



Commissioning and funding innovative research, while providing support and information for patients, carers and healthcare professionals

Melanoma Focus

Guideline Development Methodology Manual



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1 Purpose of this document

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 Uveal Melanoma guideline. This received NICE accreditation and was published in 2015. Following the success of this project, other guidelines are planned covering rare melanomas.

This document describes the methods used to develop guidelines commissioned by Melanoma Focus. Its purpose is to describe the methods used and to guide the development of future guidelines and updates.

2 Aims of the Programme

The programme to develop guidelines for various rare types of non-cutaneous melanomas aims to identify the highest standard of care based on an extensive literature review and expert consensus and will aim to promote a high quality of care for patients throughout the UK.

Most melanomas occur on the skin (cutaneous melanomas); however melanomas may occur almost anywhere on the body. Non-cutaneous melanomas pose a particular challenge as they are very rare and they are not covered in the UK (NICE) melanoma guidelines.

Clinicians who do not specialise in melanomas may never see a non-cutaneous melanoma during their career and may not recognise the signs and symptoms. Variation exists in current pathways for patients, in particular for follow-up. Novel therapies are in development and patients need to have access to the best treatments.

3 Planning a guideline

3.1 *Outline of the process*

The following steps will be followed when setting up the development of a guideline:

- a. When Melanoma Focus or another body proposes that a new guideline should be developed under the auspices of Melanoma Focus, the agreement of the charity's Trustees will be sought via the CEO.
- b. Once approval in principle has been given by the Melanoma Focus Trustees a small group (the 'Initiating Group') will be established to guide the first actions of the project. Membership of this group should include clinicians with knowledge of the condition, representatives of Melanoma Focus and guidelines specialists.

Since a guideline takes a great deal of time and money, the Initiating Group should first establish that there is a genuine need for the guideline. As a general rule, a guideline should only be developed if there is a likelihood that it will significantly improve patient care. This is more likely if there are currently:

- variations in clinical practice
- differences in outcomes
- new treatments about which the efficacy for the condition are uncertain

c. The Initiating Group reports its conclusions to Melanoma Focus. Assuming the Trustees accept the need for the guideline and approve its funding by Melanoma Focus, the Initiating Group then identifies stakeholders in the guideline. These will include clinicians who see patients with the condition as well as lay representatives (patients, relatives and carers and/or patient organisations in the field) and guideline specialists.

d. The next stage is to form a Guideline Development Group ('GDG'). A chairman and secretariat are appointed and, together with the Initiating Group, recruit suitable clinicians and lay representatives to the GDG, in particular from the identified stakeholders. (See Recruitment Section 4.2)

e. Once the GDG has been formed, Melanoma Focus will step back from further active involvement in the project, as described in Section 3.3. See Section 4 for details of the GDG's role.

3.2 Drafting the Scope

The scope sets out what the guideline will and will not cover. It will be used to communicate what the guideline will be about and to estimate the likely costs of the guideline, providing an initial budget for the project. The Initiating Group should consult with stakeholders before the GDG is set up to seek their views on priority areas.

The scope should define:

- Clinical areas to be addressed in the guideline
- Clinical areas which will not be included in the Guideline
- Population addressed by the guideline
- Target audience
- Key clinical questions which will be answered by the guideline

The sample scope in Appendix C can be used as a template.

The draft scope should be discussed and agreed by the GDG before it is finalised.

3.3 Relationship with Melanoma Focus

Melanoma Focus commissions the guideline. It does not have any vested interest in any technology or intervention, but as the funder the charity will nonetheless remain at arm's length during the development process. However the charity is concerned that the development processes should be consistent from one guideline to another, and that they adhere to the standards set out in the Melanoma Focus Guidelines Manual. It achieves these objectives in two ways:

- by retaining a common secretariat for all guidelines, to guide the GDG's deliberations and processes and advise Melanoma Focus on any departure from the methods in the Manual;
- by requesting observer status for the charity's CEO or other nominee, allowing visibility of the GDG's processes.

After each GDG meeting a report will be sent to the CEO of Melanoma Focus including the agenda, declarations of interests and minutes and giving any update on milestones. Neither the CEO nor the Trustees should comment on the content of the Guideline or on the minutes or papers from the meeting unless, in their view, the GDG is deviating from the methodology.

