Appendix

Contents

Table S1: Recruitment Sites

The ethics committee providing local approval and number of participants recruited from each site were:

- National Research Ethics Service Committee East Midlands – Derby for recruitment sites 1–5, 9–21, 23, 26–28
- University Hospital of Larissa Ethics Committee for recruitment site 6
- Ethics Committee of the Medical University of Graz for recruitment site 7
- Ethics Committee Medical Faculty Heidelberg (EKHD) for recruitment site 8
- Ethics Committee, Kanton St Gallen for recruitment site 22
- Scientific Council of the Papageorgiou Hospital of Thessaloniki, Ethics Committee for recruitment site 24
- Scientific Council of the University Hospital of Ioannina, Ethics Committee for recruitment site 25

No	Recruitment Site (code)	Principle Investigator Responsible for Site	No. of participants recruited
1	University Hospitals of Leicester NHS Trust, Leicester, UK (LEI)	Irene Gottlob	66
2	East London NHS Foundation Trust and Cambridgeshire Community Services, Bedford, UK (BED)	Payal Khandelwal	35
3	University Hospital Southampton NHS Foundation Trust, Southampton, UK (SOU)	Jay Self	28
4	Moorfields Eye Hospital NHS Foundation Trust, London, UK (MRF)	Annegret Dahlmann-Noor	27
5	University Hospitals of Derby and Burton NHS Foundation Trust, Burton, UK (BUR & DER)	Phillip Harvey (Burton) Meriel Cross (Derby)	22
6	University Hospital of Larissa, Larissa, Greece (LAR)	Elena Papageorgiou	21
7	University Hospital Graz, Graz, Austria (GRA)	Andrea Langmann	18
8	University Hospital Heidelberg, Heidelberg, Germany (HEI)	Christina Beisse	18
9	Great Western Hospitals NHS Foundation Trust, Swindon, UK (SWI)	Angie Smith	16
10	Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK (BRD)	Shegufta Farooq	16
11	North West Anglia NHS Foundation Trust, Hinchingbrooke, UK (HIN)	Rupert Bourne	10
12	Leicestershire Partnership NHS Trust, Leicester, UK (LPT)	Irene Gottlob	9

13	The Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK (NEC)	Christine Powell	8
14	Frimley Health NHS Foundation Trust, Frimley, UK (FPH)	Lorraine North	5
15	United Lincolnshire Hospitals NHS Trust, Boston & Lincoln, UK (LCH & PHB)	Brian Redmill (Lincoln County Hospital) Mohit Gupta (Boston Pilgrim Hospital)	5
16	Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK (BCH)	Joseph Abbott	4
17	East Lancashire Hospitals NHS Trust, Burnley, UK (BRN)	Meyyammai Mohan	4
18	Ashford and St Peter's Hospitals NHS Foundation Trust, Surrey, UK (SPH)	Namir Kafil-Hussain	4
19	University Hospitals of North Midlands NHS Trust, Stoke, UK (STO)	Annie Joseph	4
20	Manchester University NHS Foundation Trust, Manchester, UK (MRH)	Carly Lawler	4
21	East Kent Hospitals University NHS Foundation Trust, Kent, UK (EKH)	Hilary Webb	3
22	Kantonsspital St. Gallen, St Gallen, Switzerland (STG)	Ethics Committee, Kanton St Gallen	3
23	Mid and South Essex NHS Foundation Trust, Southend, UK (SOS)	Elizabeth Agrippa	3
24	Papageorgiou General Hospital, Thessaloniki, Greece (THE)	Asimina Mataftsi	2
25	University Hospital of Ioannina, Ioannina, Greece (IOA)	Elena Papageorgiou	2
26	Oxford University Hospitals NHS Foundation Trust, Oxford, UK (OXF)	Ravi Purohit	2
27	Salisbury NHS Foundation Trust, Salisbury, UK (SAL)	Sue Elliott	2
28	Queen Victoria Hospital NHS Foundation Trust, East Grinstead, UK (QUE)	Samer Hamada	1

Table S2: Full Inclusion/Exclusion Criteria. D = Dioptre; logMAR = logarithm of the minimum angle of resolution; SE = spherical equivalent; BCVA = best corrected visual acuity.

Inclusion criteria: all criteria required to apply for enrolment
1) Newly detected unilateral amblyopia associated with: anisometropia, strabismus or a combination of these ('mixed' amblyopia). 2) BCVA interocular difference of ≥0.3 logMAR. 3) No previous amblyopia treatment of any modality. 4) Aged 3 to <9 years of age. 5) Clinically significant refractive error. Defined as a minimum of either: a. ≥ 1.5D in at least 1 eye. b. 1D anisometropia. 6) Ability to perform Crowded Keeler logMAR test (matching card may be used if required). 7) Signed informed parental/guardian consent. 8) Parent/guardian understand study procedures/schedule and able to attend appointments.
Exclusion criteria: participant excluded from study if any of these apply
1) Any other type of amblyopia (e.g. stimulus deprivation, bilateral amblyopia). 2) BCVA in fellow eye of worse than 0.3 logMAR. 3) Presence of other ophthalmic disease. 4) Presence of neurological disease. 5) Prematurity (defined as <36 weeks gestation).
Withdrawal criteria: once enrolled in study a participant may be withdrawn for the following reasons
1) Significant protocol deviation. 2) Inability to continue participation in the trial for other medical reasons (i.e. prolonged ill health). 3) Withdrawal of informed consent by parents/guardians. 4) Any other condition which in the opinion of the investigator no longer justifies or allows the safe participation of the participant.

Figure S1: Percentage of participants reaching interocular differences in best-corrected visual acuity at baseline and at each time point spanning the patching period (with imputation of missing values).

