Uveal Melanoma Guideline Development Methodology

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1 Purpose of this document
This document describes the methods used to develop the Uveal Melanoma Guideline (‘the Guideline’) [http://melanomafocus.com/activities-2/um-guidelines-resources] in the interests of transparency and as a guide for the development of future revisions of the Guideline.

2 Background to development
The Guideline began as an initiative by clinicians involved in the care of Uveal Melanoma who thought that the care of patients with this rare condition could be improved by consistent evidence-based guidance on management and follow-up.

Melanoma Focus ([http://melanomafocus.com/]), a national charity with a professional core membership undertaking research into melanoma and providing information for the public and healthcare professionals alike, funded the development of the Guideline and will take responsibility for it after publication. The Guideline and all supporting documents, including the evidence extractions, declarations of interest of the GDG and the names of consultees and their comments will be posted on the Melanoma Focus website at the time of publication.

Its development was led by Dr Paul Nathan, a Trustee of Melanoma Focus and a medical oncologist expert in the treatment of metastatic melanoma. Other officers and Trustees of Melanoma Focus played no part in the development of the Guideline and did not comment on the Guideline prior to the public consultation stage.

3 Aims of the Guideline
Uveal melanoma is a rare condition affecting fewer than 500 people a year in the United Kingdom. It is distinct from cutaneous melanoma and is not covered in the UK melanoma guidelines.

Variation exists in current pathways for patients. Novel therapies are in development and patients need to have access to the best treatments. This multi-disciplinary guideline aims to identify the highest standard of care based on an extensive literature review and expert consensus; when introduced it will aim to promote a high quality of care for patients throughout the UK. It reviews the evidence, where available, and the diagnosis and management of the disease.

4 Scope of the Guideline
4.1 Need for the Guideline
The only published guideline on the subject that could be found was from New Zealand, published in 2008 [http://www.cancer.org.au/content/pdf/HealthProfessionals/ClinicalGuidelines/ManagementofOcularmelanomasupplementarydocument2008.pdf] This addresses primarily the management of the primary tumour.
The treatment of primary uveal melanoma is well established. There are, however, areas of uncertainty in the patient pathway, these include:

1. The use of and effectiveness of new technologies such as cytogenetics/mutational analysis.

2. The appropriate pathway for the surveillance of patients following treatment for primary uveal melanoma.


4. The use of systemic treatments

4.2 **Clinical areas covered by the Guideline**

The Guideline addresses: four main clinical topics:

- Management of the primary tumour including diagnostic investigation, staging and treatment.
- Prognostication including the roles of prognostic tools and biopsy.
- Surveillance including who should be offered surveillance, as well as its frequency and duration.
- Metastatic disease including the management of systemic disease and liver metastases.

4.3 **Clinical areas not included in the Guideline**

The Guideline does not address:

- The recognition or initial referral for a suspected uveal melanoma.
- The diagnosis and management of eyelid melanoma or orbital melanoma
- Areas of management that are common to a number of cancers such as palliative care, pain relief, management of general side-effects of chemotherapy and breaking bad news.

4.4 **Population and target audience**

The Guideline will be helpful to all health professionals who provide care for people with uveal melanoma. This includes ophthalmologists, opticians, liver surgeons, radiologists, pathologists, specialist cancer nurses and oncologists. It provides guidance to those not working in tertiary referral centres about when to refer patients and the subject of surveillance. The Guideline is also relevant to people who have received a diagnosis or who are suspected of having uveal melanoma, as well as their family and carers.

5 **Stakeholders**

Uveal melanoma is a relatively rare condition which is managed by specialists. At diagnosis of the primary tumour, care is provided to patients by specialist ophthalmic surgeons in one of three centres in England (London, Liverpool and Sheffield), with a few other centres providing treatment for metastatic disease.

5.1 **Selection and composition of the Guideline Development Group (GDG)**
The number of health professionals who provide care to patients with uveal melanoma is relatively small and the aim in selecting the GDG was to reflect a significant proportion of these. Professional GDG members were selected to represent these centres and to represent the professions involved in delivering care. General Practitioners rarely see this condition, since it is generally recognised by an optician during an eye check or at presentation at an eye casualty, so there was no GP on the GDG.

