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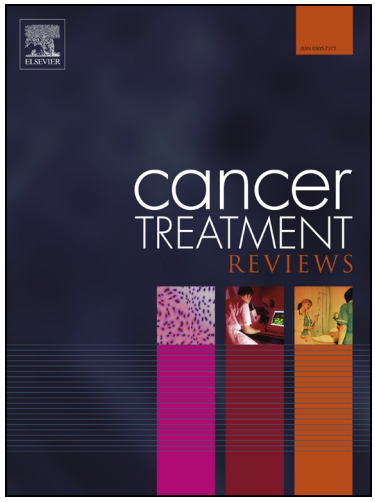

Reply to response to Wheatley et al., Surgical excision margins in primary cutaneous melanoma: A meta-analysis and Bayesian probability evaluation" Cancer Treatment Reviews April 2016;45:76

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We thank Madu et al[1] for their comments regarding our systematic review.[2] Their letter shows a serious lack of understanding of statistical methodology, especially in relation to meta-analysis. The expectation in a randomised trial is that the groups will be balanced because of the randomisation process; however, there is the possibility that, by chance, the groups could be imbalanced. This would not be a systematic error – i.e. a bias – but a random error. Meta-analysis of all the trials increases patient numbers and makes such a chance imbalance less likely. The supposition by Madu et al. that our results are due to chance differences between the arms in patient characteristics such as ulceration or sentinel lymph node biopsy (SLNB) positivity is entirely speculative. They provide no evidence for such an assertion. In fact the presence or absence of ulceration was recorded in 4 of the 6 trials and, as expected, the balance was remarkably similar between the narrow and wide margin arms (see Table 1). The validity and quality of these 6 randomised studies have until now been widely accepted by the melanoma surgical community precisely because prognostic characteristics have been well-matched. Since these same prognostic variables drive the population risk of SLNB positivity, there is no reason to believe that differences in SLNB positivity explain our findings. Moreover, if there were chance imbalances, they would be just as likely to go in the opposite direction, in which case the adverse impact of narrow surgical margins would have been underestimated. As we discuss in our paper, the misinterpretation of p-values is a major reason for the belief that narrow margins are not inferior to wider ones (a non-significant difference does not mean that there is no difference); Madu et al. fall into the same trap, whereas in fact the effects on MSS, OS and RFS are in no way inconsistent with each other despite only the first being conventionally significant.

Our data clearly show that increasing size of the surgical margin used to treat primary melanoma is associated with reduced risk of death from melanoma. As Madu et al point out, the real question is how our findings might be used. Firstly, the data are clinically relevant. They indicate that we cannot be certain that margin size has no effect on survival, and patients should be aware of this so that they can make decisions about treatment best suited to their preferences. 'Adhering to existing guidelines' should not preclude patient choice, and neither should the prior beliefs of the surgical community. Secondly, these findings should inform trial design, since otherwise an effect of margin size on melanoma survival, and the threshold for this, may well be missed. We agree that such trials should include stratification for all accepted relevant staging criteria, and this might include sentinel lymph node biopsy.

From Wheatley K, Wilson JS, Gaunt P and Marsden JR. June 2016

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Table 1. Study Characteristics – detailed table.

Trial name	Trial details	Number in trial		Population general characteristics		Melanoma characteristics		Surgical characteristics Margin width Deviations	
	Date of trial recruitment **Median follow up** **Country**	**Narrow**	**Wide**	**Narrow** **Age: median (range)** **Gender: m/f %**	**Wide** **Age: median (range)** **Gender: m/f %**	**Narrow** **Melanoma size (mm)** **Location** **Ulceration:**	**Wide** **Melanoma size (mm)** **Location** **Ulceration:**	**Narrow** **Margin width (cm)** **Deviations**	**Wide** **Margin width (cm)** **Deviations**
WHO melanoma Trial [Cascinelli N *et al.* 1998 [3] Veronesi U *et al.* 1991[2] Veronesi U *et al.* 1988[1]]				Inclusion criteria: Histologically confirmed stage I melanoma		Inclusion criteria: 2mm or less thick.		Planned width: *narrow = 1cm, wide = 3cm* Extending to muscular facia. Margins measured by surgeon.	
	1980 to 1985 Follow up data available for 12 yrs. Mean duration 91mths	n = 305	n = 307	Age yrs: n (%) 0-20: 6pts (2) 21-40 101 pts (46.5) 41-50: 84 pts(52.8) 51-65: 114pts(49.6)	Age yrs: 0-20: 0 21- 40: 116 pts (53.5) 41-50: 75pts (47.2) 51-65; 116 pts (50.4)	Median: 0.99 Range: SD 0.53 Distribution n (%) 0 - 0.5: 62 (20) 0.51 – 1.0: 123 (40) 1.1 – 1.5 : 65 (21) 1.51 – 2.0: 48 (16) ≥ 2.1: 5 (2) Unknown: 2 (1) Location n (%) Arm:60pts (49.6) Leg:124pts (49.4) Trunk: 121pts (50.4) Clark level of invasion: pts (%) I: 11 (4) II: 109 (36) III: 119 (39) IV:37 (12) V:0 Unknown: 29 (9)	Median: 1.02 Range: SD 0.49 Distribution n (%) 0 - 0.5: 50 (16) 0.51 – 1.0: 121 (39) 1.1 – 1.5: 83 (27) 1.51 – 2.0: 49 (16) ≥ 2.1: 4 (1) Unknown: 0 Location n (%) Arm:61pts (50.4) Leg: 127pts (50.6) Trunk: 119pts (49.6) Clark level of invasion: pts (%) I: 6 (2) II: 98 (32) III: 136 (44) IV: 44(14) V: 0 Unknown: 23 (8)	1cm	3cm

