COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

Cutaneous Melanoma

Invited reviewers:			**Declared Interests**
MC	Ms Marissa Collins	Researcher in Health Economics, Glasgow Caledonian University, Glasgow.	None
AD	Professor Alan Denison	Consultant Radiologist, Summerfield House, Aberdeen.	None
VD	Dr Val Doherty	Dermatologist, Royal Infirmary of Edinburgh, Edinburgh.	Shares and securities – personal shares – astra zeneca.
WF	Mrs Wilma Ford	MacMillan Skin Cancer clinical Nurse Specialist, Southern General Hospital, Glasgow.	None
MH	Dr Matthew Hough	Consultant Plastic Surgeon, Ninewells Hospital, Dundee.	None
KMac	Mrs Kirsty MacFarlane	Principal Pharmacist, Scottish Medicines Consortium, Healthcare Improvement Scotland.	None
CM	Dr Colin Malone	Locum Consultant Dermatologist, Dumfries and Galloway Royal Infirmary, Dumfries.	None
MM	Dr Megan Mowbray	Consultant Dermatologist, Queen Margaret Hospital, Dunfermline.	None
LN	Dr Lisa Naysmith	Consultant Dermatological Surgeon, Royal Infirmary, Edinburgh	Remuneration from employment – Consultant Dermatological Surgeon in NHS teaching hospital. Member of skin cancer MDM advising on the management of melanoma and non melanoma skin cancers.
MN	Dr Marianne Nicolson	Consultant Medical Oncologist, Aberdeen Royal Infirmary, Aberdeen	Remuneration from consultancy or other fee paid work – paid advisory board work for BMS, GSK, MSD, Novartis and other drug companies. Non-personal support from commercial healthcare companies,

			organisations or undertakings which may be significant to, relevant to or bear upon the work of SIGN – Research support from BMS, GSK, MSD, Novartis and other pharma companies; also pharma support to attend oncology meetings and deliver lectures at national and international oncology meetings.
MP	Professor Mary Porteous	Consultant Clinical Geneticist, Western General Hospital, Edinburgh.	None
CP	Dr Charlotte Proby	Professor of Dermatology, University of Dundee, Dundee.	None
JV	Dr James Vestey	Consultant Dermatologist, Raigmore Hospital, Inverness.	Shares and securities – possibly, but not certainly, since the management of my investments is under the control of financial advisor.

Open consultation:			
AA	Dr Andrew Affleck	Consultant Dermatologist and Mohs Surgeon, Ninewells Hospital, Dundee.	None
BAD		British Association of Dermatologists.	None.
RC	Mr Roger Currie	Consultant Oral and Maxillofacial Surgeon, Crosshouse Hospital, Kilmarnock	Remuneration from employment – Consultant Surgeon in NHS. Remuneration from self employment – Private practice as sole trader. Remuneration as a director of an undertaking – Elected Council Member of RCS, Edinburgh.
RD	Dr Robert Dawe	Consultant Dermatologist & Honorary Clinical Reader in Dermatology, Ninewells Hospital, Dundee.	None
SD	Dr Sarah Digby	Consultant Pathologist, Queen Elizabeth University Hospital, Glasgow.	None

CF	Dr Colin Fleming	Consultant Dermatologist, Ninewells Hospital, Dundee.	None
KH	Dr Khalid Hassan	Associate Specialist in Dermatology, Vale of Leven Hospital, Alexandria.	None
MH	Dr Matthew Hoghton	Medical Director of CIRC, RCGP, London.	None
KHI	Mr Kismet Hossain-Ibrahim	Consultant Neurosurgeon, Ninewells Hospital, Dundee.	None
AM	Mr Andy Malyon	Consultant Plastic Surgeon, Glasgow Royal Infirmary, Glasgow.	None
RR	Dr Ruth Ray	Associate Specialist in Dermatology, Royal Infirmary of Edinburgh, Edinburgh.	None
RCPE		Royal College of Physicians, Edinburgh.	None.
RCP&S		Royal College of Physicians and Surgeons of Glasgow.	None
SW	Mr Stuart Waterston	Consultant Plastic Surgeon, Ninewells Hospital, Dundee.	None

Section	Comments received		Development group response
General			
	LN	The authors should be commended for their hard work. It is well written and easy to follow. The updates are very helpful. It would be useful to have a flow chart of what to do with patients from referral to follow up depending on stage. I may have missed it but does it say anywhere in the guideline at that all melanomas should be discussed at an MDM?	*Thank you for your comment* *Flowcharts have been developed and are available locally, with local variation. It was not deemed necessary to include a generic flowchart in this guideline.* *The guideline mentions discussion at multidisciplinary teams in several places. A more general GPP has been added to the introductory paragraph of section 4 in relation to all melanomas.*
	RR	Excellent document. Minor point but there is inconsistency between space or no space after measurement units e.g. 5mm or 5mm.	*Thank you for your comment.* *Document checked for inconsistent spacing. Inconsistent spacing will also be identified in the editorial proofreading stage.*
	MC	I wonder if there is a need to re-appraise the original evidence given that some of the papers are from the 90's to see if they are still relevant to today. I also think that it would be useful to publish the search strategies used for the guidelines for those who may be interested in undertaking further research.	*This was a selective update, large parts of the guideline have not been updated, in these sections text and references from the original guideline are used verbatim. Areas not updated which are thought to be out of date are removed completely. The wording on the rationale for updating in the introductory chapter has be revised for clarity.* *The search strategies for each key question, as well as evidence tables and other process documentation are available on request.*
	KH	Bibliography 1. Lazovich, D. et al. Association Between Indoor Tanning and Melanoma in Younger Men and Women. JAMA dermatology (2016). doi:10.1001/jamadermatol.2015.2938 2. Tellez, A. et al. Risk factors and outcomes of cutaneous melanoma in women less than 50 years of age. J. Am. Acad. Dermatol. (2016). doi:10.1016/j.jaad.2015.11.014	*This bibliography refers to KH's comments throughout the consultation document.* *Thank you, these papers are helpful, although most were published after the guideline systematic review searches were completed. The remainder have either already been included as part of the evidence base or are of poor quality and would have been rejected.*

3. Gandini, S. et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur. J.

Cancer 41, 28–44 (2005).

4. Echeverría, B., Bulliard, J.-L., Guillén, C. & Nagore, E. Indicators for the total number of melanocytic naevi: an adjunct for screening campaigns. Observational study on 292 patients. Br. J. Dermatol. 170, 144–9 (2014).

5. Argenziano, G. et al. Twenty nevi on the arms: a simple rule to identify patients younger than 50 years of age at higher risk for melanoma. Eur. J. Cancer Prev. 23, 458–63 (2014).

6. Geller, A. C. et al. Total Nevi, Atypical Nevi, and Melanoma Thickness. JAMA Dermatology (2016).

doi:10.1001/jamadermatol.2016.0027

7. Ribero, S. et al. Prediction of high naevus count in a healthy U.K. population to estimate melanoma risk. Br. J. Dermatol. 174, 312–8 (2016).

8. Whiteman, D. C. & Olsen, C. M. Melanoma Incidence and Lethality Is Increased Following Solid Organ

Transplantation. J. Invest. Dermatol. 135, 2560–2 (2015).

9. Arron, S. T. et al. Melanoma Outcomes in Transplant Recipients With Pretransplant Melanoma. Dermatol. Surg. 42, 157–66 (2016).

10. Vyas, R., Keller, J. J., Honda, K., Cooper, K. D. & Gerstenblith, M. R. A systematic review and meta-analysis of animal-type melanoma. J. Am. Acad. Dermatol. 73, 1031–9 (2015).

11. NICE. Melanoma : assessment and management. (2015).

12. Scope, A. et al. The ‘ugly duckling’ sign: agreement between observers. Arch. Dermatol. 144, 58–64 (2008).

13. Unlu, E., Akay, B. N. & Erdem, C. Comparison of dermatoscopic diagnostic algorithms based on calculation: The ABCD rule of dermatoscopy, the seven-point checklist, the three-point checklist and the CASH algorithm in dermatoscopic evaluation of melanocytic lesions. J. Dermatol. 41, 598–603 (2014).

14. Aldridge, R. B., Naysmith, L., Ooi, E. T., Murray, C. S. & Rees, J. L. The importance of a full clinical examination:

		assessment of index lesions referred to a skin cancer clinic without a total body skin examination would miss one in three melanomas. Acta Derm. Venereol. 93, 689–92 (2013). 15. Bichakjian, C. K. et al. Guidelines of care for the management of primary cutaneous melanoma. J. Am. Acad. Dermatol. 65, 1032–1047 (2011). 16. Ribero, S. et al. Association of Histologic Regression in Primary Melanoma With Sentinel Lymph Node Status: A Systematic Review and Meta-analysis. JAMA dermatology 151, 1301–1307 (2015). 17. Coit, D. G. et al. Melanoma _ Clinical Practice Guidelines in Oncology. 7, 250–275 (2009). 18. Terushkin, V., Brodland, D. G., Sharon, D. J. & Zitelli, J. A. Digit-Sparing Mohs Surgery for Melanoma. Dermatol. Surg. 42, 83–93 (2016). 19. Pollitt, R. A. et al. Efficacy of skin self-examination practices for early melanoma detection. Cancer Epidemiol. Biomarkers Prev. 18, 3018–23 (2009). 20. Moore Dalal, K. et al. Methods of detection of first recurrence in patients with stage I/II primary cutaneous melanoma after sentinel lymph node biopsy. Ann. Surg. Oncol. 15, 2206–14 (2008). 21. Zaragoza, J. et al. High neutrophil to lymphocyte ratio measured before starting ipilimumab treatment is associated with reduced overall survival in patients with melanoma. Br. J. Dermatol. 174, 146–51 (2016).	
	CP	My main criticism is the decision to leave out areas that were 'beyond the scope of this guideline' when clearly they are very important to the detection and management of melanoma and when there has been significant new evidence or thinking since the previous SIGN guideline 72. I would particularly criticise section: 3.2 (needs stronger statement on sunbeds); 4.1 (needs to include molecular subtypes of melanoma. This is the future!); 4.2 (needs major update on dermoscopy and needs to change recommendation to include progressive skin lesions - ie behaviour of the skin	*Thank you for your comment. This guideline update was selective. The development group decided at the beginning of the process which areas of the guideline should be updated, rather than update the whole guideline. A balance needs to be struck where areas of the guideline which rely on older evidence are assessed and a decision made on whether reviewing the evidence is likely to result in a change to any recommendations or messages the guideline conveys.*

		lesion - rather than just ABCDE); 5.1 on surgical margins (significant deficiencies in this section - the recommendations are not necessarily correct and new evidence has not been reviewed or discussed); 6.2 (Lab investigations should include molecular genetics); 7.2 Immunotherapy needs to be updated; 8.8.2 (serial ultrasound should be reviewed and considered); and there is no section on melanoma in immunosuppressed patients or advice re advisability of organ transplantation in patients who have had melanoma. This is just as important as a section on pregnancy and has been left out completely.	*To take your points in order:* *3.2 table 1 in this section already mentions that sun beds are not recommended. A full evidence review would have resulted in a recommendation in its place. The group acknowledges this but felt including an evidence review at the peer review stage would result in unacceptable delay to publication.* *4.1 currently there is not enough robust evidence to make clinically relevant recommendations about molecular subtypes* *4.2 a GPP about dermoscopy has been added to the draft. The group feels ABCDE is adequate.* *5.1 surgical margin recommendations have been updated based on 2015 NICE guidelines.* *6.2 see point 4.1 above* *8.8.2 serial ultrasound was not included in the key question.* *Evidence on immunosuppression has been added at 7.3*
	AM	Generally well presented, clear & concise. Can I please register my disappointment that you only involved one plastic surgeon in a SIGN guideline on melanoma. I'm sure I could have found you at least 2 or 3 more, which might have reflected the mix of those actively involved in the management of melanoma a little better.	*Thank you for your comment.* *Group size must be limited and usually one or two specialists from a particular field are recruited onto a group.*
	WF	Overall the guidelines have been well written and presented and information on 'key topics' easily accessible and informative. Bearing in mind that the group will have been limited with the availability of supporting/up to date evidence for which they have clearly acknowledged the need for further research.	*Thank you for your comment.*
	MP	I think the draft reads well but I have limited my comments to my area of expertise - genetics. Elaine Fletcher who went through the genetic literature has not been named on the Development group - will her contribution be	*Thank you for commenting on the draft. Omitting Elaine Fletcher from the development group list was an oversight which has been corrected.*

		acknowledged elsewhere?	
	BAD	We have a number of concerns related to this melanoma, clinical guidelines update. Fundamentally there have been significant changes in melanoma management in recent years, which we feel, have not been adequately addressed in this update, in particular, in relation to the detection and management of melanoma, where there has been significant new evidence or thinking since the previous SIGN guideline 72. There is no section on melanoma in immunosuppressed patients or advice re advisability of organ transplantation in patients who have had melanoma. This is just as important as a section on pregnancy and has been left out completely. All recommendations made should be listed under section 2. We appreciate that SIGN feels it must limit it's remit and not re-write the whole SIGN 72 guideline, but where the previous guidance is no longer correct or is based on evidence that is significantly out of date and has been superseded by better evidence, it is very misleading to clinicians to bring out a new Guideline that does not correct these deficiencies.	*See response for CP above.* *Section 2 lists only key recommendations, not all recommendations. A complete list of recommendations is published separately in a quick reference guide.* *It is clear in the introductory chapter which parts of the guideline have been updated.*
	JV	Readable and easy to navigate quickly to relevant sections.	*Thank you*
	CM	Overall the draft reads well and on the whole the information is clear and relatively succinct – having experience as both a GP and Dermatologist I would find this useful in both the spheres I have worked within.	*Thank you*
	MN	Thank for asking me to contribute; I think this is a good guideline. The fantastic improvement of the effective systemic therapies has perhaps been underemphasised, since we are now seeing 5- and 10-year survivals with metastatic disease compared with an average of 8 months' median survival	*Thank you for your comment.*

