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MultifocAL COntact Lenses for Myopia (MALCOLM) control in Australian children: a study protocol for a double-blind, contralateral eye, non-inferiority, randomised controlled clinical trial

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ABSTRACT

Introduction Myopia is the most common refractive error worldwide, but each dioptre increase in myopia leads to an increased risk of degenerative eye disease and permanent vision impairment. Soft contact lens (CL) designs have been developed to slow myopia and potentially reduce long-term risk, but there is still a need for additional designs of varied materials and parameters to cater for diverse patient needs. The MultifocAL COntact Lenses for Myopia control study aims to compare the efficacy of the Acuvue Oasys for Presbyopia (AOP) CL against the Food and Drug Administration approved MiSight 1-Day multifocal CL in controlling progressive myopia in children using a non-inferiority contralateral eye design.

Methods and analysis A double-blind, contralateral eye, non-inferiority, randomised, controlled clinical trial will be conducted at University of New South Wales Sydney, Australia (UNSW). Children (6 to 12 years of age, inclusive) will be randomised to wear AOP in their right or left eye, with the MiSight 1-Day CL fitted to the contralateral eye. The primary outcome is the difference in axial length and cycloplegic objective refraction change between the two CLs over 12 months. Additional outcomes include quality of life, pupillometry and adherence to treatment. To achieve a statistical power of 80% to demonstrate non-inferiority of the AOP to the MiSight 1-Day and taking into consideration a 20% discontinuation rate, the calculated sample size is 72. This trial started recruitment during the recent COVID-19 pandemic in January 2021.

Ethics and dissemination Ethics approval has been obtained from the UNSW Human Research Ethics Committee (HC200052), and the study complies with the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines. The results of this trial will be disseminated in peer-reviewed publications and conference presentations.

Trial registration number ACTRN12620000159954, CTN-00 282–1 v2, NCT06887920.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ MultifocAL COntact Lenses for Myopia is a double-blind, contralateral eye, non-inferiority, randomised controlled trial (RCT) representing an alternative trial design to conventional, parallel group, RCTs that are commonly used in myopia control research.
⇒ The primary outcome will be the 12-month difference in myopia progression between the two CLs, measured by changes in axial length and cycloplegic objective refraction.
⇒ Secondary outcomes will include patient-reported outcome measures including quality of life and adherence to the treatment.
⇒ This study will not have sufficient statistical power to robustly assess the secondary outcomes listed, and these will be interpreted as exploratory.
⇒ Patient, parent/guardian and community representatives were not involved in the design and delivery of the current study.

INTRODUCTION

With the dramatic increase in prevalence over the last century, myopia is predicted to affect 50% of the global population by 2050.[1] Excessive axial elongation underlying myopia may increase the risk of permanent visual impairment from ocular pathologies including myopic maculopathy and retinal detachment.[2–4] This results in detrimental impacts on individual quality of life (QoL), significant healthcare costs and billions in lost productivity. Direct annual costs of myopic correction in Asian adults were estimated to reach US$328 billion in 2006,[5] with the annual global burden of myopic macular degeneration estimated to be US$6 billion in 2015.[6]

Current interventions used to slow or prevent the progression of childhood myopia include optical, pharmacological or light-based therapies, which vary in their efficacy and suitability to individual patients.[7 8] Animal studies have shown that

refractive error development is a visually guided process, that myopic retinal defocus inhibits axial elongation, and the opposite effect occurs with hyperopic retinal defocus.[9–11] Thus, optical interventions such as myopia control contact lenses (CLs) incorporate areas to correct distance refractive error to provide clear central vision and zones of relative plus power to impose myopic defocus.[9–11]

The MiSight 1-Day (CooperVision, USA) is a soft CL which is Food and Drug Administration (FDA) approved for the control of progressive myopia. It is a daily disposable hydrogel multifocal contact lens (MFCL) of dual-focus concentric ring design with a central single vision (SV) distance correction zone surrounded by two concentric rings of positive power.[12] Multiple studies have established the safety and efficacy of MiSight 1-Day[13–16] and other MFCLs for slowing progressive myopia,[8 12 17–23] but there is a need for additional CL designs of diverse materials and parameters that are able to cater for a wider variety of myopic patients. The Acuvue Oasys for Presbyopia (AOP; Johnson & Johnson Vision Care, Florida, USA) is a silicone hydrogel MFCL originally developed for presbyopic patients to provide distance and near vision correction. Alongside the MiSight 1-Day, it is one of the few commercially available concentric ring designs.[24] A meta-analysis suggests that concentric ring CLs may offer superior myopia control compared with peripheral Add MFCLs,[25] highlighting the value of providing alternatives made from diverse materials. The AOP lens is also made of silicone hydrogel material associated with a higher Dk/t (103–147 vs 28–36.7 Dk/t) and a greater modulus which can benefit patients prone to corneal hypoxia (Morgan et al., 2010) or those who find high modulus lenses easier to handle. (Wong et al., 2019) High Dk/t lenses are particularly advantageous for myopia control CLs, as children are required to wear CLs for many hours over extended years.[20–22] As such, the AOP lens is a promising concentric ring design CL with the potential to reduce the progression of childhood myopia.

