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Low-dose (0.01%) atropine eye drops to reduce progression of myopia in children: a multi-centre placebo- controlled randomised trial in the United Kingdom (CHAMP- UK) – study protocol.

Augusto Azuara-Blanco
Queens University Belfast

Nicola Logan
Aston University

Niall Strang
Glasgow Caledonian University

Peter Allen
Anglia Ruskin University

Ruth Hogg
Queens University Belfast

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Authors

Augusto Azuara-Blanco, Nicola Logan, Niall Strang, Peter Allen, Ruth Hogg, Ruth Weir, Paul Doherty, Catherine Adams, Margaret McFarland, Evie Gardner, Rejina Verghis, Jennifer Preston, James Loughman, Daniel I. Flintcroft, David Mackey, Samantha Lee, Christopher Hammond, Nathan Congdon, and Mike Clarke

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Complete List of Authors:	Azuara-Blanco, Augusto; Queen's University Belfast, Centre for Public Health Logan, Nicola; Aston University, School of Life & Health Sciences Strang, Niall; Glasgow Caledonian University, Dept. of Vision Sciences Allen, Peter; Anglia Ruskin University, UK, Optometry and Ophthalmic Dispensing Saunders, Kathryn; School of Biomedical Sciences Hogg, Ruth; Queen's University Belfast School of Medicine Dentistry and Biomedical Sciences, Centre for Public Health Weir, Ruth; Belfast Health and Social Care Trust, NICTU Doherty, Paul; Belfast Health and Social Care Trust, NICTU Adams, Catherine; Belfast Health and Social Care Trust, NICTU McFarland, Margaret; Belfast Health and Social Care Trust, Department of Pharmacy Gardner, Evie; Belfast Health and Social Care Trust, NICTU Verghis, Rejina; Belfast Health and Social Care Trust, NICTU Preston, Jennifer ; University of Liverpool, Institute of Translational Medicine Loughman, James; Dublin Institute of Technology, Optometry Department Flitcroft, Ian; Childrens University Hospital, Ophthalmology Mackey, David; Centre for Ophthalmology and Visual Science, University of Western Australia, Lions Eye Institute Lee, Samantha; Centre for Ophthalmology and Visual Science, University of Western Australia, Lions Eye Institute Hammond, Christopher; King’s College London, Department of Twin Research and Genetic Epidemiology Congdon, Nathan; Zhongshan Ophthalmic Center, Preventive Ophthalmology Clarke, Mike; Queen's University Belfast School of Medicine Dentistry and Biomedical Sciences, Centre for Public Health; Belfast Health and Social Care Trust, NICTU
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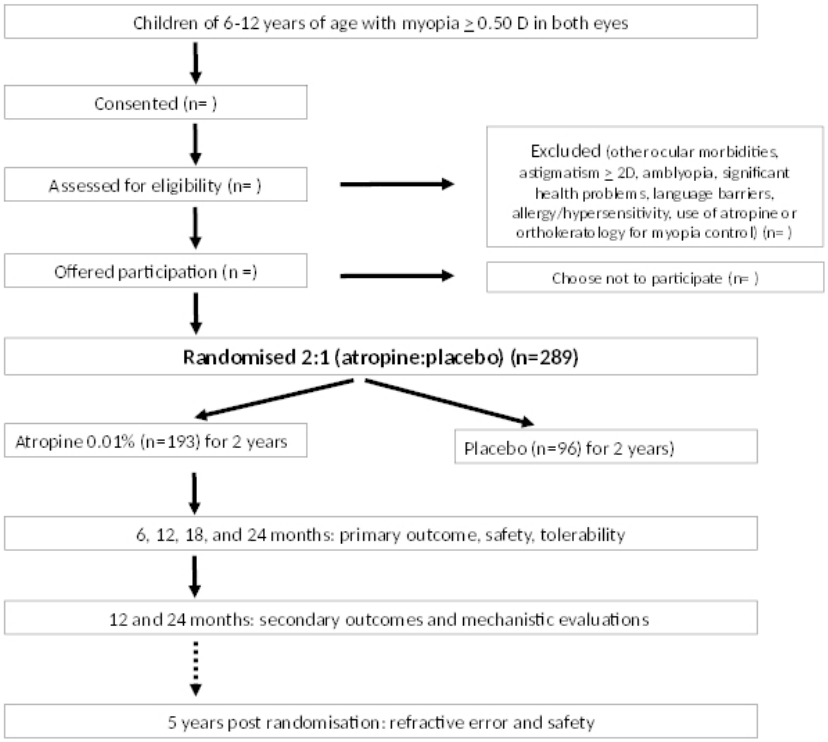