		with older fashioned drugs.	
	RCP&S	We would like to express our general support for the guidance but feel section 5.1 should be more explicit, to avoid the unintended impression that there must be a 5 mm margin of clearance.	*A change to paragraph 4 of section 5.1 has been added for clarity. Surgical margins have also been adopted from NICE guidelines.*
Section 1			
1.1	LN	Is reference '1' at end of paragraph one correct?	*This reference is correct.*
	RR	1st p'graph wording of 4th sentence 'whilst incidence rates have been rising' may need reworded as it is difficult to understand. 2nd p'graph - remove both , in 1st sentence. 2nd p'graph - 2nd sentence consider substituting "support" with "promote".	*Wording has been changed for clarity.* *The first comma was removed.* *Wording changed*
	AA	March 2016 Letter in response to the request for me to comment on the proposed SIGN guideline on cutaneous melanoma. Thank you for asking me to comment on the first draft of the revised up-dated SIGN guideline on cutaneous melanoma. I have studied the draft in detail and my initial response is of disappointment. I think there are opportunities to emphasise key areas to optimise clinical quality in this extremely important area. I propose going through the guideline making comments chronologically. Page 1 - Updating the Evidence As is the norm for the SIGN guidelines, the most recent evidence should be represented – mostly within the last 10 years – many of the references throughout the guideline are historical and so this is not optimum and does not reflect this initial intent. I will make specific references to these points as I go.	*This guideline update was selective. The development group decided at the beginning of the process which areas of the guideline should be updated, rather than update the whole guideline. A balance needs to be struck where areas of the guideline which rely on older evidence are assessed and a decision made on whether reviewing the evidence is likely to result in a change to any recommendations or messages the guideline conveys.*
	RC	Yes, need updated.	*Thank you for your comment*
	AM	No issues.	*Thank you for your comment*
	VD	No comment.	*Thank you for your comment*
	MM	Unable to find information relating to mortality rates in reference 1, may well be included but not in the primary	*Mortality data in supplementary tables of ref 1.*

		document as far as I can see.	
	RD	No comments.	*Thank you for your comment*
	CF	No comment, other than to recognise value and work behind this guideline.	*Thank you for your comment*
	JV	Well stated in the document.	*Thank you for your comment*
	AD	Agreed.	*Thank you for your comment*
	CM	Relevant guideline for dermatologists, GPs and other Heath Care Professionals.	*Thank you for your comment*
	RCPE	The authors of this guideline have taken into account recent NICE guidance (June 2015) on melanoma and included the same tables in relevant sections – leading to little risk of divergence of practice within UK.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
1.1.1	MC	Why was the original supporting evidence not re-appraised? This suggests that this evidence is still valid and applies to this condition.	*This guideline update was selective. The development group decided at the beginning of the process which areas of the guideline should be updated, rather than update the whole guideline. A balance needs to be struck where areas of the guideline which rely on older evidence are assessed and a decision made on whether reviewing the evidence is likely to result in a change to any recommendations or messages the guideline conveys.*
	CP	I have a concern that this guideline has left areas verbatim from SIGN 72 that are now significantly out of date and should have been updated. I refer for instance to 4.2: Clinical Diagnosis and 6.2: Laboratory Investigations.	*This guideline update was selective. The development group decided at the beginning of the process which areas of the guideline should be updated, rather than update the whole guideline. A balance needs to be struck where areas of the guideline which rely on older evidence are assessed and a decision made on whether reviewing the evidence is likely to result in a change to any recommendations or messages the guideline conveys. Section 4.2 was not updated. Only the wording of the recommendation was updated at 6.2 but the evidence was not reviewed.*
	RC	Most helpful.	*Thank you for your comment*
	AM	No issues.	*Thank you for your comment*

	VD	Clear.	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	RD	No comments.	*Thank you for your comment*
	CF	The partial approach to update taken with this guideline weakens the SIGN process, and reduces the potency of SIGN advice. Many of those sections which have not been updated now have out of date references and advice which is not consistent with other international guidelines. This will be regarded by international observers as odd, and by extension unreliable. This is a real pity as those areas which have been updated have produced good up to date recommendations.	*Partial updating is part of SIGN methodology and is detailed in SIGN 50. This methodology has been used regularly for a number of years.*
	JV	Entirely appropriate.	*Thank you for your comment*
	AD	Agreed.	*Thank you for your comment*
	CM	Appropriate.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
1.2.1	RC	These have been addressed.	*Thank you for your comment*
	AM	No issues.	*Thank you for your comment*
	VD	Uncontroversial.	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	I agree.	*Thank you for your comment*
	AD	These are clear.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
1.2.2	CP	No comment for 1.2.2, but what about 1.2.3?? We need to be allowed to comment on Summary of Updates, by Section because this is the main omission from this guideline...	*See comments in general comments section*
	RC	Difficult should cover all core members of MDT as well as GP's and patients if we can as the Pt Info leaflet. Also support groups and palliative care.	*Added further interested parties*
	AM	No issues.	*Thank you for your comment*

	VD	Satisfactory.	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	RD	No comments apart from that very ambitious (aiming to be helpful to a very wide target audience).	*Thank you for your comment*
	JV	Comprehensive.	*Thank you for your comment*
	AD	This should be expanded to include Radiologists and Nuclear Medicine Physicians.	*Added further interested parties*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
Section 2			
General	AM	No issues.	*Thank you for your comment*
	CF	Recommendations consistent with guideline.	*Thank you for your comment*
	JV	I agree with all the key recommendations.	*Thank you for your comment*
	CM	Agreed.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
2.1	LN	Why are the recommendations different to NICE 2015 NG14? NICE recommends considering SLNB for melanomas more than 1mm stage IB-IIC but SIGN advises greater or equal to 1mm for the same stage?	*See comment responses in chapter 5. The recommendation has been changed to align with NICE.*
	AA	Management of Regional Lymph nodes. I think it is important to state that sentinel lymph node biopsy has no proven therapeutic value.	*The GDG feel the wording stating this, while not prominent, is sufficient.*
	CP	Agreed	*Thank you for your comment*
	RC	Worried about the resource implication of this with SLNB. Potential for large numbers with limited evidence of benefit.	*The GDG feel the wording on SLNB in chapter 5 is sufficient.*
	VD	Would be worth explicitly stating that the information should be given then reasonable time allowed for patient and carer decision making. The pros and cons in this setting are difficult.	*The GDG feel that the pros and cons stated in chapter 5 are sufficient.*
	MM	No comment, agree with guideline. A change from previous guideline in light	*Thank you for your comment.*

		of new evidence.	
	RD	I am going through the guideline in order, so hopefully will find more justification for the recommendation regarding SLNB later. I initially misread this as a strong recommendation (because of the word "should") but on re-reading understand it is not to be considered as such a strong recommendation (the "considered" weakening the recommendation). Nevertheless, as far as a negative can be "proved" I think that the study by Morone et al. (NEJM, 2014) has shown that SLNB is of no value, so I am uncomfortable with it even being advised as a "to be considered recommendation" as this seems to flt a bit in the face of the evidence. I realise that the recommendation relates to staging, but surely a staging intervention should only be recommended if it adds something useful to patient care (such as improving survival). I have sometimes had difficulty helping patients in deciding whether to have SLNB or not, so I estimated likelihood ratios for death if SLNB positive or negative (based on the Morton et al study) and have tended to use the Cochran model (as in the previous SIGN guideline) to estimate pre-test risks. So, for a 40 year old man, 1.3 mm Breslow thickness, non-ulcerated melanoma on arm he has an estimated 9% chance of dying of his melanoma within 5 years. If he has a positive SLN, this rises to a 22% chance of dying within 5 years. If SLN is negative he has a 7% chance of dying of melanoma within 5 years. Expressed more positively, he can be told that he has a 90% chance of being alive in 5 years. If he has SLN biopsy and it is positive he still has a 78% chance of being alive in 5 years. If he has SLN biopsy and it is negative he has a 93% chance of still being alive in 5 years.For most people in this situation the extra information from SLNB probably does not help (certainly not enough to warrant the morbidity of 'completion lymphadenectomy', which is often done if SLNB is positive). Or for a 65 year old man, 8 mm Breslow thickness, non-ulcerated melanoma on back, he has (using Cochran model) an estimated 84% chance of dying of his melanoma within 5 years. If he has a	*Thank you for your comments. The guideline group are happy with current wording of recommendations.* *The GLG acknowledge that although performing SLNB has no impact on prognosis it is still reasonable to consider using it as a staging technique.* *The GDG acknowledge the difficulties in assessing suitability for SLNB but we did not assess the evidence of the use of additional prognostic models*

		positive SLN, this rises to a 96% chance of dying within 5 years. If SLN is negative he still has a 79% chance of dying of melanoma within 5 years. Expressed differently, he can be told that he has a 16% chance of being alive in 5 years; but if he has SLNB and it is positive he has a 4% chance of being alive in 5 years and if f he has SLNB and it is negative he has a 21% chance of still being alive in 5 years. Possibly, with new treatments offering a bit more hope some would want to know, but I think for most again SLNB does not really add to the knowledge that the prognosis is very poor. I think (and again this may be covered later in the guideline, as I am going through it in sequence) "Patients should be given detailed verbal and written information regarding the possible advantages and disadvantages of the SLNB procedure to allow them to make an informed decision." is perhaps not enough - I think it would be reasonable to suggest that more taylored information be given and it should perhaps be recommended that it be explicitly stated that, currently, SLNB is only a test that can give prognostic information and there is good evidence that it does NOT improve prognosis (although, reassuringly [given the concerns that disrupting immune responses to melanoma by SLNB might worsen prognosis] it also does not seem to make the prognosis worse).	*Information on disadvantages of SLNB in table 8 states "There is no good evidence that people who have the operation live longer than people who do not have it"*
	MH	"SLNB should be considered as a staging technique in patients with a primary melanoma ≥1 mm thick in patients with IB-IIC melanoma." This statement is slightly confusing as patients with melanoma less than 1mm thick may also be included in some circumstances.	*Wording has been amended to better reflect NICE 2015 guideline recommendations.*
	CF	Agree – reasonable phrasing.	*Thank you for your comment*
	JV	Ditto.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
2.2	LN	Recently the tendency at our MDM has been to carry out staging CT for exceptionally thick melanomas that may	*See response to comments on this recommendation in chapter 6*

		not necessarily have been ulcerated. If a melanoma is very, very thick (for example greater than 10mm) but non ulcerated (T4a) - does this mean staging CT is not indicated?	
	AA	Imaging Techniques I suggest a statement regarding the use of PET CT scan here would be helpful. I think this is covered in the body of the document but I think it should also be a stand-alone statement in this summary section.	*The GPP on PET CT has now been included as a key recommendation.*
	CP	Agreed	*Thank you for your comment*
	RC	Clear	*Thank you for your comment*
	VD	It is not clear to me why brain is not included in staging as an unsuspected positive finding would certainly influence decision making.	*See response to comments on this recommendation in chapter 6*
	MM	No comment, agree with guideline. A very useful statement in view of difference in practice with regards scanning melanoma patients.	*Thank you for your comment*
	CF	Agree.	*Thank you for your comment*
	JV	Ditto.	*Thank you for your comment*
	AD	These are clear. It might be helpful to include "FDG PET/CT is not of proven value in the initial staging of melanoma and is not recommended".	*Wording in chapter 6 text altered taking account of this comment. The wording of the recommendation remains unchanged.*
	KHI	I can understand why CT scanning of the head is not included in the staging CT (Key Recommendations 2.2, page 5) due to the risk:benefit ratio (described in section 8.8.2, Table 11, pages 28-29). However, neither sections 2.2 nor 6.1.2 (page 25) (Identifying brain metastases) explicitly state that a CT of the head +/- contrast should be performed on any patient with persistent headache, new seizures or neurological deficit. I think that this should be mentioned somewhere in the guideline, even though it may seem obvious. CT scanning of the head should also be included in any patient with metastases elsewhere, as melanoma is the third commonest metastasis seen in the brain (accounting for 12-20% of all metastases in the brain) but are actually found in 36-54% of metastatic melanoma patients at autopsy	*The key recommendation has now been removed from this section. The group felt this was not required in chapter 6.* *CT head is now recommended as part of staging investigations in patients with stage IIC malnoma or above.*

		and in up to 73% of patients who die from disseminated cutaneous melanoma (de la Monte et al, 1983; Sampson et al, 1998) – i.e. we are under-diagnosing them. Ref 1: Staudt et al., Determinants of survival in patients with brain metastases from cutaneous melanoma. Br J Cancer (2010) Apr 13; 102(8): 1213-1218 – which also states that in a series of 265 patients, 64% were asymptomatic and diagnosed brain mets during surveillance scans. A favourable independent prognostic factor was administered therapy (neurosurgery or SRS vs other (P<0.002) Ref 2:Donohoe et al (2010) Up To Date (web address: http://www.uptodate.com/contents/imaging-studies-in-melanoma.	
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok but what about PET-CT whihc is more sensitive in picking up distant disease thus preculsing resection where inappropriate?	*See chapter 6 GPP at 6.1.1*
2.3	CP	This will soon be out of date.	*Thank you for your comment*
	VD	Given this is a rapidly changing field should there be mention of made of the future introduction of other options?	*Chapter 9 covers the development of new therapies at 9.1 and the statement at the end of 7.2*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	CF	Agree.	*Thank you for your comment*
	JV	I agree.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	BRAF inhibitor therapy in BRAF mutant advanced disease patients is generally best as first line in those with CNS disease, rapidly progressive tumours and/or elevated LDH. Otherwise, the standard first line therapy even in BRAF mutant patients is immunotherapy. Agree immunotherapy is standard first line in BRAF wild type patients. I do not have a reference, but this is 'best practice'.	*We can only make recommendations which concur with SMC advice. No change proposed.*
Section 3			
General	AA	Prevention, surveillance and genetics. I think this part is well written.	*Thank you for your comment*