Melanoma Focus will place a notice on its website stating that the development is taking place and, later, encouraging users to participate in the consultation. Melanoma Focus will publish the guideline, with its logo, on the website and in other formats as appropriate.

The charity will need to be in a position to state: 'Melanoma Focus commissioned and funded this Guideline, but played no part in its development and did not comment on the Guideline prior to the public consultation stage'.

4 Guideline Development Group (GDG)

The members of the GDG will be responsible for developing the guidance in the guideline. They will:

- Agree the scope,
- Develop clinical questions to be answered in the guideline
- Advise the methodologists within their area of expertise
- Discuss the evidence presented for each question and formulate the recommendations
- Assist with the drafting of the guideline
- Plan and facilitate the dissemination and implementation the guideline.

Members will be expected to set aside enough time to prepare for and attend meetings. Members will be co-authors on publications.

4.1 *Composition*

Ideally, the GDG should be made up of no more than 15 members in order to facilitate discussion.

The healthcare professionals on the GDG should include those professions and specialisms which provide the care to be covered in the scope. Clinical members of the GDG are expected to have the following skills:

- Experience of caring for patients with the condition
- Ability to work with a group to deliver a complex piece of work
- Ability to understand and interpret research

See the Information in the Specimen Application pack in Appendix A

Lay representatives, a patient, carer or relative, or a member of a relevant patient organisation, bring the patient's perspective to the guideline. The GDG should aim for at least two lay representatives – as they

can help one another. If this proves difficult, a wider lay consultation should be sought with special efforts made to seek comments from patients, carers and support groups in the consultation. This may be achieved through other cancer charities as well as through Facebook or other social media groups.

The GDG should have at least one member well versed in the guideline development process. It is also worth considering appointing a clinically trained rapporteur (e.g. a trainee in a relevant specialty) at meetings to document the discussion and the transition of the evidence into recommendations.

4.2 Recruitment

Open recruitment, rather than selection, is preferable so that everyone who is interested has the opportunity to apply, thus avoiding claims of cronyism. The recruitment can be advertised on relevant websites (including by Melanoma Focus) and via emails to the relevant professional organisations and individuals asking them to cascade the information to anyone who might be interested.

4.2.1 Application

Those interested should be sent an application pack consisting of an application form, declarations of interests policy and form (Appendix A), the draft scope and relevant information about the guideline and the application (see the specimen documents in Appendix B). The deadline for returning the application must be clear.

4.2.2 Selection

The Initiating Group should agree the process and criteria for selecting candidates in advance of receiving applications. This should include a review of candidates' declarations of interest and their application. The chairman should have no conflicts of interest related to the topics being covered in the guideline and must not be a Melanoma Focus Trustee. Applicants for membership who have conflicts of interests which, in the view of the Initiating Group, would preclude them participating in a significant number of topics, will not be invited to join the GDG.

4.3 Planning meetings

It is helpful for members if GDG meeting dates are agreed well in advance. As a rule of thumb there will need to be one introductory meeting, one consultation meeting and one meeting for every 2-3 questions; for example if there are 12 questions, plan for 6-8 meetings. As members are likely to be coming from all over the country, a full day meeting makes best use of time and resources. Allow enough time between meetings to carry out the work needed to present at the meetings. Generally this is 6-8 weeks, depending on resources. Very infrequent meetings risk losing the interest of the members.

5 Methodology

5.1 Question development

The Working Group should draft the clinical questions based on the scope. These can be circulated with the scope for comment by GDG members, in advance of meetings, and by stakeholders. Once the clinical questions are agreed, they should be refined to PICO questions. These define the **P**opulation, **I**ntervention

or Investigation, Comparator and important Outcomes. This work may be done at the first GDG meeting or drafted in advance and agreed at the meeting.

Samples of PICO are available in the NICE Methodology Manual Chapter 4

<https://www.nice.org.uk/process/pmg20/chapter/developing-review-questions-and-planning-the-evidence-review>

5.2 Search

As the body of evidence for rare forms of melanoma is small, it may be more efficient to carry out one broad search and then to sift references for each question. A broad search should look for all evidence within the scope of the guideline. This usually means searching for the condition, using all synonyms, based on general filters or limits, e.g. excluding animal studies, case studies, and papers published before a given year.