There were 19 members of the GDG. These included

- 3 patient representatives
- 2 interventional radiologists
- 2 hepatic surgeons
- 3 ophthalmic surgeons
- 1 pathologist
- 4 oncologists
- 1 Specialist Registrar trainee ophthalmic surgeon who helped with development
- 1 project manager

OcuMel, which is the only patient organisation in Britain exclusively involved in supporting patients with OM, was approached to provide patient representation on the GDG. The general manager of OcuMel and the chairman of the board (who is also a patient with uveal melanoma) shared attendance and meetings. In addition two people with the condition who were identified through clinician contacts served on the GDG to provide a wider perspective. Both the project manager and the general manager of OcuMel supported the patient representatives. Unfortunately, one representative resigned in January 2013 for health reasons. It was felt too late to replace him but he was invited to comment on the draft.

### 5.2 Lay involvement

The OcuMel representatives were involved in the development from its inception. Throughout the process they have commented on the scope, developed questions and other members of the charity have been involved in commenting on what should be in the Guideline. Several presentations were made to the GDG on patients’ experience of their care and what is important to patients.

Melanoma Focus and Cure OM (an American charity), both charities involved in research, were invited to comment on the Guideline. Individual patients were also invited to comment, having been recruited via clinicians involved in the Guideline and through the consultation being advertised on the Melanoma Focus website.

### 5.3 Consultation and peer review

Relevant professional and patient organisations, as well as key individuals, were nominated by the GDG and invited to comment at the consultation stage. The Guideline consultation was advertised on the Melanoma Focus website for several months and people registered if they wished to comment. Several months in advance of the consultation, all the professional organisations involved in UM as well as the leading researchers and clinicians worldwide were contacted and invited to review the Guideline.

A total of 25 individuals and six professional organisations agreed to comment, these are listed in appendix A. In addition, all the professional members of Melanoma Focus were invited to comment.
Consultation

On 17 June 2014 the Guideline and the evidence extractions were sent to all individuals and organisations who had agreed to comment and to the Melanoma Focus professional membership. An invitation to anyone who wished to comment was posted on the Melanoma Focus website at the same time. In addition OcuMel also invited its members to comment. The deadline for the return of comments was 21 July.

All comments were collated into a table and sorted into the page order of the Guideline. The comments were reviewed by the lead for each topic and responses were drafted by them or the chair. The GDG reviewed those comments that would entail changes to the Guideline and discussed these by email. A table showing all comments and responses is available on the Melanoma Focus website.

5.4 Declarations of interest

Before the first meeting in April 2012, all GDG members completed a declaration of interest (DOI) form requesting details of work related to the topic of the Guideline in the following areas:

- the member or any member of their immediate family commercial interests, sponsorships or paid consultancy work
- any financial support for their department of unit
- any consultancies or memberships of national bodies, charities or pressure groups
- published opinion
- editorial fees on commissioned articles
- patents

The forms were reviewed by the chairman.

The DOIs were read out at the first meeting. Many of the GDG members work with pharmaceutical and technology companies both in conducting trials and on advisory boards. The management of conflicts of interest were discussed. In such a small field, there was concern that if members were asked to leave the room their expertise would be lost to the GDG. It was agreed at this first meeting that if a member had declared a financial interest in a company manufacturing a drug or technology in question, they would remain in the room but not participate in the discussion or the formulation of recommendations. They could answer direct questions from the GDG in the capacity of an ‘expert witness’.

At subsequent meetings any new interests or any competing interests for the subject matter of the meeting were declared. All declarations were recorded in the minutes.

Members were asked to re-complete the entire DOI form in July 2013. The table of DOIs is available in appendix D of the Guideline.

Competing interests were as follows:

- Three clinical members of the group were advisors to OcuMel.
Many members were involved in trials of pharmaceuticals or other technologies. These were declared but no action was taken.

Two members served on advisory boards to pharmaceutical companies but, since specific drugs were not discussed, no action was taken.

One member was on the advisory board and was sponsored by a technology company. When treatment in the clinical area involving this product was discussed, this member did not participate in the discussion and this member did not contribute to the formulation of recommendations.

6 Methodology

As most of the work on the guideline was carried out by the members of the Guideline Development Group (GDG) on a volunteer basis with limited funding being provided by Melanoma Focus primarily for the Project Manager and additional reviewing support, decisions on methods and guideline development had to recognise the limited time and funding available.