3.1	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Certainly.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
3.2	CP	There is significantly more known/published now about sunbeds and risk of skin cancer. This section is out of date. A missed opportunity!	*See comment response in general section*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	RD	For the next SIGN revision I would consider the new information regarding sunbeds and some drugs.	*See CP comment response in general section*
	CF	More information regarding sunbeds available.	*See CP comment response in general section*
	JV	I have no problem with any of this section.	*Thank you for your comment*
	BAD	Need stronger statement on sunbed use as risk factor for melanoma.	*See CP comment response in general section*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
3.3	AA	Table 1: Prevention of Melanoma. The 4th bullet point I think one should reword to '(SPF) of 30 and 4 or 5 UVA stars' rather than "or" as, in my recollection, they are 2 separate entities protecting against UVB or UVA so both should be protected.	*Changes made as suggested*
	CP	Delighted to see that you recommend minimum SPF 30.	*Thank you for your comment*
	VD	Given the high profile of vitamin D I wonder about introduction of an explicit comment on availability of evidence of any relationship between low vitamin D and high levels of sun avoidance.	*This section was not within the remit of the update.*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	RD	Perhaps, worth considering this section for the future. Some of the guidance is rather vaguely worded and could even be interpreted, for example, as saying that everyone should wear a topical sunscreen (the irst point emphasising clothing is good though, althou even	*Thank you for your comment*

		better, I think, if discussing sunlight exposure reduction measures, would be to systematically cover all 4 main areas (behavioural, environmental, clothing sunscreen).	
	RR	SPF 30 and 4 or 5 star UVA protection (not SPF 30 or 4 or 5 UVA star protection).	*Changes made as suggested.*
	JV	I agree with this.	*Thank you for your comment*
	BAD	Intense sunlight is not just around midday and should advise avoidance at least 11am-3pm.	*Changes made as suggested*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
3.3.1	CP	This section is way out of date now and should have been updated. In terms of effectiveness, the Skin Cancer Prevention Committee for the British Association of Dermatologists believes that the use of brochures and leaflets has been largely superseded by use of Apps and other on-line devices.	*This section was not within the remit of the update.* *Recommendation wording altered and additional statement added on up to date resources.*
	VD	Perhaps a sentence to acknowledge availability of apps, web sites, etc, nowadays rather than leaflets only.	*See CP comment response above*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	RD	Perhaps, worth considering this section for the future. I agree entirely that leaflets should not be alarmist. Some currently around ones are, and are also no evidence-based. One even implies that sunburn in childhood causes melanoma which is untrue (a. people diagnosed with melanoma recall severe childhood sunburns more than do people not diagnosed with melanoma and b. even if people with melanoma have genuinely had more severe childhood sunburns than others this might just be because people with the type of skin prone to bad sunburn are more prone to melanoma than because sunburn actually causes melanoma). I particularly dislike this information sheet (I cannot recall who produces it) because I have seen people with newly diagnosed melanoma really upset about it – it implies that people themselves, or their parents, have caused their melanomas.	*This section was not within the remit of the update.*

	CF	This is an example where publication of this section, in a way that has not been updated, will risk the guideline being widely disregarded.	*Thank you for your comment*
	JV	No problem with any of this.	*Thank you for your comment*
	BAD	There should be greater emphasis and recommendations made regarding education programs for schools.	*This section was not within the remit of the update.*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
3.4	BAD	The recommendation that healthcare professionals and member of the public should be aware of risk factors for melanoma needs further expansion on how this is to be achieved.	*This section was not within the remit of the update.*
3.4.1	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	I agree.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	There was a paper published this year indicating that 5 moles or more on the right arm conferred a higher risk; not sure where peer reviewed/published or if worth adding to this section?	*Evidence not reviewed for this section*
3.4.2	KH	The incidence in younger individuals is increasing due to indoor tanning. This is based on a population based case–control study that evaluated the role of indoor tanning in the development of melanoma in younger patients (defined as those between the ages of 25 and 50)1. Indoor tanning was strongly associated with melanoma in women younger than 30 years (OR, 6.0), with 61/63 cases in this age range reporting a history of indoor tanning. Associations between indoor tanning and melanoma were less clear in men. In both cases and controls, a lower proportion of men reported less indoor tanning (44.3%) compared with women (78.2%). Pregnancy-associated melanoma ((PAMM), diagnosed with melanoma while pregnant or within 1 year following delivery) has a higher rate of metastasis, recurrence, and death compared with non-pregnant patients. This retrospective study of 462 female	*This section and chapter 10 was not within the remit of the update.*

		patients <50 years old (mean age, 34.7) diagnosed with melanoma between 1988 and 2012 assessed risk factors and outcomes in those followed for more than 2 years2. Patients in the youngest age category (<19 years) were less likely to have invasive melanoma than those in other age categories. The 40- to 49-year age group had the higher recurrence rates, metastatic disease, positive sentinel node status, and death rates compared with the other age groups. Pregnancy-associated melanoma (PAMM) was diagnosed in 41 patients. Patients with PAMM had a 9.2 increase in the odds of recurrence (based on 11 recurrences total in the study), a 6.7 increase in the odds of metastasis, and a 5.1 increase in the odds of mortality compared with non-pregnant patients. These findings suggest that routine skin exams during and after pregnancy should be recommended. Total body nevus count remains an important risk factor for melanoma and can be predictive of patients at higher risk3,4,5. Total body nevi can be estimated quickly by counting the nevi on one arm to identify patients at higher risk of melanoma. This study 6 suggests younger patients with more than 5 AN should receive appropriate counselling and education regarding their risk for melanoma. A multi-centre study surveyed 566 patients with newly diagnosed melanoma to better understand the relationship between total nevi (TN) and atypical nevi (AN) and tumour thickness. The majority of patients had 0 to 20 TN (66.4% patients) and no AN (73.3% patients). The mean melanoma thickness was 2.33 mm in patients with 0 to 20 TN, compared with a mean melanoma thickness of 1.12 mm in patients with more than 50 TN in crude analysis. In multivariable logistic regression, the presence of more than 50 TN was associated with a reduced risk for thick melanoma in patients younger than 60 years (OR, 0.32 age-adjusted; OR, 0.35 fully adjusted). There was an association between the presence of more than 5 AN and thicker melanoma (OR, 2.43 age-adjusted; OR, 2.89 fully adjusted). The authors of this cohort study7 of 3694 female twins evaluated the body site	

		most predictive of total body nevus count. They found that the total body nevus count can be accurately estimated using the arm as a proxy and that women with 11 or more nevi on the right arm were nine times more likely to have more than 100 total nevi. The right and left arm correlation coefficients were 0.50 and 0.51, respectively. The authors of this study8 suggest that higher rate of melanomas and greater risk of death from melanoma are consistent with the hypothesis that immunosuppression allows melanoma to evade normal immune responses and cause worse outcomes. This study showed that pre-transplant melanoma is associated with increased melanoma-specific mortality, overall mortality, and incident melanoma after transplant9. They evaluated the outcomes of transplant recipients with a history of pre-transplant melanoma. There were 336 out of 185,039 (0.18%) US transplant recipients with pre-transplant melanoma; 5 had regional metastases and 2 had distant metastases. Pre-transplant melanoma patients had significantly increased risk of melanoma-specific mortality (27-fold increased risk; absolute risk difference, 1.17% and 2.97% at 5 and 10 years, respectively), overall mortality, and incident melanoma after transplant.	*Immunosupression and melanoma is covered in 7.3*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Agree with this.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
3.5	LN	Should be a space on first line between '1-2% of'. Last line paragraph 2 should be 'taking a family history'.	*Changes made as suggested*
	CP	Again, out of date. There are new GWAS studies that are not mentioned and we know much more about the 'at risk' genetic groups.	*A systematic review based on the original key question was carried out.*
	VD	For the recommendation need clarity of what type of family members. Also need comment about what would be outcome of a positve test in terms of	*Added 'first degree' to recommendation* *This would require a further key question rather than a new search*

		lifestyle / follow up etc.	*based on the original key question. No action required.* *Unfortunetaly recommendations regarding patients with positive genetic test would require further key questions not within the scope of the current guideline update.*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	MP	The phrasing of paragraph 2 of this section is slightly confusing. In some families CDKN2A mutations can be associated with pancreatic cancer but in others the mutation does not segregate with the pancreatic cancer. I would therefore phrase the second sentence second paragraph to say "Mutations in CDKN2A are also associated with a risk of pancreatic cancer in some families and therefore a family history of pancreatic cancer and melanoma may increase the likelihood of identifying a CDKN2A mutation." In the R paragraph I think it is important to state that any genetic testing be performed on an affected individual so "Genetic testing for CDKN2A can be offered to an affected individual who has a first degree relative affected by melanoma or pancreatic cancer"	*Changes made as suggested*
	CF	Out of date.	*A systematic review based on the original key question was carried out.*
	JV	This is our practice too.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	paragraph 2: is it Making a family history or Taking a FH?	*Thank you for your comment. This paragraph has since been reworded.*
Section 4			
General	AA	This is arguably the most important part of the whole document and I am disappointed it is not more detailed and with more recent seminal papers summarised and referenced.	*Thank you for your comment. Sections 4.1.5 & 4.1.6 are new, 4.5 & 4.7.8 have minor updates, 4.6.1, 4.7, 4.7.4, 4.7.6, 4.7.9 & 4.9 have been updated and 4.7.1 & 4.10 have been completely revised. The rest of the chapter remains unchanged.*
	MM	No reference for these comments – site.	*Sections 4.1.5 & 4.1.6 are additional statements based on new evidence. The chapter sections up to and including 4.1.4 are taken verbatim from SIGN 72 and have no*

			references in the original text.
	JV	I agree with all of this.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	ok; good that unknown primary is mentioned (although not quaantified).	*Thank you for your comment*
4.1	AA	I think it would be helpful to have a paragraph on hypomelanotic melanoma – this is especially relevant in Scotland with a large type 1 skin photo type in the population who tend to produce pink or minimally pigmented melanoma which may be missed as it often does not conform to the ABCDE screening criteria.	*Thank you for your comment. This section has been reworded at the introduction.*
	CP	The Cancer Genome Atlas (ICGA) network have published a definitive melanoma genome classification (Chin L, et al. Cell. 2015 Jun 18;161(7):1681-96) that is hugely important and subdivides melanoma into 4 genetic categories or sub-types. These will define treatment strategies as this classification identifies the biological drivers of the disease (eg. BRAF, NRAS, NF1 or Triple Wild type). This new and important knowledge should be included in this guideline.	*This reference is included in the intro to chapter 9.*
	MM	Include reference for incidence of types. SCAN data 2014/2015 shows SSMM>lentigo MM>Nodular	*This was not referenced in the original guideline and the text appears verbatim from that version.*
	CF	Need now to consider melanoma subtypes in term of the 4 basic genotypes- BRAF, NF1, NRAS or wild typex3.	*See intro to chapter 9*
	JV	All standard.	*Thank you for your comment*
	BAD	Need to include molecular subtypes of melanoma.	*Intro chap 9*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.1.1	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	All fine.	*Thank you for your comment*
	JV	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*

4.1.2	MM	See note above.	*Thank you for your comment*
	JV	All fine.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.1.3	RC	Agree more difficult to be dogmatic re. marine in large areas on HN.	*Thank you for your comment*
	LN	'lentigo maligna' should be lower case in second last line	*Changes made as suggested*
	MM	See note above.	*Thank you for your comment*
	JV	Agree.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.1.4	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Fine.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.1.5	LN	In the last sentence '..wider margins should be considered..' does this mean the wider local excsion margins should be greater than for non DM? What should the margins be? Is the recommended managemet of this subtype (in terms of SLNB) the same as other subtypes?	*Change made to last sentence for clarity given lack of evidence to support specific recommendations for margins for SLNB.*
	VD	Should mention this is uncommon.	*Thank you for your comment. This section has been reworded.*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Fine.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.1.6	LN	Line 2 should this be 'hypermelanotic' rather than 'hypomelanotic'? Should these melanomas be treated the same as other types of melanoma?	*Thank you for your comment. This section has been reworded.* *Yes, noted and small change made to wording.*

