CHAMP UK

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

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Ethics Reference Number:	18/NI/0164
Chief Investigator:	Augusto Azuara-Blanco Centre for Public Health Institute of Clinical Sciences B Queen's University Belfast Grosvenor Road Belfast BT12 6BA

CHAMP-UK

PROTOCOL AUTHORISATION

Protocol Title	Low-dose atropine eye drops to reduce progression of myopia in children in the United Kingdom
Protocol Acronym (if applicable)	CHAMP UK (Childhood Atropine for Myopia Progression in the United Kingdom)
Protocol Number	17097AB-AS
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A review of the protocol has been completed and is understood and approved by the following:

Augusto Azuara-Blanco	See attached email	____ / ____ / ____
Chief Investigator	Signature	Date

Cliona McDowell	See attached email	____ / ____ / ____
Study Statistician	Signature	Date

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Full Wording
ACTRN	Australian New Zealand Clinical Trials Registry
AE	Adverse Event
AR	Adverse Reaction
BCdVA	Best Corrected Distance Visual Acuity
BHSCT	Belfast Health and Social Care Trust
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
D	Diopter
DMC	Data Monitoring Committee
DMP	Data Management Plan
EME	Efficacy and Mechanism Evaluation
EQ-5D Y	EQ-5D youth version
ETDRS	Early Treatment Diabetic Retinopathy Study
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GEE	Generalised estimating equations
HCl	Hydrochloride
IB	Investigator brochure
ICC	Interclass Correlation Coefficient
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IQR	Inter-quartile range
IRB	Institutional Review Board
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number Register
LogMAR	Logarithm of the Minimum Angle of Resolution
MACRO	Clinical Trials Database
MEMS	Medical Events Monitoring System
MHRA	Medicine and Healthcare Products Regulatory Agency
mmHg	Millimetre of mercury
MMI	Multimedia information resource
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICRF	Northern Ireland Clinical Research Facility
NICTU	Northern Ireland Clinical Trials Unit
NIHR	National Institute of Health Research
OCT	Optical Coherence Tomography
PI	Principal Investigator
PIS	Participant Information Sheet
QUB	Queen's University Belfast
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction

SD	Standard Deviation
SDV	Source Data Verification
SER	Spherical equivalent refractive error
SPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWAT	Study Within A Trial
TMF	Trial Master File
TMG	Trial Management Group
TRECA	TRials Engagement in Children and Adolescents
TSC	Trial Steering Committee
U	University
UAR	Unexpected Adverse Reaction
UK	United Kingdom
VA	Visual Acuity
WA	Western Australian
WHO	World Health Organisation

2 STUDY SUMMARY

Scientific title	Low-dose atropine eye drops to reduce progression of myopia in children
Public title	Low-dose atropine eye drops for children with myopia
Health condition(s) or problem(s) studied	Myopia
Study Design	STUDY DESIGN: multicentre, randomised, double-masked, placebo-controlled superiority trial. STUDY POPULATION: Children aged 6-12 years with myopia of -0.50 diopters (D) or greater in both eyes. RANDOMISATION PROCEDURES: All eligible children will be randomised and allocated a unique participant ID number via sealedenvelope.com. Randomisation will be minimised by centre, ethnic background (white/non-white) and severity of myopia in the eye with more severe myopia (less than -3D versus -3D or greater). The unit of randomisation will be the participant (not the eye). The primary and safety outcomes will be measured every six months during the treatment period. The mechanistic evaluations will take place at 12 and 24 months.
Study Aim and Objectives	Aim: to evaluate the efficacy and safety of low dose atropine (0.01%) eye drops to reduce progression of myopia in children. The primary objective is: - to evaluate the efficacy of 0.01% atropine eye drops to reduce the progression of myopia in children after 24 months of treatment. The secondary objectives are: - to evaluate the safety, side effects and tolerability of low dose atropine eye drops in terms of difficulties with near vision and reading, local discomfort and stinging of eye drops, photophobia, and occurrence of allergic reactions - to determine the mechanism of action of atropine eye drops. Specifically, we will evaluate if atropine has an effect on central axial length of the eye, position of the lens, peripheral retinal defocus and use of spectacle correction. The exploratory objective is: - to explore the influence of other factors in the progression of myopia, including accommodation,