5.2.1 Documentation

The following details should be recorded for each search and included in the methods of the guideline:

- Date of search
- Search terms and limits
- Databases searched
- Number of papers found
- Agreed inclusion and exclusion criteria
- Number of papers included for review
- Number of papers excluded from review

5.2.2 Mapping the evidence

An assessment should be made of the quality and quantity of the evidence by mapping the evidence to each question to develop a review strategy. The review strategy should document for each question:

- the types of studies which will be considered. This should include the ideal study type (e.g. randomised controlled studies) but also what types of studies will be considered if there are no good quality studies (e.g. whether case series will be considered as well as cohorts)
- whether recent conference abstracts will be considered
- the minimum sample size of the studies and, for case series, whether these need to be multi-site.
- whether studies with mixed populations will be considered if sub-group data is not available
- whether extrapolated evidence (e.g. from other melanomas) will be used

From the evidence map, a decision should be made as to the most efficient method of assessing and extracting the evidence for presentation to the GDG and inclusion in the guideline. GRADE is generally considered the best method of assessing the good randomised control trial (RCT) evidence. However, it is unlikely to improve the review if there are only a limited and poor quality evidence base and GRADE requires more time and expertise to undertake. Guidance on methods, including an algorithm for determining study type and therefore review strategy is available in Appendix H of the NICE Methodology Manual <https://www.nice.org.uk/process/pmg20/chapter/appendices>

If there are any relevant economic studies, these should be reviewed. Checklists are available in the NICE Manual Appendix H.

If no direct evidence is available and indirect or extrapolated evidence is not relevant, the GDG may develop recommendations based on experience and expertise. It may be helpful to have one member or a subgroup present a paper setting out the issues and the options for the GDG to discuss.

5.2.3 **Sifting**

Once a search is complete, it is usual to carry out an initial sift to remove irrelevant and extraneous records such as letters, subject matter not related to the guideline, etc. In general, the search is confined to human studies and, in the interest of costs, English language only.

A second sift should be carried out on the basis of the evidence map. Any record excluded at this point should not be deleted. A list of excluded references should be sent to the GDG to ensure that no relevant papers have been excluded.

5.3 **Review of the evidence**

For each question for which there is evidence, either a GRADE report or an extraction table with the relevant information from each paper should be completed and sent to the GDG. Appendix H of the NICE Methodology Handbook <https://www.nice.org.uk/process/pmg20/chapter/appendices> contains guidance on GRADE methodology, checklists and sample extraction tables for different studies.

The extraction table generally includes:

- Bibliographic reference
- Study type
- Study quality
- Intervention/Investigation
- Comparator
- Method of allocation
- Setting
- Number of participants
- Participant characteristics
- Length of follow-up
- Methods of analysis
- Results
- Limitations
- Additional comment

The GDG may request additional information.

5.4 **Development of recommendations**

For each question, the GDG will review the evidence tables and discuss the evidence. Evidence statements which reflect the general conclusions from the evidence should be derived. The GDG will then draft recommendations for practice. These are based on the evidence, where available, but take into account

the experience and expertise on the GDG. Recommendations should be clearly written, easily identifiable and unambiguous. The GDG should consider the following in making decisions:

- benefits and harms
- patient preferences (drug regimen may be more inconvenient/unpleasant),
- clinical significance (although it is statistically significant, the actual clinical benefit is minimal taking into account other factors)
- Feasibility of implementation
- Cost effectiveness or cost impact (very expensive for the minimal increase in benefit)
- When making choices between alternative interventions, consider clinical and cost effectiveness

With rare melanomas, consideration should be given particularly to balancing survival with quality of life.

When drafting recommendations, it is useful if they are typed and displayed on a screen so that the GDG can see them and agree them at the meeting. Usually, with discussion and revision, a form of words can be agreed. The chairman should, however, agree with the GDG, in advance (e.g. at the first meeting) what they will do if the GDG cannot agree; this may mean a majority vote.

5.4.1 Evidence to recommendations

In drafting each recommendation, the discussion and GDG considerations which resulted in the recommendations should be documented and included in the guideline. This allows the guideline user to understand why the GDG reached a particular conclusion. Some guideline groups recruit a trainee doctor to act as a rapporteur and write up this section. If GDG members have differing views and arguments, these may be written up in this section.