			It is acknowledged that this section focuses on clinical features rather than specific treatment recommendations.
	KH	This is a systematic review10 and meta-analysis of animal-type melanoma (n=190 cases); 7.9% (n=15) loco-regional recurrence, 3.2% of cases had distant metastases (n=6) and 2.6% died (n=5). Consider discussing atypical spitzoid naevi at the specialist skin cancer multidisciplinary team meeting11.	*Inclusion would not change content of section.* *Evidence for this section was not reviewed.*
	VD	Should mention this is very uncommon.	*Thank you for your comment. This section has been reworded*
	JV	Unusual but well recognised; relatively common in 'grey' horses.	*Thank you for your comment. This section has been reworded*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.2			*The GDG acknowledge that not including KQs on dermoscopy in this update is a weakness. The evidence was not reviewed for this section so this makes it difficult to include the suggested changes and issues raised in the comments below. Some issues have been addressed but changes were limited in the this section to address the issues the group thought could be addressed without adding further delay to the process by carrying out further evidence review after peer review.*
	AA	4.2 Clinical Diagnosis. Considerable weight should be put on the history and risk factors that the patient presents with. This should be emphasised in my view. Also it is worth stating that a proportion of melanomas will be picked up during routine follow up in a Secondary Care clinic (or during an incidental examination in GP). I do think it is important to have a paragraph discussing the so-called melanoma incognito (see attached paper) and micro-melanoma, both of which can defy clinical detection unless there is a high index of suspicion and an experienced skin cancer diagnostician.	*In the intro to the chapter it acknowledges the importance of all health professionals being aware of the signs of melanoma and the diagnostic difficulty associated with atypical presentations such as non-pigmented melanoma.*

		In the middle paragraph it should read 'accuracy of diagnosis does vary' (rather than may vary). There are many papers that have found that dermatologists are the best at diagnosing skin lesions (which one would expect due to their training and day-to-day clinical experience). This should be stated in the guideline. Indeed the gold standard would be a dermatologist with a special interest in skin cancer who is also an expert in dermoscopy. 'High magnification' - this is not necessary (10x magnification is most often used with the commonest dermoscopes used in practice) and the preferred term is dermoscopy as used by the International Dermoscopy Society, the biggest organisation with all the main research contributors. Dermoscopy has been established now for over 10 years and most dermatologists use this as a diagnostic aid (see attached paper). I don't know how the group chose the dermoscopy papers that they reference but I suggest 2 much more recent and evidence-based papers which should be read and referenced. The gold standard for diagnosis of any skin lesion is a trained expert who would tend to be a dermatologist and dermoscopy is unequivocally useful and that is why it is recommended in both the recently updated NICE guideline and the excellent Australian and New Zealand guideline on melanoma (see attached papers). NICE melanoma update - "Assessing melanoma • Assess all pigmented skin lesions that are referred for assessment or identified during follow-up using dermoscopy carried out by healthcare professionals trained in this technique". Australasian melanoma guideline - "Training and utilisation of dermoscopy is recommended for clinicians routinely examining pigmented skin lesions evidence level A". In my view, the SIGN guideline should follow the suggestions made by these 2 guidelines with at least "good clinical practice" level recommendations in the use of dermoscopy. There are recent studies looking at	*The GDG think current "may vary" is acceptable.* *The GDG felt that stating that "dermatologists are the best at diagnosing skin lesions" could not be supported without formally reviewing the evidence. No change to wording.* *GPP added to reflect NICE GL. Included NICE recommendation on dermoscopy*

		reflective confocal microscopy which would have been helpful to look at and summarise. The excellent paper by Argenziano et al which I have already mentioned above emphasises the need for clinicodermascopic correlation to minimise the chance of missing melanoma – this is a key “good clinical practice” point and would be helpful to reference. It is obvious that imaging modalities like ultrasound and MRI would be not sensitive enough and so it is not that “this specialist equipment is available”, it is that it is going to be unhelpful in clinical practice. This is in contrast to the possible benefit of much more sensitive imaging like confocal microscopy. It is also worth stating that dermoscopy also helps to distinguish benign lesions from malignant lesions therefore avoids the unnecessary excision benign skin lesions eg. melanocytic naevi. It can be used to follow up lesions, looking for any evolution which could then point towards excision. Menzies published an excellent recent review of this important topic - Dermatol Clin. 2013 Oct;31(4):521-4, vii. doi: 10.1016/j.det.2013.06.002. Epub 2013 Jul 23. Evidence-based dermoscopy. Menzies SW1. Author information • 1Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050,Australia; Discipline of Dermatology, Sydney Medical School, The University of Sydney, NSW 2006, Australia. Electronic address: scott.menzies@sswahs.nsw.gov.au. Abstract Dermoscopy has been shown in meta-analyses to improve the diagnostic accuracy of melanoma unequivocally compared with naked eye examination and to reduce excision rates of benign melanocytic lesions in clinical trials. Sequential digital dermoscopy imaging (SDDI) allows the detection of dermoscopic featureless melanoma. When used in high-risk individuals or on individual suspicious melanocytic lesions, it has a gross impact for detecting melanoma in clinical practice, with a range of 34% to 61% of melanomas	*Some changes made to 4.2 wording.*

		detected exclusively using SDDI in these patients. Furthermore, SDDI has been shown to reduce the excision of benign lesions when used in combination with dermoscopy. Good practice point - clinicians should keep a note of their “numbers needed to treat” i.e. benign:malignant / severely dysplastic or in situ melanoma ratio as a marker of good clinical practice and diagnostic accuracy. This is a good clinical audit area for clinicians involved in diagnosis of skin cancer. It would be considered in my view (and as stated in other guidelines) unacceptable in 2016 to simply accept naked-eye examination of skin lesions “in a good light”. Also worth mentioning the gold standard referral – Thorough history including risk factors, benefit of teledermatology – attached macroscopic and dermoscopic ephotographs – then triaged by an expert in skin cancer Dx / dermoscopy to facilitate clinically indicated triage priority – this reflects recent “Detect cancer early” funding which in Tayside we plan to develop exactly this – with training of GPs in dermoscopy and help in facilitating dermoscopic images as part of e-referral.	
	KH	The ugly duckling helps to identify melanomas, because naevi in the same individual tend to resemble one another and melanomas often do not fit the individual’s naevus pattern12. This study was to compare the sensitivity, specificity, and diagnostic accuracy rates of the ABCD rule of dermoscopy, the seven-point checklist, the three-point checklist, and the CASH algorithm in the diagnosis and dermoscopic evaluation of melanocytic lesions on the hairy skin13. The ABCD rule of dermoscopy showed sensitivity of 91.6%, specificity of 60.4%, and diagnostic accuracy of 66.9%. The seven-point checklist showed sensitivity, specificity, and diagnostic accuracy of 87.5, 65.9, and 70.4%, respectively; the three-point checklist 79.1, 62.6, 66%; and the CASH algorithm 91.6, 64.8, and 70.4%, respectively. “Without a Total Body Skin Examination Would Miss One in Three Melanomas”. This paper14 was based on two prospective studies of over 1,800 sequential patients in two UK centres it shows that over one third of	*This section was not within the remit of the update.*

		melanomas detected in secondary care are found as incidental lesions, in patients referred for assessment of other potential skin cancers.	
	CP	There are serious omissions / inadequacies in this section. The use of dermoscopy has become common place and you MUST update this part of the guideline to include the up to date evidence in this area. To be using references from 1995 to 1999 (references 46 - 53) is inexcusable when there is now better evidence available. The Recommendation to use the ABCDE checklist is also out of date. Whilst these are useful things for patients to consider when undertaking mole surveillance, the advice should be to look for progressive skin lesions that are clearly changing over weeks (see GP Toolkit developed by the British Association of Dermatologists together with doctors.net and CRUK.)	*See AA comment response above* *GDG disagree. ABCDE checklist still valid. E= evolution (of lesions).*
	VD	There needs to be inclusion of diagnosis of nodular +/- non pigmented lesions and those around nails.	*This section was not within the remit of the update.*
	MM	Recent publication from Georgia group detailing alternative method of examining for melanoma, ?should be included in this section Stuart M. Goldsmith, MD,a and Armand B. Cognetta, Jr, MDb Time to move forward after the report of the AAD Task Force for the ABCDEs of Melanoma JAAD Oct 2015 vol 73 issue 4 pe149 Georgia Society of Dermatology and Dermatologic Surgery. Available from: URL: gaderm.org. Accessed March 24, 2015.	*This section was not within the remit of the update.*
	RD	It is a pity that this section could not be updated particularly given all the newer evidence regarding hand-held dermoscopy. Also, it is probably time to de-emphasise the ABCDE criteria as particularly the D can be counter-productive (we do not want to only be diagnosing the wider diameter melanomas).	*This section was not within the remit of the update.*
	CF	Dermoscopy is now practised by >95% of UK dermatologists and is recommended in all major updated international guidelines. It would be better not to publish non-updated areas of this guideline than to recycle dated	*This section was not within the remit of the update.*

		advice ABCDE checklist advice is dated.	
	BAD	Need major update on dermoscopy. The increased role of dermoscopy in routine clinical practice to help in the diagnosis of melanoma (and to diagnose non-melanoma skin cancer and benign skin lesions) needs to be emphasized and recommended so the best outcomes are achieved. There are many recent key papers published in dermoscopy since 2003, which the SIGN group appear to have been omitted. In addition, need to highlight importance of a changing progressive skin lesion – i.e. behaviour of the skin lesion.	*See AA and CP comments above*
	JV	No update needed.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.3	MM	No comment, agree with guideline.	*Thank you for your comment*
	CF	Again, useful recent literature omitted; weakens guideline.	*This section was not within the remit of the update.*
	BAD	The recommendation Health professionals should be encouraged to examine patients' skin during other clinical examinations, needs rewording - with increasing time constraints, do we really have evidence to support this? We also have particular concern about anything that puts an onus on dr's dermatologists or others to carry out a general skin examination for skin cancer at routine consultation. The time constraints on dealing with the referral issue let alone anything else does not allow this, especially considering specialty shortfalls in dermatology and primary care. Possibly in an ideal world this would be the case but that is not what we have and would produce unsustainable/ unaffordable effects on the ability to deal with patients generally.	*This section was not within the remit of the update.* *Not removed as GDG feel this is still valid.*
	JV	Ditto.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.4	AA	It would be helpful to discuss evidence (or lack of) of patient self-examination in detecting melanoma. Also patients can	*This section was not within the remit of the update.*

		be encouraged to photograph skin lesions themselves and use this as an aid looking for any change.	
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Ditto.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.5	RR	Having discussed this with several colleagues who perform dermatological surgery we consider longitudinal or oblique excision over joints preferable to transverse excision.	*Thank you for your comment. This section has been reworded.*
	AA	The statement that excision with a 2mm margin "allows direct wound closure" is unhelpful as the type of defect reconstruction will be determined by the nature of the defect which will vary enormously according to the size and anatomical location so I would remove this unhelpful comment. Lentigo maligna and lentigo maligna melanoma merit a separate stand-alone paragraph as they bring with them many different challenges both diagnostically and therapeutically. Dermoscopy can be especially helpful as an aid to the diagnosis of pigmented skin macules with good evidence of discriminatory dermascopic features which can be an aid to choosing the most representative parts to biopsy (see attached paper). Recommendation - the term 'full thickness' is vague. It would be better to be more specific to say 'diagnostic biopsy either scalpel incisional or punch(es), including epidermis, dermis and at least superficial subcutis is advised'. I think it would have been helpful to have a section on MDT and specifically what type of cases should be discussed (aim for the best possible scenario to get best possible patient outcomes – may attract funding if in a guideline). Ideally all cases of melanoma in situ (including LM) and invasive melanoma as well as difficult borderline lesions like Spitz naevi and highly dysplastic naevi.	*Thank you for your comment. This section has been reworded* *LM and LMM are covered in section 5.1 para 4* *Thank you for your comment. This section has been reworded* *Noted but not required in terms of biopsy.* *GPP added to beginning of chapter.*
	KH	When carrying out a biopsy of a suspicious nail lesion, it is worth highlighting the nail matrix should be	*This was not part of the key question.*

		sampled15.	
	RC	Clear message.	*Thank you for your comment*
	MM	No comment, agree with guideline. Re-iterate that as per QPI guideline and scottish skin cancer referral guidelines a GP should not excise a suspicious pigmented lesion.	*Thank you for your comment.*
	JV	Unchanged.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
	MH	GPs should refer urgently all patients in whom melanoma is a strong possibility rather than carry out a biopsy in primary care". Whilst this recommendation exits in current NICE guidance it follows no logical pathway. GPs are expected to undertake clinical diagnosis which represents the most demanding aspect of melanoma management but not primary excision, the most simple aspect (excision with a 2 mm margin). The former takes time, training and with dermoscopy expensive equipment and for no financial return. The latter provides the financial incentive for the former as well as increasing GP engagement into diagnostic accuracy and the development of locality expertise. Our soon to be published (May BJGP) paper questions the evidence that suggests GPwSIs are any less skilled than secondary care at diagnostic accuracy and surgical skill. Melanoma is the most simple skin cancer to treat surgically in the first instance. The real skill is in the diagnosis. (Dr Jonathan Botting).	*Noted, however common clinical practice still supports GPP*
4.6.1	VD	Helpful.	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	CF	Overall, fairly happy with path section.	*Thank you for your comment*
	JV	Agree.	*Thank you for your comment*
	SD	In the selection of tissue block section, it states on one line that cruciate blocks should not be selected (very definitive) but on the next line, states cruciate blocks can be used in very large LM excisions. It might be better to state on	*Thank you for your comment. This section has been reworded*

		that first line, cruciate blocks should not routinely be selected unless considered for a LM excision and then on the next line, can state cruciate blocks can be used for large LM excisions.	
	MN	Ok.	*Thank you for your comment*
4.7	LN	The first 3 lines would benefit from rewording as it's repetitive.	*Thank you for your comment. This section has been reworded*
	RC	After SIGN 140 vast improvement in pathology reports with data set.	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Agree with all of this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.7.1	LN	'pigment synthesising melanoma' should be lower case.	*Thank you for your comment. This section has been reworded*
	CP	Agreed	*Thank you for your comment*
	VD	Not sure where there is clear evidence of LMM playing a role in likelihood of recurrence vs other types.	*Thank you for your comment. This section has been reworded*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Ditto.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Should state whether LMM, PSM and PDM confer HIGHER chance of recurrence rather than simply ' ...play a role in determining likelihood of recurrence'?	*The clinical characteristics of these subtypes are covered in 4.1.5 & 4.1.6*
4.7.2	CP	Agreed	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Ditto.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.7.3	RC	Clearly written re. 1A/B	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Ditto.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*