The six panels represent the main time points across the trial (compare G0, P0, P6, P12, P18 and P24 in Figure 1). For each panel the percentages of participants reaching the thresholds of improvement indicated on the y-axis are provided for the EOT group to the left of the panel (shown in gold colours) and for the EP group to the right of the panel (shown in blue colours). Different shades of colour represent the breakdown for the type of amblyopia (anisometropic, mixed, strabismic) for each time point across the whole trial. The % values provided are for all participants in each group. Statistical comparisons between EOT and EP groups using Chi-square tests are shown.

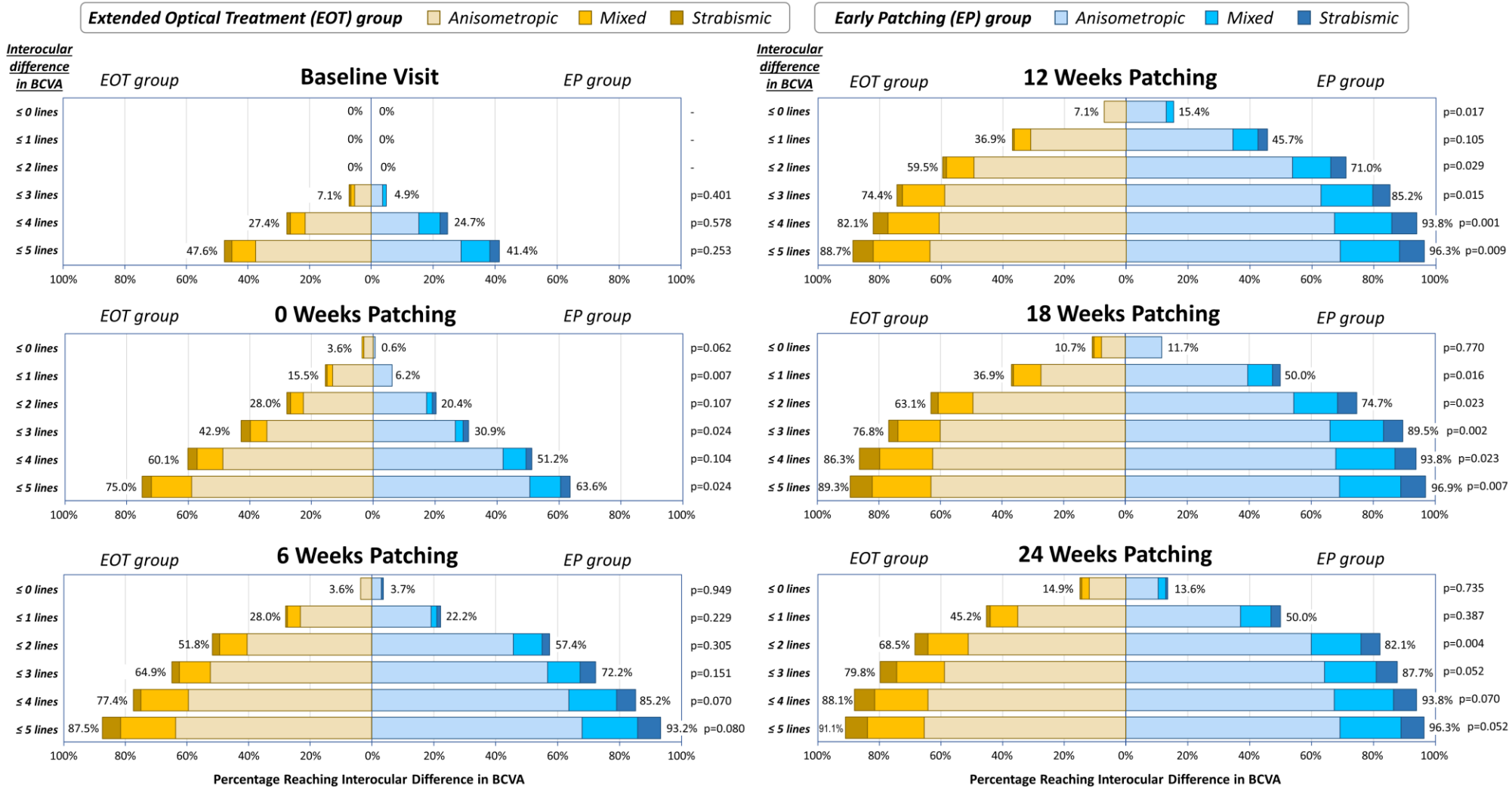


Figure S2: Time course of changes in interocular differences in BCVA across the study without imputation of missing values and excluding study dropouts.

Mean and standard deviations of interocular differences in best-corrected visual acuity (BCVA) are shown, where EOT = Extended Optical Treatment group with data shown in gold squares and EP = Extended Patching group with data shown in blue circles. G0, G6 and G12 indicate weeks of glasses wear whereas P0, P6, P12, P18 and P24 indicate weeks of patching.