Trial name	**Trial details**	**Number in trial**		**Population general characteristics**		**Melanoma characteristics**		**Surgical characteristics** **Margin width** **Deviations**	
	Date of trial recruitment **Median follow up** **Country**	**Narrow**	**Wide**	**Narrow** **Age: median (range)** **Gender: m/f %**	**Wide** **Age: median (range)** **Gender: m/f %**	**Narrow** **Melanoma size (mm)** **Location** **Ulceration:**	**Wide** **Melanoma size (mm)** **Location** **Ulceration:**	**Narrow** **Margin width (cm)** **Deviations**	**Wide** **Margin width (cm)** **Deviations**
Swedish I MSG Trial Swedish Cohn-Cedermark G *et al.* 2000[5] Ringborg U et al. 1996[4]				Inclusion criteria: Histologically proven curtaneous, malignant melanoma.		Inclusion criteria: >0.8mm to ≤2.0mm on trunk or extremity excluding hands & feet.		Planned width: *narrow = 2cm, wide = 5cm* *Excision down to the muscular facia..* *Surgery within 6 weeks of primary diagnostic procedure.*	
	1982 – 1990 Median follow up: 132mths (11yrs) Range: 7 – 17 yrs Sweden	476	513	Age: 52 (16-81) Gender: 47/53%	Age: 51 (16-84) Gender: 48/52	Median: 1.2 Range: 0.4 – 2.9 Distribution % ns Location n (%) Head – neck:6 (1) Arm:61 (13) Leg:140 (29) Trunk: 265 (56) Hand:2 (0.4) Foot:2 (0.4) Clark level of invasion: pts (%) I: 0 II: 53(11) III: 297 (62) IV:114 (24) V:1 (0.2) Unknown:11 (2) From Cohn-Cedermark Ulceration n (%) Yes:36(18) No:153 (78)	Median: 1.2 Range: 0.3 – 2.0 Distribution % ns Location n (%) Head – neck:3 (0.4) Arm:75 (15) Leg:150 (29) Trunk:282 (55) Hand:1 (0.2) Foot:2 (0.4) Clark level of invasion: pts (%) I:1 (0.2) II: 80 (16) III: 304 (59) IV: 120 (23) V: 0 Unknown: 8 (2) From Cohn-Cedermark Ulceration n (%) Yes:33 (17) No:158 (79)	Margin of excision Median: 2cm <2cm: 57pts (12%) 2cm: 357pts (75%) >2cm: 61pts (13%) Unknown: 1pt (0.2%) If 2cm had been excised at biopsy pt did not need to have further surgery. Numbers not stated.	Margin of excision Median: 5cm <5cm: 106pts (21%) 5cm: 377pts (73%) >5cm 27pts (5%) Unknown: 3pts (1%)

