to pemetrexed for different histological subgroups, and this individualising of treatment will develop with increasing analysis of large databases.
3	What is the best way to monitor patients with diffuse pleural thickening and a negative biopsy who are considered to have a high risk of developing mesothelioma (e.g. repeat biopsies, imaging, etc.)?	Patients with pleural thickening are known to be at high risk of developing mesothelioma.
4	In mesothelioma patients, what is the best second line treatment (i.e. what chemotherapy drugs should be used if a cancer has recurred following first line chemotherapy, usually with cisplatin and pemetrexed)?	Although most patients respond to 1st line chemotherapy, the effect is usually short lived, and identification of the best 2nd line treatment is urgently needed.
5	Which is the most effective current treatment for ascites (excessive accumulation of fluid in the abdominal cavity) (e.g. peritonoevenous shunt, tunnelled indwelling peritoneal catheter, etc.) in patients with peritoneal mesothelioma?	A major symptom of peritoneal mesothelioma is the recurrent build up of fluid in the abdominal cavity, which requires regular draining. Finding the best way to do this would improve patients' quality of life.
6	What are the relative benefits of immediate standard chemotherapy compared to a watch and wait policy for mesothelioma patients?	Given the small benefit with chemotherapy, and the potential side effects, there may be a case for delaying treatment, in some patients. Defining the patients and the point at which to start treatment would be beneficial.
7	For mesothelioma patients, what is the best follow-up strategy post-treatment, to identify and treat emerging side effects and other problems?	Post-treatment survival is often measured in weeks, but patients are often given 3 month follow-up appointments. What is the most effective strategy to ensure quick treatment when symptoms and side effects appear?
8	In mesothelioma, is there a role for intrapleural immunostimulants (a drug designed to stimulate an anti-cancer immune response, such as corynebacterium parvum extract) in addition to any other treatment?	Delivering immuno-stimulants directly to the pleural or peritoneal cavity may be more effective than systemic (iv) treatments.
9	Does an annual chest X-ray and/or CT scan and medical examination in high-risk occupations (e.g. carpenters, plumbers, electricians, shipyard workers) lead to earlier diagnosis of mesothelioma?	Is it cost-effective to try and identify and regularly screen workers in high risk occupations?
10	What, if any, are the benefits of pleurectomy (pleurectomy/decortication) compared to no surgery, and which mesothelioma patients might benefit?	The value of radical surgery has been called into question by the results of the MARS trial, but a less radical procedure might be beneficial. The planned MARS2 trial will attempt to answer this question.
11	Can PET scans (which produce 3D images of the inside of the body) help to diagnose mesothelioma (as well as aiding the assessment of response to treatment)?	Diagnosis, and monitoring changes in the disease, are currently mainly done by CXR or CT, but using PET-CT scans might be more helpful.
12	How can the levels of mesothelin (a protein present in mesothelioma cells that can be measured in the blood) best be incorporated in the diagnosis, response and progression of mesothelioma?	Although mesothelin has been shown to be a useful marker, more work is needed to improve the sensitivity and specificity of the test.
13	What is the best current treatment for breathlessness in mesothelioma patients (e.g. exercise, handheld fans, etc.)?	Breathlessness is the most common, and most debilitating, symptom of mesothelioma, and yet little research has been done into ways to relieve distress.

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consensus on the top 10 research priorities, and a recommendation that a further three questions should be highlighted as being worthy of consideration. Therefore these 13 questions are listed in Table 1, along with indications of why they were considered important.

5. Discussion

There are numerous reasons why research into the diagnosis, treatment and care of patients with mesothelioma is important. The incidence of mesothelioma continues to rise, confounding earlier predictions that the number of new cases in the UK would peak around the turn of the century. However, even with over 2500 new cases a year in the UK, the relative rarity of mesothelioma makes it difficult to run large randomised trials. The dearth of reliable evidence about mesothelioma can be gauged from the fact that searches in October 2014 (searching for 'mesothelioma' in the Trials section of the Cochrane Library, and for papers with 'mesothelioma' and 'randomised' in their title in Pubmed) only identified a total of 48 relevant randomised trials (20 fully published, nine presented at meetings, four completed, 12 ongoing and three planned but not yet started). For information, the 29 published and presented trials are listed in Table 2.