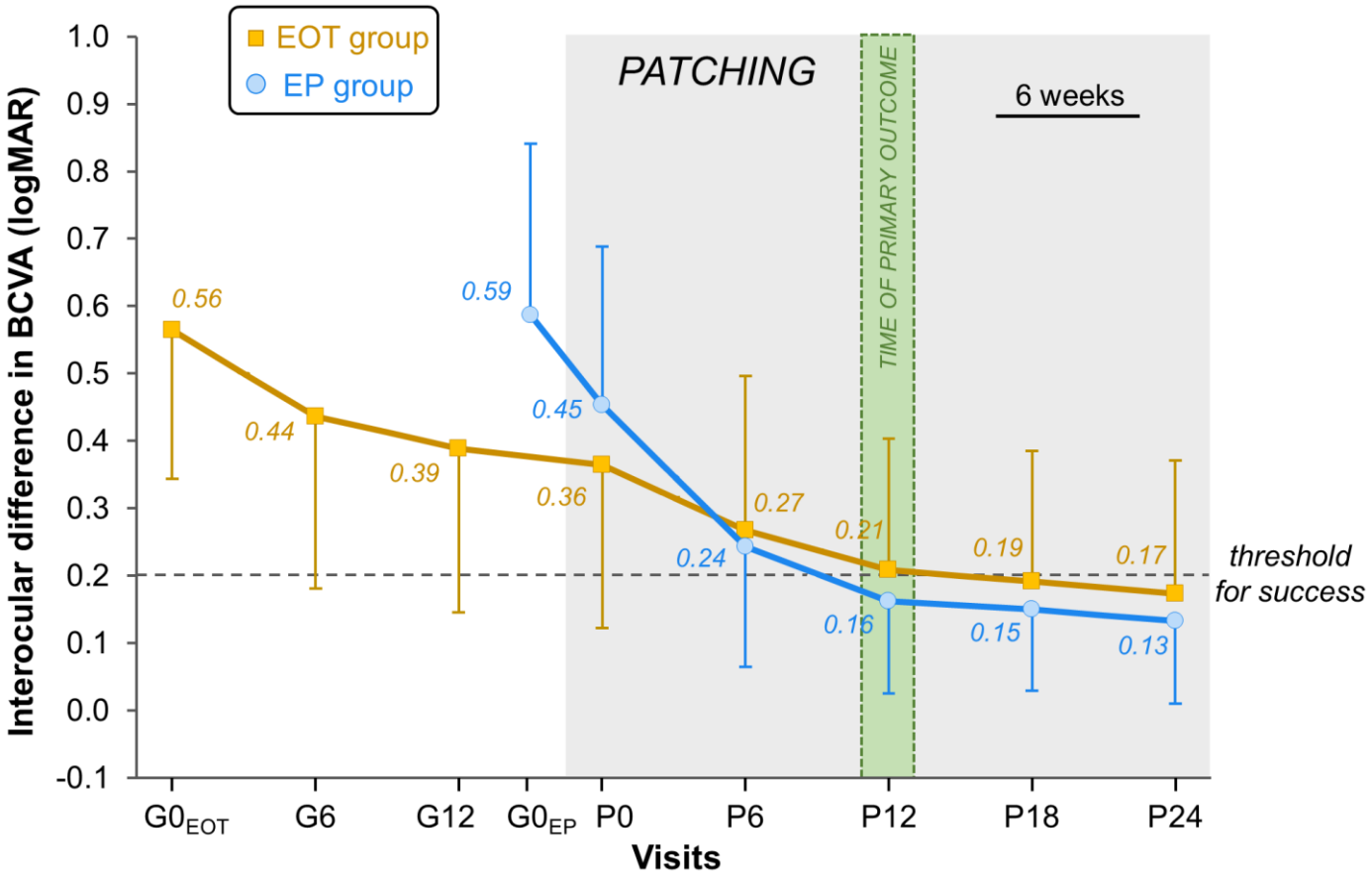


Table S3: Success / failure defined at three different thresholds, with statistical comparisons, (A) without, and (B) with imputation of missing values.

'Start of patching' corresponds to the Week 18 (EOT) and Week 3 (EP) examinations, i.e. the final orthoptic examination prior to patching commencing. The EP group has a significantly higher percentage of success at the primary and two secondary endpoints. Chi-square tests were used to compare difference in proportions between EOT and EP groups.

A. Success / failure without imputation of missing values

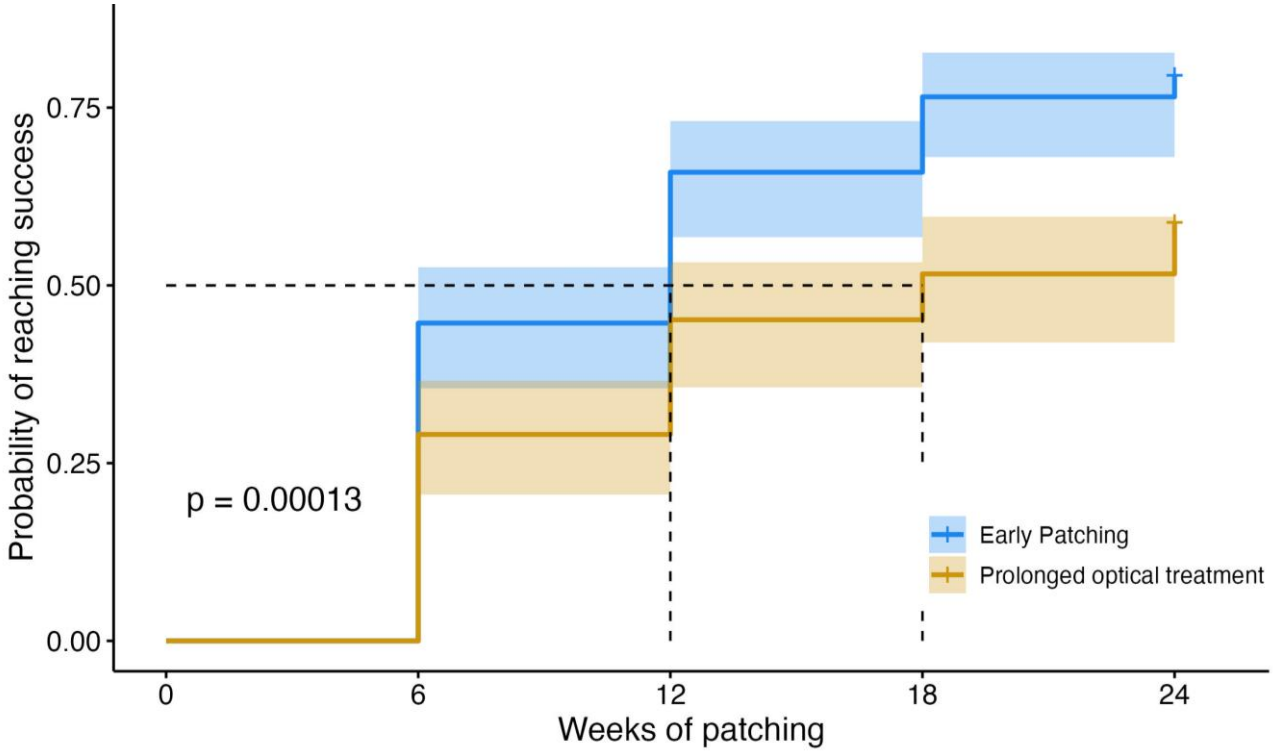
	Start of Patching (P0)		12 Weeks Patching (P12)		18 Weeks Patching (P18)		24 Weeks Patching (P24)	
	% success	*n success / total*	*% success*	*n success / total*	*% success*	*n success / total*	*% success*	*n success / total*
1-line residual amblyopia or better								
EOT group	14.63%	24 / 164	32.91%	52 / 158	36.36%	56 / 154	41.36%	67 / 162
EP group	5.63%	9 / 160	44.03%	70 / 159	47.20%	76 / 161	47.83%	77 / 161
	0.0073		*0.0420*		*0.0512*		*0.2423*	
2-lines residual amblyopia or better								
EOT group	26.83%	44 / 164	54.43%	86 / 158	57.14%	88 / 154	60.49%	98 / 162
EP group	18.75%	30 / 160	67.30%	107 / 159	71.43%	115 / 161	75.78%	122 / 161
	0.0833		*0.0189*		*0.0081*		*0.0032*	
3-lines residual amblyopia or better								
EOT group	40.85%	67 / 164	67.09%	106 / 158	68.18%	105 / 154	67.28%	109 / 162
EP group	28.75%	46 / 160	79.87%	127 / 159	83.23%	134 / 161	81.37%	131 / 161
	0.0223		*0.0099*		*0.0018*		*0.0038*	