Interventional myopia control clinical trials have often employed a randomised controlled trial (RCT) study design, comparing novel to conventional treatments that only correct the myopic refractive error such as SV spectacles or SV CLs.[8 12 17–23] Although long considered the gold standard, the appropriateness of this design has recently come into question given the ethics of enrolling children into a placebo group receiving SV correction while there are known effective treatments for progressive myopia.[8 26 27] The risk of myopic sequelae increases with every increased dioptre of myopia,[3] and allowing children to progress in their myopia will irreversibly increase their risk of vision impairment.[2–4] In addition, the potential for allocation into the SV placebo group may also act as a barrier to enrolling their children into myopia control RCTs, creating recruitment challenges. Non-inferiority studies represent an alternative with a superior safety profile for participants as they compare the study intervention to an active control of proven efficacy, ensuring that there are no children designated to a placebo group with no effective treatment.[28 29]

An additional emerging challenge in myopia control trials is the difficulty in recruiting participants who have never used any myopia control interventions.[17] This is a particular challenge in settings such as Australia where myopia has a relatively low prevalence compared with Asia, combined with a high uptake of myopia control interventions from community clinics.[30 31] A contralateral study design presents an alternative in which each participant acts as their own control, allowing for paired data analysis with a reduced sample size.[27] Myopia control research has the unique potential for contralateral eye study designs as natural ocular growth is highly correlated between eyes,[32] making the two eyes excellent comparison groups. Additionally, both known and unknown confounders such as family history, outdoor time and near work will be matched between eyes.[17 27] Many animal and human studies have shown that myopia and refractive development are locally regulated, suggesting that treatment of one eye does not affect the other.[27 33–36]

In this double-blind, contralateral eye, non-inferiority RCT, the efficacy of AOP MFCL will be evaluated and compared with the MiSight 1-Day CL in myopic children aged 6 to 12 years. The hypothesis is that eye growth in myopic eyes treated with AOP and MiSight 1-Day MFCL will be similar over the course of 12 months.

METHODS AND ANALYSIS

This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials guidelines (online supplemental material 1), and the intervention is described with reference to the Template for Intervention Description and Replication (online supplemental material 2) checklist.[37 38] The trial was registered with the Australian New Zealand Clinical Trials Registry (identifying number ACTRN12620000159954) on 13 February 2020, the Australian Therapeutic Goods Administration (CTN: CTN-00282–1v2) on 30 January 2020 and clinicaltrials.gov on 26 March 2025. This is protocol version 7.3, dated 28 September 2023.

Study design and setting

The MultifocAL COntact Lenses for Myopia (MALCOLM) clinical trial is a prospective, double-blinded, non-inferiority RCT, with the aim to compare the effect of AOP to MiSight 1-Day MFCL on axial elongation in myopic children over 12 months. The study will take place at a single site at the School of Optometry and Vision Science, UNSW Sydney, Australia. It will use a 1:1 allocation ratio with a contralateral eye study design where participants will be randomised to wear in their right or left eye the experimental treatment AOP CL and the control treatment MiSight 1-Day MFCL in the fellow eye.

The primary sponsor-investigators of the study are UNSW Sydney who are responsible for regulatory compliance, conducting the study including study design, data

Table 1 Measurements and data to be collected at each MultifocAL COntact Lenses for Myopia (MALCOLM) study visit

Procedures	Screening/baseline	Lens fitting and dispensing	1-week CL check	1-month CL aftercare visit	6 and 12-month visits	3 and 9-month teleconsultations*
Timepoint	Day −14 to day −1	Day 0	Week 1 (−2/+3 days)	Week 4 (±7 days)	Week 26 and 52 (±7 days)	Week 12 and 48 (±7 days)
Primary outcomes						
Axial length measurement	Y	-	-	Y	Y	-
Cycloplegic objective and subjective refraction	Y	-	-	-	Y	-
Secondary outcomes						
Outdoor time and near work questions	Y	-	-	Y	Y	Y
Quality of life*	Y	-	-	-	Y	-
Adherence to intervention	Y	Y	Y	Y	Y	Y
Safety/dispensing outcomes						
Anterior eye assessment	Y	Y	Y	Y	Y	-
Anterior eye photos*	-	Y	Y	Y	Y	-
CL assessment and fit	-	Y	Y	Y	Y	-
Accommodation and binocular vision assessment	Y	-	Y	Y	Y	-
Exploratory outcomes						
Pupillometry	Y	-	-	Y	Y	-
Corneal topography	Y	-	-	Y	Y	-
Anterior eye optical coherence tomographer	Y	-	-	Y	Y	-
Widefield posterior eye imaging	Y	-	-	Y	Y	-
Intraocular pressure	Y	-	-	-	Y	-
Informed consent and eligibility assessment	Y	-	-	-	-	-