Figure 1

60x45mm (300 x 300 DPI)

Low-dose (0.01%) atropine eye drops to reduce progression of myopia in children: a multi-centre placebo-controlled randomised trial in the United Kingdom (CHAMP-UK) – study protocol.

Augusto Azuara-Blanco (Centre for Public Health, Queen's University Belfast, Belfast, UK)
Nicola Logan (Optometry School, Aston University, Birmingham, UK)
Niall Strang (Optometry School, Glasgow Caledonian University, Glasgow, UK)
Kathryn Saunders (Optometry School, Ulster University, Coleraine, UK)
Peter Allen (Optometry School, Anglia Ruskin University, Cambridge, UK)
Ruth Weir (Northern Ireland Clinical Trials Unit, Belfast, UK)
Paul Doherty (Northern Ireland Clinical Trials Unit, Belfast, UK)
Catherine Adams (Northern Ireland Clinical Trials Unit, Belfast, UK)
Evie Gardner (Northern Ireland Clinical Trials Unit, Belfast, UK)
Ruth E Hogg (Centre for Public Health, Queen's University Belfast, Belfast, UK))
Margaret McFarland (Department of Pharmacy, Belfast Health and Social Care Trust, Belfast, UK)
Jennifer Preston (Institute of Translational Medicine, University of Liverpool, Liverpool, UK)
Rejina Verghis (Northern Ireland Clinical Trials Unit, Belfast, UK)
James Loughman (Optometry School, Technological University Dublin, Dublin, Ireland)
Ian Flitcroft (Optometry School, Technological University Dublin, Dublin, Ireland)
David Mackey (Lions Eye Institute, University of Western Australia, Perth, Australia)
Samantha Lee (Lions Eye Institute, University of Western Australia, Perth, Australia)
Chris Hammond (St Thomas' Eye Hospital, King's College London, London, UK)
Nathan Congdon (Centre for Public Health, Queen's University Belfast, Belfast, UK; Orbis International, New York, USA; and Zhongshan Ophthalmic Centre, Sun Yat-sen University, Guangzhou, China)
Mike Clarke (Centre for Public Health, Queen's University Belfast, Belfast, UK and Northern Ireland Clinical Trials Unit, Belfast, UK)

Corresponding Author: Augusto Azuara-Blanco, PhD, FRCS(Ed), FRCOphth
Centre for Public Health, Institute of Clinical Sciences - Block A, Grosvenor Road, Belfast BT12 6BA.
Ph: 02890976460. E-mail: a.azuara-blanco@qub.ac.uk

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Acronym: The Childhood Atropine for Myopia Progression in the UK study (CHAMP-UK)

Trial registration: ISRCTN99883695, NCT03690089.

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Precis

We report the protocol of a multicentre placebo-controlled randomised trial that will evaluate the efficacy, safety and mechanism of action of low dose atropine (0.01%) eye drops to reduce myopia progression in children with myopia.

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Abstract

Background/Aims: To report the protocol of a trial designed to evaluate the efficacy, safety and mechanism of action of low dose atropine (0.01%) eye drops for reducing progression of myopia in UK children.

Methods: Multicentre, double-masked, superiority, placebo-controlled, randomised trial. We will enrol children aged 6-12 years with myopia of -0.50 diopters or worse in both eyes.

We will recruit 289 participants with an allocation ratio of 2:1 (193 atropine; 96 placebo) from five centres. Participants will instil one drop in each eye every day for two years and attend a research centre every six months. The vehicle and preservative will be the same in both study arms.

