Frank A Proudlock, Michael Hisaund*, Gail Maconachie, Eleni Papageorgiou, Ali Manouchehrinia, Annegret Dahlmann-Noor, Payal Khandelwal, Jay Self, Christina Beisse, Irene Gottlob, on behalf of the EUPatch study group†*

A b y i , h e s t e i s u i r e t h i h e , i s u b i d h e c e r . A e t e e i c t r e t b e r e t h i s r e e p e b y h e c i i c u i e i e s s e r e u t i e s . h e i p h i s s u y s t e r e i t e s i e t h i r e i e , i h i h u t e t e e i c t r e t e t (E O) , i r i s e e t r e t i p .

E i P t h s r i s e e t r e t i e u c t e i 3 0 h s i t s i h e K , G r e e c e , A u s t r i , G e r y , S i t e r . G i r e e 3 8 y e r s i h e y e t e c t e , u t r e p t e b y i (e e s i t e r u r i e r e c e _ 0 . 3 0 i h h e i i u e r e s u f r M A R] b e s t e r r e c t e i s u u i t y [B C V A]) u e t i s e t r i , s t r l i s u s , r b h t e r e e i i b e . P r i d t s e r e r y s s i e (1 : 1) i e u t e r - e e r t e s q u e c e t i h e r h e E O r u (1 8 e e s s s e s u s e b e r e t h i) r t h e e r y t h i r u (3 e e s s s e s u s e b e r e t h i) , s t r f i e r t y e s e e i t y b y i . A r i d t s p e r e i i f y p r e s c i b e i t e s i e t h i p r e i e (1 0 h / y , 6 y s e r e e) , s u e e t e i h p f p t e i s . h e t h i e r s u t 2 4 e e s . P r i d t s , r e t s r u r i s p s s e s s r s , h e t i s t f s i d e r e t p s e t t r e t e t p c h . h e i r y u t e p e s u c c e s s u t r e t e t (e , 0 . 2 0 M A R i t e r u r i e r e c e i B C V A) t e r 1 2 e e s p t h i . e i r y y s e s e r e e u c t e : h e i y s i s i u e r i d t s , i u i h e s e h e r p e e u t , h t e p u e h e s e h e i t r i e u t e e t t e e 1 2 r e i e e h e s u y , h e h t e r y s i s i u t e t h i s i s s i t . A e i i b e p r e y s s i e r i d t s e r e s s e s s e e r e r s e e e t s . h i s s u y s r e i s t e r e i h h e I t e r f S t r R e i s e p C t p e i N i b e r r e i s t r y (I S R C N 5 1 7 1 2 5 9 3) i s e e r r e c u i f .

B e t e e u j e 2 0 , 2 0 1 3 , M r h 1 2 , 2 0 2 0 , t e r e u s e e i h t r i d t s u i e i i b e t e r e t i e s c r e e i , e r e y s s i e 3 3 4 r i d t s (1 7 0 t h e E O r u p 1 6 4 t h e e r y t h i r u) , i u i 1 8 8 (5 6 %) b y s , 1 4 6 (4 4 %) p i r s , p t (1 %) r i d t s p h e s e s s t r e e r e . 3 1 7 p r i d t s (1 5 8 i h e E O r u 1 5 9 i h e e r y t h i r u) p e r e y s e e r h e i r y u t e e

Correspondence to:
Prof Irene Gottlob, Department of Neurology, Cooper University Health Care, Cooper Medical School of Rowan University, Camden, NJ 08103, USA

Current outcomes of patching treatment for unilateral amblyopia are poor. In the UK, for example, 30% of children treated with patching do not reach the best corrected visual acuity (BCVA) of 6/12 (ie, the ability to read, at a distance of 6 m, something that someone with no visual impairment can read from 12 m away) in the amblyopic eye, often after several thousand hours of prescribed patching.[6] Poor adherence to patching, which can happen as a consequence of reduced vision while patching the contralateral eye or of social and educational issues, has been identified as an important barrier to the attainment of improvement in BCVA.[7] In addition, personalised approaches for the treatment of amblyopia on the basis of factors such as age, type of amblyopia, and baseline visual deficit are not widely available.[3] Such personalised approaches could potentially increase the likelihood of treatment success and reduce the duration of treatment, costs, and burden of amblyopia on individuals, their families, and health-care services.[8]