B. Success / failure with imputation of missing values

	Start of Patching (P0)		12 Weeks Patching (P12)		18 Weeks Patching (P18)		24 Weeks Patching (P24)	
	% success	*n success / total*	*% success*	*n success / total*	*% success*	*n success / total*	*% success*	*n success / total*
1-line residual amblyopia or better								
EOT group	15.48%	26 / 168	36.90%	62 / 168	36.90%	62 / 168	45.24%	76 / 168
EP group	6.17%	10 / 162	45.68%	74 / 162	50.00%	81 / 162	50.00%	81 / 162
	0.0067		*0.1055*		*0.0164*		*0.3865*	
2-lines residual amblyopia or better								
EOT group	27.98%	47 / 168	59.52%	100 / 168	63.10%	106 / 168	68.45%	115 / 168
EP group	20.37%	33 / 162	70.99%	115 / 162	74.69%	121 / 162	82.10%	133 / 162
	0.1070		*0.0289*		*0.0230*		*0.0041*	
3-lines residual amblyopia or better								
EOT group	42.86%	72 / 168	74.40%	125 / 168	76.79%	129 / 168	79.76%	134 / 168
EP group	30.86%	50 / 162	85.19%	138 / 162	89.51%	145 / 162	87.65%	142 / 162
	0.0241		*0.0149*		*0.0021*		*0.0527*	

Figure S3: Kaplan-Meier survival analysis of probability of time to reach treatment success.

A. Kaplan-Meier Survival analysis plot showing the probability of reaching success (defined as ≤0.200 logMAR interocular difference) in the early patching (EP) compared to the extended optical treatment (EOT) group with weeks of patching. The estimated median time (± 95% confidence interval) is shown by the dashed black lines.



B. Result of a multivariable Cox proportional hazard regression model assessing the association between clinical and demographic variables and probability of success after patching. The hazard ratio is shown graphically and numerically with the 95% confidence interval.

Variable		N	Events	Hazard ratio	p
Age (years)		255		0.76 (0.67, 0.87)	<0.0001
Sex	F	111	81	Reference	
	M	144	96	0.83 (0.62, 1.12)	0.22
Group	POT	124	73	Reference	
	EP	131	104	2.00 (1.47, 2.72)	<0.0001
Type of amblyopia	Anisometropic	170	128	Reference	
	Mixed	63	35	0.77 (0.52, 1.13)	0.18
	Strabismic	22	14	0.72 (0.40, 1.27)	0.25
Initial Visual Acuity		255		0.12 (0.05, 0.27)	<0.0001

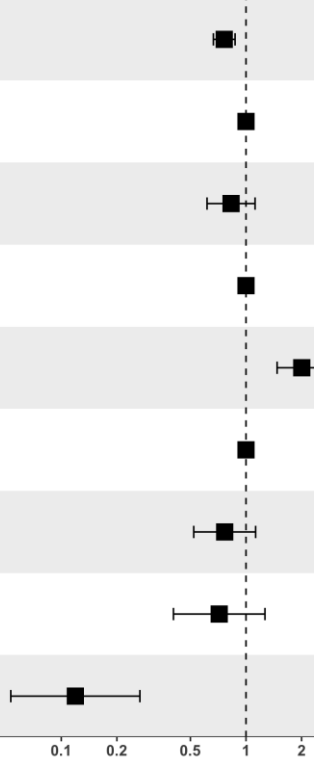


Figure S4: Density distribution histograms of the key factors determining success to extended optical treatment (EOT) after 18 weeks glasses wear.

Children reaching success by 18-weeks glasses wear are shown in pink in contrast to those who do not (fail) in cyan. AE = amblyopic eye, FE=fellow eye, logMAR = logarithm of the minimum angle of resolution.