The primary outcome is spherical equivalent refractive error of both eyes measured by autorefractor under cycloplegia at two years (adjusted for baseline). Secondary outcomes include axial length, best corrected distance visual acuity, near visual acuity, reading speed, pupil diameter, accommodation, adverse event rates and allergic reactions, quality of life (EQ-5D-Y), and tolerability at two years. Mechanistic evaluations will include: peripheral axial length, peripheral retinal defocus, anterior chamber depth, iris colour, height and weight, activities questionnaire, ciliary body biometry and chorio-retinal thickness. Endpoints from both eyes will be pooled in combined analysis using generalised estimating equations to allow for the correlation between eyes within participant. Three years after cessation of treatment, we will also evaluate refractive error and adverse events.

Conclusions: CHAMP-UK will be the first randomised trial reporting outcomes of low-dose atropine eye drops for children with myopia in a UK population.

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Introduction

In Europe, myopia prevalence has risen dramatically over the last few decades. [1-6] Myopia appears to be occurring at a younger age and its severity has increased by an average of approximately 1 dioptre (D) among European-derived populations in one generation. [4, 7] In UK the proportion of myopic children has doubled in the last 50 years.[6] In the USA myopia prevalence increased from 25% to 42% in a generation.[7]

In the UK, most people with myopia have normal visual acuity when appropriately corrected, but myopia still has significant public health consequences from a variety of perspectives, educational, financial and psychological, as well as the risks of visual impairment. [8-10] Myopia is a risk factor for myopic maculopathy, retinal detachment, cataract and glaucoma in adult life, [9, 11, 12] and the risk increases with the degree of myopia. All these conditions are more challenging to treat than myopia itself, and reducing the risk for any of them requires interventions to slow myopia progression and thus decrease a child's severity of myopia in the long term rather than correct it optically with spectacles. Children with myopia also require frequent eye tests and change of spectacles that are funded primarily by taxpayers in the UK. Strategies to control progression of myopia are particularly meaningful in the context of World Health Organisation (WHO) initiatives to eliminate preventable causes of blindness.

Atropine at low concentration has been shown to be safe and effective in slowing myopia progression in children of Chinese ethnicity, [13-17] but its safety and effectiveness in European-derived populations has not been adequately assessed in a controlled trial. Therefore, the objective of the current study is to evaluate the efficacy, safety, and mechanism of action of low dose atropine (0.01%) in UK children with myopia. This paper describes the protocol of the randomised controlled trial called CHAMP-UK (The Childhood Atropine for Myopia Progression in the UK study).

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Materials and methods

This is a multicentre, randomised, double-masked, placebo-controlled, superiority trial, with 2:1 allocation of intervention and control (atropine:placebo). We followed the SPIRT guidelines https://www.spirit-statement.org/) for reporting trials protocols.

Participants: Children will be eligible to participate in the study if they are 6-12 years of age at the time of consent, with myopia of -0.50 D or greater (spherical equivalent refractive error) in both eyes, best-corrected distance visual acuity (BCDVA) 0.20 logMAR or better in both eyes, and no other significant ocular or systemic morbidities (see Table 1). Children with myopia ≥ -10.00 D or astigmatism ≥ 2.00 D in either eye will be excluded.

Table 1: Inclusion and Exclusion Criteria:

Inclusion Criteria

1. 6-12 years of age (at the time of consenting)
2. Myopia of -0.5D or greater (spherical equivalent refractive error) in both eyes
3. Best-corrected distance visual acuity (BCDVA) 0.20 logMAR or better in both eyes

Exclusion Criteria

1. Children with other ocular morbidities*
2. Myopia of -10D or greater in either eye
3. Astigmatism of 2D or higher in either eye
4. Amblyopia
5. Significant health problems that can compromise the ability to attend research visits or complete the trial
6. Other factors that may compromise the ability to attend the research appointments
7. Parents or children with poor understanding of the English language
8. Children enrolled in other interventional trials
9. Allergy or hypersensitivity to atropine or excipients
10. Prior or current use of atropine or orthokeratology contact lenses