4.7.4	CP	Agreed	*Thank you for your comment*
	MM	Useful clear comments.	*Thank you for your comment*
	JV	Helpful, relatively new criterion.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.7.5	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Agree.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.7.6	LN	Paragraph 5, line 1 - can't be 'stage I' if >3mm thick	*Thank you for your comment. This section has been reworded*
	CP	Agreed	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Important to include as stated.	*Thank you for your comment*
	CM	In paragraph 5 should thick be (>3mm) or should it read (>4mm)??	*Thank you for your comment. This section has been reworded*
	MN	Ok.	*Thank you for your comment*
4.7.7	CP	Agreed	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Ditto.	*Thank you for your comment*
	CM	No issues regarding this section	*Thank you for your comment*
	MN	Are there no referenced statements for vertical growth phase to contrast with the good prognosis of radial GF?	*This section was not within the remit of the update.*
4.7.8	CP	Agreed	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Ditto.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.7.9	AA	A recommendation as in the minimum data set should be to state the presence or absence of regression as a yes or no then state whether features suggestive of early or late regression as far as I am aware.	*GDG happy with the recommendation as stated. No change required.*

	KH	Histologic regression is a possible protective prognostic factor based on the lower incidence of SLN positivity. This literature review and meta-analysis16 addresses the incidence of sentinel lymph node (SLN) positivity in patients with histologic regression of primary melanoma. It is debated whether histologic regression is a poor vs protective prognostic factor in melanoma. Fourteen studies were included, with a total of 10,098 patients. Patients with a histologic regression of primary melanoma had a lower likelihood of SLN positivity (OR, 0.56) compared with patients without regression.	*This paper was published after the evidence review.*
	CP	Agreed	*Thank you for your comment*
	VD	Last sentence of second paragraph is suggesting modification of current practice in terms of MDT inclusion . not clear on what basis this statement is being made. Recommendation reads rather oddly. Surely regresssion is either present or absent ?	*This section states RCPath recommendations.* *GDG happy with wording. no change required.*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Most important.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	R: should it read presence OR (rather than and) absence of regression...?	*Changes made as suggested*
4.7.10	LN	third last line should be 'mitoses' not 'mitotes'	*Changes made as suggested*
	CP	Note spelling mistake of ‘mitoses’	*Changes made as suggested*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	No worry with this.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.8	AA	Good practice point - where there is diagnostic doubt refer to an expert dermatopathologist.	*A GPP has been added*
	CP	Agreed	*Thank you for your comment*
	RC	Fully support all NMSC and Melanoma in	*Thank you for your comment*

		interested ‘hands’.	
	VD	Are there well recognised panels of experts?	*The wording of this section has been changed for clarification.*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Not my area of expertise.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.9	LN	Should 'tumour stage (pT)' be on a separate line, in the last line of column two of table 5?	*Changes made as suggested*
	MM	No comment, agree with guideline.	*Thank you for your comment*
	JV	Ditto, but structured reports, as developed locally, are very helpful and avoid omissions.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	Ok.	*Thank you for your comment*
4.10	LN	last line page 16, first line page 17 suggest: 'which should be recorded include the exact number of total nodes...' Page 17 paragraph 5, line 1 should be: 'Additional...' Page 17 paragraph 5, line 2, should 'SLNB' be replaced with 'SLN'?	*Changes made as suggested*
	CP	Agreed	*Thank you for your comment*
	MM	Consider providing a link to the RCP dataset in this section.	*The group did not feel this was necessary*
	JV	Not my area of expertise.	*Thank you for your comment*
	CM	No issues regarding this section.	*Thank you for your comment*
	MN	paragraph 3: '....exact number of nodes total identified..' Should be number of nodes or no of nodes IN total?	*Changes made as suggested*
Section 5			
5.1	LN	Paragraph 4 line 3- should this be 'lentigo maligna' rather than 'lentigo melanoma'? Same for paragraph 5 line 2? Why are the wide local excision margins different to those recommended by NICE 2015 NG14.	*Changes made as suggested* *NICE recommendation now used.*

		'The majority of melanomas should be excised with direct wound closure..' does this mean the primary excision or the wide local excision?	
	AA	Page 18 Surgical management and staging. There are several recent article comparing 2 different peripheral margins – Ann Surg Oncol. 2016 Mar 8. [Epub ahead of print] Is a Wider Margin (2 cm vs. 1 cm) for a 1.01-2.0 mm Melanoma Necessary? Doepker MP1, Thompson ZJ2, Fisher KJ2, Yamamoto M3, Nethers KW1, Harb JN1, Applebaum MA1, Gonzalez RJ1, Sarnaik AA1, Messina JL4, Sondak VK1, Zager JS5. Author information Abstract BACKGROUND: The current NCCN recommendation for resection margins in patients with melanomas between 1.01 and 2 mm deep is a 1-2 cm radial margin. We sought to determine whether margin width had an impact on local recurrence (LR), disease-specific survival (DSS), and type of wound closure. METHODS: Melanomas measuring 1.01-2.0 mm were evaluated at a single institution between 2008 and 2013. All patients had a 1 or 2 cm margin. RESULTS: We identified 965 patients who had a 1 cm (n = 302, 31.3 %) or 2 cm margin (n = 663, 68.7 %). Median age was 64 years, and 592 (61.3 %) were male; 32.5 and 48.7 % of head and neck and extremity patients had a 1 cm margin versus 18.9 % of trunk patients (p < 0.001). LR was 2.0 and 2.1 % for a 1 and 2 cm margin, respectively (p = not significant). Five-year DSS was 87 % for a 1 cm margin and 85 % for a 2 cm margin (p = not significant). Breslow thickness, melanoma on the head and neck, lymphovascular invasion, and sentinel lymph node biopsy (SLNB) status significantly predicted LR on univariate analysis; however, only location and SLNB status were associated with LR on	*Thank you for submission of additional papers, however these were published after the evidence review process or have already been included.* *NICE recommendations now used.*

		multivariate analysis. Margin width was not significant for LR or DSS. Wider margins were associated with more frequent graft or flap use only on the head and neck (p = 0.025). CONCLUSIONS: Our data show that selectively using a narrower margin of 1 cm did not increase the risk of LR or decrease DSS. Avoiding a 2 cm margin may decrease the need for graft/flap use on the head and neck. In the 3rd paragraph I am unclear what the group are meaning when they state that “other techniques can be considered” in the treatment of lentigo maligna melanoma and I note the reference they quote for this is 36 years old. This surely is out of date. In the next paragraph on lentigo maligna, the final sentence suggests that ‘Mohs micrographic surgery may reduce the size of the defect’. This is true but also this may reduce the chance of recurrence which is the primary indication for Mohs surgery. Dermatol Surg. 2015 Feb;41(2):211-8. doi: 0.1097/DSS.0000000000000248. Five-year outcomes of wide excision and Mohs micrographic surgery for primary lentigo maligna in an academic practice cohort. Hou JL1, Reed KB, Knudson RM, Mirzoyev SA, Lohse CM, Frohm ML, Brewer JD, Otley CC, Roenigk RK. Author information Abstract BACKGROUND: Wide local excision with 5-mm margins is the standard of care for lentigo maligna (LM). Mohs micrographic surgery (MMS) is used increasingly to treat this tumor. OBJECTIVE: To study the authors' experience with these 2 approaches. MATERIALS AND METHODS: Primary LM cases treated at the authors' institution from January 1, 1995, through December 31, 2005, were studied retrospectively. Main outcome measures were recurrence and outcomes after treatment for recurrence.	*Paragraph removed* *GDG are happy with wording. No change required.*

		RESULTS: In total, 423 LM lesions were treated in 407 patients: 269 (64%) with wide excision and 154 (36%) with MMS. In the MMS group (primarily larger head and neck lesions with indistinct clinical margins), recurrence rates were 3 of 154 (1.9%). In the wide excision group (primarily smaller, nonhead and neck, or more distinct lesions), recurrence rates were 16 of 269 (5.9%). Each of the 16 recurrences was biopsy proven and treated surgically: 6 by standard excision and 10 by MMS. CONCLUSION: This follow-up study of LM surgical treatments shows excellent outcomes for wide excision and MMS. Because this is a nonrandomized retrospective study, no direct comparisons between the 2 treatments can be made. When recurrences occurred, repeat surgery, either standard excision or MMS, was usually sufficient to provide definitive cure. In clinical practice other forms of margin control can be considered as well as staged surgical excision. Also in some cases simple observation using macroscopic and dermascopic images may be appropriate for individual patients due to the general indolent biological behaviour of LM and patient choice. Patients should be involved in decision making regarding their care. Regarding recommendations for surgical excision margins, I agree with the Australian guidelines and in clinical practice in the last 10 years of me attending our Skin Cancer MDM, as far as I can recall, we have never recommended more than a 2cm wide peripheral margin so I would not favour a 3cm margin being in the guideline which should represent usual practice (although as in any guideline, there could be the rare occasion when a clinician/ and /or MDT decide that 3cm would be best). pT1 – 1cm pT2 – 1 – 2cm pT3 – also 1 to 2cm pT4 – 2cm This is in keeping with the evidence. Indeed there is some evidence that	*These points are addressed by using NICE recommendations.*

		suggest that excision margins less than 1cm are safe for thin melanomas less then 0.76mm, especially those in radial growth phase. In clinical practice all individual variables should be considered when deciding on the peripheral margin due to the range of thickness of melanoma in each individual group and anatomical location. A sensible approach can be to take 1.5cm margin at times. Clearly, the deeper the invasion, the more likely there could be benefit in pushing out the peripheral margins to reduce the chance of local recurrence. In the final paragraph the 2nd last sentence is not backed by any evidence stating that 'the majority of melanomas should be excised with direct wound closure'. Perhaps, inserting "initially" before excised would clarify this statement? As I said before the choice of surgical defect reconstruction (especially the WLE) depends on many variables and often direct wound closure is not used e.g. local skin flaps on the face and scalp and body as well as full thickness and split thickness skin grafts. Of course, most small width melanomas can be initially excised with the defect closed directly but the WLE may require a complex reconstruction depending on anatomical site and defect size.	*Changes made as suggested.*
	KH	I think it is important to be clear that the margins quoted in studies are surgical margins noted at the time of surgery and not histological margins. The studies carried out used clinically measured surgical margins which do not need to correlate with histologically negative margins15,17. Mohs micrographic surgery (MMS) for digital melanomas allowed patients to avoid amputation without negatively affecting survival. This was a retrospective series of 62 digital melanomas (57 primary and 5 recurrent) treated with MMS18. Of these melanomas, 5 recurred locally within 6.5 years of follow-up, and 3 were treated with additional MMS. Local recurrence-free survival rates for patients with digital melanoma at 5 and 10 years were 91.8% and 82.6%, respectively. Melanoma-	*GDG are happy with current wording. No change required.* *There was no key question on MMS in this update.*

		specific survival rates at 5 and 10 years were 95% and 81.2%, respectively.	
	CP	This evidence (and Recommendation) for surgical margins is very out of date. For up to date discussion please see: http://authors.elsevier.com/sd/article/S0305737215001991 There has also been a Cochrane review of this topic in 2009. It seems very remiss that you haven't included that. The reference is: Sladden MJ, Balch C, Barzilai DA, Berg D, Freiman A, Handiside T, et al. Surgical excision margins for primary cutaneous melanoma. Cochrane Database Syst Rev2009;4:CD004835. http://dx.doi.org/10.1002/14651858.CD004835.pub2.	*GDG have adopted NICE recommendations on surgical margins.*
	RC	Well written with clear evidence and tissue sparing.	*Thank you for your comment*
	AM	Would it be possible to consider clarification of the surgery for Tis melanoma? I have had the previous edition of this guideline quoted to me as justification for a 5mm re-excision of an already completely excised melanoma in-situ. Perhaps adding something to the effect that pathological complete excision is the aim, with a suggestion that this would usually be achieved by a 5mm surgical margin?	*GDG have adopted NICE recommendations on surgical margins.*
	VD	Is the 5th paragraph not out of place in the surgical section?	*GDG feel it should remain, however it has been included as a second paragraph with the previous evidence statement.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	MH	3cm margins for the thicker lesions are frequently difficult to close primarily and are associated with increased morbidity. Where the aim is local control this margin frequently seems excessive, and would contradict the statement which folows it "The majority of melanomas should be excised with direct wound closure (see section 4.5). Perhaps the text should be softened here to allow more leeway in margin size for the thicker lesions.	*GDG have adopted NICE recommendations on surgical margins.*
	CF	Worth reviewing AND CONSIDERING. http://www.sciencedirect.com/science/arti	*GDG have adopted NICE recommendations on surgical*

		cle/pii/S0305737215001991	*margins.*
	SW	The discussion of the evidence (or lack of) for surgical margins >2cm is absent and I am concerned that the way the AJCC data is presented in table format, without prior discussion of the lack of good evidence for margins >2cm, then this will be taken as 'what should be done' when in fact it is uncommon to take margins >2cm in practice. In the 2010 'UK' guideline there is much more detailed discussion of the evidence surrounding surgical margins, including the fact that there is only 1 RCT looking at 1 vs 3cm margins for MM >4mm and the the trials looking at 2 v 4cm and 1 v 3cm for thinner melanomas are not directly comparable. I think it would be useful to highlight the lack of clarity here and that the final decision should be informed by anatomical site, reconstructive requirements, and both MDT and patient discussion.	*GDG have adopted NICE recommendations on surgical margins.*
	BAD	The surgical margins recommendations are questionable. There are significant deficiencies in this section and new evidence has not been reviewed or discussed. An article by Jerry Marsden and colleagues which summarizes important new evidence on surgical excision margins in primary cutaneous melanoma isn't considered at all in this guidance. http://authors.elsevier.com/sd/article/S0305737215001991 M.J. Sladden, C. Balch, D.A. Barzilai, D. Berg, A. Freiman, T. Handiside, et al. Surgical excision margins for primary cutaneous melanoma Cochrane Database Syst Rev, 4 (2009), p. CD004835 http://dx.doi.org/10.1002/14651858.CD004835.pub2 Recommendations regarding Lentigo Maligna are ambiguous. Firstly it states that it should be surgically removed but then there is discussion regarding other treatment options but no indication when other options should be considered.	*GDG have adopted NICE recommendations on surgical margins.* *Please see comment response for VD above.*
	JV	Agree with this.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*