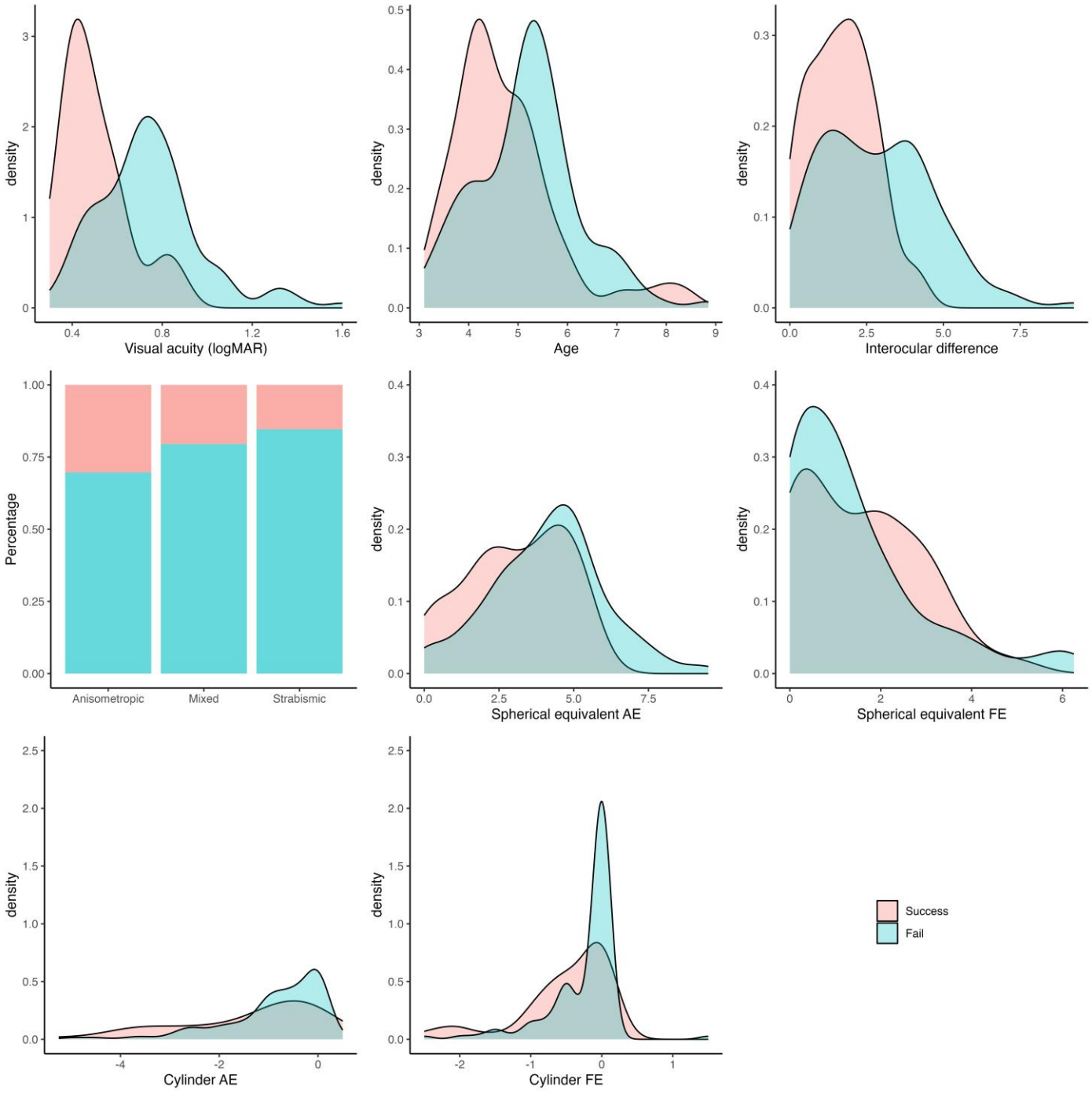


Figure S5: Change in stereoacuity between the baseline visit and after 12 weeks of prescribed patching.

Differences in number of octaves change in stereoacuity for each participant are given for the two groups where EOT = extended optical treatment and EP = early patching.