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** Ocular co-morbidities refer to any disease that can potentially compromised vision or that may require ocular surgery, including diabetes mellitus.*

Setting: Clinical research facilities from the following five academic departments of medical or optometry schools and NHS Trusts in Northern Ireland, England and Scotland:

- Wellcome Trust-Wolfson Northern Ireland Clinical Research Facility (NICRF): Belfast Health and Social Care Trust, Queen's University Belfast and Ulster University, Northern Ireland
- Department of Optometry at Glasgow Caledonian University and NHS Greater Glasgow and Clyde,

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Scotland

- School of Optometry at Aston University and Birmingham Women and Children's NHS Foundation Trust, England

- Department of Vision and Hearing Sciences at Anglia Ruskin University and Cambridge University Hospitals NHS Hospital Trust, England

- Moorfields Eye Hospital NHS Foundation Trust, England

Study Interventions: The intervention group will receive preserved 0.01% atropine sulfate eye drops, administered at home once daily in both eyes for two years. The control group will receive placebo eye drops on the same dosing schedule, with the same preservative (benzalkonium chloride 0.01% w/v in sterile water) and pH. Atropine and placebo bottles will be identical, and thus participants and investigators will be masked to study group assignment.

Outcomes: The primary outcome is spherical equivalent refractive error (SER) (i.e. myopia severity) of both eyes after 24 months measured by autorefractor under cycloplegia, adjusted for baseline. Participants will have 1-2 drops of 1% cyclopentolate HCl instilled in each eye at least 20 minutes before autorefraction and another drop will be instilled if full cycloplegia has not been achieved. The autorefractor derives an average of five readings to produce the SER. The spherical equivalent refractive error (i.e, the spherical power plus half the cylindrical power) will be recorded for each eye.

Secondary outcomes of both eyes include the following: axial length (measured with partial coherent interferometry), best corrected distance visual acuity (uniocular and binocular), uniocular and binocular near visual acuity (ETDRS), reading speed (Wilkins), pupil diameter (by autorefractometer), accommodation (using a near target), spectacle correction power, adverse event rates and allergic reactions, quality of life (EQ-5D-Y),[18] and tolerability at two years.

The mechanism through which atropine inhibits myopia remains uncertain. Possible sites of action include the lens and ciliary muscle, the sclera, choroid and the retina. [11] A variety of tests will be done, according to their availability in the research units, to explore the effect of atropine on ocular anatomy and function. In experimental models, atropine reduces myopia and ocular elongation via a non-accommodative mechanism. [19] However, an accommodative effect cannot be ruled out in humans. [20] We will study the effect of atropine on the lens and ciliary muscle by measuring the anterior chamber depth with laser biometry and assessing changes in ciliary muscle using anterior-segment optical coherence tomography (OCT).

Altering the amount of defocus in the peripheral retina appears to be one mechanism influencing growth rate of the eye in myopia progression. [21] Whether topical atropine also has some

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influence in the peripheral retina is unknown. Changes in peripheral eye length and off-axis measures of refraction are two ways in which the peripheral properties of the eye can be assessed. In the posterior eye, subfoveal choroid thinning is correlated with the degree of myopia. Changes in subfoveal choroidal thickness may occur in response to imposed retinal defocus. [22-24] We will study choroidal thickness using OCT. This will enable differences in choroidal thickness resulting from atropine use to be compared with normal myopic growth. We will also explore the influence of parental myopia using parents' current spectacle prescription power, and time spent on different activities (Table 2).

Table 2. Diary used to record time spent indoor or outdoor.

Activity, to nearest whole hour	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
Hours indoors: classroom, music etc							
Hours outside: sport, training, walking / cycling to or from school							
Hours reading, homework, video / computer / tablet / mobile phone use							
Hours outside: sport, training, walking / cycling to or from school							

Compliance will be assessed using electronic monitoring with a MEMS device (AARDEX Group Ltd, Switzerland). The MEMS Cap is a plastic container with a screw top in which the eye drop bottle is stored until needed for drop instillation. [25] When the top is unscrewed the device electronically records the date and time, and this is downloaded, analysed and taken as a surrogate for having administered the medication.