*Amendment to protocol after study commencement.
-, not conducted; CL, contact lens; Y, procedure conducted.

collection and management, analysis, interpretation of data, writing of the report and submitting the report for publication. The study team will comprise both masked and unmasked investigators who will be appropriately trained before commencing the study. Unmasked investigators will perform all CL-related tasks following randomisation. Masked investigators will be responsible for the assessment of primary, secondary and exploratory investigational outcomes (table 1).

Participants

The eligibility criteria are summarised in table 2. A maximum age of 12 years was chosen to ensure that by the end of the trial, participants may still be reasonably expected to be experiencing myopia progression.[8 17 39] An upper spherical equivalent myopic refraction limit of −5.00DS was selected due to MiSight 1-Day MFCLs only being available up to −6.00DS at the time of planned trial commencement. This will also ensure that a baseline spherical equivalent refraction of −5.00DS with potential myopia progression to −6.50DS by the end of the study can be dispensed CLs with vertex adjusted correction. Astigmatism will be limited to −1.00DC to ensure acceptable vision with both CLS which provide spherical refractive error correction only.[8 17]

Interventions

The experimental intervention is the AOP CL with +2.50 Add, and the control intervention is the MiSight 1-Day MFCL. The AOP is commercially available in three Add powers, of which the HIGH (+2.50) Add was chosen, due to its comparability in optical design to the control lens. Power profiles for both CLs measured with the NIMO^{EVO} aberrometer using the 'ISO Ophthalmic Optics – Contact Lenses – part 3: Measurement methods 18369–3 2017'[40]

Table 2 Inclusion and exclusion criteria for the MultifocAL COntact Lenses for Myopia (MALCOLM) clinical trial

Inclusion criteria	Exclusion criteria
Aged 6–12 years (inclusive)	Strabismus at distance or near, amblyopia or significant anisometropia (>1 D)
Is willing to wear soft contact lenses daily	Systemic or ocular conditions that may affect contact lens use (eg, allergy) or that may affect refractive development (eg, ptosis)
Spherical equivalent myopic refractive error between −0.50 and −5.00D in each eye and astigmatism ≤1.00D	Previous history of ocular surgery, trauma or chronic ocular disease
Best corrected LogMAR visual acuity of 0.1 or better in both eyes	Contraindications to contact lens use
Good ocular and general health	Ocular or systemic medication use which may interfere or interact with contact lens wear or ocular development
No previous use of myopia control interventions for more than 1 month or within the last 30 days	Plans to migrate or move during the study
Competent enough in English to be able to fully understand the participant information and consent form	Child, parent/guardians not willing to comply with treatment and/or follow-up schedule

D, dioptres.

are shown in figure 1, and other CL characteristics are detailed in table 3.

While the AOP CL is typically prescribed as a fortnightly replacement lens, both CLs will be dispensed with instructions for daily disposable wear. When required, participants will also be supplied with preservative-free artificial lubricants (Systane Ultra preservative-free unit dose eye drops, Alcon Laboratories Inc), at no cost. Participants will not be given CL multipurpose solution or cases to ensure adherence to the daily CL replacement schedule.

Participants will be taught appropriate insertion, removal and care of CLs by a trained masked investigator and advised to wear their prescribed CL for at least 10 hours a day for 6 days a week. The initial trial CL prescription will be based on participants' cycloplegic objective refraction conducted at the baseline visit, and −0.25DS will be incrementally added until there is no further improvement in visual acuity of at least 3 LogMAR letters of the same size. Minimum acceptable monocular and binocular distance visual acuity criteria will be 0.20 LogMAR units and 0.16 LogMAR units, respectively, and binocular near visual acuity of 0.20 LogMAR units or better. Participants will be advised of the signs and symptoms of adverse events related to CL wear including eye infections and inflammations and to promptly notify their parent/guardian and a member of the study team so that appropriate care may be provided. They will also be advised to refrain from using any other myopia control interventions throughout the duration of the study. Participant retention will be promoted by dispensing a CL supply that is sufficient until the next study visit only,