The limited available evidence suggests that none of the usual oncological modalities (surgery, radiotherapy and chemotherapy) have made much impression on improving survival rates or quality of life. Thus new ideas and new incentives are required to investigate and discover new effective treatments, and to support patients through this distressing disease.

It is therefore timely that this JLA PSP was set up to specifically incorporate patients', carers' and health professionals' views, as Chalmers and Glasziou [33] have argued strongly for a more efficient research culture in which scientists study health conditions that address questions about interventions and outcomes that patients and clinicians consider to be the most important.

Inevitably, such large collaborative projects raise numerous issues, and a few aspects require greater discussion:

- Given the incapacitating symptoms and short survival, finding patients to sit on the Steering Group was a major challenge. Although we were fortunate to involve two long-term survivors (one of whom sadly died during the project), it could be argued that they were not typical patients.
- Although attempts were made to formulate the research questions in lay language, in some situations it proved to be extremely difficult to do this in a concise fashion. This represented a major challenge for most patients and carers and, at the final workshop, many indicated they felt disadvantaged by their lack of understanding of the complex medical issues.
- Mediating the contrast between patients' expectations of speedy and major progress, and clinicians' and researchers' awareness that progress is slow and usually involves small cumulative steps, proved difficult.
- Total scores were generated for each question for both the initial prioritisation survey, and the initial subgroup session of the final prioritisation workshop (see online Tables A and B). It may appear overly simplistic to add the positions together (as an outlying rank may skew the combined position), but, interestingly, alternative options (taking the median score, or the highest score) give very similar results, and thus it was felt the method used was valid.
- The importance of some questions varied significantly between the initial and final prioritisation lists, and Fig. 1 shows the cross-tabulation of the initial and final rank of each question. The diagonal line indicates what the picture would have been if the interim and final ranks were identical, but as can be seen, the rank position of some questions changed significantly. This

Table 2
Published randomised trials in mesothelioma.

Summary	Pts	Reference
Fully published papers		
Doxorubicin vs cyclophosphamide	32	Sorensen et al. Cancer Treat Rep 1985;1431–2
Platinum analogues JM8 vs JM9	16	Cantwell et al. Cancer Chemother Pharmacol 1986;286–8
Cyclophosphamide/adriamycin ± imidazole carboxamide	76	Samson et al. JCO 1987;86–91
Cisplatin/mitomycin vs cisplatin/doxorubicin	79	Chahinian et al. JCO 1993;1559–65
Local radiotherapy	40	Boutin et al. Chest 1995;754–8
Surgery ± intraoperative photodynamic therapy and postoperative immunochemotherapy	63	Pass et al. Ann Surg Oncol 1997;628–33
Pemetrexed	456	Vogelzang et al. JCO 2003;2636–44
Radiotherapy for tract metastases	58	Bydder et al. BJC 2004;9–10
Raltitrexed	250	van Meerbeeck et al. JCO 2005;6881–9
Early vs delayed chemotherapy	43	O'Brien et al. Ann Oncol 2006;270–5
Intervention site radiotherapy	61	O'Rourke et al. Rad Oncol 2007;18–22
Maintenance pemetrexed	243	Jassem et al. JCO 2008;1698–704
Active Symptom Control ± chemotherapy	409	Muers et al. Lancet 2008;1685–94
Aprotinin for blood loss	20	Norman et al. Cancer 2009;833–41
Extra-pleural pneumonectomy (EPP) vs No EPP	50	Treasure et al. Lancet Oncol 2011;763–72
Bevacizumab	115	Kindler et al. JCO 2012;2509–15
Maintenance thalidomide	222	Buikhuisen et al. Lancet Oncol 2013;543–51
VATS pleurectomy vs talc	196	Rintoul et al. Lancet 2014;1118–27
Pemetrexed/cisplatin ± CBP501	65	Krug et al. Lung Cancer 2014;429–34
Nurse education	177	Nagamatsu et al. Nurse Educ Today 2014;1087–93
Meeting abstracts		
Onconase vs doxorubicin	157	Vogelzang et al. ASCO 2000;577a (abs 2274)
Interleukin-2	14	Pitako et al. ASCO 2003;230 (abs 920)
ICE ± hyperthermia	27	Bakhahandeh et al. ASCO 2004;685 (abs 7288)
Doxorubicin ± onconase	413	Reck et al. ASCO 2009;383 (abs 7507)
Second line vorinostat	660	Krug et al. EJC 2011;47(Suppl. 2):2–3
Pemetrexed/gemcitabine vs pemetrexted/carboplatin	32	Millenson et al. ASCO 2010;28 (abs e18053)
Axitinib	26	Buikhuisen et al. ASCO 2013;31 (abs 7528)
ADI-PEG20 vs placebo	68	Szlosarek et al. ASCO 2014;32 (abs 5707)
Hemithoracic radiotherapy post chemotherapy and surgery	54	Stahel et al. abs ESMO 2014 (abs LBA37)