At five years after randomisation, we will post a questionnaire to participants' parents and ask for details of any possible complications and adverse events after trial completion. We will also request information from their children's optometrists regarding their eye health, visual acuity, and refractive error data.

Sample size: We anticipate that the underlying progression in the control group and the effect of atropine eye drops in a UK population will be smaller than the reported effect in Chinese populations, [17] but assuming that atropine reduces the progression of myopia by at least 40%, using SD=0.7, an intra-class correlation coeficient between the two eyes of 0.9 and a variation

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inflation factor of 1.9, we will need 97 participants in each group. Considering a dropout rate of 15% and that 10% of recruited children will be Chinese, we will need a total of 289 participants: 193 atropine, 96 placebo (152 atropine, 76 placebo inflated by a variance inflation factor of 1.9) to detect this difference in the non-Chinese UK population with 90% power.

Allocation: Randomisation will be computer-generated using a minimisation algorithm to ensure balanced allocation of participants across the two treatment groups, and that each participant's allocation is fully concealed from everyone involved in recruiting them to the trial. Minimisation will be by centre, ethnic background (white/non-white), and severity of myopia (less than -3.00 D in either eye / -3.00 D or greater in the eye with more severe myopia). The unit of randomisation will be the participant (not the eye). The randomisation list will be generated by sealed envelope (sealedenvelope.com) and group allocation will only be visible to those with administrator access in the trial management team in NICTU. Local researchers will access the automated randomisation system to obtain the kit number for each participant.

Adverse events/Safety reporting: Serious adverse events (SAEs) related to participants' participation in the trial are reported in accordance with the guidance from The European Clinical Trials Directive 2001/20/EC (https://ec.europa.eu/health/human-use/clinical-trials/directive_en).

Timeline of procedures: Table 3 displays the timing of the trial's outcome measurements. Participants will attend a research centre every six months (+/- two weeks) across the 2-year follow-up as illustrated in Figure 1 (see Table 3 for details). Following completion of the 2-year trial, participants will then again be contacted at the 5-year time point (three years after cessation of eye drops) to evaluate their refractive error and possible adverse events.

Recruitment strategy: We will ask community optometrists and paediatric ophthalmologists to inform parents of children with myopia about the trial. We will aim to recruit approximately 60 participants per centre.

Data collection: The chief investigator (CI) and NICTU will provide training to site staff on trial processes and procedures, including the completion of the clinical research form (CRF) and data collection through investigator meetings and site initiation visits. All data for an individual participant will be collected by the local principal investigator (PI) or designee and recorded in the CRF for the study. Participant identification on the CRF will be through their unique trial identifier, allocated at the time of recruitment. Data will be collected and recorded on the CRF and

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questionnaires by the local PI or designee. Case report forms and questionnaires will be submitted to the NICTU in a timely manner.

Data management: Study data will be entered onto a web-based Clinical Trial Database and processed electronically as per NICTU standard operating procedures and the study specific data management plan. Data queries will be generated for site staff as required to clarify data or request missing information. All queries will be responded to and resolved within the study database. Any amended information will then be entered in the study database. All study documentation (including participant medical records) and data will be archived as per regulatory requirements and those responsible for archiving will be noted on the sponsor delegation framework.

Statistical analysis: The primary analysis will be performed based on the intention to treat principle. A p-value <0.05 is considered as statistically significant. Baseline characteristics will be summarised as mean and standard deviation (SD), median and inter-quartile range (IQR) or numbers and proportions (%) as appropriate, depending on the scale of measurement and distribution. Endpoints from both eyes will be pooled in combined analysis using generalised estimating equations to allow for the correlation between eyes within participant. Difference in the myopia progression and other continuous outcomes between the atropine and control groups will also be tested for significance using independent t-test. Analysis of covariance will be performed to adjust for baseline characteristics and other covariates. Fisher's exact test will be used to test the difference in the proportions between the groups for the categorical variables. Exploratory subgroup analyses will be performed on the primary outcome using 99% confidence intervals and interaction terms (treatment group by subgroup) for the following subgroups: age (6-9 and 10-12 years at randomisation), ethnic background (white versus non-white), and severity of myopia (less than -3D in either eye versus -3D or greater myopia). Sensitivity analyses will assess the impact of missing data for the primary outcome by imputing extreme values (lowest and highest). A detailed Statistical Analysis Plan will be completed before the final analysis is started.