	chorio-retinal thickness at the macula, peripheral axial length hours of outdoor activity, iris colour, ethnicity, and family history.
Study Intervention	INTERVENTION: 0.01% atropine sulfate eye drops, one drop once a day for 24 months in each eye. CONTROL: placebo eye drops, (10mls of a clear colourless solution of benzalkonium chloride 0.01% the same preservative as intervention eye drops w/v in sterile water), one drop once a day for 24 months in each eye.
Primary Outcome	At 24 months: spherical equivalent refractive error (i.e. myopia severity) of both eyes measured by autorefractor under cycloplegia (adjusted for baseline).
Key Secondary Outcomes	At 24 months: axial length, best corrected visual acuity (uniocular and binocular), near visual acuity (uniocular and binocular), reading speed, pupil diameter, spectacle correction, adverse event rates and allergic reactions, quality of life, and tolerability.
Exploratory Outcomes/Mechanistic Evaluations	At 24 months: peripheral axial length, peripheral retinal defocus, anterior chamber depth, accommodation, iris colour, height and weight, activities questionnaire, ciliary body biometry and chorio-retinal thickness.
Key Inclusion and Exclusion Criteria	Inclusion criteria: children aged 6-12 years with myopia of -0.5D or greater (spherical equivalent refractive error) in both eyes and good best-corrected distance visual acuity (0.20 logMAR or better) in both eyes. Exclusion criteria: children with other ocular morbidities, astigmatism of 2D or higher, myopia greater than -10D, amblyopia, hypersensitivity to the active substance or to any of the excipients of the eye drops, significant health problems, other factors that may compromise the ability to attend the research appointments, children enrolled in other interventional trials or have previously used atropine eye drops or prior or current use of Ortho-K contact lenses or contact lenses with dual focus, multifocal or extended depth of focus lens design, children or parents / guardians with latex allergy as the dropper used to administer the eye-drop contains latex. If a child or their parents have a poor understanding of the English language, they will be excluded.
Countries of Recruitment	UK
Study Setting	Clinical research facilities at academic departments of ophthalmology or optometry and NHS facilities.
Target Sample Size	We will recruit a total of 289 participants with an allocation ratio of 2:1 (193 atropine: 96 placebo).

Study Duration	This project will last 54 months. Safety data will be gathered five years after randomisation (approximately seven years after the start of the study).

3 STUDY TEAM

Chief Investigator	Augusto Azuara-Blanco Centre for Public Health, Queen's University Belfast Institute of Clinical Sciences B Grosvenor Road, Belfast BT12 6BA a.azuara-blanco@qub.ac.uk
Co-Investigators	**(1) Co-applicants and Co-Investigators:** Peter Allen (Anglia Ruskin U) Mike Clarke (QUB and NICTU) Nathan Congdon (QUB) Evie Gardner (NICTU) Chris Hammond (Kings College London) Ruth Hogg (QUB) Nicola Logan, co-chief investigator (Aston U) Margaret McFarland (BHSCT) Jennifer Preston (Liverpool U) Kathryn Saunders (Ulster U) Niall Strang (Glasgow Caledonian U) Cliona McDowell (NICTU) **(2) Members of the NICTU**: Clinical Trial Manager Clinical Trial Co-ordinator Data Manager Database Developer Clinical Research Monitor **(3) Members of DIT (MOSAIC trial)**: James Loughman and Ian Flitcroft have joined the research team to be able to share trial protocols and facilitate prospective meta-analysis. (4) **Members of WA (WA-ATOM trial)**: David Mackey and Samantha Lee have joined the research team to be able to share trial protocols and facilitate prospective met-analysis.
Statisticians	Cliona McDowell (NICTU)Head of Statistics, Northern Ireland Clinical Trials Unit (NICTU), 1st Floor Elliott Dynes Building, The Royal Hospitals, Grosvenor Road, Belfast, BT12 6BA
Clinical Trials Unit	Northern Ireland Clinical Trials Unit (NICTU) 1st Floor Elliott Dynes Building, Royal Hospitals Grosvenor Road, Belfast, N. Ireland, BT12 6BA
Primary Sponsor	Belfast Health & Social Care Trust (BHSCT) Royal Hospitals, Grosvenor Road, Belfast, N. Ireland, BT12 6BA
Primary Sponsor's Reference	17097AB-AS
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Contact for scientific queries	Augusto Azuara-Blanco Centre for Public Health, Queen's University Belfast Institute of Clinical Sciences B Grosvenor Road, Belfast BT12 6BA a.azuara-blanco@qub.ac.uk

4 FUNDING

This trial is funded by the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation (EME) Programme.