5.5 *Guideline format*

It is helpful to agree a structure for the guideline early in the process. The full guideline should contain all of the information needed to allow the reader to track how the guideline was developed and how the conclusions were reached. In addition to an introductory and methods chapters, there will be clinical chapters for each topic or stage. As meetings are held, the reviews, evidence statements, recommendations and discussion are put into the chapter. The Guideline should also contain a care pathway and implementation guidance.

5.6 *Consultation and peer review*

5.6.1 Recruiting Peer Reviewers

A draft of the guideline should be circulated for review. Relevant professional and patient organisations, as well as key individuals, should be invited to comment. The Guideline consultation should be advertised on the Melanoma Focus website for several months in advance so that people may register if they wish to comment. A cascade email to relevant healthcare professionals and patient organisations, requesting peer reviewers, should also be sent.

5.6.2 Consultation

Reviewers should be notified in advance when to expect to receive the draft guideline.

Reviewers might want to comment by editing the document and inserting changes with tracking and/or inserting comments. This is however extremely time consuming to collate to present to the GDG and

should be discouraged if at all possible. It will save a great deal of time and avoid confusion if the draft guideline is laid out with page numbers and line numbers and reviewers are asked to note their comments on a table by page and line number. A sample comments table is in Appendix D.

The guideline, comments table and a deadline for return should be sent out with the draft. Four weeks is usually allowed for return of comments, with a reminder sent one week before the deadline.

Upon receiving comments, each reviewer should be sent a Declaration of Interests form to complete. These can be held and made available on request.

5.6.3 Reviewing comments

As comments are returned they should be compiled into a single table listing the reviewer/organisation, page number, line number and comment. The table can then be sorted into page and line order to enable the GDG to review all of the comments on a given topic together. Sections of the guideline may be allocated to different GDG members, who may either recommend a change to the text of the guideline or draft a response defending the GDG position. When this process is finished, the revised guideline and the Consultation table (with comments and responses) should be sent to the GDG for approval. It may be necessary to have a final meeting to discuss any controversial changes. The final consultation table should be posted on the Melanoma Focus website when the guideline is published.

6 Final draft and Publication

At the consultation stage, Melanoma Focus will assess the guideline against this methods manual and the NICE Accreditation checklist and raise any concerns. Before the guideline is published a formal appraisal will be undertaken to ensure that the guideline complies with this manual and the NICE Accreditation checklist (Appendix E) which will be presented to and signed off by the Melanoma Focus Board.

Once the full guideline is complete, a Summary, containing the recommendations and care pathway, should be abstracted for ease of use by clinicians. A Patient/Carer version which reflects the contents of the guideline should also be developed. At publication, the following should be published on the Melanoma Focus website:

- Full Guideline
- Patient/Carer Version
- Summary Version
- Scope
- Consultation Table
- Declaration of Interests
- Implementation guidance (see below)

Each version of the guideline should clearly state the publication and review dates.

7 Implementation

Implementation plans should be discussed at a GDG meeting several months before the guideline is due to be published. The aim is to make relevant healthcare professionals aware of the guideline and facilitate its use. A plan for contacting professionals should be developed.

Tools and guidance which aid implementation include:

- Journal articles
- A slide-set to assist GDG members and others to present the guideline at conferences and departmental meetings
- Patient/Carer version of the guideline to facilitate dialogue and involvement in care
- Identification of potential organisational and financial barriers in implementing the guideline
- Audit criteria to assist users in monitoring compliance

8 Updating

Upon publication, Melanoma Focus will take administrative responsibility for the guideline. The chairman, or a designate, will take clinical responsibility for maintaining the guideline. GDG members should 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 clinical area. 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 need to meet. Updates of the guideline should follow the methodology detailed in this document.

Appendix

A. Declaration of Interest Policy



What is an interest?

An *interest* is defined as any activity, arrangement or opinion which might affect, or might be interpreted as affecting, a member's objectivity or decisions. While in the vast majority of cases, members will not be influenced by their interests, it may not be so interpreted when the guideline is published. Conflicts of interest or perceived conflicts of interest can detract from the authority of the guideline and its implementation. It is important, therefore, that all interests are declared both in the interests of transparency and to allow an objective assessment of what is a conflict.