Amblyopia is usually treated first with a period of glasses use to correct for refractive errors, followed by patching of the contralateral eye. Several studies, including a meta-analysis, found a moderate to large e ect size from the glasses-only period before commencing patching,[9–15] which significantly decreased for children who commenced treatment when they were older.[9] However, whether parameters such as severity of amblyopia or refractive error and type of amblyopia have a role in the success of treatment with glasses is unclear.

These reported results have led to the notion that all children with amblyopia should be prescribed an extended period of glasses use (also called extended optical treatment [EOT] or refractive adaptation) before the start of the patching treatment.[12] The rationale behind this approach is to improve vision before patching,

obtained from each participant's parent or guardian and assent was obtained from children whenever applicable (ie, usually on children older than 4 years).

[redacted]

Participants meeting the inclusion criteria were randomly assigned (1:1) to the EOT group (ie, use of glasses for 18 weeks followed by patching and use of glasses for 24 weeks) or to the early patching group (use of glasses for 3 weeks followed by patching and use of glasses for 24 weeks), with a stratified, balanced block design with a block size of four (ie, EOT with electronic monitoring of patching or glasses use; EOT without monitoring; early patching with monitoring; and early patching without monitoring). 50% of participants in each treatment group were randomly allocated electronic dose monitors for assessment of adherence to glasses use and patching. Stratification was done according to type (anisometropic, strabismic, or mixed) and severity (severe [ie, amblyopic eye BCVA ≥0·60 logMAR] or mild to moderate [ie, <0·60 logMAR]) of amblyopia. Randomisation was not stratified on the basis of the centre due to the small number of participants in some centres.

Randomisation was done by the local investigator using a secure online randomisation service (Sealed Envelope, London, UK) that assigned participants to treatment groups and could be accessed locally at sites. The local investigator communicated the assigned group information to the participants and was responsible for subsequent examinations and treatment. Participants, parents or guardians, assessors, and the trial statistician were not masked to study treatments.

[redacted]

Before enrolment, potential participants received a full ophthalmological examination, including a cycloplegic refraction. At this examination, participant information for the study was provided and the glasses prescription was issued but not yet worn. After informed consent was obtained, participants were enrolled in the study, randomly assigned to a treatment group, and requested to wear glasses during all waking hours from the date of first examination (time G0; figure 1). Both groups were prescribed an intensive patching regimen, supplemented with motivational materials to improve adherence to the use of glasses and patching. Participants in the EOT group were assigned 18 weeks of full-time glasses use, followed by 24 weeks of combined patching and glasses use. Participants in the early patching group were assigned 3 weeks of full-time glasses use followed by 24 weeks of combined patching and glasses use.

Patching was initially recommended for 10 h per day, 6 days per week (with one non-occluding day chosen by families), with the patching hours modified at the discretion of the orthoptist or ophthalmologist after improvement of visual acuity, if the treatment endpoint was reached, or if adverse e ects occurred. In participants assigned electronic monitoring, electronic dose monitors were placed on the frame of glasses or between two occlusion patches (Ortopad Elite, Pietrasanta Pharma, Lucca, Italy) to monitor glasses use and patching.[22] All data from electronic dose monitors were analysed in the University of Leicester (Leiceister, UK); feedback from the monitors was not provided to participants or treating orthoptists at any time.

The EOT group received eight orthoptic assessments over 42 weeks and the early patching group received six assessments over 27 weeks (figure 1). A deviation of 1 week for each orthoptic assessment was permitted. Each 6-weekly assessment included measurements of uniocular BCVA with the logMAR Crowded test and stereoacuity (a measure of depth perception) with the Frisby Near Stereotest (Stereotest, Thame, UK). Many participants were unable to resolve the 6 mm plate at 30 cm (ie, the lowest stereoacuity measurement, equivalent to 600"), especially for early examinations, and were assigned a value of 1200" to enable statistical analysis. After the trial, children returned to clinical care if further treatment was required.