Monitoring: On-site monitoring will be an on-going activity from the time of initiation until trial closeout and will comply with the principles of Good Clinical Practice (GCP). On-site monitoring visits during the trial will check the accuracy of entries on CRFs against the source documents, the adherence to the protocol, study procedures and GCP. The local PI or designee will ensure that access to all trial related documents including source documents (to confirm their consistency with CRF entries) are available during monitoring visits. The extent of source data verification will be documented in the monitoring plan.

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Ethics and governance: The trial will comply with the principles of GCP, the requirements and standards set out by the EU Directive 2001/20/EC and the applicable regulatory requirements in the UK, the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the UK Policy Framework for Health and Social Care Research. CHAMP-UK has been reviewed and approved by a Research Ethics Committee (18/NI/0164). Local NHS Research and Development (R&D) approvals will be obtained prior to commencing the trial at the participating sites. An independent data and safety monitoring committee will oversee the trial. A Clinical Trial Authorisation was obtained from the Medicines for Human Use Regulatory Authority (MHRA) before the start of the trial.

Protocol Compliance: A protocol deviation is defined as an incident that deviates from the normal expectation of a particular part of the trial process. Any deviations from the protocol will be fully documented on the protocol deviation form in the CRF.
A serious breach is defined as a deviation from the trial protocol or GCP which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the subjects of the trial; or

(b) The scientific value of the trial

Protocol compliance will be monitored by the NICTU.

Protocol Amendments: Changes to the protocol will require regulatory authority/ethics committee approval/favourable opinion prior to implementation.

Participant Confidentiality: All study reports and communication regarding the study will identify the participants by the assigned unique trial identifier only. Computers where information will be stored will be password-protected. Participant confidentiality will be maintained at every stage and identifying data will not be made publicly available to the extent permitted by the applicable laws and regulations.

Post-trial Care: Administration of study eye drops will stop after 24 months of trial participation. At the end of the trial, participants' myopia will be managed in accordance with standard clinical practice.

Dissemination Policy: The final study data report will be provided by the Trial Statistician. It is anticipated that the study findings will be published in peer reviewed journals and these articles will

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be led by the CI. The CI will secure a searchable compendium of these publications and make the results readily accessible to the public and healthcare professionals. In addition, study findings may be presented at both national and international meetings and to appropriate patient groups.

Data Sharing Statement: Requests for data sharing will be reviewed on a case by case basis by the CI and Trial Management Group. We will share trial data with the CI of the MOSAIC trial (ISRCTN36732601) and the WA ATOM trial (ACTRN12617000598381) to facilitate prospective individual participant data meta-analysis once the results of the CHAMP-UK trial are accepted for publication. **MOSAIC and WA-ATOM are placebo-controlled trials evaluating 0.01% atropine eye drops. WA-ATOM will enrol 150 children aged 6-16 years with progressive myopia. MOSAIC will enrol 250 children aged 6-16 years with progressive myopia (phase 1). All participants initially assigned to the placebo (n=83) crossover to the intervention arm of the study for Phase 2, and from month 24 to 36, instil 0.01% atropine eye drops in both eyes once nightly.**

Funder: The trial is funded by a grant awarded by NIHR Efficacy and Mechanism Evaluation (project 15/48/59). CHAMP-UK is registered (ISRCTN99883695, NCT03690089). The Belfast Health and Social Care Trust sponsors the trial and provides the necessary trial insurance.