For the purposes of this programme, interests in the past 36 months or known of in the next 24 months should be declared. The following interests types of should be declared

Personal financial interests constitute a significant benefit to the individual, partner of that individual or their immediate family. They include:

- a financial benefit (of £500 or greater), to the person.
- ownership of stock in companies whose products, or competitors' products, may be considered in the guideline.

Generally, but not exclusively, this might include:

- holding of shares in commercial organisations (pharmaceutical/equipment manufacturers for example), but excluding those held in pooled investment funds.
- sponsorship or payment of expenses by commercial organisations. (Note: while they should be declared, the payment of reasonable expenses to attend a conference will not affect a member's status on the group)
- patents (existing and pending) held by the individual.
- editorial fees for publications (written or electronic).

Non-personal financial interest a financial benefit (of £500 or greater) to the practice or department in which the person is directly employed. Generally, but not exclusively, this might include:

- donations, sponsorship or similar from pharmaceutical firms and equipment manufacturers
- consultancies and fees paid to the practice or department.
- funding of research grants or a research nurse.

- patents (existing and pending) held by the organisation.

Personal non-financial interest are strongly held opinions which might unduly influence the outcome of the guideline, where there may be contention opinion. These might include

- membership of any national body, charity or pressure group which lobbies for or against a particular treatment.
- publication of personal opinions

Declarations of interest

All applicants will complete a Declaration of Interest (Appendix A) form as part of their application to join the Guideline Development Group (GDG). These will be reviewed by the Initiating Group. The chairman should have no conflicts of interest related to the topics being covered in the guideline. Applicants for membership who have conflicts of interests which, in the view of the Initiating Group, would preclude them participating in a significant number of topics, will not be invited to join the GDG.

All members will declare orally new interests at the beginning of each meeting and these will be recorded.

Before publication of the guideline, all members will check the declaration of interest form again for completeness.

Records of interest

Declarations of interests for each GDG member will be recorded in a table and updated at each meeting; this will be available to all members of the GDG. A table containing all declarations will be published on the Melanoma Focus website at the time of the publication of the guideline.

Conflicts of Interest

Prior to each meeting, the chairman will review members' declarations of interests to identify any possible conflicts relating to the topics being covered and discuss these with the member. Where there is an interest, in all cases the member should declare this at the beginning of the meeting. The following actions should then be taken:

- *Personal financial interest* – the chairman will decide whether the member should leave the room while the topic is discussed or can remain in the room and act as an *expert witness* i.e. respond to direct questions but take part in the discussion or decisions.
- *Non-personal financial interest* - the chairman will decide whether the member may participate in the discussion and decisions or act as an *expert witness*.
- *Personal non-financial interest* – in most cases, members would participate in the discussion or decisions. In exceptional cases the chairman may decide that the member act as an *expert witness*.

Tick One	Yes	No
Personal Financial Interest		

Do you, your partner (if applicable) or any member of your immediate family have any commercial interest such as personal shares etc. with any companies that are, or could be, involved in the above named guideline?		
If Yes, please give details		
Do you, your partner (if applicable) or any member of your immediate family receive sponsorship or paid consultancy work within commercial organizations that are, or could be, involved in the above named guideline?		
If Yes, please give details		
Do you receive significant editorial fees for commissioned articles for publication (in any format) or are you paid editorial work for any publication related to the above named guideline?		
If Yes, please give details		
Non-personal Financial Interest		
Does your department or unit receive financial support from commercial organizations that are, or could be, involved in the above named guideline?		
If Yes, please give details		
Do you or your department hold a patent (existing or pending) related to the above named guideline?		
If Yes, please give details		
Personal Non-financial Interest		
Are you a consultant to or a member of any national body, charity or pressure group whose work is related to the above named guideline?		
If Yes, please give details		
Have you published your opinion on topics covered in the above named guideline?		
If Yes, please give details		

Name:

Title:

Role in guideline development:

Signature:

Date:

B. Sample Application Information

a. Information for Applicants

Introduction

Melanoma affecting the uro-genital tract and ano-rectum is rare, with only 437 cases recorded in England in the 4 years from 2010. Nonetheless, there is no consensus about how such patients should be managed. Surgery at all stages frequently involves complex decisions about risk and benefit, and the value of adjuvant treatment – drug therapy or radiotherapy - is unclear. Medical treatment of advanced melanoma is rapidly evolving, and its relevance to this group of patients requires clarification. There is no agreement about diagnostic imaging techniques, and follow-up protocols. There is therefore a need for clinical guidance in this area.