	MN	Para 4 need to lose comma before ...(variant of...); also 'Currently 5mm MARGINS? are recommended...	*Changes made as suggested.*
	RCP&S	Should be more explicit, to avoid the unintended impression that there must be a 5mm margin of clearance.	*GDG have adopted NICE recommendations on surgical margins.*
5.2	LN	Table 6a) T4 should be greater than 4.0mm not less than Table 6b) Stage IIC shouldn't have T4a for both clincal and pathological staging	*Changes made as suggested.*
	AM	There are transcription errors in the staging tables: Table 6a: T4 tumour should be >4.0 (not <4.0) Table 6b: Stage IIc is T4bN0M0 only, delete next line (T4aN0M0, which is IIb)	*Changes made as suggested.*
	MM	Consider including more detail regarding definitions from AJCC, eg 'regional lymph nodes' and 'distant metastasis'.	*Table reproduced from AJCC. They do not include definitions with tables.*
	AD	There is a minor typo in the last sentence on page 24 ("PET-CT should be considered for patients with indeterminate findings on CT orfor those who are being considered for a major surgical resection." I suggest this is changed to "PET-CT should be considered for patients with indeterminate findings on CT or for those who are being considered for a major surgical resection. The decision on PET-CT and the rationale should normally be made within a specialist melanoma multidisciplinary meeting and with the support of the ARSAC certificate holder". The reasoning behind this is that - in law - the final decision on justification on nuclear medicine studies lies not with the responsible melanoma clinician but with the FDG certificate holder.	*See chapter 6*
	JV	Ditto.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	RCPE	There is an opportunity missed by simply pasting the TNM classifications of melanoma without effort to integrate within one table a clearer outline of staging that patients/GPs might more easily follow.	*Thank you for your comment. We were limited in our permission to reproduce these tables but without adapting or altering them.*

	Mn	Ok.	*Thank you for your comment.*
5.3	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Satisfactory.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
5.3.1	AA	Fine needle aspiration/open biopsy If this is unsatisfactory or negative and clinical suspicion persists it is reasonable to repeat with the help of ultrasound guidance I suggest.	*Changes made as suggested.*
	RC	Updated and sensible.	*Thank you for your comment.*
	MM	Consider including detail that FNA can be US guided.	*Changes made as suggested.*
	MH	The section on therapeutic lymph node dissection includes the statement "Groin nodes include a superficial group of inguinal nodes below the inguinal ligament and the obturator and iliac group of nodes which lie deeper in the pelvis. Ilioinguinal dissection offers a survival benefit in patients with palpable positive inguinal nodes compared with inguinal block dissection of the femoral triangle node." This suggests that we should possibly be doing ilioinguinal node dissections in all cases, whereas I don't think this reflects my experience of current practice. Could this issue be clarified slightly?	*This section was deleted as the GDG agreed that this statement was controversial but had not been the subject of a key question.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	R '...referred to a lymphoedemIC specialist' or lymphoedemA?	*Changes made as suggested.*
5.3.2	LN	I think it needs to be clearer, preferably in the first paragraph under SLNB, that SLNB is a staging procedure, not a therapeutic procedure, and has no survival advantage. Paragraph 3 should this be 'The standard for sentinel lymph node biospy (SLNB)..' Table 7 and table 8 should be labelled 'Possible advantages...	*It is stated in first paragraph that SLNB is a staging technique.* *Changes made as suggested.*

		How much additional prognostic information is gained from SLNB when factors such as Breslow thickness, ulceration and mitoses have been excluded? Under 'R' 'SLNB should be considered ... greater or equal 1mm thick in patients with IB-IIC melanoma,,,' the recommendations are different to NICE, why?	*Updated the wording in recommendation.*
	AA	Table 7 – Advantages and disadvantages of SLNB In the final sentence of the advantages I don't think it is ethical to say that 'These trials often cannot accept people who haven't had this operation'. Rather I would tone this down to say 'some clinical trials may not accept people who have not had a sentinel lymph node biopsy'. Table 8 – Possible disadvantages (middle paragraph) I think it should read, following a positive SLNB, 'In 4 out of 5 people further melanoma cancer will not be found in the remaining lymph nodes' – rather than 'will not develop' as one can't make that statement, but rather only 1 in 5 people will have any further positive lymph nodes after a positive sentinel lymph node. In my view there are some misleading comments here, especially the comment that 'In thick melanomas it can identify a subset of "good" prognosis melanomas which are node negative'. No thick melanoma has a good prognosis e.g. a patient may have an estimated 60% chance of death over 5 years after the diagnosis of a thick e.g. 5mm thickness melanoma. If she has a positive sentinel node the chance of dying will increase to about 80%. If the sentinel lymph node is negative the chance of dying will reduce only slightly to e.g. 55% chance of death within 5 years i.e. still a poor prognosis i.e. a negative sentinel lymph node in this context does not really give any reassurance and more people will still likely die within 5 years. Some discussion on this area would have been helpful as well as a review of the existing survival estimate calculations based on Cochrane's formula, 2 of which are available free to use online – 1 from America and 1 from the Birmingham, UK	*Tables are reproduced with permission from NICE guidelines.* *Wording changed for clarity to "better".* *This was not part of the key question for this update.*

		Centre, both of which I find useful in clinical practice to share with patients. Regarding a positive sentinel lymph node biopsy, it is helpful to expand on this with the commentary that prognostic value depends on the precise site of the positive melanoma i.e. intracapsular v. extracapsular and the extent of nodal involvement and I suggest you quote the N-Score study which tries to stratify risk after a positive sentinel node to detect the group where perhaps watchful waiting would be reasonable with or without ultrasound surveillance of the nodal basin. This would be an obvious area for a prospective RCT.	
	CP	As per NICE guidelines 2015	*Thank you for your comment.*
	VD	Final recommendation implies all patients may need lymphodema services . given that this problem usually arises later and is by no means universal is there not argument for alerting patient to early signs of this problem thus prompting early onward referral.	*GDG happy with wording. No change.*
	MM	I welcome tables 7 & 8 which simplifies a difficult area.	*Thank you for your comment.*
	RD	The section here answers some of my comments earlier in the guideline regarding SLNB. A statement I find worrisome is "People who have had the operation may be able to take part in clinical trials of new treatments for melanoma. These trials often cannot accept people who haven't had this operation." This might be true but probably, I think, should not be (as it must be unethical to insist on this operation with, as detailed in this section of the guideline, a fairly high risk of complications, as prerequisite for participating in therapeutic trials), and I think (and I do realise there are uncertainties and this topic must have been discussed in detail by the guideline development group) that an opportunity could be taken in this guideline to be 'stronger' on what the evidence is, so saying "There is no evidence that people who have the operation live longer than people who do not have it" rather than the current "There is no good evidence that people who have the operation live longer than people who do not have it", and discouraging insistence on SLNB as a staging test insisted upon for entry to	*Tables are reproduced with permission from NICE guidelines. The GDG think the wording is sufficiently clear.*

		any therapeutic trials. In the discussion here it may be worth also including discussion of the serious worries that disrupting the local lymphatic drainage system, especially with such an immune-response generating tumour, by SLNB might worsen the chances of survival, even if mainly to say that to date most studies have been reassuring from this point of view. There is a typo near the end of page 22 - lymphodema should be lymphoedema.	*Typo corrected.*
	MH	The statement "SLNB should be considered as a staging technique in patients with a primary melanoma ≥1 mm thick in patients with IB-IIC melanoma." should be clarified as there are some patients with melanomas less than 1mm who should be considered for SLNB.	*This point has been addressed in above comments for this section.*
	CF	WORTH REFERRING TO NICE 2015 advice.	*Thank you for your comment.*
	JV	The place of SLNB is still hotly debated and the points made are valid and helpful in the discussion.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	RCPE	The question of SLNB remains a confusing area for patients - the SIGN guideline has taken the same approach as NICE in tabulating the advantages and disadvantages - whether this actually helps the patient is uncertain, but at least is consistent, until further studies clarify benefit.	*Thank you for your comment.*
	MN	R under completion lymphadenectomy - counselLing?	*Changes made as suggested.*
Section 6			
General	CP	You have not included molecular testing of the primary (and/or metastatic) tumour tissue. This is now an extremely important investigation that directs therapy. It should be included in this section and is a serious omission.	*See CP comment response at 6.2*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	CF	Have I missed genotyping of melanoma in this?	*Covered in section 3.5 of the guideline.*

	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
6.1.1	LN	typo second last line - '..on CT or for..'	*Amended*
	RC	Recognition of limited PET in NHS Scotland.	*This has been noted in wording of final paragraph.*
	AM	A very sensible & pragmatic approach – agree entirely.	*Thank you for your comment.*
	VD	If the main reservation about PET CT is weak evidence that should be stated . amalgamating reasons for not advising it alongside cost and lack of availability is unhelpful. Need to say what is most important reason.	*This has been noted in wording of final paragraph.*
	AD	Agree regarding RCT. See above for my comments on PET/CT.	*Thank you for your comments.*
	BAD	We would question the decision to recommend the use of CT of chest, abdomen, and pelvis for staging rather than PET CT, because of cost and limited availability. The advice on brain CT for initial staging is missing. It states, “neck should be included for head and neck melanomas”, but what about brain imaging. The next section says Brain CT for brain mets, but does not say if this is for initial staging or only when a brain met is suspected.	*GDG are happy with amended wording.*
	JV	CT remains standard; PET-CT :can only be used in selected cases till it is more widely and quickly available and the data supporting its use stronger.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	ref my earlier comments on imaging - they are addressed here; need to tie together for consistency?	*Thank you for your comment.*
6.1.2	RC	MRI supported.	*Thank you for your comment. The GDG is happy with the current wording of this section.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*