5 ROLES AND RESPONSIBILITIES

The Chief Investigator (CI) will have overall responsibility for the conduct of the trial. The Northern Ireland Clinical Trials Unit (NICTU) will undertake trial management including all clinical trial applications (Ethics, Research Governance and Competent Authority), site initiation and training, monitoring, analysis and reporting. The NICTU Trial Co-ordinator will be responsible on a day to day basis for overseeing and co-ordinating the work of the multidisciplinary trial team, and will be the main contact between the trial team and other parties involved.

Before the trial starts, site training will take place to ensure that all relevant essential documents and trial supplies are in place and that site staff are fully aware of the trial protocol and procedures. The NICTU will assist and facilitate in the setting up and coordination of the trial committees including the Trial Management Group (TMG), Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMC).

5.1 Contributorship

AAB and NS conceived the study. AAB, NL, NS, RH, MC and EG initiated the study design and all co-applicants and the Belfast Health and Social Care Trust (BHSCT) clinical trial pharmacist contributed to the refinement of the study protocol. EG and MC provided statistical and methodological expertise in trial design.

5.2 Sponsor

The BHSCT will act as Sponsor for the study and the CI will take overall responsibility for the conduct of the trial. Separate agreements will be put in place between the Sponsor and each organisation who will undertake Sponsor delegated duties in relation to the management of the study.

5.3 Committees

5.3.1 Trial Management Group (TMG)

A TMG will be established and Chaired by the CI. The TMG will include representation from the NICTU and other investigators or collaborators who are involved in the study and provide trial specific expertise (e.g. trial statistician). This group will have responsibility for the day to day operational management of the trial. Regular meetings of the TMG will be held to discuss and monitor progress. The discussions of the TMG will be formally minuted and a record kept in the Trial Master File (TMF). A TMG Charter will be drawn up to detail the terms of reference of the TMG, including roles and responsibilities of the members.

5.3.2 Trial Steering Committee (TSC)

The conduct of the trial will be overseen by a TSC. The TSC is a group that act as the oversight body for the trial on behalf of the Sponsor and Funder. Throughout the trial, the TSC will take responsibility for monitoring and guiding overall progress, scientific standards, operational delivery and protecting the rights and safety of trial participants.

The TSC will include an independent Chair, at least two independent clinicians or trialists, at least one patient representative and the CI. Representatives of the Sponsor/Funder and the NICTU may attend TSC meetings as observers and at the discretion of the Chair. The TSC Charter will outline the terms of

reference of the TSC including roles and responsibilities, membership, organisation of meetings, reporting, decision making and the relationship with the other trial committees.

As the frequency of DMC meetings will be dependent on recruitment rates (see below), TSC meetings will be arranged to coincide with these and will be convened to discuss issues and recommendations raised by the DMC.

5.3.3 Data Monitoring Committee (DMC)

A DMC will be appointed with responsibility for safeguarding the interests of trial participants. The DMC will monitor the main outcome measures including safety and efficacy and assist and advise the TSC to protect the validity and credibility of the trial. The DMC will include two clinicians and a statistician who are independent of the trial. The DMC Charter will outline the terms of reference of the DMC including roles and responsibilities, membership, organisation of meetings, reporting, decision making (including stopping rules if applicable) and the relationship with the other trial committees. In the light of interim data and other relevant evidence, the DMC will inform the TSC if, in its view, there is proof beyond reasonable doubt that the data indicate that the trial should be terminated.

A joint TSC and DMC inaugural meeting will be held prior to recruitment commencing. Subsequent meetings will be scheduled at regular intervals.

The Trial Statistician will produce reports for the DMC and TSC which may include recruitment, baseline data, adverse events, compliance and outcome data to enable them to monitor the trial and guide overall progress.

5.3.4 User Involvement or any other relevant committees

The participant information sheets (PIS) have been reviewed by the NIHR Medicines for Children Research Network and parent representatives. In addition, two parent representatives sit on the TSC.

6 BACKGROUND AND RATIONALE

6.1 Background Information

Myopia is a condition that causes poor vision when looking at distant objects. This is generally due to a physical change in the structure of the eye, typically an increased axial length. Myopia typically appears in childhood and tends to become more severe over time. It can be corrected (e.g. with glasses, contact lenses or surgery) but myopic eyes have an increased risk of developing co-morbidities such as glaucoma (Marcus 2011), retinal detachment, and choroidal neovascularisation at the macula that can cause blindness (Flitcroft 2012). Importantly, the risks of associated co-morbidity and blindness are associated with the degree of myopia.