The Amblyopia Treatment Index questionnaire, developed by the Pediatric Eye Investigator Group (PEDIG), was administered after 12 weeks and 24 weeks of prescribed patching to record the attitudes towards treatment of parents or guardians (appendix pp 16–19).[23] Some questions were modified to include perspectives on the use of glasses in addition to patching. The children's perspectives were recorded with the Smiley Face Likert scale. Data were recorded at each site and collated and analysed centrally at the University of Leicester, UK.

[redacted]

The primary outcome was the proportion of successfully treated children (ie, reaching ≤0·20 logMAR interocular di erence in BCVA) after 12 weeks of prescribed patching. A threshold of success of logMAR of less than or equal to 0·10 was originally planned, as stated in the protocol. However, this threshold falls within the normal variability of BCVA measurements in children.[24] Hence, a decision was made by lead investigators to adjust this threshold to less than or equal to 0·20 on May 13, 2021. This amendment was made before the statistician viewed the data and commenced statistical analysis. Children who dropped out of the study were recorded as not having responded to treatment without data imputation. Prespecified secondary exploratory outcomes were the proportion of successfully treated children after 18 weeks and 24 weeks of prescribed patching; total hours of prescribed patching required; electronic dose monitor-measured compliance to glasses use and patching; and responses of parents, guardians, and children to questionnaires about the treatment. Post-hoc secondary exploratory outcomes were the proportion of successfully treated children according to other definitions of

treatment success (ie, ≤0·10 and ≤0·30 logMAR interocular di erence in BCVA); the proportion of successfully treated children after imputation of missing values by use of multiple imputation methods for study dropouts or missed visits; time to reach successful treatment, assessed with a time-to-event analysis; the determination of characteristics of participants most likely to respond to EOT treatment without patching by constructing a decision tree with a recursive partitioning method; and changes in stereopsis between baseline and after 12 weeks of patching.