6.2	CP	You have not included molecular testing of the primary (and/or metastatic) tumour tissue. This is now an extremely important investigation that directs therapy. It should be included in this section and is a serious omission.	*This is only routinely used in one health board in Scotland.*
	RC	Recognition of LDH, without over burdening the system.	*Thank you for your comment.*
	VD	Does there need to be explicit level at which LDH elevation is relevant?	*The GDG is happy with the current level of detail.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	BAD	Lab investigations should include molecular genetics.	*This is only routinely used in one health board in Scotland.*
	JV	Accepted view.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
Section 7			
General	CP	Agreed. Ideally we need to identify biomarkers of risk (other than SLNB) that can stratify patients for adjuvant therapy, but we are not there yet.	*Thank you for your comment.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Mainly for consideration in the context of RCTs as yet.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Given use of adjuvant Ipilimumab in US, should there not be a specific statement on that/the evidence? If not mentioning drugs, then at least classes eg CTLA4, checkpoint inhibitors, etc.	*We can only make comment on use of medicines as approved by SMC.*
7.1	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
7.2	BAD	Immunotherapy needs to be updated.	*Paragraph added noting ongoing trials.*
7.2.1	CP	You need some comment in this section that trials are imminent / ongoing for use of anti-PD1/anti-PDL1 immune checkpoint inhibitors in an adjuvant	*Paragraph added noting ongoing trials.*

		setting because these will be of FAR more clinical relevance than interferon or IL2 or vaccine studies.	
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	ok, but I stil think it is remiss in a 2016 guideline to fail to mention the newer immunotherapy agents, as above	*Paragraph added noting ongoing trials.*
Section 8			
8.1	AA	Chapter 8 Table 9 there is a spelling mistake – it should be recurrence with an e and not an a.	*Typo corrected.*
	MM	Include comma, bullet point 4.	*Typo corrected*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
	RC	Agree	*Thank you for your comment.*
8.2	MM	No comment, agree with guideline.	*Thank you for your comment.*
	RD	"Patients who have had melanoma in situ do not require follow up." is a recommendation. "Patients with an invasive melanoma should have a period of follow up." is a good practice point. Although not in the "scope of the current guideline" this should probably be reviewed and discussed for the next version. I sometimes follow up someone who has had a melanoma in situ (if, for example, they have multiple melanocytic lesions and BCPs, and I have jusdged that they would be reassured by one more visit and a whole-body skin examination. I do not absolutely always follow up someone who has had a good prognosis just invasive melanoma removed - for some individuals follow generates anxiety and risks turning someone from being healthy into someone who is "diseased". I mostly follow the old SIGN guideline but do use it as a guideline only, not following it exactly, but I think this (follow-up) is an	*The recommendation and GPP have been amended to two GPP without further review of the evidence.*

		area where many like me would welcome an up-to-date summary of the (limited) evidence and to know what a current guideline development group thinks.	
	KHI	I think it worth mentioning that this section describes the risks of cancers secondary to radiation from CT and added anxiety to the patient, stating that together, they outweigh the benefit of CT-screening of the brain and cervical spine. However, this was decided before the advent of immunotherapy – e.g. nivolumab and ipilimumab – which have been shown to successfully treat metastastic melanoma (refs: Larkin et al., N Engl J Med 2015; 373:23-34 ;https://www.nice.org.uk/guidance/indevelopment/gid-tag522). Moreover, adoptive cell therapy has also been shown to successfully treat melanoma brain metastases (Hong JJ, et al. Successful treatment of melanoma brain metastases with adoptive cell therapy. Clin Cancer Res. 16(19):4892-8,2010.) Is it now worth trying to screen for brain mets upon disease recurrence or at 5 years? I understand the lack of evidence for its efficacy but I feel that, with more efficacious medical treatment of brain mets available, the risk:benefit ratio since SIGN 72 has changed. My suggestion is not to screen with every CT C/A/P but at disease recurrence (anywhere) and/or 5 years, as these are the patients typically seen in the neurosurgery department with brain mets.	*The recommendation and GPP have been amended to two GPP without further review of the evidence.*
	JV	I feel that pts with in situ MM & LM should be followed once at 6 months, to ensure they are practicing "Safe Sun", that the scar has healed well, confirm what changes in lesions should prompt their seeking further med. advice and that they are clear how to monitor the scar and draining nodes. I have seen many patients with second lesions and other skin cancers; several pts who developed recurrences and a few who developed invasive disease.	*The recommendation and GPP have been amended to two GPP without further review of the evidence.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
8.3	MM	No comment, agree with guideline.	*Thank you for your comment.*

	JV	Fine as is.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
8.4	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Ditto.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	second para just at ref 160 '...five yearS.....'	*Typo corrected.*
8.5	AA	Follow up recommendations. I think it is poor that the group have simply quoted the BAD guideline. Of course it is impossible to get the ideal guideline and a guideline is merely a guideline. However helpful statements like 'follow up of an individual should be tailored to their specific melanoma risk of recurrence and risk of a new primary melanoma. In clinical stage 1a melanoma there will be a heterogeneous group from micro-invasive to less than 1mm with no ulceration, so up to 1 year follow up would seem appropriate with 2 to 4 clinic visits as per the need and then discharge if there is nothing else outstanding. However then it seems strange that a patient with a 1b melanoma or just into a 2a i.e. 1.01mm with no ulceration is then subject to such intensive follow up as suggested. Perhaps a clinic FU frequency of 3 to 6 monthly for 3 years and then 6 monthly for up to 5 years depending on the individual risk I think would be more sensible. Going back to the sentinel node, I don't think you have mentioned the MSLT-II study results and the fact that the interpretation of the results in the paper was criticised widely.	*Adopted NICE guideline recommendations on follow up.* *Where possible recently published guideline recommendations are considered rather than duplicating the work to make similar recommendations.*
	KH	All patients with a past history of melanoma should be educated on self examination of their skin19,20 and in addition how to examine for nodal disease15. Consider measuring vitamin D levels routinely at diagnosis and during follow up of melanoma. We should also provide advice on vitamin D supplementation if needed11.	*This is mentioned in GPP at 8.2 and in the checklist at 11.4 in the guideline.* *Thank you for your comment. This update did not include a key question on vitamin D supplementation.*

	CP	There is new thinking in this area that has been left out. It could be better referenced.	*Now adopted NICE guideline recommendations on follow up.* *Where possible recently published guideline recommendations are adopted rather than duplicating the work to make similar recommendations.*
	RC	Sensible but need to identify resource. Significant increase with NMSC after SIGN 140.	*It is not within SIGN's remit to comment on resources in NHS.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	BAD	Table 10 – 5th bullet point should be 111B not 11B.	*Now adopted NICE guideline recommendations on follow up.*
	JV	All accepted practice.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	ok; no mention made of who should follow patients eg unresectable stage 4 'according to need'?? I know this is BAD guideline but perhaps a comment would be helpful re 'by treating clinician/oncologist'?	*Adopted NICE guideline recommendations on follow up.* *Where possible recently published guideline recommendations are adopted rather than duplicating the work to make similar recommendations.* *The evidence around who should be doing follow up was not reviewed.*
8.6	AA	Psychological and emotional support. Excessive frequency of follow up in a low risk melanoma could cause patients unnecessary anxiety e.g. a thin stage T2 without ulceration of 1.1mm.	*Thank you for your comment. This section was not updated.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Satisfactory.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	ok but would be helpful to mention the great role of skin specialist nurses here - as well as at the teaching examination part? Maybe they have not yet published evidence for the benefits to patients of their role?	*Thank you for your comment. This section was not updated.*
8.7	KH	Patients with primary melanoma should be monitored for the development of subsequent melanomas, with more intensive screening beginning in the first year following diagnosis, then continuing over the longer term.	*Thank you for your comment. This section was not updated.*

		Kaiser Permanente Northern California records were used to identify all 16,570 patients diagnosed with melanoma from 1996 to 2011 in order to determine incidence rates and examine risk factors associated with the development of cutaneous multiple primary melanoma (MPM). Of the 16,570 patients identified, 1122 had MPM. Some patients developed a third melanoma (172 patients), while 63 were diagnosed with four or more melanomas. Review of patient records was used to distinguish recurrent melanomas from subsequent melanomas. The average time to diagnosis of subsequent primary melanomas was 3.83 years (SD, 3.61; median, 2.82). Subsequent melanomas were thinner when invasive, more likely to be in situ, and more likely to develop on the head and neck. The lower rate of invasiveness in subsequent melanomas may be biological but may also be a result of increased monitoring. Risk of developing a subsequent melanoma was greatest in older, white (non-Hispanic), partnered men. The risk of development of a subsequent melanoma was greatest in the first year after diagnosis (2%) and stable at approximately 1% for the 15 years of follow-up.	
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	I agree with this; it underlines the importance of the above points.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
8.8	CP	Again, huge deficiencies in not updating this section.	*Thank you for your comment.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	CF	Needs updated as previously commented.	*Thank you for your comment.*
	JV	Ditto.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
8.8.1	CP	The laboratory tests cited are VERY insensitive especially LDH and other biomarkers need to be explored as with	*Thank you for your comment. The GDG acknowledge other biomarkers need to be explored but this section*

		the TRACER-X study. This includes circulating tumour cells.	*was not updated.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Ditto.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
8.8.2	LN	Duplicated in 6.1.1 ? refer to this section??? Last paragraph before 'R' should it be the 'local' or specialist MDT that decides on follow up imaging?	*6.1.1 refers to investigation and staging, this section refers to post treatment follow up. Change of wording removes mention of MDT and states MCN rather than local MDT.*
	CP	There is evidence that serial ultrasound may be a sensitive, cheap and non-invasive method for detection of melanoma recurrences. This evidence should have been included and discussed.	*Serial ultrasound was not included in the key question.*
	VD	Would decision on follow up imaging not fall into remit of specialist MDT rather than local.	*Change of wording removes mention of MDT and states MCN rather than local MDT.*
	MM	Table 11 is useful and could be adapted for use as patient information.	*Thank you for your comment.*
	AD	The recommendation " Decisions on routine follow up imaging in patients with Stage IIB-III should be made by the local multidisciplinary team." is vague and not consistent with the tone of the NICE guidelines. This potentially will facilitate the development of an unstructured approach to followup which will add nothing to the evidence base that will inform future use. I strongly advocate using recommendation 1.9.16 of the NICE (2015) melanoma guideline, which provides clarity and will temper demand for imaging investigations for which there is no evidence of tangible value. ie, I suggest: Consider surveillance imaging as part of follow‑up for people who have had stage IIC melanoma with no sentinel lymph node biopsy or stage III melanoma and who would become eligible for systemic therapy as a result of early detection of metastatic disease if: •there is a clinical trial of the value of	*The GDG acknowledge that this is a challenging area to give detailed recommendations and believe that this section adequately addresses the main issues involved albeit the final recommendation is not as detailed as that given by NICE. This section has been updated with a change of wording to state MCN rather than local MDT and to make it clear that PET CT is not recommended in this setting*

		regular imaging or •the specialist skin cancer multidisciplinary team agrees to a local policy and specific funding for imaging 6‑monthly for 3 years is identified. Finally, I (and the SCIN PET cttee) strongly advise that it should be made clear that PET/CT has no routine role in surveillance imaging in Stage IIB-III patients. There has been a rise in melanoma PET referrals across NHS Scotland following informal adoption by it by some clinicians, which requires to be reversed, given that there is no evidence of benefit.	
	BAD	The recommendation for follow up imaging to be made by local MDT should relate to stage 11C-111 not stage 11b as stated. The role of ultrasound should be discussed.	*Thank you for your comment. Wording of recommendations have been corrected.* *Ultrasound was not included in the key question.*
	JV	I agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	RCPE	Presumed typographical error here - IIC and III for MDT discussion - confusing overlap as stated: “Routine Surveillance imaging should not be offered to patients with stage I-IIB melanoma. Decisions on routine follow up imaging in patients with Stage IIB-III should be made by the local multidisciplinary team”.	*Thank you for your comment. Wording of recommendations have been corrected.*
	MN	Ok but refer back to your own document identical paragraph previously in this guideline also/instead?	*Thank you for your comment. Wording of recommendations have been corrected.*
Section 9			
General	CP	Not just BRAF mutation testing. Also NRAS. If ALM should include c-KIT.	*Thank you for your comment. The GDG acknowledge that further molecular testing is available in some centres but given the absence of approved and locally available treatments for these other molecular subtypes, routine testing for NRAS and c-KIT could not be recommended at this time outwith clinical trials.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Now standard practice.	*Thank you for your comment.*

	MN	Ok.	*Thank you for your comment.*
9.1	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Fine.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
9.2.1	KH	The neutrophil to lymphocyte ratio (NLR) appears to be a simple and inexpensive prognostic biomarker of aggressive disease which could be used to select patients for ipilimumab treatment. This retrospective study21 of consecutive series assessed if the NLR prior to initiating ipilimumab was associated with overall survival (OS) in patients with melanoma. Patients with a NLR >4 had poorer OS compared with patients with a NLR <4 (Univariate analysis: HR, 2.79; multivariate analysis: HR, 2.20).	*Thank you for your comment.* *The referenced study was published after the evidence review, appraisal and summary.*
	CP	You should include the evidence (and advice) about use of BRAF inhibitors in patients with BRAF mutation that is not V600E. This is an important area where clinicians need guidance.	*The GDG agree that it was an oversight that this was not included in key questions.*
	RC	Really useful and SMC input useful. Whilst delay in reporting BRAF status should be considered for data set.	*Thank you for your comment.*
	MM	Useful summary for the non-oncologist.	*Thank you for your comment.*
	CF	I would add in the word 'only' to the summary sentence relating to SMC advice – as much of the discussion above also includes combination BRAF and MEK inhibitors i.e. "Vemurafenib and dabrafenib are accepted for use by the SMC only as monotherapy for the treatment of patients with BRAF V600 mutation positive unresectable or metastatic melanoma as first line therapy (see Section 12.4). SMC advice on the use of combined BRAF and MEK inhibitors is awaited. "	*Statement wording has been slightly amended for clarity.*
	JV	Amazing advances during last 3 yrs or so: now standard practice and rapidly developing field.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok, mention clinical trials as an option?	*GPP added to beginning of chapter.*

9.2.2	CP	Agreed	*Thank you for your comment.*
	KMac	In the discussion, there is some reference to combinations so I think the SMC advice should be clarified as below. Nivolumab advice is also now published: "While there is evidence of efficacy for novel immunotherapies, optimal choice, sequence and combination of therapies are still to be determined. Ipilimumab monotherapy and pembrolizumab monotherapy (with restrictions) have been considered and accepted for use by the SMC (see Section 12.4). Advice on nivolumab is awaited" - This advice has now been published in March 2016".	*Thank you for your comment. Minor text changes have been made.*
	JV	I agree.	*Thank you for your comment.*
	CM	Will the average GP or clinician know what "gp100" means without any explanation? - I doubt it This section is heavy on facts and figures but not necessarily a criticism.	*Thank you for your comment.*
	MN	Ok, mention clinical trials as an option?	*A good practice point has been added to the beginning of the chapter.*
9.3	AA	I think there should have been a bit in 9.3 on Isolated Limb Infusion which does have some evidence and there is less morbidity than isolated limb perfusion. Cryotherapy and Aldara can also be used for local management of skin metastases as needed. There is a disproportionate section of electrochemotherapy with no evidence of superior efficacy to other ablative methods as far as I am aware.	*Thank you for comments.* *The GDG did not include this in key questions for this section.*
	CP	Agreed.	*Thank you for your comment.*
	RC	Limited use must be in one centre.	*Thank you for your comment.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Fine.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	No definition of 'significant number'?	*Text changed to 'high' for clarity.*
9.3.1	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*