Myopia is more prevalent in East Asia but recent epidemiological studies show increasing rates of myopia among adolescents in European populations and suggest myopia is occurring at an earlier age than in previous generations. Myopia currently affects 30.6% of adults in Europe, but among younger people (25-29 years), myopia occurs in 47% (Williams 2015).

Juvenile-onset myopia typically develops at approximately six to ten years of age. The progression of myopia is usually faster at younger ages but myopia onset, progression, and stabilization vary widely among individuals and are influenced by a wide range of variables including environment, lifestyle, parental refractive history and ethnicity (Williams 2015, Donovan 2012).

Interventions to reduce the progression of myopia have been investigated. Multifocal spectacles, undercorrection of myopic refractive error and peripheral defocus contact lenses have at best a very mild effect on myopia progression (Walline 2011). However, cycloplegic agents, such as atropine,

significantly reduce myopic progression (Walline 2011) and are widely used in some East Asian countries for treating children with myopia, but the mechanism by which they act is unknown. Furthermore, because myopia onset and progression are known to be influenced by ethnicity and environment, it is not clear how effective atropine treatment would be for slowing myopic progression in UK children.

A 2011 Cochrane Review found topical anti-muscarinic agents to be more effective than refractive interventions in the inhibition of myopic progression (Walline 2011). The trial team recently updated the evidence base for this review (entitled "Interventions to slow progression of myopia in children" (Walline 2011)) by searching the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and MEDLINE, as well as the clinicaltrials.gov website. Search dates were from October 2011 (last search date of the Cochrane Review (Walline 2011) to December 2015. Two independent investigators assessed the titles and abstracts identified in the searches as per the Walline criteria for considering studies for this review. Each record was classified as (1) include, (2) unsure or (3) not include. The full text of studies that were classified as include or unsure was assessed by two investigators and a decision was then made on whether to include the study or not. A third review investigator helped to resolve disagreements. Data were extracted by two investigators. This updated search found one additional randomised trial (Chia 2012), evaluating the effectiveness of low dose of atropine (3 different concentrations) in Singaporean children of Chinese race. A very low dose of 0.01% was associated with better tolerability and efficacy. Recent publications from the ATOM-2 study (Chia 2014, Chia 2015, Loh 2015) reported on the long-term efficacy of low-dose atropine in children from Singapore and risk factors for myopia progression. A small retrospective case-control study from the USA also suggested that low-dose 0.01% atropine reduced myopia progression in children of other ethnicities: White, African-American, and Hispanic (Clark and Clark 2015). Another recent systematic review and network meta-analysis (Huang 2016) also confirmed muscarinic antagonists (atropine and pirenzepine) as the most effective interventions for myopia control in children.

In conclusion, there is robust evidence that treatment with atropine eye drops is effective to control myopia in Chinese children; but there is limited evidence from UK children and those of white race on how effective atropine will be to prevent myopia progression.

Atropine is an anti-cholinergic agent that is relatively selective for muscarinic receptors. As an eye drop, atropine 1% instillation causes pupil dilatation by blocking the muscarinic receptors in the pupillary sphincter musculature. Atropine also reduces or paralyses contraction of the ciliary muscle resulting in blurred proximal vision from loss of accommodation (cycloplegia). Traditionally this cycloplegic effect was used to aid paediatric eye examinations. Aside from individual response differences due to pigmentation, the severity and persistence of the atropine response is also dose related; instilling lower concentrations of the eye drop lessens adverse effects such as photophobia, blurred near vision and allergic reaction.

Systemic side effects to 1% atropine eye drops are associated with its anti-muscarinic activity and can include severe ataxia, restlessness, excitement and hallucinations.

Other adverse effects may include a dry mouth with difficulty in swallowing and talking, flushing and a dry skin, transient bradycardia followed by tachycardia, palpitations and arrhythmias, reduced bronchial secretions, urinary urgency and retention and constipation. Side effects that occur occasionally include confusion, nausea, vomiting and giddiness. Frequency of systemic side effects with a 0.01% formulation would be expected to be considerably reduced in comparison to the 1% formulation.

6.2 Rationale for the Study

Myopia currently affects one in three people in the UK. In Europe, myopia prevalence has risen dramatically over the last few decades (Rudnicka 2016), with nearly half (47.2%) of young adults aged

24-29 years reported as myopic (Williams 2015). Myopia appears to be occurring at a younger age and its severity has increased by an average of approximately 1 diopter (D) in one generation (Vitale 2008).