6.1 Evidence search

Question development

Questions were drafted based on input from GDG members. At the first meeting the GDG members divided into four subgroups corresponding to each of the four topics addressed in the Guideline to draft the clinical questions. These were refined to PICO questions defining the Population, Intervention or Investigation, Comparator and important Outcomes. The draft PICO questions were then discussed by the full GDG at the meeting and further refined by email for agreement by GDG members.

Questions

The PICO questions for each area were as follows.

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are appropriate pre-operative investigations for the primary tumour?</td>
<td>Patients with possible primary uveal melanoma</td>
<td>Biopsy</td>
<td>With each other/ With observation only</td>
<td>Selection of appropriate treatment modality (see Q 3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-ultrasound sonography (USS) Photography</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorescein angiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Optical Coherence Tomography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Should patients be staged before primary treatment?</td>
<td>Patients with primary uveal melanoma</td>
<td>Any staging investigation</td>
<td>No staging</td>
<td>Change of treatment of primary tumour</td>
</tr>
<tr>
<td>• Which patients should be staged before primary treatment, and how and when?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• What is the</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Prognostication**

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is there a preferred prognostic tool?</td>
<td>• Patients with diagnosed primary uveal melanoma with and without clinical evidence of metastatic disease</td>
<td>Clinical variables Histomorphological features Immunohistochemical features Genetic data Serological markers</td>
<td>Each other</td>
<td>Survival (hazard ratio for prognostic factors)</td>
</tr>
<tr>
<td>What is the role of the prognostic biopsy?</td>
<td>Patients with uveal melanoma with and without clinical evidence of metastatic disease</td>
<td>Intraocular biopsy</td>
<td>With no biopsy</td>
<td>Patient surveys and satisfaction</td>
</tr>
</tbody>
</table>

**Surveillance**

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Test/Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should all patients be offered surveillance?</td>
<td>Patients who have been treated for a primary uveal melanoma</td>
<td>LFT USS MRI (liver, contrast enhanced) Laparoscopy</td>
<td>With each other</td>
<td>Metastasis Survival</td>
</tr>
<tr>
<td>Should there be a risk-adapted</td>
<td>Patients who have been treated for a primary uveal melanoma</td>
<td>LFT USS</td>
<td>Comparing different risk</td>
<td>Sensitivity and specificity of</td>
</tr>
</tbody>
</table>
strategy for surveillance?

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the optimal imaging modality for surveillance? What is the interval?</td>
<td>Patients who have been treated for a primary uveal melanoma</td>
<td>USS MRI (liver, contrast enhanced)</td>
<td>Compared to each other</td>
<td>Sensitivity and specificity of metastasis detection Survival</td>
</tr>
<tr>
<td>What is the duration of surveillance?</td>
<td>Patients who have been treated for a primary uveal melanoma</td>
<td>USS MRI (liver, contrast enhanced) 5 years versus 10 years versus life-long</td>
<td>Compared to each other</td>
<td>Sensitivity and specificity of metastasis detection Survival</td>
</tr>
</tbody>
</table>

Metastatic disease

Initially, this was treated as two topics – liver disease and systemic disease, but due to the overlap and duplication of evidence they were merged into one topic.