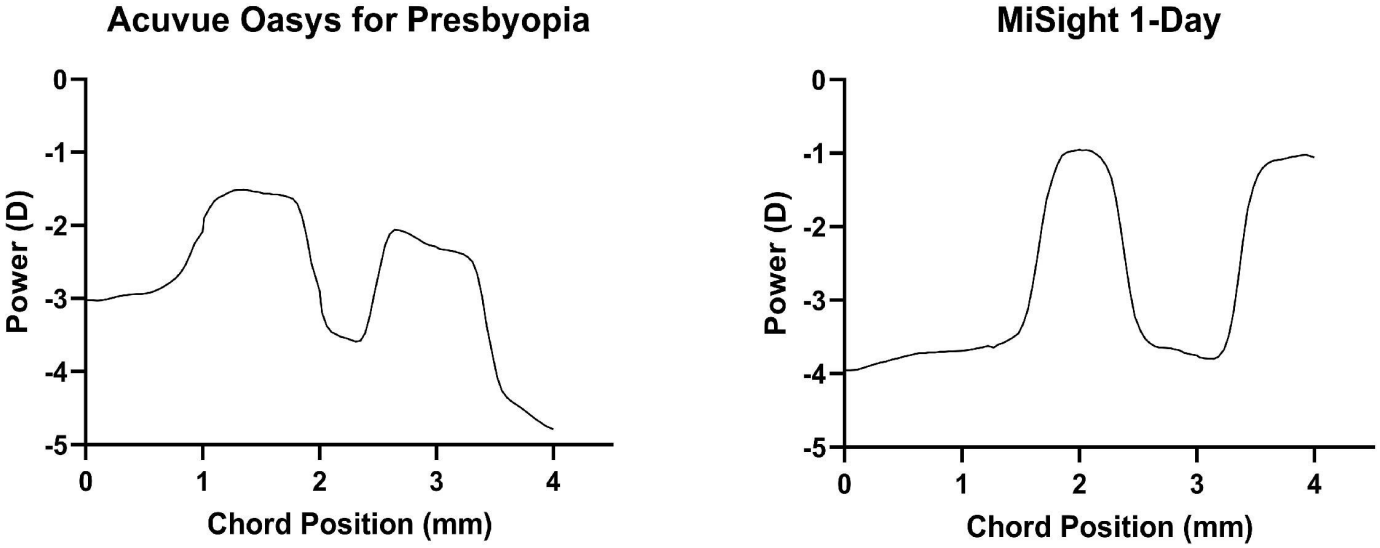

Figure 1 Measured power profiles of Acuvue Oasys for Presbyopia High Add (left panel) and MiSight 1-Day (right panel) for −3.00DS contact lenses. Measured power is plotted against the chord position from the centre of the lens (mm) to the periphery.

Table 3 Specifications for the MiSight 1-Day and Acuvue Oasys for Presbyopia HIGH Add contact lenses

Contact lens	MiSight 1-Day	Acuvue Oasys for Presbyopia HIGH Add
Manufacturer	CooperVision	Johnson & Johnson
Material	Omafilcon A	Senofilcon A
Base curve (mm)	8.7	8.4
Diameter (mm)	14.2	14.3
Water content (%)	60	38
Manufacturer lens design	Concentric ring, ActivControl technology	Multi-zonal aspheric design, HIGH Add

encouraging participants to return on a timely basis to renew their CL supply.

Participants may be permanently discontinued from the trial if it is deemed to be in their best interest by the study team. Criteria for discontinuation include development of anisometropia >1.00D, persistent clinical trial-related symptoms/complaints that are not correctable, serious adverse event that is eye/lens related that requires withdrawal, voluntary withdrawal by the participant, loss to follow-up, lack of adherence to interventions/visits or repeated protocol violations/deviations.

Amendments to the protocol after study commencement

This study commenced recruitment in January 2021. The COVID-19 global pandemic forced temporary cessation of recruitment and face-to-face visits between 16 June 2021 and 11 October 2021.

In addition, several changes were made to the protocol after study commencement. Initially, study visits consisted of face-to-face visits at baseline, 1 month, 3 months, 6 months and 12 months. From August 2022, the 3-month face-to-face study visit was switched to a teleconsultation, and a 9-month teleconsultation was also added to improve retention of study participants during the long interval between the 6- and 12-month face-to-face study visits. Additional secondary study outcomes were added including anterior eye photos (May 2021) and QoL measures (October 2022). Additional recruitment strategies were cumulatively added including recruitment from local businesses (June 2021), social media advertising (April 2022), participant referral scheme (September 2022) and a practitioner referral scheme (May 2023).

All protocol changes were submitted and approved by relevant parties including the Institutional Human Research Ethics Committee before implementation. The protocol described in this paper includes these approved changes.