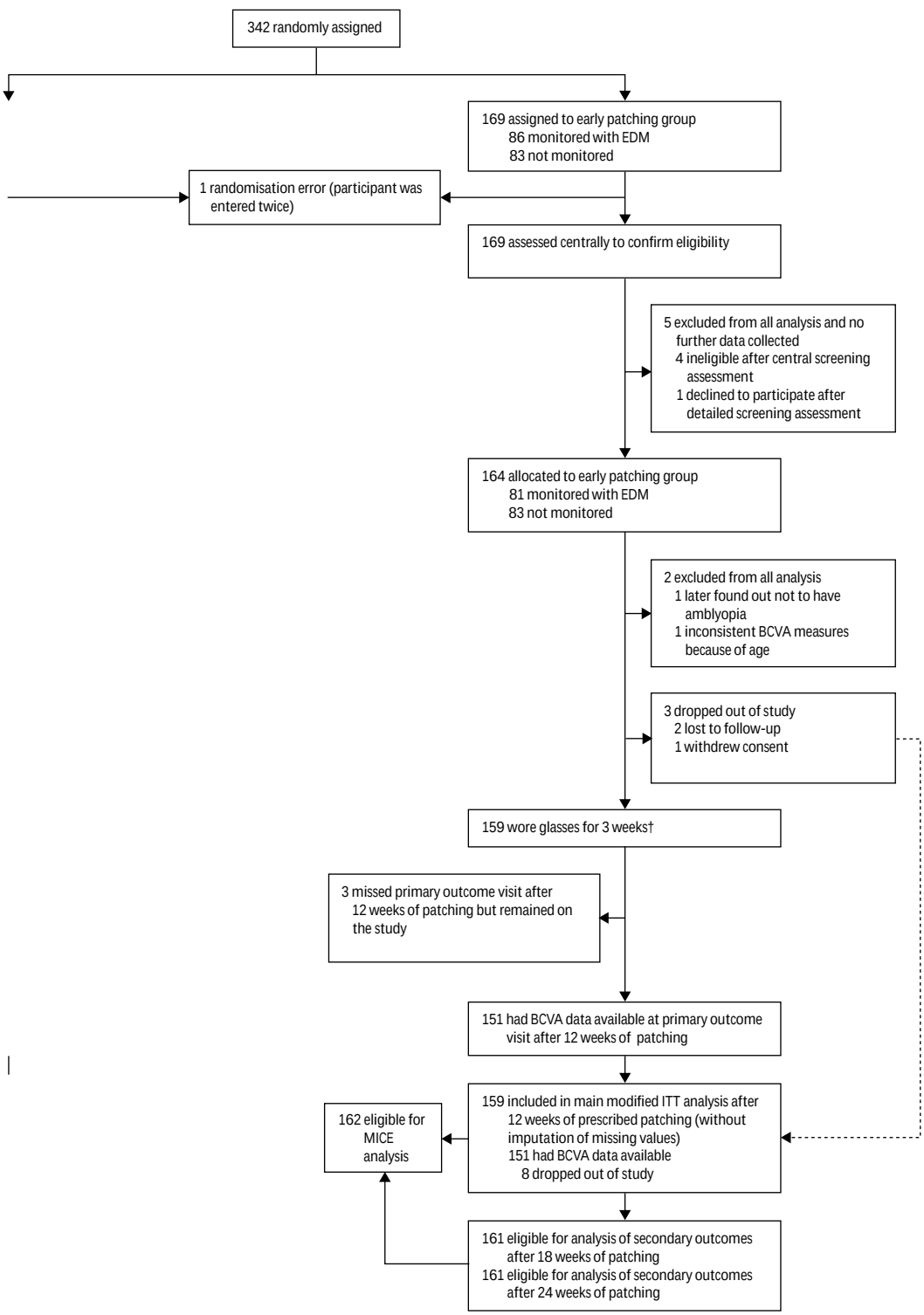
The sample size was based on our previous studies[19,20] recording BCVA outcomes over a 12-week patching timeframe. In Pradeep and colleagues' study,[20] success after 12 weeks of patching without EOT (10 h/day, 6 days per week) was 23% (≤0·10 logMAR interocular di erence in BCVA). Accordingly, a 15% di erence in success—the same di erence in success observed between the two patching regimens in Awan and colleagues[19]—required 173 participants in each arm (two-sided α of 0·05, power 80%, and a 15% dropout rate).

The primary analysis was done in a modified intention-to-treat (mITT) population consisting of all randomly assigned participants, including those who dropped out, but excluding those who were deemed ineligible after randomisation. A full ITT analysis of all randomised participants was initially planned; however, we did not anticipate the randomisation of several ineligible participants after glasses had been prescribed and worn. Hence, a decision was made by the lead investigators on May 13, 2021, to use the mITT design outlined here, performed both with and without imputation of missing values. The main primary analysis was performed in all participants in the mITT population for whom data were available for the primary outcome visit with no imputation for missing values (treatment was deemed unsuccessful in participants who dropped out of the study), and another analysis was performed including all participants in the mITT population, imputing missing data with the multiple imputation by chained equations approach for missing values. Pearson's χ^2 tests were used to compare success rates for the primary outcome after 12 weeks of prescribed patching, after 18 weeks and 24 weeks of prescribed patching, and with other definitions of success (ie, ≤0·10 and ≤0·30 logMAR interocular di erence in BCVA).

Several secondary analyses were decided post-hoc because a formal statistical analysis plan was not included at the time the trial was originally planned. A Kaplan–Meier analysis was used to estimate median time from the initiation of patching (ie, start and origin) to time of treatment success or end of follow-up (at week 24 of patching). The analysis included all participants, from both study groups, who provided measurements at the visit at which patching commenced (ie, P0; figure 1), along with at least one follow-up visit, but excluded participants who had already reached success by P0. The median time to treatment success between groups was compared with the log-rank test. The probability of treatment success was calculated with the formula recommended by Spruance and colleagues[25] (ie, probability=HR/[1+HR]), with HR being the hazard ratio from a Cox regression model, adjusted for age at baseline, sex, type of amblyopia (ie,

term between time (in 6-week intervals) and group. Electronically monitored glasses use and patching were compared with χ^2 tests.