<table>
<thead>
<tr>
<th>Question</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is the optimal method of staging?</td>
<td>Patients with uveal melanoma with suspected metastatic disease</td>
<td>LFT USS CT chest abdo pelvis MRI (whole body, liver, contrast enhanced) FDG PET CT Bone scan Laparoscopy</td>
<td>With each other</td>
<td>Assess the extent of disease</td>
</tr>
<tr>
<td>What is the most robust prognostication (known prognostic factors for survival)?</td>
<td>Patients with uveal melanoma with metastatic disease</td>
<td>Clinicopathological variables; Performance status CRP Platelet/lymphocyte ratio Other Treatment variables: Regional therapy Systemic therapy</td>
<td>Each other</td>
<td>Survival (hazard ratio for prognostic factors)</td>
</tr>
<tr>
<td>Question</td>
<td>Patients with uveal melanoma with specific disease</td>
<td>Surgery Ablation Regional therapy eg. liver isolation perfusion, TACE, other Systemic therapy Combination of the above Best supportive care</td>
<td>With each other</td>
<td>Primary - Overall survival Progression free survival Disease free survival Response rate Toxicity Quality of life Second line treatment</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>What is the optimal management of systemic metastases?</td>
<td>Patients with uveal melanoma with systemic +/- liver metastatic disease</td>
<td>Surgery Ablation Regional therapy eg. liver isolation perfusion, TACE, other Systemic therapy Combination of the above Best supportive care</td>
<td>With each other</td>
<td>Response toxicity, QOL, PFS, Overall survival Quality of life Second line treatment response rate, PFS, OS</td>
</tr>
<tr>
<td>What is the optimal management of oligometastatic disease outside the liver?</td>
<td>Patients with uveal melanoma with oligometastatic disease outside the liver</td>
<td>Surgery RFA Radiotherapy</td>
<td>With each other</td>
<td>Primary - Overall survival Progression free survival Disease free survival Response rate Toxicity Quality of life Second line treatment</td>
</tr>
<tr>
<td>What is the optimal management of liver only metastases?</td>
<td>Patients with uveal melanoma with liver only metastatic disease</td>
<td>Surgery Ablation Regional therapy eg. liver isolation perfusion, TACE, other Systemic therapy Combination of the above Best supportive care</td>
<td>With each other</td>
<td>Primary - Overall survival Progression free survival Disease free survival Response rate Toxicity Quality of life Second line treatment</td>
</tr>
<tr>
<td>Is regional liver therapy more effective than systemic therapy?</td>
<td>Patients with uveal melanoma with liver +/- systemic metastatic disease</td>
<td>Surgery Ablation Regional therapy eg. liver isolation perfusion, TACE, other Systemic therapy Combination of the above Best supportive care</td>
<td>With each other</td>
<td>Primary - Overall survival Progression free survival Disease free survival Response rate Toxicity Quality of life Second line treatment</td>
</tr>
<tr>
<td>What is the role of surveillance following metastatic treatment?</td>
<td>Patients with uveal melanoma following resection or regional treatment</td>
<td>USS CT MRI</td>
<td>Each other</td>
<td>Survival Ability to identify disease recurrence or new metastatic disease</td>
</tr>
</tbody>
</table>
Search

As the clinical area and the associated body is small, it was decided to do one all-encompassing search and then to sift references for each topic.

The original search was carried out by the Royal College of Physicians on 27 March 2012 and the search repeated to identify new evidence on 21 June 2013 and further update search was carried out on 16 April 2014. The search strategy is in appendix B of this document. Some papers of relevance which were before the search time limits were added by the GDG members.

Sifting – inclusion and exclusion criteria

About 4,000 references were retrieved from the initial search. The database was sifted for each of the topics and then reviewed to answer the questions. As this is a rare and serious condition with a high mortality rate, there are difficulties in recruiting to well-designed RCTs. Therefore much of the evidence used was from case series. When reviewing these, all human, adult only, Phase I/II/III studies were included. All study types were included except for case reports, which were excluded. Review articles combined with case reports were included if they provided new evidence. Limits on the minimum number in a case series were applied and these are discussed in the individual chapters where applicable. Papers about techniques or technologies which are now obsolete due to more recent advances (unless useful for discussion of the history of development of techniques), where techniques have changed, or where papers had been superseded by more contemporary results, were excluded. Further detail is given in the individual chapters.

6.2 Review of the evidence

The Guideline used the SIGN (1999-2012) Methodology as a guide including the checklists, evidence and recommendation grading. An example of the checklist and the grading system used are in appendices C and D respectively. Other methodologies, for example GRADE, were unlikely to have improved the evidence review with the limited and poor quality evidence base for this condition and would have required more time and been more difficult for the GDG members.

All references were put into an Access database. The review, grading and extraction of the evidence was carried out primarily by GDG members with support from a NICE-trained Guideline methodologist who extracted references when GDG members did not have time. Once the data had been sifted, each reviewer was sent a personal database of the references they were to review. They could extract directly into the database which had the relevant SIGN forms. Where this was not possible, they returned the results, which were input into the database by the project manager.

As most of the evidence consisted of small case series, many of the questions on the quality of the evidence were not relevant. For some questions, additional criteria were applied to appraise quality among the different reports of case series, in particular whether the case series included patients from more than one centre. This did not affect the grading of case series studies, which are all Level 3 by the SIGN conventions, but gave it more weight in discussion.
The subgroups presented the evidence review and extraction tables, generated by the database, to the full GDG at the group’s meetings. The full GDG discussed the evidence and formulated evidence statements and recommendations. A great deal of work was done electronically and following update search revisions all GDG members were sent several drafts of chapters for comment.