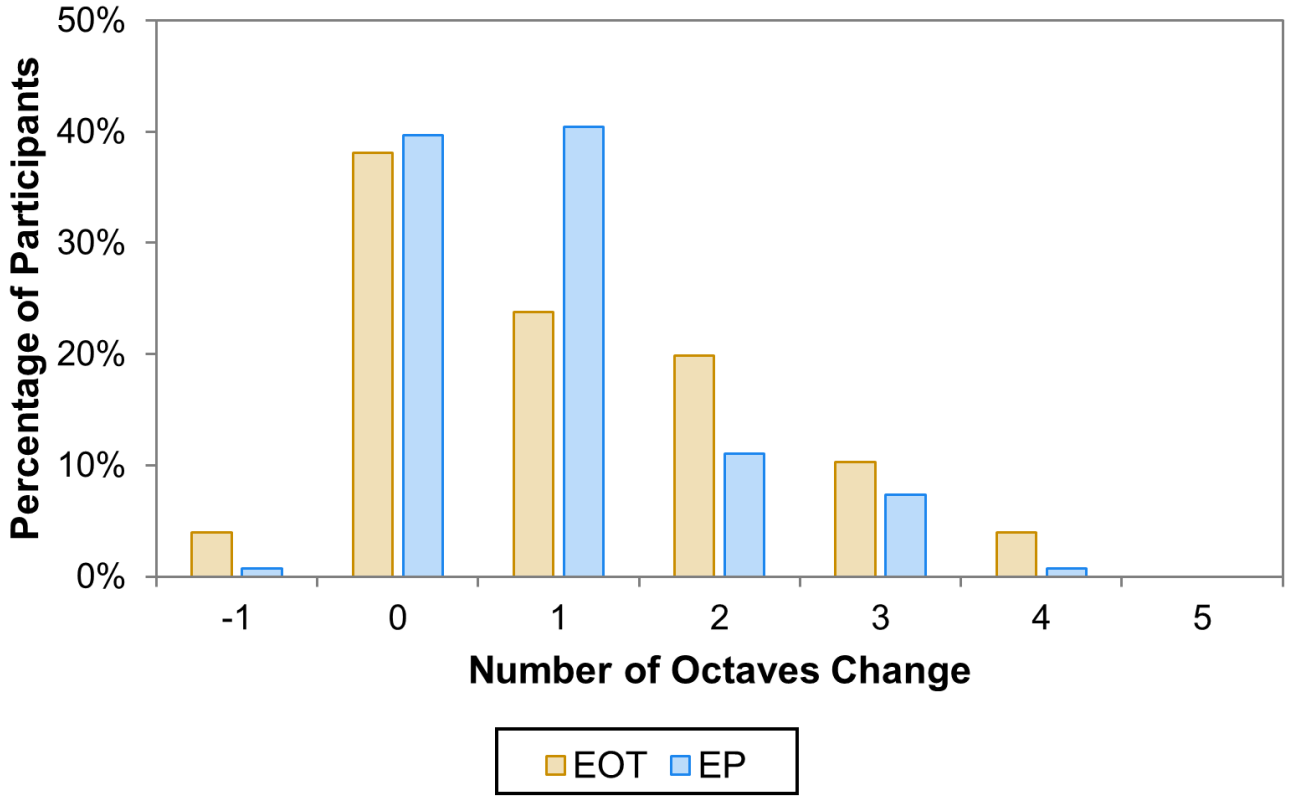
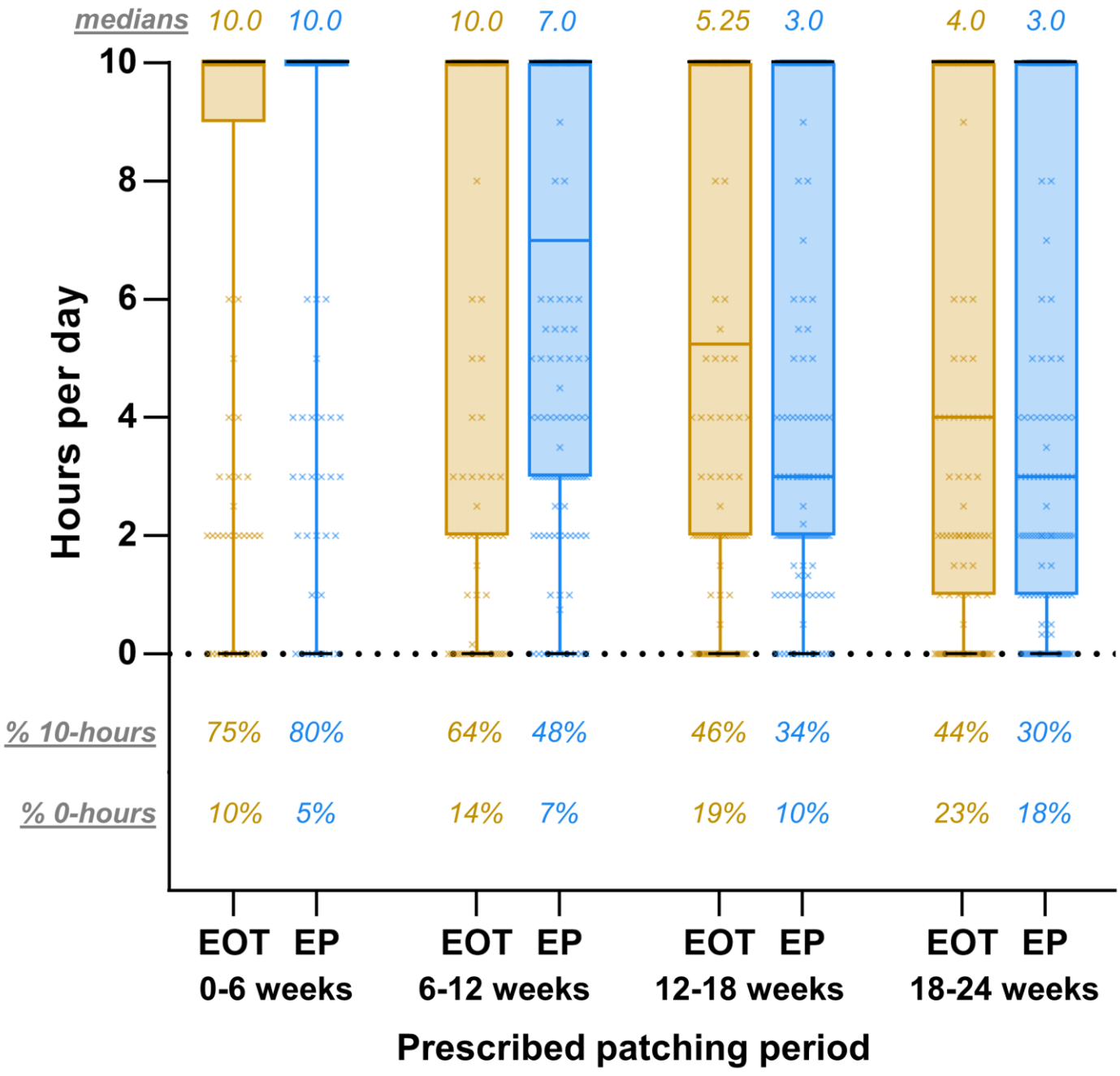


Figure S6: Box and whisker plots of (A) prescribed patching and (B) electronically monitored adherence to glasses wear and patching.