The between-group di erences in the change in the number of octaves of stereoacuity (a measure of depth perception analysed in octave changes—distinct from



visual acuity measured in logMAR) for each participant between baseline and after 12 weeks, 18 weeks, and 24 weeks of patching were compared with Kruskal's γ statistic.

Questionnaire data from parents or guardians and children were analysed by aggregating individuals' responses into a single score, reflecting an overall perception of the intervention (appendix pp 16–19). This score was then dichotomised into positive (including positive and strongly positive responses) and negative (including strongly negative, negative, and neutral). We compared the di erence in the proportion of individuals in the two categories at the primary timepoint and the final visit between groups using the χ^2 test.

For all randomly assigned participants, adverse events were reported to clinicians at study sites during research visits and compared descriptively between the groups.

All statistical tests were two-sided (significance threshold p=0·05). R (version 4.1; survival, rpart, and caret packages) was used for data management and data analysis. The trial is registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN51712593) and is no longer recruiting.

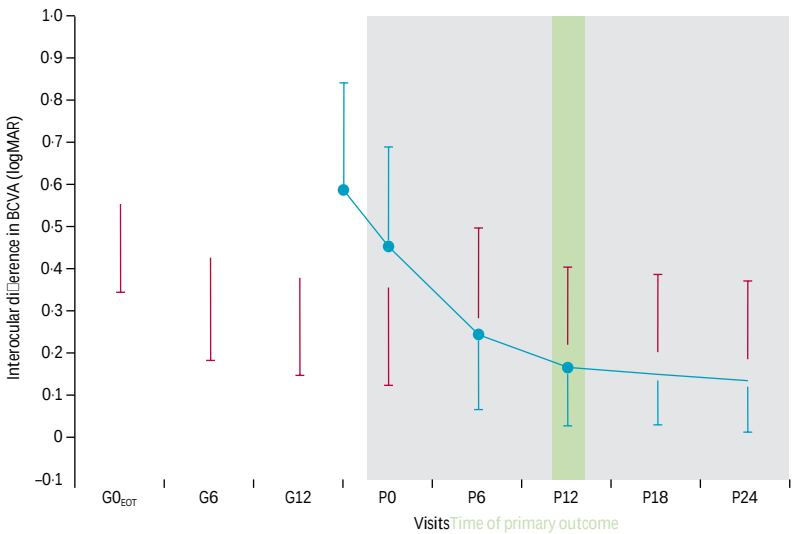
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Between June 20, 2013, and March 12, 2020, after an initial eligibility assessment by the local centre, 342 participants were recruited and randomly assigned (173 to the EOT group and 169 to the early patching group; figure 2). Recruitment was interrupted by the start of restrictions due to the COVD 7l9.7atcersmic0 0 9 343

which 136 participants (86%) from the EOT group and 151 participants (95%) from the early patching group provided BCVA measurements; 22 participants (14%) from the EOT group and eight participants (5%) from the early patching group were lost to follow-up. Treatment success or failure could not be accurately assessed in ten participants (6%) from the EOT group and three participants (2%) from the early patching group because they missed the primary outcome visit and so these participants were excluded from the main primary analysis but were included in the imputation analysis.

The baseline characteristics of allocated participants are shown in the table. Median follow-up was 42 weeks (IQR 42–42) in the EOT group and 27 weeks (27–27) in the early patching group.

For the primary outcome, a significantly larger proportion of children had a successful treatment (ie, ≤0·20 logMAR interocular di erence in BCVA) in the early patching group (107 [67%; 95% CI 60–75] of 159) than in the EOT group (86 [54%; 46–62] of 158) after 12 weeks of prescribed patching (13% di erence; p=0·019). Similar patterns were observed with the imputation of missing values (appendix p 6). A breakdown of children reaching thresholds from 0·00 to 0·50 logMAR interocular di erence in BCVA in 0·1 increments, including for di erent types of amblyopia, after 12 weeks and 24 weeks of patching is shown in figure 3. Results at baseline and at each visit spanning the patching period, without and with imputation of missing values, are available in the appendix (pp 5–6). The time course of improvement in mean interocular di erence in BCVA across the study without imputation of missing data is shown in figure 4; equivalent data with missing data imputed are also shown in the appendix (p 7). The improvement in interocular di erence in BCVA during EOT, with glasses use only, occurred mostly during the first 6 weeks, with the mean change of 0·127 logMAR (SD of