Study visits and outcomes

The study visits are shown as a flow diagram in figure 2 according to the CONsolidated Standards Of Reporting Trials recommendations. At the beginning of the screening/baseline visit, written and informed consent (online supplemental 3) will be obtained from parent/guardians, before any study measures are taken. Participants will then be asked to return for fitting of CL and to be taught CL handling and care, which will be scheduled within 2 weeks of the screening/baseline visit. Following this, a 1-week CL aftercare safety visit will be scheduled within 5 to 10 days.

In-person study visits will be conducted at 1, 6 and 12 months (primary end point) after initiation of treatment. Teleconsultations will be conducted at 3 and 9 months. These visits will be scheduled within a range of ±7 days from the exact calculated study visit date. Study measurements at each visit are summarised in table 1. Serious or adverse event assessments can be scheduled at any time at the request of the participant or study team.

If participants choose or are required to withdraw, they will be asked to return for a final study visit, at which time all the study procedures for the closest intended study visit will be completed, as well as any safety procedures required.

Primary outcomes

The primary outcome of this trial will be the 12-month difference in myopia progression between the two CLs, measured by changes in axial length and cycloplegic objective refraction. Axial length will be measured prior to cycloplegia with the IOLMaster 700 (Carl Zeiss Meditec AG, Jena, Germany). Cycloplegia will be achieved with the instillation of one drop of 0.4% oxybuprocaine eyedrops followed by one drop of 1.0% cyclopentolate eyedrops in each eye. Objective refraction will be conducted at least 30 min after drop instillation. Objective refraction will be measured using the Shin-Nippon NVision-K 5001 free-space autorefractor (Shin Nippon, Japan).

Secondary outcomes

At each study visit, participants and parent/guardians will be asked questions to ensure no additional myopia control treatments such as myopia control spectacle lenses (eg, lenslets) or light-based therapies are being used. Information about the average time spent outdoors and on near work during weekdays and weekend will be asked verbally by investigators at each face-to-face study visit and teleconsultation.

Two QoL instruments will be administered: the Pediatric Refractive Error Profile 2 (PREP2) and the Pediatric Eye Questionnaire (PedEyeQ).[41 42] The PREP2 includes questions for the child participant and a section for the parent/guardian-proxy. The PedEyeQ includes three sections with questions for the child participant, parent/guardian-proxy and the parent/guardian. Both