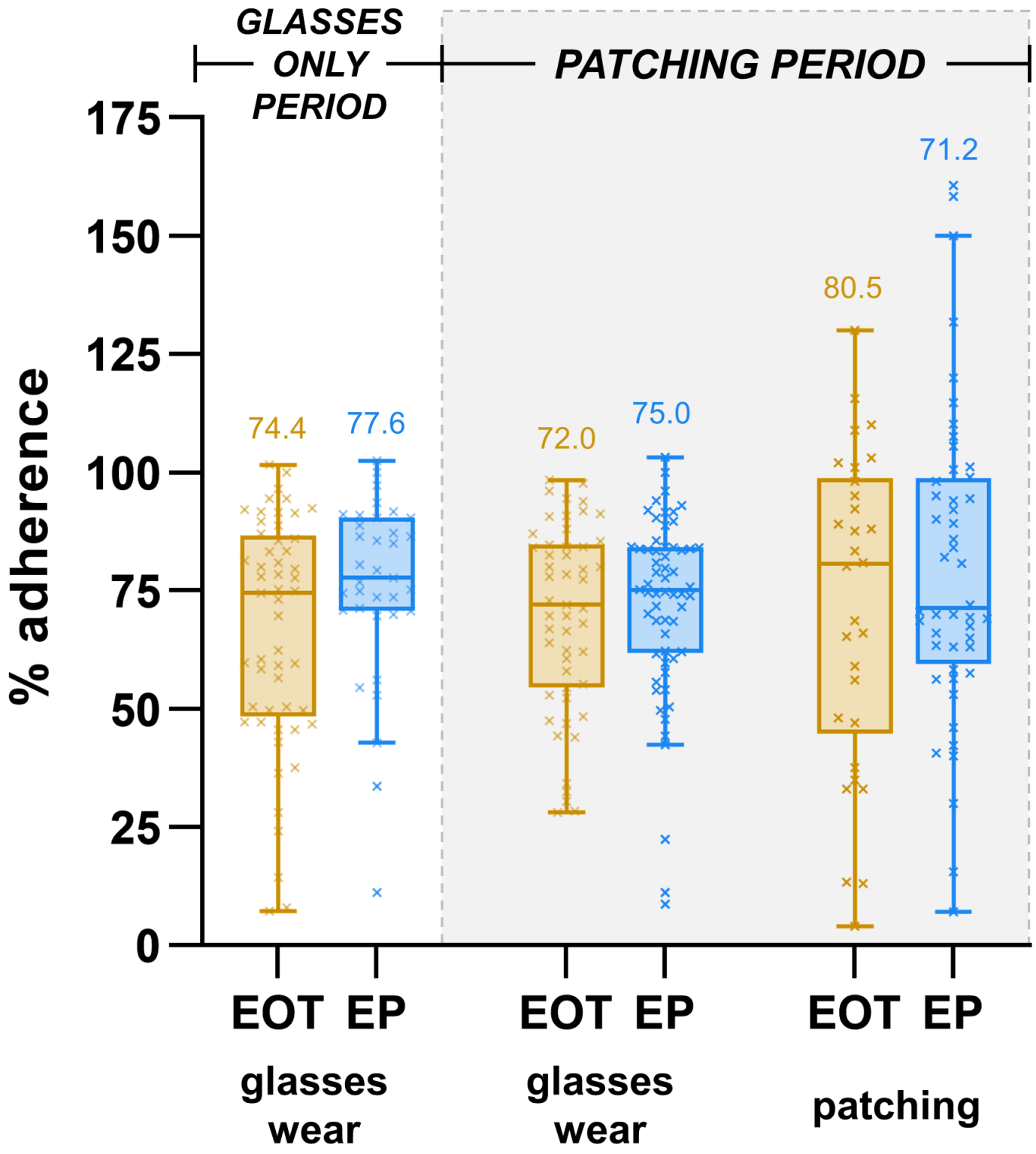
The boxes indicate medians and interquartile ranges, the whiskers show the range of values. The median values are added above each box and whisker. EOT = extended optical treatment and EP = early patching. Waking hours were determined from data published by Galland et al., *Sleep Med Rev.* 2012;**16**(3):213-22. Outliers were determined using the Tukey method.

Recordings were not available for 45·0% (749/1664) electronic monitor measurements (45·5% in EOT group and 44·5% in EP group) because:(i) there were technical errors (27·0%); (ii) EDMs were not tolerated (12·2% overall: 8·4% for glasses wear and 17·6% for patching), and (iii) EDMs were not returned (5·8%).

A. Prescribed patching



B. Electronically monitored glasses wear and patching



Lazy Eye Treatment Questionnaire – Parents Response

The questionnaire is a modified version of the Amblyopia Treatment Index questionnaire, developed by the Pediatric Eye Investigator Group (PEDIG) to include perspectives on glasses wear in addition to patching. Questions that were not relevant to glasses wear were excluded.

For parents/guardians, only the specified questions were considered in the analysis: (i) 15 questions marked with † related to patching, and (ii) 15 questions marked with ‡ concerning glasses wearing.

For children, we focused on the two marked questions deemed most equivalent to those posed to parents and guardians regarding (i) § patching and (ii) ¶ glasses wearing for children.