The extraction tables are in appendix A (separate document) of the Guideline. This includes many references that were reviewed but not included in the final document as the GDG felt that these might be of relevance to the reader.

**Strengths and limitations**

The small number of UM patients results in very few good quality studies. Due to the rarity of UM, its poor prognosis and the expense of the treatment, there is very little good research evidence. Most evidence of treatments consisted of small case series with ten or fewer patients. Larger studies were scrutinised carefully for a survival bias as mortality is so high. With regard to the treatment of primary tumours, the equipment is so expensive that each centre only has one type of treatment available. While the centres compare their results, there are no RCTs based in the UK. Therefore the limitations of the evidence were considerable.

**6.3 Development of recommendations**

For each topic, members of the subgroup presented the evidence found. The GDG also reviewed the evidence tables and discussed the evidence to agree the evidence statements. These are detailed in the Guideline. They then formulated the recommendations, drafting them collectively on screen until satisfied. The GDG considered the health benefits, side effects and risks in formulating recommendations. With uveal melanoma, consideration was given particularly to balancing survival with quality of life. The recommendations were circulated after the meeting and reviewed and edited where relevant. Recommendations were graded according to SIGN nomenclature listed in appendix E. The plan was to hold one meeting per topic, but there was a need for two additional meetings to complete the task.

Consensus methods sufficed for agreeing recommendations, with re-drafting of wording at the meetings until agreement was reached. The GDG then reviewed them following the meeting, with a subsequent review at a final meeting. Suggestions made by consultees were either agreed by the GDG or a reason for rejection documented.

The GDG had agreed that, should consensus not be possible, voting would be used. Where there were differing points of view, these are reflected in the ‘Linking Evidence to Recommendations’ section of each chapter.

**6.4 GDG meetings**

The Guideline was started in February of 2012, with the first Guideline Development Group meeting held in April 2012; in all, seven full day meetings were held over a period of two years. The first few meetings were held at the different centres in an effort to be even handed (Liverpool, Sheffield and London) but
members decided that meetings held in London were more convenient where all subsequent meetings were held.

### 6.5 Guideline format

The Guideline was published electronically as a full document including care pathway, recommendations, evidence reviews, and linking evidence to recommendations and implementation guidance. In addition, a patient version and a shorter version for ease of use in clinics were developed.

### 7 Funding

The Guideline was developed on a limited budget but the decision was made at the outset not to accept funding from any organisation with a vested interest in the content of the guideline. The GDG therefore turned down offers for funding from a number of pharmaceutical and technology companies. Many of the professional members of the GDG paid their own expenses to meetings. The centre hosting the meeting met room expenses and, on some occasions, the hospitality expenses. The first meeting was hosted by the rare melanoma sub-group of the NCRI melanoma CSG. The additional costs of the Guideline, including the costs of the project manager and reviewer and hospitality and travel expenses were met by the Melanoma Study Group which then merged with Melanoma Focus to become a single national melanoma charity who agreed to fund the guideline. Melanoma Focus does not have any vested interest in any technology or intervention. The trustees of the charity agreed that development of national guidelines for the management of Uveal Melanoma would improve and make care equitable across the UK and was therefore an appropriate initiative for the charity to support. After each meeting a report was sent to the funder stating that the meeting took place, which topics has been addressed and giving any update on milestones. Funders did not comment on content of the Guideline, before the public consultation stage, nor the minutes or papers of the meetings and did not participate the development of the Guideline. Melanoma Focus placed a notice on of its website stating that the development was taking place and, later, encouraging users to participate in the consultation.

### 8 Applicability

Tools and guidance to aid implementation were developed. This included:

- Publishing support tools including a slide-set to assist GDG members at conferences and patient information to facilitate dialogue and involvement in care.
- Identification of potential organisational and financial barriers in implementing the guideline.
- Development of audit criteria to assist users in monitoring compliance.