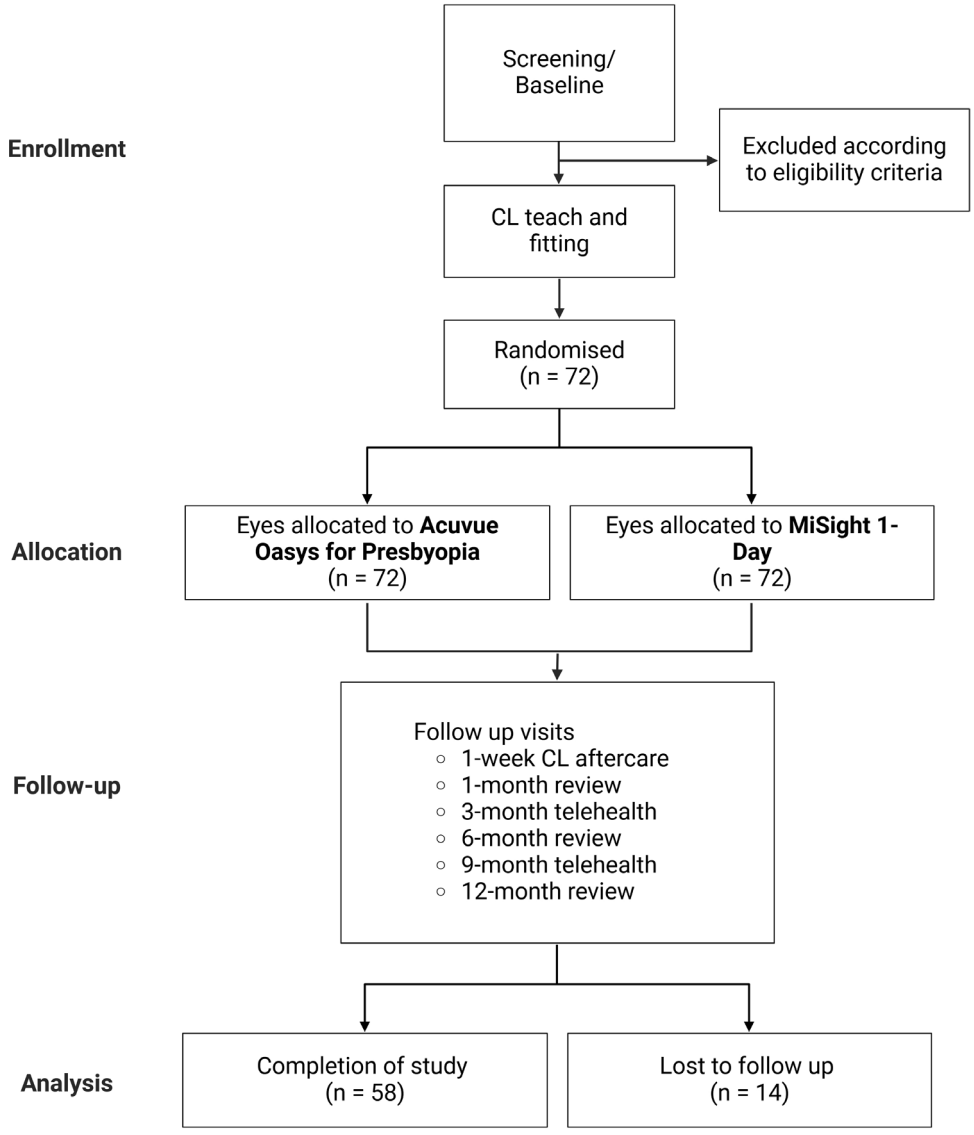

Figure 2 Anticipated MultifocAL COntact Lenses for Myopia (MALCOLM) non-inferiority trial CONsolidated Standards Of Reporting Trials (CONSORT) flow diagram. CL, contact lens.

QoL instruments will be administered electronically in random order at baseline, 6-month and 12-month study visits. Investigators will advise the participant and parent/guardian to answer questions independently of each other, taking care not to influence each other's answers. The child participant will be shown how to answer an example question and advised to ask the investigator or parent/guardian for help if a question is incomprehensible or beyond the child's vocabulary.

Adherence to intervention data will be collected in three ways: verbal retrospective self-report questions, text-message 'snapshot' self-report surveys and counting of CL labels. Participants and parent/guardians will be verbally asked about CL wear habits by investigators at face-to-face study visits and teleconsultations. The verbal questions are as follows:

1. On average, how many days a week have you been wearing your CLs?
2. On an average day, what time do you usually wake up?
3. On an average day, what time do you usually go to sleep?
4. On an average day, what time will you put your CL in?
5. On an average day, what time will you take your CL out?

Adherence to interventions will also be assessed via text-message surveys, with the option of sending it to either the child participant or their parent/guardian's mobile phone number. The process of completing the text-messaging survey will be demonstrated in-office with the child participant or parent/guardian to ensure that they are familiar with the process. It will be sent at periodic intervals at 8:00 in the morning, aimed at capturing data retrospectively for the previous day. Text-message surveys will be sent out daily for 7 days during the first week of each month for the 12-month duration of the study, that is, weeks 1, 5, 9, etc, allowing for 'snapshot' sampling of 84 out of 365 days while participants are enrolled in the trial. This 'snapshot' design is aimed at preventing fatigue

of text messages, minimising errors due to recall and maximising adherence to study protocol. The questions for the text-message survey are listed below:

1. Did [participant name] wear their contact lenses yesterday?
2. What time did [participant name] INSERT their contact lenses YESTERDAY? Please enter the time to the closest hour in 24h time e.g. 8:15am as '8' or 9:45pm as '22'.
3. What time did [participant name] REMOVE their contact lenses YESTERDAY? Please enter the time to the closest hour in 24h time e.g. 8:15am as '8' or 9:45pm as '22'.

Participants will also be asked to return all used and unused CL packaging and labels at scheduled visits so that the study team can manually count the number of CLs used to estimate the number of days CLs were worn between study visits. Although this method relies on participants adhering to recommended replacement frequencies, it ensures that no products are discarded or given away.

Safety outcomes

Visual acuity will be measured using standard LogMAR charts calibrated for 6 m and 40 cm. Slit lamp biomicroscopy examination will be performed to evaluate CL fit and monitor anterior eye health using the Efron grading scale.[43] Anterior eye photos will be taken to assess contact lens centration using image analysis with a custom MATLAB programme.[44]

Accommodation and binocular vision will be assessed by the unmasked investigator to ensure good visual function while fitted with different CLs in each eye. Near point of accommodation will be measured using the Royal Air Force (RAF) near point rule. Near point of convergence will also be measured with the RAF rule using the vertical line and dot target. Horizontal heterophorias will be conducted at 3 m and 33 cm with the Howell card. Stereopsis will be assessed with the Randot Stereo test and fixation disparity with the Saladin card, both conducted at 33 cm. All accommodation and binocular vision assessments will be conducted while the participant is corrected for their distance refractive error.