Melanoma Focus is the UK's leading melanoma charity. Its remit includes the development of clinical guidance, so it is well-placed to sponsor the development of proposed new guidelines, which will be developed in compliance with the requirements published by NICE and published in relevant medical journals.

Role of Guideline Development Group (GDG) members

The Guideline Development Group will comprise healthcare professionals and patients/carers or patient organisations with expertise in uro-genital and ano-rectal mucosal melanoma supported by methodologists. Members contribute to the group as individuals, drawing on their own areas of experience and representing a particular organisation. Members will be co-authors of the guideline and other relevant publications.

Members will be expected to set aside enough time to attend committee meetings and contribute to the development of the guideline by:

- Preparing for the topics being discussed at the meeting and contributing to the discussion taking full account of the evidence in developing recommendations
- Assisting with the drafting of the guideline

Remuneration

Reasonable out-of-pocket expenses, including standard class rail fares and, when necessary, hotel costs will be paid to support attendance at committee meetings.

Time commitment

The overall time commitment for this guideline is approximately 18-24 months with 9-12 one-day meetings taking place during that period. Methodologists will undertake the evidence searches, appraisal and extractions. For each meeting, members will be expected to read through the papers, including evidence reviews, which will take approximately 2-4 hours. Members will also be expected to contribute to the drafting of the guideline, in particular the introductory background and epidemiology for each clinical area.

The first meeting of the GDG is planned for July

How to apply

Please submit the following

- A completed application form
- A short C.V.
- Declaration of interest form

To [Chairman] [Email] by [Date]

GDG members will be chosen [Date] and the first meeting is planned for [Date].

b. Application

<u>Full name</u>	
<u>Address</u>	
<u>Contact phone number</u>	
<u>Email address</u>	
<u>Why do you want to be a member of this Guideline Development Group? (100 words maximum)</u>	
<u>Please comment briefly on the scope and questions of the guideline. Which question do you think is the most important and why. (150 words maximum)</u>	

Please send the completed application along with:

- A short CV (max 5 pages)
- A completed Declarations of Interest Form

To [Chairman] [Email] by [Date]

C. Sample Scope

Ano-uro-genital Melanoma Guideline Scope

1. Guideline title

Assessment and management of ano-uro-genital melanoma

2. Short title

Ano-uro-genital Melanoma

3. The remit

Melanoma Focus will develop a clinical guideline on the assessment and management of ano-uro-genital melanoma.

4. Clinical need for the guideline

4.1 Epidemiology

Mucosal melanoma occurs at 2 main sites – the upper aerodigestive tract, and the ano-rectum and urogenital tracts. The latter group is the subject of this guideline. Data from Public Health England (PHE) shows that between 2010 and 2013 there were 437 cases of melanoma affecting anorectal and urogenital sites. Of these, 121 cases involved the vulva; 49 cases were vaginal melanoma; and 105 cases involved the ano-rectum. Surveillance, Epidemiology, and End Results Program (SEER) data shows that age-adjusted incidence rates increased between 1992 and 2011 ($p < .05$) for both women and men, with estimated annual percentage changes of 3.02% and 5.08% respectively. There were 2,203 deaths from melanoma in 2010, and about 100 deaths from ano-uro-genital melanoma.

There may be variations in survival across different cancer networks, and poorer survival may be attributable to late presentation or delays in diagnosis and initiation of treatment.

4.2 Current practice

It is unclear to what extent current practice for skin melanoma should inform decisions for people with ano-uro-genital melanoma. It is also unclear how the American Joint Committee on Cancer (AJCC)

cutaneous melanoma staging system applies to this group. <https://cancerstaging.org/references-tools/quickreferences/documents/melanomasmall.pdf>

The majority of ano-uro-genital melanomas are diagnosed as a result of appearance, in the case of vulval melanoma, or by bleeding from the ano-rectum or uro-genital tracts. Many will be referred via the 2-week wait process.

Most will have either a biopsy or, less commonly, complete excision of the melanoma, pathological analysis and subsequent wide local excision. There remains some uncertainty about optimal final excision margins for cutaneous melanoma, and this topic is the subject of current research. This is especially relevant to this group, who are more likely to have more advanced primary disease.