### 9 Updating

Melanoma Focus will take administrative and the chairman, or a designate, will take clinical responsibility for maintaining the guideline. GDG members will be asked to notify the chairman at any time, if new evidence makes any aspect of the Guideline unsafe. Annually, the chairman or designate will write to the GDG members and the consultees, who comprise many of the leaders in the field, asking if there has been any new evidence which would change the recommendations. At three year intervals, there will be a full
search of the literature from the date of the last search to identify any new evidence which would change a recommendation. This will be reviewed by the chairman, or designate, and experts from the each of the four GDG sub-groups (Primary treatment, Prognostication, Surveillance and Metastatic disease) For any section of the Guideline which needs updating, the members of that subgroup will meet to review the evidence and agree changes. The re-drafted sections of the Guideline will be sent to the full GDG for agreement before publication. Only if there are several sections that need updating will the full GDG meet. Updates of the guideline should follow the methodology detailed in in *Uveal Melanoma Guideline Development Methodology* (Link), which also contains further details of the update methods.
Appendix

A. Stakeholders invited, or who requested, to review the draft Guideline

Organisations

- The British Society of Interventional Radiology
- The Royal College of Radiologists
- EORTC Ocular Group
- BOPSS (British Oculoplastic Surgery Society)
- National Collaborating Centre for Cancer
- Ocular Oncology Group
- CUREOM
- Royal College of Ophthalmologists
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
- Optometrists
- International Society of Ocular Oncology
- International Eye Cancer website
- Melanoma Focus

Individuals

- Mr Marios Andreou
- Dr Ruth Board
- Mr Tom Brown
- Dr Richard Carvajal
- Dr Trevor Cleveland
- Dr Pippa Corrie
- Professor Angus Dalgleish
- Dr Sarah Danson
- Ms Becky Dennis
- Dr Joseph Fell
- Professor Paula Ghaneh
- Professor Robert Hawkins
- Dr Stephen Houston
- Dr Rhona Jacques
- Dr Nasir Khan
- Dr Tero Kivela
- Dr James Larkin
- Mr Ali Majeed
- Dr Hardeep Singh Mudhar
- Professor Ruth Plummer
- Ms Teresa Reid
- Mr Mandeep Sagoo
- Mr Arun Singh
- Dr Karen Sisley
- Dr Neil Steven

B. Search Strategies
Medline (total results 2987 initial search)

1. exp *Eye Neoplasms/
2. Conjunctival Neoplasms/
3. Iris Neoplasms/
4. Choroid Neoplasms/
5. *Ciliary Body/
6. exp Uveal Neoplasms/
7. or/1-6
8. Melanoma/
9. and/7-8
10. ((ocular or uvea$ or conjunctiv$ or iri$ or choroid$ or ciliary) adj3 (melanoma$ or malignant neoplasm$)).ti,ab.
11. or/9-10
12. letter/
13. exp historical article/
14. Anecdotes as Topic/
15. comment/
16. case report/
17. exp animals/ not humans/
18. Animals, Laboratory/
19. exp animal experiment/
20. exp animal model/
21. exp Rodentia/
22. or/12-21
23. 11 not 22
24. limit 23 to (english language and yr="1980 -Current")

Embase (total results 3188 initial search)

1. exp *eye tumor/
2. exp *conjunctiva tumor/
3. exp *iris tumor/
4. exp *ciliary body tumor/
5. or/1-4
6. *melanoma/
7. and/5-6
8. exp *choroid melanoma/
9. exp *uvea melanoma/
10. ((ocular or uvea$ or conjunctiv$ or iri$ or choroid$ or ciliary) adj3 (melanoma$ or malignant neoplasm$)).ti,ab.
11. or/7-10
14. letter/
15. note.pt.
16. case report/
17. case study/
18. animal/ not (animal/ and human/)
19. nonhuman/
C. Guidance given to GDG for at beginning of development.

Sifting, Appraising, Extracting and Distilling Evidence

The job of the subgroups is to review the evidence and present it to the GDG. For the guideline to get NHS evidence accreditation (which means it is kite-marked as rigorous and is on their website), it must comply with the AGREE criteria [http://www.agreetrust.org/].

Paying particular attention to Domain 3 – rigour of development. The criteria in that section are:

1. Systematic methods were used to search for evidence.
2. The criteria for selecting the evidence are clearly described.
3. The strengths and limitations of the body of evidence are clearly described.
4. The methods for formulating the recommendations are clearly described.
5. The health benefits, side effects, and risks have been considered in formulating the recommendations.
6. There is an explicit link between the recommendations and the supporting evidence.
7. The guideline has been externally reviewed by experts prior to its publication.

Therefore, the subgroup, should comply with the bolded criteria above in reviewing the evidence.

The key criteria in developing guidelines are to be systematic and transparent. Readers can see how it was developed and why the group reached their conclusions.