Exploratory outcomes

Pupillometry will be conducted using the NeurOptics PLR-300 (NeurOptics, Laguna Hills, CA, USA), with the protocol set to positive pulse stimulus, 180 uW pulse intensity and 0 uW background stimulus. Corneal topography will be captured using the Medmont E300 corneal topographer (Medmont International Pty Ltd), with three standard scans per eye. Anterior eye OCT will be conducted with the 3D CAS-OCT SS-1000 (Tomey, Nagoya, Japan) using three 2-dimensional scans and a single 3-dimensional scan per eye. Widefield posterior eye imaging will be taken with the Optos Daytona (Optos PLC, Dunfermline, UK) on each eye using both colour and autofluorescence mode and intraocular pressure measured with the iCare IC200 (Tiolat Oy, Helsinki, Finland) or non-contact tonometry using the TONOREF III (NIDEK Co, Gamagori, Japan).

Sample size

A sample of 60 participants completing the study will yield 80% power to reject the null hypothesis that AOP is inferior to MiSight 1-Day MFCL. This calculation is based on a 0.05 level of significance, assuming a treatment difference of 0.0 mm, a SD of 0.12 mm and a non-inferiority margin of 0.05 mm.[23] To account for a 20% discontinuation rate, a target sample size of 72 participants was set.

Recruitment

Recruitment of this study will be facilitated through a number of methods:

1. Recruitment from the university community including paper flyers and posters displayed around the university. Online advertisements will also be placed on university intranet forums and emailed to school staff and students.
2. Recruitment from the UNSW Optometry Clinic including paper flyers given to potential participants by reception staff and online advertisements on associated Facebook pages.
3. Online advertisements on Facebook or local newspapers
4. Third-party participant recruitment agencies
5. Recruitment from local businesses including libraries, dance schools, swim schools and tutoring centres.
6. A participant referral scheme in which current participants can refer potential new participants into the study.
7. A practitioner referral scheme in which practising optometrists can refer potential new participants into the study.

Data management and monitoring

Study data will be collected and managed using the Research Electronic Data Capture (REDCap) tool hosted and managed by Research Technology Services at UNSW, Sydney. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages and (4) procedures for data integration and interoperability with external sources.[45 46] Participant data will be kept confidential, and access to the REDCap platform will only be given to authorised and trained investigators via individually assigned user identification and passwords. REDCap will also allow electronic validation of data type and length. Study data will be the property of the study sponsor, UNSW, but the study funders, Johnson & Johnson, USA, will also have unrestricted access and use as applicable by law.

Data monitoring and trial conduct audit will be conducted by an independent study monitor as outlined in a study monitoring plan. The study monitor will be independent from the sponsor and competing interests. Health records are to be maintained in compliance with the institutional review board and retained for at least 15 years after publication of the study.

The trial will be terminated on completion of the final visit by the last active participant. It may be stopped early if clinical trial monitoring reveals unacceptable levels of device-related adverse events (>5%) or lack of protocol adherence. On early termination of the trial, the Institutional Human Research Ethics Committee will be notified.

Randomisation and masking

Randomisation

Randomisation will be conducted by designated unmasked investigators. Only the designated unmasked investigators will be privy to the intervention assignment, and they will not be responsible for measuring primary study outcomes. The randomisation sequence will be computer-generated by an investigator not involved in data collection, using a variable block size of either 2, 4 or 6,[47] and uploaded onto REDCap.[45 46] As participants will be acting as their own controls, they will not be stratified. Intervention assignment will be concealed until participant eligibility is verified, at which time REDCap will produce the next allocation in the sequence.

Masking and unmasking

The masked investigators and study participants will remain blinded to the assigned treatment group for the duration of the study, and unmasked investigators will perform all CL-related tasks following randomisation. Participants and their parent/guardians will be advised not to discuss their CL wear with the masked investigator. If participants or parent/guardians believe that they have become unmasked, investigators will be instructed not to confirm their suspicions. Masked investigators and participants will remain masked unless knowledge of the intervention assignment is deemed essential to maintain participant safety and well-being such as in the event of a serious adverse event or a product recall.

Over-labels will be used to mask CL design, prescription and lot number information (figure 3). Over-labels will match the shape of the manufacturer's lens label and coded red for the right eye and blue for the left eye, as either lens type can be allocated to either eye. The over-label will code to an internal lens lot number which is stored on a secure document which only the unmasked practitioner will be able to access.

Despite over-labelling, there will be differences in the shape of the CL packaging which cannot be concealed and from which masked study investigators may discern the lens design. To minimise the risk of treatment identification, all CL products and labels will be carefully stored and removed from consultation rooms before the entry of any masked investigators.