Note: Does not include trials which included a subset of mesothelioma patients.

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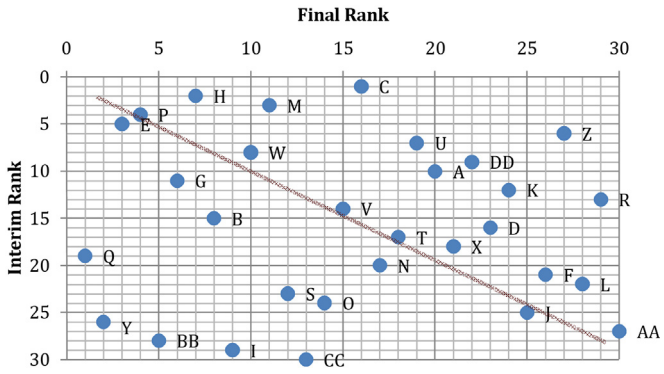

Fig. 1. Comparison of interim vs final ranking of top 30 questions. Note: the letters (A–Z, and AA–DD) correspond to the 30 research questions (see online Tables A and B), and the figure indicates the change between the interim and final prioritisation (for example question Q was ranked 19th at the interim stage, but 1st in the final list).

suggests that there was a gradual shift in emphasis over the successive stages of the project, away from the more patient and carer orientated concerns (e.g. fatigue) towards more complex interventions.

- At the final workshop, trying to put every single question in order of importance proved to be the most difficult part of the process. The discussion focused on the top 13 questions, and therefore it might be better to consider these as a group of equally important questions.

However, despite the above concerns this JLA PSP succeeded in its aim of bringing together patients, carers, and health professionals to identify, discuss, and prioritise the important unanswered research questions in mesothelioma. This rigorous, transparent and person-centred approach reflects what matters most to people affected by mesothelioma and health professionals dealing with this disease. The top 10 research priorities include a wide portfolio of potential research projects (including immunotherapy, chemotherapy and surgery, as well as questions about the role of PET scans, screening and monitoring patients, and the management of ascites in peritoneal mesothelioma).

6. Conclusions

The research priorities highlighted by this JLA PSP present clear directions for future interventional research, and it is important that researchers and funders in the UK, and globally, take note of this list and establish studies that will ultimately improve the experience and the current poor outlook of patients with mesothelioma.

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Author's contribution

The paper was drafted by RS, and all the Steering Group Members read and commented on drafts and approved the final version.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2015.05.021

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