The SIGN methodology handbook, [www.sign.ac.uk/methodology/index.html](http://www.sign.ac.uk/methodology/index.html) is a recognised structure for ensuring this. The steps are:

- **SIFT** - after a systematic search of the literature, the first step is to go through and shortlist the references against explicit criteria. What these criteria are will depend on the clinical question that
has been asked. It may be English language only, no animal studies. But it may also be RCT or metanalyses only. In Ocular Melanoma, you will be considering cohort studies, but you might want to consider how small a case series will yield any meaningful results. Did they find anything meaningful in small case series for systemic disease? If you can legitimately set the bar higher you will save yourself a lot of work. Sifting is usually done on the basis of title and abstract, you don’t need to have the full paper.

- **APPRAISE** – some studies that meet your sifting criteria may be poor quality – e.g. biased, unrepresentative, not directly related to the questions you are trying to answer. The SIGN checklists give a structure to assess objectively the quality. (Quality isn’t assessed on whether you personally respect the author or the journal!)

   After reading the paper, complete Sections 1 (Internal Validity) & 2 (Overall Assessment) of the relevant SIGN checklist for each sifted paper, giving the reasons for including or excluding it.

- **EXTRACT** – the GDG will need to see the key information from the studies in order to be able to make their own decisions about the evidence to formulate recommendations.

   After reading the paper, complete Section 3 (Description of the Study) should be completed for all included studies. NOTE: you need to record if there are key subgroups or confounders within the study. This information is then presented in tabular form to the GDG.

- **DISTILL** – Bring the evidence together to ‘answer’ the questions that were asked. This is usually done as a presentation for the GDG and then written as a narrative for the guideline. NOTE: this is still an objective presentation – the reviewer is serving as a ‘witness’ for the evidence. It does not involve your clinical experience or opinion. These come into the discussion in developing the recommendations. Once the recommendations are drafted, it is important to document the considerations that lead to the recommendations. They usually don’t match the evidence exactly and this needs to be explained. It might be that the evidence was poor and then the discussion of the GDG is captured (this is what I try to do in the final column). Or the evidence may have been good and the GDG chose not to give it as strong and endorsement. For example, there might be strong RCT evidence that drug A was more effective than drug B. But in considering the evidence the GDG might consider –

  - Clinical significance – although it is statistically significant, the actual clinical benefit is minimal taking into account other factors
  - Side effects/harms,
  - Patient preferences (drug regimen may be more inconvenient/unpleasant)
  - Cost effectiveness or cost impact (very expensive for the minimal increase in benefit)

**PRACTICALITIES**

- Sifting is done through the Excel spreadsheet put the relevant number (1=Primary, 2=Prognosis, 3=Liver 4= Systemic) in the QID column of all references you want to include. You will see that each reference has an RID number. This is the database assigned number but as long as we are careful, it
is a good shorthand for referring to the reference. FYI – RID stands for Reference Index Number and QID stands for Question Index Number.

- You will need the full paper for each included reference. If you can get these yourself, that’s great. If not, please give Nancy the RID’s of references needed
- For appraising and extracting, I have developed a database which contains all of the checklists. It is very easy to use and makes it much easier to complete the checklists and much quicker to present them in tabular form. If you want to have a go, let Nancy know. Alternatively, you can complete one checklist per paper (Nancy can send them to you – these are slightly adapted from the ones on the SIGN website) and send them to Nancy to put in.

Send Nancy to document in the guideline:
- Excel spreadsheet of included/excluded references
- Selection Criteria
- Checklists

D. SIGN checklists

An example of a SIGN checklist

<table>
<thead>
<tr>
<th>Methodology Checklist 3: Cohort studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIGN</strong></td>
</tr>
<tr>
<td>Study identification (Include author, title, year of publication, journal title, pages)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Guideline topic:</th>
<th>Key Question No:</th>
</tr>
</thead>
</table>

**Before** completing this checklist, consider:

1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question □ 2. Other reason □ (please specify):

Checklist completed by:

**SECTION 1: INTERNAL VALIDITY**

**In a well conducted cohort study:**

In this study the criterion is:
<table>
<thead>
<tr>
<th></th>
<th>The study addresses an appropriate and clearly focused question.</th>
<th>Well covered</th>
<th>Adequately addressed</th>
<th>Poorly addressed</th>
<th>Not addressed</th>
<th>Not reported</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.</td>
<td>Well covered</td>
<td>Adequately addressed</td>
<td>Poorly addressed</td>
<td>Not addressed</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1.2</td>
<td>The study indicates how many of the people asked to take part did so, in each of the groups being studied.</td>
<td>Well covered</td>
<td>Adequately addressed</td>
<td>Poorly addressed</td>
<td>Not addressed</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1.3</td>
<td>The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.</td>
<td>Well covered</td>
<td>Adequately addressed</td>
<td>Poorly addressed</td>
<td>Not addressed</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1.4</td>
<td>What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>Comparison is made between full participants and those lost to follow up, by exposure status.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6</td>
<td>The outcomes are clearly defined.</td>
<td>Well covered</td>
<td>Adequately addressed</td>
<td>Poorly addressed</td>
<td>Not addressed</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1.7</td>
<td>The assessment of outcome is made blind to exposure status.</td>
<td>Well covered</td>
<td>Adequately addressed</td>
<td>Poorly addressed</td>
<td>Not addressed</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1.8</td>
<td>Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.</td>
<td>Well covered</td>
<td>Adequately addressed</td>
<td>Poorly addressed</td>
<td>Not addressed</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1.9</td>
<td>The measure of assessment of exposure is reliable.</td>
<td>Well covered</td>
<td>Adequately addressed</td>
<td>Poorly addressed</td>
<td>Not addressed</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1.10</td>
<td>Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.</td>
<td>Well covered</td>
<td>Adequately addressed</td>
<td>Poorly addressed</td>
<td>Not addressed</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1.11</td>
<td>Exposure level or prognostic factor is assessed more than once.</td>
<td>Well covered</td>
<td>Adequately addressed</td>
<td>Poorly addressed</td>
<td>Not addressed</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>1.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.13</td>
<td>The main potential confounders are identified and taken into account in the design and analysis.</td>
<td>Well covered</td>
<td>Adequately addressed</td>
<td>Poorly addressed</td>
<td>Not addressed</td>
<td>Not reported</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

### STATISTICAL ANALYSIS

1.14 | Have confidence intervals been provided? |

#### SECTION 2: OVERALL ASSESSMENT OF THE STUDY

2.1 | How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect? *Code ++, +, or −* |

2.2 | Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention? |

2.3 | Are the results of this study directly applicable to the patient group targeted in this guideline? |

2.4 | **Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. |

#### SECTION 3: DESCRIPTION OF THE STUDY

**PLEASE PRINT CLEARLY**

3.1 | How many patients are included in the study?  
List the number in each group separately? |

3.2 | What are the main characteristics of the population(s)?  
*Include all relevant characteristics – for example, age, sex, ethnic origin, comorbidity, disease status, community/hospital based* |

3.3 | What environmental or prognostic factor is being investigated in this study? |

3.4 | What comparisons are made in the study?  
Are comparisons made between presence or absence of an environmental/prognostic factor, or different levels of the factor? |

3.5 | How long are patients followed up in the study? |

3.6 | What outcome measure(s) are used in the study?  
*List all outcomes that are used to assess the impact of the chosen environmental or prognostic factor.* |
| 3.7 | **What size of effect is identified in the study?**  
List all measures of effect in the units used in the study - e.g. absolute or relative risk. Include p values and any confidence intervals that are provided. Note: Be sure to include any adjustments made for confounding factors, differences in prevalence, etc. |
| 3.8 | **How was this study funded?**  
List all sources of funding quoted in the article, whether Government, voluntary sector or industry. |
| 3.9 | **Does this study help to answer your key question?**  
Summarise the main conclusions of the study and indicate how it relates to the key question. |
| 3.10 | **Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question. *(Much of this is likely to be contributed by GDG members).* |

### E. Levels of Evidence

The grading of the evidence is based on the Scottish Intercollegiate Guidelines Network (SIGN) grading system 1999-2012 [http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html](http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html)

<table>
<thead>
<tr>
<th>Levels</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1++</strong></td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td><strong>1+</strong></td>
<td>Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td><strong>1-</strong></td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td><strong>2++</strong></td>
<td>High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
</tr>
<tr>
<td><strong>2+</strong></td>
<td>Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td><strong>2-</strong></td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>Non-analytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

### F. Grade of recommendations

The grading of recommendations is also based on SIGN 199-2012:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
</tr>
</tbody>
</table>
**GPP**  Recommended best practice based on the clinical experience of the guideline development group