Trial name	**Trial details**	**Number in trial**		**Population general characteristics**		**Melanoma characteristics**		**Surgical characteristics** **Margin width** **Deviations**	
	Date of trial recruitment **Median follow up** **Country**	**Narrow**	**Wide**	**Narrow** **Age: median (range)** **Gender: m/f %**	**Wide** **Age: median (range)** **Gender: m/f %**	**Narrow** **Melanoma size (mm)** **Location** **Ulceration:**	**Wide** **Melanoma size (mm)** **Location** **Ulceration:**	**Narrow** **Margin width (cm)** **Deviations**	**Wide** **Margin width (cm)** **Deviations**
						Not assessed: 8 (4)	Not assessed: 9 (5)		
Intergroup Melanoma Trial Intergroup [Balch CM *et al.* 2001 [8] Karakousis CP *et al.* 1996[7] Balch CM *et al.* 1993[6]]				Inclusion criteria: *Clinically localized primary melanoma stages I, II.*		Inclusion criteria: *1 to 4mm thick, on trunk, & above knee & elbow.*		Planned width: *narrow = 2cm, wide = 4cm Excision down to the muscular facia..*	
	1983-1992 Median follow up; 10yrs	n = 244	n = 242	Age:45.3 (19-73) Gender:57/43%	Age:47.6 (18-81) Gender:57/43%	Median:1.8 Range: ns Distribution n (%) 1.0 – 1.99: 142(58) 2.0 – 2.99: 12 (30) 3.0 – 4.0: 29(12) Location n (%) Limb (Proximal): 90 (37) Trunk: 154 (63) From Balch 1993 Ulceration (%) Yes: 56 (23) No: 188 (77)	Median: 1.8 Range: ns Distribution n (%) 1.0 – 1.99: 131 (54) 2.0 – 2.99: 68 (28) 3.0 – 4.0: 44 (18) Location n (%) Limb (Proximal): 94 (39) Trunk: 148 (61) From Balch 1993 Ulceration (%) Yes: 56 (23) No: 186 (77)	2cm	4cm

Trial name	**Trial details**	**Number in trial**		**Population general characteristics**		**Melanoma characteristics**		**Surgical characteristics** **Margin width** **Deviations**	
	Date of trial recruitment **Median follow up** **Country**	**Narrow**	**Wide**	**Narrow** **Age: median (range)** **Gender: m/f %**	**Wide** **Age: median (range)** **Gender: m/f %**	**Narrow** **Melanoma size (mm)** **Location** **Ulceration:**	**Wide** **Melanoma size (mm)** **Location** **Ulceration:**	**Narrow** **Margin width (cm)** **Deviations**	**Wide** **Margin width (cm)** **Deviations**
European Trial French [Khayat D *et al*. 2003[9]]				Inclusion criteria: *Primary malignant melanoma.*		Inclusion criteria: *<2.1cm thick, not on toes, nail, or finger.*		Planned width: *narrow = 2cm, wide = 5cm* *Excision down to the muscular facia..* *Surgery within 1mth of excision biopsy.*	
	Start date 1981 Median follow up: 192 mths (range 1 to 228 mths) Data collection complete 2000. 9 European centres	n =161	n = 165	Age: 43 Gender: 38/62	Age: 45 Gender: 37/63	Median: Range: Distribution n (%) ≤0.5:8 (5) 0.51-1.0:72 (45) 1.01-1.5:51 (32) ≥1.51:30 (18) Location n (%) Head & neck:10 (6) Arm:32 (20) Leg: 55 (34)	Median: Range: Distribution n (%) ≤0.5:10 (6) 0.51-1.0: 69 (42) 1.01-1.5: 55 (33) ≥1.51: 31 (19) Location n (%) Head & neck: 6 (4) Arm:36 (22) Leg: 73(44)	2cm If biopsy excision had a 2cm margin no further surgery required: number not given.	5cm

Trial name	**Trial details**	**Number in trial**		**Population general characteristics**		**Melanoma characteristics**		**Surgical characteristics** **Margin width** **Deviations**	
	Date of trial recruitment **Median follow up** **Country**	**Narrow**	**Wide**	**Narrow** **Age: median (range)** **Gender: m/f %**	**Wide** **Age: median (range)** **Gender: m/f %**	**Narrow** **Melanoma size (mm)** **Location** **Ulceration:**	**Wide** **Melanoma size (mm)** **Location** **Ulceration:**	**Narrow** **Margin width (cm)** **Deviations**	**Wide** **Margin width (cm)** **Deviations**
						Trunk: 47 (29) Other: 5 (3) Missing: 12 (8) Clark level of invasion n (%) I: 8 (5) II: 72 (45) III: 51 (32) IV: 30 (18)	Trunk: 46 (28) Other: 0 Missing: 4 (2) Clark level of invasion n (%) I: 10 (6) II: 69 (42) III: 55 (33) IV: 31 (19)		
UK Trial BAPS/MSG [Thomas				Inclusion criteria: *Single primary localized cutaneous melanoma.*		Inclusion criteria: 2mm or greater *on trunks or limbs where a 3cm excision margin was possible. (not palms of hands or soles of feet).*		Planned width: *narrow = 1cm, wide = 3cm*	