Imaging (for example CT, MRI or positron emission tomography PET-CT) for staging purposes is indicated for all people diagnosed with ano-uro-genital melanoma. Sentinel node biopsy (SNB) is used to stage skin melanomas according to the AJCC staging system. It is also used to identify people who might be eligible for adjuvant therapy clinical trials and to stratify during analysis of those trials. However, SNB has not been shown to confer any survival advantage and the cost effectiveness of SNB is uncertain. Its applicability to people with ano-uro-genital melanoma is unclear. There is thought to be variation in practice in the use of CT and PET-CT imaging for people with more advanced disease.

Adjuvant chemotherapy and immunotherapy are not currently indicated for the management of skin melanoma and continue to be the subject of research trials. Adjuvant radiotherapy for stage IIIB and IIIC melanoma is used on the basis of one randomised study showing reduced risk of loco-regional recurrence, but it does not appear to confer a survival advantage. The relevance of these findings to people with ano-uro-genital melanoma is uncertain, especially as the sites of their disease frequently limit the extent of curative surgical resection. Some people with small numbers of apparently localised metastases to other organs may also be offered surgical resection, although this is not supported by randomised trial evidence.

People whose metastatic melanoma carries cKIT mutations may be treated with specific cKIT inhibitors. Other drugs used in people with advanced skin melanoma, such as BRAF and MEK inhibitors, are less likely to be relevant to people with ano-uro-genital melanoma. These drugs have a very rapid effect on tumours but unfortunately the majority of people who take them develop resistance and the tumour relapses.

People with systemic metastases whose tumours are not found to carry BRAF mutations are usually treated with immunotherapy using ipilimumab, or with a PD1 inhibitor. The utility of these treatments for patients with ano-uro-genital melanoma is uncertain. Chemotherapy with dacarbazine may be used but response rates are low.

Radiotherapy may be used to treat isolated cerebral metastases and for palliation.

5. The guideline

The guideline will be developed to fulfil the AGREE II Criteria http://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf

used for accreditation by NICE <https://www.nice.org.uk/about/what-we-do/accreditation/accreditation-process>.

5.1 Population

5.1.1 Groups that will be covered

- Children, young people and adults with ano-uro-genital melanoma.
- Subgroups identified as needing specific consideration will be considered during development of the guideline.

5.1.2 Groups that will not be covered

- People with primary ocular melanoma.

5.2 Healthcare setting

All secondary and tertiary care settings in which NHS-funded care is provided.

5.3 Clinical management

5.3.1 Key clinical issues that will be covered

- The specific information and support needs of people with ano-uro-genital melanoma and their carers at diagnosis, at treatment planning, and during and after treatment.
- The best approach to increasing clinical diagnostic accuracy and appropriate prompt excision.
- The best approach to resolving clinico-pathological diagnostic uncertainty for borderline melanocytic lesions.
- The best approach for mutation testing of tumours for prognostic and predictive purposes.
- The most effective method of staging melanoma:
 - the role of sentinel lymph node biopsy in newly diagnosed melanoma.
 - imaging for newly diagnosed and recurrent melanoma.
- The most effective surgical treatment for stage 0-II melanoma.
- The most effective surgical treatment for stage III melanoma (including the effectiveness of sentinel lymph node biopsy).
- The indications for adjuvant radiotherapy for stage I-III melanoma after resection.
- The most effective treatment for relapsed loco-regional melanoma metastases.
- The role of surgery, stereotactic radiotherapy and image guided ablative techniques including radioembolisation in stage IV melanoma.
- The role of systemic anti-cancer therapy in the treatment of metastatic melanoma including targeted treatment and immunotherapy
- The optimum methods, setting and frequency of follow-up for people with melanoma.
- Management of other intercurrent conditions with drug therapies which may increase the risk of death from melanoma (for example, immunosuppressants, levodopa, metformin).

5.3.2 Clinical issues that will not be covered

- Referral from primary care with suspected melanoma.

- Awareness and prevention of melanoma.
- End-of-life care.
- Complementary therapies.

5.4 *Main outcomes*

- Overall survival.
- Disease-free survival.
- Progression-free survival.
- Melanoma-related morbidity.
- Melanoma-related mortality.
- Treatment-related morbidity.
- Treatment-related mortality.
- Psychological wellbeing.
- Number and length of admissions to hospital after diagnosis.
- Number and severity of adverse events.
- Health-related quality of life.
- Cost effectiveness.
- Patient-reported outcomes.