Figure 3 The Acuvue Oasys for Presbyopia and MiSight 1-Day multifocal contact lenses with red and blue over-labels indicating the right (R) and left (L), respectively, for a given participant, as will be used in the MultifocAL COntact Lenses for Myopia (MALCOLM) clinical trial.

Statistical analysis

Statistical analysis will be performed with R statistical software (R Core Team) with the RStudio integrated development environment (RStudio Team) or IBM SPSS Version 27.0 2020 for Windows.

Comparison between ocular factors at baseline between eyes will be assessed using Student's t-test for continuous variables. The primary outcome will be the difference in axial length progression from baseline to 12 months between the AOP and MiSight 1-Day CL. A non-inferiority margin of 0.05 mm was chosen on the basis that a 0.05 mm difference in the change in axial length is clinically meaningful and is at the upper limit of where the two eyes can be said to have progressed similarly. A mixed model including a random effect for individual and fixed effects of CL type, study visit and the interaction between the two eyes will be used to calculate the adjusted change in axial length and cycloplegic refractive error. Then, the two one-sided test procedures will be used to assess whether the difference between the two treatments is not larger than the non-inferiority margin.

Secondary outcomes will be analysed using a linear mixed model with interaction to assess their effect on myopia control. A linear mixed model, including a random effect for individual and fixed factors such as CL type, sex, study visit and their interactions, will be used to compare the adjusted change in axial length and cycloplegic refractive error.

Data will be analysed on an intention-to-treat basis. As a sensitivity analysis, multiple imputations will be used to examine the impact of missing data.

Intervention storage and dispensing

CL interventions will be handled and stored in a secure location that only unmasked investigators can access.

Participants and parents/guardians will be advised to return all used and unused CLs at each study visit. The designated unmasked investigators will maintain an accurate log of all used and unused, dispensed and returned CLs. At the end of the study period or at the early termination of the study period, all unused inventory will immediately be returned to the funder or disposed of according to local regulations.

Harms

Adverse events will be assessed by the study's qualified medical expert, with a physical examination of the participant as required. They will then categorise the event as an adverse event, adverse reaction, serious adverse event and expected or unexpected serious adverse reaction and document and report as necessary to the principal investigator, UNSW's delegate, UNSW Human Ethics Research Committee or the Australian Therapeutic Goods Administration. The trial management group is responsible for reviewing the safety information to identify serious emerging safety concerns and develop a plan to minimise participant risk if required. The UNSW Human Research Ethics Committee and UNSW's delegate will be consulted before the implementation of any plan.

ETHICS AND DISSEMINATION

Study protocols and procedures will be approved by UNSW Human Research Ethics Committee (HC20052) which are in accordance with the ethical standards and regulations of the Helsinki Declaration and Good Clinical Practice. All protocol modifications will be submitted to the UNSW Human Research Ethics Committee before implementation. Written consent will be obtained by parent/guardians for the child participant by a trained member of the study team involving a verbal explanation of the risks and benefits of study participation, requirements of the study and process of withdrawal. While written consent will not be obtained directly from child participants, study procedures and requirements will be carefully explained, and children will not be enrolled or discontinued from the study if unwilling to participate.

The findings of the MALCOLM trial will be shared with the sponsor, in peer-reviewed publications and at conferences. Participants will be able to opt in if they would like to receive a copy of the trial publication. Investigators will provide the funders, Johnson & Johnson, USA, a copy of the draft manuscript, allowing 60 days for review before submission for publication.

Necessary personal information will be collected and stored only on secure REDCap databases before, during and after cessation of the trial. Access to this information will be restricted to and not shared outside of authorised members of the study team. Datasets will not be made accessible to the public but will be shared on reasonable request. In accordance with local regulations, clinical trial, professional indemnity and general and product liability insurances will be obtained.

STUDY STATUS

Recruitment commenced in January 2021 and is expected to end in December 2024. At the time of this manuscript submission, 36 participants have been recruited and randomised to treatment. Planned recruitment was severely impacted by the COVID-19 pandemic-related lockdowns in 2021. The last follow-up appointment is expected to take place during 2025. Data analysis and reporting of results will begin when all data from the primary endpoint have been collected (December 2025). This study is currently ongoing.

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Competing interests PK has received research funding from Meta Platforms Technologies, LLC, and honoraria from Asia Optometric Congress, Optometry Australia, Fudan University Eye & ENT hospital, Shanghai, China, Aspen Pharmacare, Australia and Zeiss, Germany. IJ does not have any paid consultancies with pharmaceutical or optical companies and is not a member of the Speaker's panel of any company. AH has received lectureship honoraria from Johnson & Johnson and has served as a consultant for Argos Vision. RD has received honoraria from Asia Optometric Congress. DK, MV and NB have no competing interests to declare.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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