Trial name	**Trial details**	**Number in trial**		**Population general characteristics**		**Melanoma characteristics**		**Surgical characteristics** **Margin width** **Deviations**	
	Date of trial recruitment **Median follow up** **Country**	**Narrow**	**Wide**	**Narrow** **Age: median (range)** **Gender: m/f %**	**Wide** **Age: median (range)** **Gender: m/f %**	**Narrow** **Melanoma size (mm)** **Location** **Ulceration:**	**Wide** **Melanoma size (mm)** **Location** **Ulceration:**	**Narrow** **Margin width (cm)** **Deviations**	**Wide** **Margin width (cm)** **Deviations**
JM *et al.* 2004[10]]	1993-2001 60 mths UK	n = 453	n = 447	Age: 57 (16-86) Gender: 54/46	Age: 58 (19-92) Gender: 49/51	Median: 3.0 Range: 1.7 – 18.0 Distribution *n* (%) <2.0: 0.2 2.0 – 2.5: *160* (35) 2.6 – 3.0: *83* (18) 3.1 – 4.0: *91* (21) >4.0: *116* (26) Location (%) Limb: *248* (55) Distal: *139* (31) Proximal: *109* (24) Trunk: *205* (45) Ulceration n (%) Yes: 63.4% No : 36.6% Not assessed: 59 (13)	Median: 3.1 Range: 1.0 – 17.0 Distribution *n* (%) <2.0: 0.4 2.0 – 2.5: *145* (32.5) 2.6 – 3.0: *76* (17) 3.1 – 4.0: *99* (22.2) >4.0: *127* (28.3) Location (%) Limb: *239* (54) Distal: *142* (32) Proximal: *97* (22) Trunk: *208* (46) Ulceration n (%) Yes: 60.2% No: 157 (35)39.8% Not assessed: 58 (13)	1cm If 1mm initial margin then 1cm excision: 82.1% If 1cm initial margin then no further tx: 17.9%	3cm If 1mm initial margin then 3cm excision: 82.8% If 1cm initial margin then no further tx: 17.2% (77pts)
Swedish II [Gillgren P *et al*. 2011[11]]				Inclusion criteria:		Inclusion criteria:		Planned width: *narrow = 2cm, wide = 4cm* *Excision down to the muscular facia..* *Surgery within 8 wks of excision biopsy.*	
	1992 – 2004. Had to stop early due to recruitment	n = 465	n = 471	Age:59 (49-68) Gender : 62/38	Age:60 (50-68) Gender:66/34	Median: Range: Distribution n (%) ≤3mm: 250 (50)	Median: Range: Distribution n (%) ≤3mm: 230 (49)	2 cm Excision biopsy could be either 1-	4cm 46 pts only had one excision. (10%)

Trial name	Trial details	Number in trial		Population general characteristics		Melanoma characteristics		Surgical characteristics Margin width Deviations	
	Date of trial recruitment **Median follow up** **Country**	**Narrow**	**Wide**	**Narrow** **Age: median (range)** **Gender: m/f %**	**Wide** **Age: median (range)** **Gender: m/f %**	**Narrow** **Melanoma size (mm)** **Location** **Ulceration:**	**Wide** **Melanoma size (mm)** **Location** **Ulceration:**	**Narrow** **Margin width (cm)** **Deviations**	**Wide** **Margin width (cm)** **Deviations**
	problems – trial originally planned as equivalence study with 2000 pts. Median follow up: 6.7 yrs. Swedish cohort followed to 2011 giving 11.8 yrs follow up. . Sweden, Denmark, Estonia, Norway.					>3mm: 233 (50) Location n (%) Neck: 2 (<1) Trunk: 273 (59) Arm: 69(15) Leg:119 (26) Sole:2 (<1) Clark level of invasion n (%): Ii: 6 (1) IIi: 107 (23) IV: 294 (63) V: 34 (7) Data unavailable: 24 (5) Ulceration n (%) Yes:210 (45) No: 194 (42%) Not assessed: 61 (13)	>3mm: 241 (51) Location n (%) Neck: 0 Trunk:292 (62) Arm:74 (16) Leg:104 (22) Sole:1 (<1) Clark level of invasion n: II: 9 (2) III: 121 (26) IV: 282 (60) V: 37 (8) Data unavailable: 22 (5) Ulceration n (%) Yes:224 (48) No:188 (40) Not assessed: 59(12)	3mm or 2cm. If 2cm no further surgery required. N = 70 pts (15%) 74 protocol deviations reported	71 protocol deviations reported

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Conflicts of interest statement:
The authors declare that there are no conflicts of interest.

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