We would like to thank you for letting your child participate in the study looking at the role of glasses and patch in the improvement of amblyopia treatment. As part of the study, we would like to receive some feedback so we can improve treatment by involving your experience of the treatment. Please take time to answer the following questions.
Please **tick** which box relates most to how you feel:

Questions about patching:	**Strongly agree**	**Agree**	**Neither agree or disagree**	**Disagree**	**Strongly Disagree**
† My child does not seem to mind wearing the patch once it is on.					
† I worry that by wearing the patch, my child may miss out on fun activities (such as games and parties).					
† Wearing the patch makes it hard for my child to play outside, such as running, jumping or riding a bike/tricycle					
† I have trouble putting on my child's patch (and keeping it on)					
† Wearing the patch is a source of tension or conflict in my relationship: a) with my child b) with another family member c) with my child's babysitter or teacher					
† Wearing the patch makes it difficult for my child to draw, colour, or write					
† My child can see well when wearing the patch					
† Wearing the patch makes my child's eye or eyelids red or irritated					
† I worry that my child does not wear the patch enough					
† My child is more clumsy and uncoordinated than usual when wearing the patch.					
† I notice that other children stare at my child when the patch is on.					
† I believe that wearing the patch will improve my child's vision.					

† Wearing the patch makes it difficult for my child to play with blocks or toys.					
† I sometimes forget to put the patch on my child					
† I worry that wearing the patch will make my child feel different from other child					
Questions about the Glasses	**Strongly agree**	**Agree**	**Neither agree or disagree**	**Disagree**	**Strongly Disagree**
‡ My child does not seem to mind wearing glasses					
‡ I worry that by wearing glasses, my child may miss out on fun activities (such as games and parties)					
‡ Wearing glasses makes it hard for my child to play outside, such as running, jumping and riding a bike/tricycle					
‡ Wearing glasses is a source of tension or conflict in my relationship: a) with my child b) with another family member c) with my child's baby sitter or teacher					
‡ My child can see well when wearing glasses					
‡ My child complains when it is time to wear their glasses					
‡ I worry that my child does not wear their glasses enough					
‡ I notice that other children stare at my child when their glasses are on					
‡ I believe that wearing glasses will improve my child's vision					
‡ I sometimes forget to remind my child to wear their glasses					
‡ I worry that wearing glasses will make my child feel different from other children					
‡ I felt my child wore their glasses for the right amount of time before starting patching					

Questions about treatment	**Very difficult**	**Difficult**	**Neither difficult nor easy**	**Easy**	**Very Easy**
For myself and my child's carers, we found the experience of amblyopia treatment					
My Child's experience of the amblyopia treatment was:					

Questions about treatment	**Not very worth it**	**Not worth**	**Neither worth nor not worth it**	**Worth it**	**Very worth it**
I found that the experience of amblyopia treatment was:					

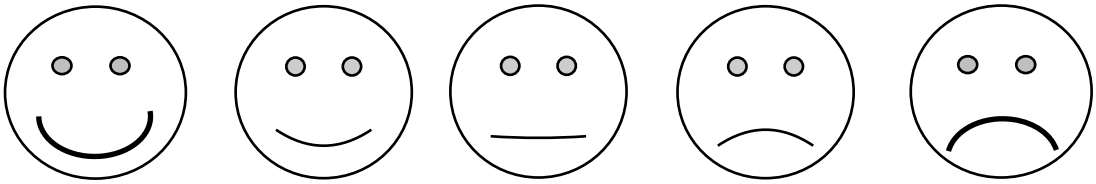
My Child's experience of the amblyopia treatment was:					

If you have any further relevant information about the experience of the amblyopia treatment, for you or your child, please comment below:

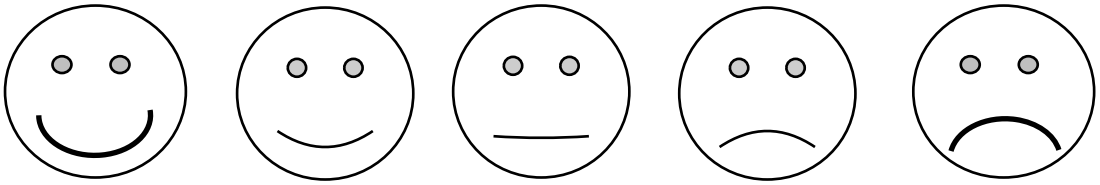
Thank you for taking the time to complete this.

If you are happy for your child to take part, and they are happy to help us too, please ask them to colour in one face that shows how they felt at different times:

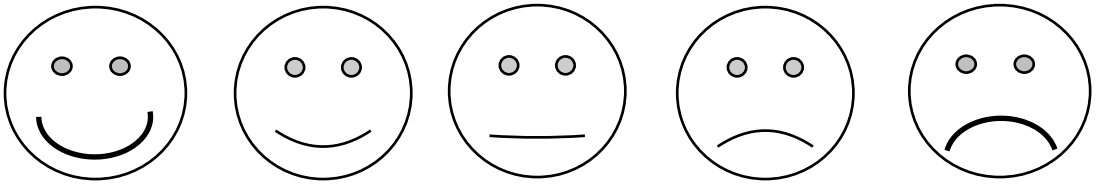
Which Face is like you most of the time?
Colour in one face



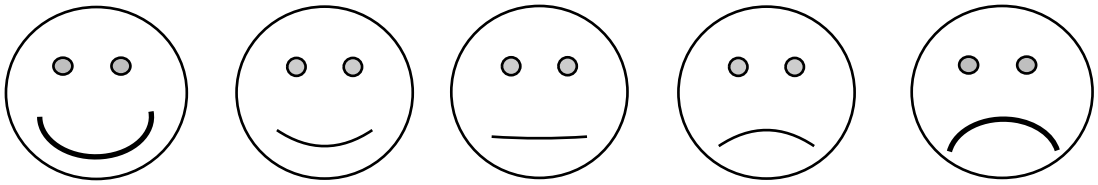
§ **What face is like you when you have to put your patch on?**
Colour in one face



Which face is like you when you take your patch off?
Colour in one face



¶ **Which face is like you when you wear your glasses?**
Colour in one face



Which face is like you when you take your glasses off?
Colour in one face