5.5 *Economic aspects*

- Developers will search for evidence of both clinical and cost effectiveness and take this into account when making recommendations involving a choice between alternative interventions.

6. Draft review questions Ano-uro-rectal Melanoma Guideline

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Note that these review questions are draft versions and will be finalised with the Guideline Development Group.

1. What is the best approach to staging patients with Stage 1-3 disease
2. What is the optimal method frequency of follow-up for patients who have undergone potentially curative surgical treatment for Stage 1-3
3. What is the most effective surgical treatment for Stage 1, 2 and 3 disease (covered this morning)
4. What is the effectiveness of imiquimod in the treatment of Stage 1 and 2 disease

Domain	1 Scope and purpose is concerned with the overall aim of the guidance, the specific clinical questions and the target population.	<i>Assessment from Final Accreditation Report</i>
Criteria	These criteria consider whether the guidance producer has a policy in place and adhered to that requires them to explicitly detail:	
	1.1 The overall objective of the guidance	
	1.2 The clinical, healthcare or social questions covered by the guidance	
	1.3 The population and/or target audience to whom the guidance applies	
	1.4 That the producer ensures guidance includes clear recommendations in reference to specific clinical, healthcare or social circumstances	
Domain	2 Stakeholder involvement focuses on the extent to which the guidance represents the views of its intended users.	<i>Assessment from Final Accreditation Report</i>
Criteria	These criteria consider whether the guidance producer has a policy in place and adhered to that means it includes:	
	2.1 Individuals from all relevant stakeholder groups including patients groups in developing guidance	
	2.2 Patient and service user representatives and seeks patient views and preferences in developing guidance	
	2.3 Representative intended users in developing guidance	
Domain	3 Rigour of development relates to the process used to gather and synthesise information and the methods used to formulate recommendations and update them.	<i>Assessment from Final Accreditation Report</i>
Criteria	These criteria consider whether the guidance producer has a clear policy in place and adhered to that:	
	3.1 Requires the guidance producer to use systematic methods to search for evidence and provide details of the search strategy	
	3.2 Requires the guidance producers to state the criteria and reasons for inclusion or exclusion of evidence identified by the evidence review	
	3.3 Describes the strengths and limitations of the body of evidence and acknowledges any areas of uncertainty	
	3.4 Describes the method used to arrive at recommendations (for example, a voting system or formal consensus techniques like Delphi consensus)	
	3.5 Requires the guidance producers to consider the health benefits, side effects and risks in formulating recommendations	
	3.6 Describes the processes of external peer review	
	3.7 Describes the process of updating guidance and maintaining and improving guidance quality	
Domain	4 Clarity and presentation deals with the language and format of the guidance.	<i>Assessment from Final Accreditation Report</i>

Criteria	These criteria consider whether the guidance producer ensures that:	
	4.1 The recommendations are specific, unambiguous and clearly identifiable	
	4.2 The different options for the management of the condition or options for intervention are clearly presented	
	4.3 The date of search, the date of publication or last update and the proposed date for review are clearly stated	
	4.4 The content of the guidance is suitable for the specified target audience. If patients or service users are part of this audience, the language should be appropriate.	
Domain	5 Applicability deals with the likely organisational, behavioural and cost implications of applying the guidance.	<i>Assessment from Final Accreditation Report</i>
Criteria	These criteria consider whether the guidance producer routinely considers:	
	5.1 Publishing support tools to aid implementation of guidance	
	5.2 Discussion of potential organisational and financial barriers in applying its recommendations	
	5.3 Review criteria for monitoring and/or audit purposes within each product.	
Domain	6 Editorial Independence is concerned with the independence of the recommendations, acknowledgement of possible conflicts of interest, the credibility of the guidance in general and their recommendations in particular.	<i>Assessment from Final Accreditation Report</i>
Criteria	These criteria consider whether the guidance producer:	
	6.1 Ensures editorial independence from the funding body	
	6.2 Is transparent about the funding mechanisms for its guidance	
	6.3 Records and states any potential conflicts of interest of individuals involved in developing the recommendations	
	6.4 Takes account of any potential for bias in the conclusions or recommendations of the guidance	