F

Means and SDs of interocular differences in BCVA are shown, with the EOT group data shown in red squares and the early patching group data shown in blue circles. G0, G6, and G12 indicate weeks of glasses use; P0, P6, P12, P18, and P24 indicate weeks of patching. The threshold for successful treatment is indicated by the dashed line. BCVA=best corrected visual acuity. EOT=extended optical treatment. $G0_{EP}$=week 0 of glasses use in the early patching group. logMAR=logarithm of the minimum angle of resolution.

differences 0·161) from 0 weeks to 6 weeks being almost twice as large as that occurring between 6 weeks and 18 weeks (mean change 0·061 logMAR [0·120]). The change of 0·127 logMAR (0·161) in the EOT group from 0 weeks to 6 weeks was similar to that occurring in an even shorter period from 0 weeks to 3 weeks in the early patching group (mean change 0·133 logMAR [0·170]). For the participants who reached a 0·10 logMAR difference in BCVA or less after EOT, 14 participants were prescribed 0 h/day of patching, eight were prescribed 2–4 h/day of patching, and two were prescribed 10 h/day of patching for the initial 6 weeks of patching. Neither of the two participants who were prescribed 10 h of patching showed reverse amblyopia; one of these participants improved in stereoacuity by two octaves and the other remained stable.

During 18 weeks of EOT, the mean improvement was 0·190 logMAR (SD of differences 0·183; effect size 1·035 [95% CI 0·835–1·232]) for the interocular difference in BCVA, and 0·255 logMAR (0·191; 1·337 [1·116–1·557]) for BCVA in amblyopic eyes. When patching commenced, the mean interocular difference in BCVA was better in the EOT group than in the early patching group, but accelerated improvement in the early patching group resulted in better interocular difference in BCVA after 12 weeks of prescribed patching, which continued to the end of the trial. After 12 weeks of prescribed patching, the mean interocular difference in BCVA was worse in the EOT group (0·209 logMAR [SD 0·195]) than in the early patching group (0·162 logMAR [0·157]; p=0·026).

For secondary outcomes without imputation of missing data, significantly more children had treatment success in the early patching group than in the EOT group after 18 weeks and 24 weeks of prescribed patching (figure 3; appendix p 8). Similar patterns were observed with imputation of missing values (appendix pp 6, 8). Statistically significant differences between groups were also apparent in the proportion of children having successfully reached 0·30 logMAR interocular difference in BCVA or better (except after 24 weeks of patching with imputation of missing values; appendix p 8). For the proportion of children having successfully reached 0·10 logMAR interocular difference in BCVA or better, significant differences between the groups were only observed after 12 weeks of patching without imputation of missing values and after 18 weeks of patching with imputation of missing values.

In the time-to-event analysis, the Kaplan–Meier estimate (n=255) of the median time from start of patching to treatment success was 12 weeks (95% CI 6–12) in the early patching group and 18 weeks (12–not calculable) in the EOT group (p=0·0001; appendix p 9). Children in the early patching group had a 67% (95% CI 60–73) higher probability of treatment success after commencing patching compared with the EOT group. The multivariable Cox proportional hazards regression model found that older age and higher amblyopic eye BCVA at baseline were significantly associated with a longer time to success (appendix p 10).