Discussion

Myopia typically starts to develop in childhood and although the vision can be corrected with glasses, contact lenses or surgery, myopic eyes have an increased risk of developing co-morbidities such as glaucoma, cataract, retinal detachment, and choroidal neovascularisation at the macula. [9, 11] Importantly, the risks of associated co-morbidity and visual loss are associated with the degree of myopia, and cannot be reduced with optical correction alone. Myopia is more prevalent in East Asia. Recent epidemiological studies show increasing rates among adolescents in European populations and suggest myopia is occurring at an earlier age than in previous generations. [3-5] Myopia usually progresses faster at younger ages, but myopia onset, progression, and stabilisation vary widely among individuals and are influenced by a range of variables including environment, lifestyle, parental refractive history and ethnicity. [4, 26]

A number of interventions to reduce the progression of myopia have been investigated. Multifocal lenses and under-correction of myopic refractive error have at best a weak effect on myopia correction. While orthokeratology and peripheral defocus contact lenses may have some effect on axial length progression, atropine, even at low doses, appears to be the most effective intervention in Asian children to reduce progression of myopic refractive error. [27,28] Low dose atropine is now

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widely used in some East Asian countries for treating children with myopia, but has not been tested in European populations.

Atropine is an anti-cholinergic agent that is relatively selective for muscarinic receptors. Topical use of high-concentration atropine (0.5 to 1.0%) causes pupil dilatation by blocking the muscarinic receptors in the pupillary sphincter musculature and reduces or paralyses contraction of the ciliary muscle. Both of these result in adverse effects, e.g., photophobia and blurred near (reading) vision that are highly undesirable in a school-age population. Additionally, cessation of topical high-concentration atropine for myopia control has been associated with rapid myopia progression towards original, un-treated levels ("myopia rebound"). [15]

The effectiveness of low dose atropine (three different concentrations) in children of Chinese race has been evaluated. [13-16] The lowest tested dose of 0.01% was associated with better tolerability and efficacy, with minimum rebound effect. [14] A systematic review and network meta-analysis has confirmed muscarinic antagonists as the most effective interventions for myopia control in children of Chinese ethnicity. [27] However, there is limited evidence from European populations on atropine effectiveness in controlling myopia progression. We will also evaluate the possible mechanisms of action of atropine, and gather information regarding central and peripheral axial length, accommodation, lens position, ciliary body biometry, chorio-retinal thickness and daily activities.

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Trial sponsor: Belfast Health and Social Care Trust.

Trial steering committee: Richard Wormald, John Buchan, Hetal Buckhurst, Hema Radhakrishnan, Helen Normington.

Data and safety monitoring committee: Jennifer Burr, David Cooper, Jeremy Guggenheim

Competing interests:

Augusto Azuara-Blanco (CI): none.

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Authors' contributions:

All authors have contributed to the conception and design of the trial.

All authors have contributed to drafting the paper or revising it critically for important intellectual content.

All authors have approved the submitted draft and agree to be accountable for all aspects of the work.

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Legends

Figure 1: Study flow chart with outcome timeline.

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Table 3. Schedule of Assessments

	Baseline	6 months	12 months	18 months	24 months
Adverse events		✓	✓	✓	✓
Tolerability		✓	✓	✓	✓
EQ-5D-Y questionnaire	✓	✓	✓	✓	✓
Activities questionnaire- to be sent home with participant for completion	✓	✓	✓	✓	✓
Best corrected VA (logMAR ETDRS)	✓	✓	✓	✓	✓
Near VA (near logMAR ETDRS)	✓	✓	✓	✓	✓
Iris colour	✓				
Reading speed (Wilkins Rate of Reading Test)	✓	✓	✓	✓	✓
Pupil diameter prior to cycloplegia (autorefractor)	✓	✓	✓	✓	✓
Accommodation (autorefractor)	✓	✓	✓	✓	✓
Peripheral retinal defocus (autorefractor)	✓		✓		✓
Anterior chamber depth (laser biometer)	✓	✓	✓	✓	✓
Cycloplegic refractive error (autorefractor)	✓	✓	✓	✓	✓
Ciliary body biometry (AS-OCT)*	✓		✓		✓
Central axial length (laser biometer)	✓	✓	✓	✓	✓
Peripheral axial length (laser biometer)	✓		✓		✓
Chorio-retinal thickness (SD-OCT)	✓	✓	✓	✓	✓

✓✓: Before and after cycloplegia

*: if instrumentation is available

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