	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
9.3.2	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok but mention better/more standard now to use improved systemic therapies?	*Thank you for your comment.*
9.4	AA	There is no evidence of carbon dioxide laser being superior to cryotherapy or indeed any physical ablative technique e.g. surgical excision of the individual metastases.	*Only electrochemotherapy evidence was reviewed in this section. Additional wording to address this comment.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	MH	"Carbon dioxide laser ablation can be considered for multiple lesions of trunk or abdomen and for limb disease when ILP is not appropriate". It can be more appropriate sometimes than ILP.	*Only electrochemotherapy evidence was reviewed in this section. Additional wording to address this comment.*
	SW	A minor point, but CO2 laser is not the only ablative laser that is effective for the albation of cutaneous melanoma metastases. Erbium:YAG laser is also effective, and this is what is used at Ninewells Hospital. Interestingly I cannot find any reference for this, but the technique is exactly analogous to CO2 laser.	*Only electrochemotherapy evidence was reviewed in this section. Additional wording to address this comment.*
	JV	Fine.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok but as above.	*Thank you for your comment.*
9.5	CP	Agreed.	*Thank you for your comment.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Interesting option in the setting mentioned.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*

9.6.1	CP	Agreed.	*Thank you for your comment.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
9.6.2	CP	Agreed	*Thank you for your comment.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	RD	Perhaps some more details about the quality of radiotherapy advised would be useful, not to correct any factual inaccuracy but to make this section clearer to dermatologists like myself only familiar with doses in Gy for grenz rays, an ionising radiation of very different qualities to the sorts which can be used for plliative therapy of metastases. Also, if this section is revised in the future it would be interesting to have comment on whther other radiation treatments (radioisotopes, interstitial brachytherapy) have, or have not, any role.	*The GDG felt that they could not be prescriptive about radiotherapy given the evidence under consideration.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
9.6.3	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok but mention urgent BRAF check and targeted therapy in new cases?	*Added GPP includes these suggestions.*
9.6.4	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	para 3: I think it merits restating the guidance in this site-specific section; patients with BRAF mutation should preferentially receive targeted therapy since these drugs do cross the BBB. R: I do not think these statements are complete enough in these days of BRAF targeted therapy availability (as above).	*Thank you for your comments. Wording in GPP has been altered to include targeted therapy when surgery is not an option.*

9.7	RC	Most important.	*Thank you for your comment.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Really good and important section.	*Thank you for your comment.*
Section 10			
10.1	AA	Melanoma in women. The last sentence 'Pregnant women who present with evolving pigmented skin lesions rather than growing or changing which sounds rather lay-person orientated.	*The only change to this chapter was removal of one sentence in section 10.1, the evidence was not reviewed and text appears verbatim from the original guideline.*
	RC	Good review of literature. Risk in context.	*Thank you for your comment.*
	VD	Is it not more a question of full discussion around pregnancy timing post diagnosis rather than advising a delay?	*The only change to this chapter was removal of one sentence in section 10.1, the evidence was not reviewed and text appears verbatim from the original guideline.*
	MM	Useful information and conclusions for clinical practice.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
10.2	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Fine as stands.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
10.3	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
Section 11			
11.1	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree.	*Thank you for your comment.*

	CM	Fine.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
11.2	MC	What is communication skills training for healthcare professionals? The list of potentially effective communication tools is a bit confusing as it includes measures for gathering data and some tools for communication. But I'm not sure how these would be used in practice and the type of communication training that would be required. I would have thought that healthcare professionals receive this type of training throughout their career.	*Thank you for your comment*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	CM	Fine.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
11.3	CP	Agreed.	*Thank you for your comment.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
11.4	MC	This makes more sense to me, making sure that the patient has all the information they need and you can use a checklist to make sure of that and other materials that can be given to the patient.	*Thank you for your comment.*
	CP	Highly desirable, but we need much longer outpatient appointment times to achieve this and greater resource in terms of Skin Cancer Nurse Specialists.	*Thank you for your comment*
	VD	It is not necessary to explain melanoma fully in primary care at time of referral surely. it should be raised as a possible diagnosis and reason for urgent referral . how / why they develop is something which would follow a definite diagnosis.	*GDG and patient rep are happy with this checklist as it is.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	WF	Primary care – reads that patient should be fully informed of melanoma prior to referral to specialist centre. Do not agree that patients should be given this level of information until confirmed diagnosis. Many patients are referred as 'urgent suspected cancer' or 'melanoma' by a GP and then present with a banal lesion.	*Thank you for your comment. The patient reps agree with comment and this bullet has been removed from the first section of the table.*

		Therefore limited information at referral stage until diagnosis confirmed will help reduce unnecessary anxiety. Patients would not be given this level of information within the Specialist Clinic until confirmed diagnosis. Feel this sentence needs reworded or removed.	
	BAD	It does not seem appropriate recommending that Melanoma is explained fully in Primary care even before the diagnosis has been confirmed.	*Thank you for your comment. The patient reps agree with comment and this bullet has been removed from the first section of the table.*
	JV	All fine.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	ok, but is this the first mention of photo triage? Also, need to introduce the BRAF mutation status as essential information which is relevant to all high risk patients.	*The GDG is happy with wording and did not think BRAF should be added specifically.*
11.5.1	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Comprehensive.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok (none checked).	*Thank you for your comment.*
11.5.2	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Ditto.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok (none checked).	*Thank you for your comment.*
11.5.3	MM	Include details of Macmillan Scottish base.	*Thank you for your comment, details have been added.*
	JV	Ditto.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok (none checked).	*Thank you for your comment.*
11.5.4	MM	SCAN does not have a support group, not sure about WOSCAN and NOSCAN.	*Thank you for your comment.*
	JV	Ditto.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
Section 12			
12.1	RC	As per SIGN 140.	*Thank you for your comment.*

	MM	No comment, agree with guideline.	*Thank you for your comment.*
	JV	Agree; we await the final text with enthusiasm.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok, but opportunity to mention QPI is missed.	*QPIs are mentioned in 12.3*
12.2	MC	There is no information in this section so unsure of the resource implications at this stage.	*Thank you for your comment.*
	RC	Possibly significant re. SLNB.	*Thank you for your comment.*
	MM	No recommendation documented?	*Thank you for your comment.*
	JV	Agree – much of this is in place.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	RCPE	There appear to be a low financial impact of the revised guidelines - No recommendations are considered likely to reach the £5 million threshold which warrants full cost impact analysis. However, there is an increased interest towards considering interval scanning - this should be evaluated within a study setting with requests from MDT meetings rather than individuals.	*Thank you for your comment.* *This appears in research recommendations and within the guideline that local MDT should consider interval scanning, as it is not evidenced at this time.*
	MN	This does not look complete.	*Thank you for your comment. This section was unfinished at the time of peer review.*
12.3	MC	This is important and understanding of current clinical practice is key before implementing further guidelines. However, this section appears unfinished. I would recommend a review of the current spend on this disease area and how resources (money, staff, equipment) are used currently before looking at how this guidelines may affect the use of such resources and where changes may need to be made in the allocation of those resources. This could then link to the resource implications section. Outlining resource use in this way, would also allow for the outline of a current pathway and if this fits with the guidelines.	*Thank you for your comment. This section was unfinished at the time of peer review.*
	RC	Ongoing via MCN's.	*Thank you for your comment.*

	MM	No recommendation documented?	*Thank you for your comment.*
	JV	Much better structured with advent of QPI's, MDTs etc universally.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	No mention of QPI; does not look to be complete	*Thank you for your comment. This section was unfinished at the time of peer review.*
12.4	MC	The use of the acronym PAS needs to be consistent. In the first paragraph in this section it is not clear what PAS stands for. One question from this section would be, what happens if the PAS is stopped by the company? What are the potential implications of this and is anything built in to the budgets if this happens? Does the inclusion of a PAS result in the cost per QALY of the drug to be cost-effective i.e. without the PAS it would not be cost-effective?	*This has been corrected.* *Further changes are not possible as this section quotes published SMC advice.*
	VD	Will this not need to be updated on line all the time? Should that be flagged in guideline?	*The guideline will have minor additions made on a periodic basis dependant on SMC advice.*
	MM	No comment, agree with guideline.	*Thank you for your comment.*
	KMac	With regards to the additional advice section from SMC – I assume you only publish positive advice as there is some advice omitted e.g. Nivolumab (published 7 March 2016) and Pembrolizumab for patients previously treated with ipilimumab (published 09 November 2015). There is also an error here as ipilimumab advice (No 997/14) was published on the 10 November 2014 and not October as is stated. The description of the accepted pembrolizumab advice in this section is much shorter and does not contain the same detail as for the other SMC advice. It would be better and more complete if it included the same level of information as the other advice.	*Thank you for your comment. More recent advice has been added and a correction made where indicated. No change to shorter 10 November 2014 advice.*
	JV	Understood.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
Section 13			
13.1	RR	Need to insert years for XXXX-YYYY	*Thank you for your comment. This*

			has been corrected.
	MC	Please state the year range. Can the search strategies be included in an appendix? This would help with future research.	*Thank you for your comment. This has been corrected. The search strategies are available on request.*
	MM	No comment.	
	JV	Standard, gaps need to be filled.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	RCPE	Correction needed for reference 250: currently "!!! INVALID CITATION !!! 250-255."	*This has been corrected.*
	MN	Years to be added.	*Thank you for your comment. This has been corrected.*
13.1.1	MC	This seems to have been included slightly out of context. There is not enough information to understand what the patient issues may be and why this had been included.	*Thank you for your comment.*
	MM	No comment.	*Thank you for your comment.*
	JV	Ditto.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*
13.2	AA	There is a whole load of further research that would be desirable. There was a call for a multi-centre world-wide study looking at 1cm versus 2cm wide local excision for intermediate thickness in melanoma which I don't think has quite taken off but this is a highly desirable study for the T2 and even the T3 group. There is also a need for a large study looking at 3 or 4 different treatment modalities for lentigo maligna comparing standard excision with different margins and excision with margin control and also probably using radiotherapy and perhaps using Aldara.	*Thank you for your comment. It is acknowledged that there are other important research questions but those included in this chapter were felt to be the priority areas*
	CP	I disagree with some of these. For instance, it makes more sense to treat first with BRAF inhibitors to gain tumour control and then follow with immune checkpoint inhibitor. Trials on the sequencing of immune agents and targeted agents is very vague. An important area to study is the spectrum of neo-antigens in advanced melanoma	*The GDG disagree - the sequencing of BRAF inhibitors and immunotherapy is important as patients often relapse rapidly after BRAF inhibitors. For slower growing tumours it may be better to sequence immunotherapy first.*

		and whether these can be used to employ adjuvant treatments that will significantly increase the efficacy of immunotherapies.	
	WF	The group clearly identifies Key areas for further research.	*Thank you for your comment.*
	AD	The research questions for imaging are excellent and I strongly support their inclusion.	*Thank you for your comment.*
	JV	Nil to add.	*Thank you for your comment.*
	CM	No issues regarding this section.	*Thank you for your comment.*
	MN	Please see earlier comments; also would add that we need evidence for the (undoubted!) benefit of having melanoma specialist nurses in each secondary/tertiary practice.	*Thank you for your comment. It is acknowledged that there are other important research questions but those included in this chapter were felt to be the priority areas*
Annex			
	AA	I hope the group take on board my comments which if incorporated in to the guideline, I believe will make it better. All my comments are well-meant and I hope are taken as constructive criticism. Some comments are my own personal opinion but as much as possible I have included key studies and recommendations from other guidelines to support my suggestions. Thanks. I look forward to the "unveiling" of the guideline which I would hope would be similar to the format we had for the recent update in the cutaneous SCC guideline which I was involved in.	*Thank you for your comments.*
	KH	Consider minimizing or avoiding immunosuppressants for people with melanoma11.	*Section added in chapter 7 on immunosuppression*
	CP	Mixed in quality, but mostly good.	*Thank you for your comment.*
	VD	Overall useful guideline. Would be worth perhaps including comment around relatively good prognosis of melanoma compared to other malignancies and also good outcomes in scotland compared with other countries . if you were reading the guideline as a non specialist some indication of percentage of good outlook lesions, numbers developing metastases etc would be helpful.	*Thank you for your comment.*
	MM	Well thought out key questions which have helped direct a clinical useful	*Thank you for your comment.*

		guideline update.	
	RD	I think this is a good draft. Having been involved in the psoriasis SIGN guideline I hope that I understand some of the constraints of the process. Having the guideline addressing specific focussed questions as in Annex 1 is mostly good but when used like this for a revision it has led to a rather patchy guideline with some aspects not updated (and now out of date) and other parts that are new. This is not a criticism of this particular guideline but I do wonder if the process for updates of SIGN guidelines should be considered: would it be better to have some updating of most of the guideline as well as, possibly fewer, new questions addressed? I realise that this would be even more work.	*Thank you for your comment.* *SIGN has now moved away from updating guidelines to producing new and more focussed guidelines where there are gaps or lack of parity.*
	JV	What a lot of hard work, well done all.	*Thank you for your comment.*
	CM	Nil to add.	*Thank you for your comment.*
	MN	Ok.	*Thank you for your comment.*