In the EOT group (without imputation of missing values), 44 (27%) of 163 children had treatment success (ie, ≤0·20 logMAR interocular difference in BCVA) after 18 weeks of glasses use before commencement of patching (appendix p 8). Age, amblyopic eye BCVA at baseline, and interocular difference in spherical equivalent (but not type of amblyopia) were identified as the most important variables by the partitioning model to assess success of EOT before patching (appendix p 11). A decision tree showing probabilities of success, including these variables, is given in figure 5. The decision tree had 83% (95% CI 76–88) internal accuracy, 68% (52–81) sensitivity, and 88% (81–94) specificity. External validations of the decision tree were assessed in 326 participants from the US PEDIG collaborative[10,15] (of which 103 met our inclusion criteria [appendix p 4]), 223 participants from the UK MOTAS and ROTAS collaborative[14,27,28] (of which 18 met our inclusion criteria), and 40 participants from the Ulverscroft Eye Unit group in Leicester, UK[22] (of which 32 met our inclusion criteria). The UK data, which used similar visual acuity tests to the current study, generated a higher accuracy score (90% [95% CI 78–97]; sensitivity 67% [38–88]; specificity 100% [90–100]) compared with the US data (62% [52–72]; sensitivity 52% [37–67]; specificity 70% [57–82]).

There were no significant differences between groups in stereoacuity improvement from baseline to 12 weeks

(p=0·34; appendix p 12), 18 weeks (p=0·11), or 24 weeks (p=0·11) of patching.

The median hours of prescribed patching dropped from the first 0–6 weeks of the patching period to the final 18–24 weeks in both groups (appendix p 13). However, possibly because of a higher rate of improvement in the early patching group, the reduction in prescribed patching hours was more pronounced in the early patching group than in the EOT group (interaction between group and time p=0·0063).

Electronic dose monitor measurements were unavailable for 749 (45%) of 1664 recordings (appendix pp 13–14). Median electronically recorded adherence to

the early patching group). This anticipated problem was built into the study design with an mITT approach in which all participants lost to follow-up and those who deviated from the protocol were included in the analysis. Although a full ITT analysis was not possible in this

2 Stewart CE, Shah S, Wren S, Roberts CJ. Paediatric eye services: how much of the workload is amblyopia-related? *Strabismus* 2016; **24:** 109–12.

3 Birch EE, Kelly KR. Amblyopia and the whole child. *Prog Retin Eye Res* 2023; **93:** 101168.

4 Rahi J, Logan S, Timms C, Russell-Eggitt I, Taylor D. Risk, causes, and outcomes of visual impairment after loss of vision in the non-amblyopic eye: a population-based study. *Lancet* 2002; **360:** 597–602.

5 Koklanis K, Abel LA, Aroni R. Psychosocial impact of amblyopia and its treatment: a multidisciplinary study. *Clin Exp Ophthalmol* 2006; **34:** 743–50.

6 Awan M, Proudlock FA, Grosvenor D, Choudhuri I, Sarvananthan N, Gottlob I. An audit of the outcome of amblyopia treatment: a retrospective analysis of 322 children. *Br J Ophthalmol* 2010; **94:** 1007–11.

7 Dixon-Woods M, Awan M, Gottlob I. Why is compliance with occlusion therapy for amblyopia so hard? A qualitative study. *Arch Dis Child* 2006; **91:** 491–94.

8 The Lancet. Personalised medicine in the UK. *Lancet* 2018; **391:** e1.

9 Asper L, Watt K, Khuu S. Optical treatment of amblyopia: a systematic review and meta-analysis. *Clin Exp Optom* 2018; **101:** 431–42.

10 Cotter SA, Edwards AR, Arnold RW, et al. Treatment of strabismic amblyopia with refractive correction. *Am J Ophthalmol* 2007; **143:** 1060–63.

11 Cotter SA, Edwards AR, Wallace DK, et al. Treatment of anisometropic amblyopia in children with refractive correction. *Ophthalmology* 2006; **113:** 895–903.

12 Moseley MJ, Fielder AR, Stewart CE. The optical treatment of amblyopia. *Optom Vis Sci* 2009; **86:** 629–33.

13 Steele AL, Bradfield YS, Kushner BJ, France TD, Struck MC, Gangnon RE. Successful treatment of anisometropic amblyopia with spectacles alone. *J AAPOS* 2006; **10:** 37–43.

14 Stewart CE, Moseley MJ, Fielder AR, Stephens DA, Cooperative M. Refractive adaptation in amblyopia: quantification of e ect and o0m6catc26903. 37–43.