In the UK, the majority of people with myopia have normal vision with appropriate correction but myopia still has significant public health consequences from a variety of perspectives; educational (Ma 2014), financial and psychological, as well as the risks of blindness (Flitcroft 2012). Myopia is a risk factor for myopic maculopathy, retinal detachment, and glaucoma, and the risk increases with the degree of myopia. Children with myopia also require frequent eye tests and changes of glasses that are funded primarily by the NHS.

Myopic maculopathy is a progressive condition in which severe visual loss develops from atrophy of the retinal pigment epithelium and choroidal neovascularisation. In the Blue Mountains Eye Study, myopic retinopathy appeared in 25.3% of myopes with greater than -5 D of myopia (Vongphanit 2002). According to NICE there are approximately 200,000 people with pathological myopia in the UK (https://www.nice.org.uk/guidance/ta298).

A similar relationship has been observed between increasing myopia and retinal detachment. The current incidence of retinal detachment is about 10–15 per 100,000 people, which equates to an estimated 7,300 new cases in the UK each year. Retinal detachment requires urgent vitreo-retinal surgery and can lead to severe visual loss if surgery is unsuccessful. The majority of non-traumatic detachments in eyes without previous surgery are attributable to myopia. In the Eye Disease Case-Control Study Group, myopia was identified as a major risk factor for retinal detachment, with an adjusted odds ratio for refractions in the range -1 to -3D of 4.4 (95% Confidence Interval (CI) 2.9–6.6), increasing to 9.9 (95% CI 6.6–14.8) in the range -3 to -8D. For any degree of myopia (above -1D), the corrected odds ratio was 7.8 (95% CI 5.0–12.3).

Myopia has also been shown to increase the risk of glaucoma. Glaucoma affects 2% of the adult population in the UK and the NHS spends over £500 million on glaucoma care each year. A recent systematic review of myopia as a risk factor for glaucoma pooled data from 11 different studies and concluded that for low myopia (myopia up to -3D), the odds ratio was 1.65 (95% CI 1.26–2.17). The odds ratio was higher still at 2.46 (95% CI 1.93–3.15) for higher levels of myopia (in excess of -3D) (Marcus 2011).

The dose–response relationships between myopia severity and ocular diseases observed in epidemiological studies indicates that there would be substantial benefits to the NHS from reducing the degree of myopia, even if the overall incidence of myopia is unaltered.

Myopia also has the potential to impede educational attainment. A recent randomised trial (Ma 2014) showed that Chinese children with uncorrected myopia have significantly worse school outcomes than their visually corrected peers. This situation was significantly improved by provision of spectacle correction. In the UK, O'Donoghue et al (2010) demonstrated that failure of school children to bring myopic spectacles to school is the most common cause of visual impairment amongst teenagers.

Strategies to control progression of myopia gain importance in the context of the 'Vision 2020' initiative by the World Health Organisation (WHO) to eliminate preventable causes of blindness, including risks associated with high myopia, by the year 2020. In several countries, myopic children are now treated routinely with low dose atropine eye drops but these drops are not available in the UK and there have been no trials to determine their efficacy in (mainly) white populations.

Two other trials, one in Dublin and one in Western Australia have been funded to evaluate the efficacy of low dose atropine in myopia progression. We will collaborate with the Dublin and Western Australia teams and will use similar protocols to facilitate prospective individual participant data meta-analysis.

6.3 Rationale for the Intervention

Atropine 1% is very effective in slowing myopia progression, but it is not popular because of its unwanted side effects of pupillary dilation and cycloplegia and possible rebound effect (see below).

In a placebo-controlled trial evaluating 1% atropine drops used daily for two years in 400 children aged 6-12 years, no serious adverse events related to atropine were observed (Chua 2006). There was no deterioration in best-corrected visual acuity. Similarly intraocular pressure changes were within 5.5 mmHg, with no absolute readings of more than 21 mmHg. No lenticular, optic disc or macular changes were noted. However some tolerability issues resulted in withdrawal of participants. These included allergic or hypersensitivity reactions or discomfort (4.5%), glare (1.5%), and blurred near vision (1%).

In a trial comparing efficacy and safety of three different concentrations of atropine, 0.5%, 0.1% and 0.01% instilled daily for two years in 400 children aged 6-12 years there were no serious adverse events (Chia 2012, Chia 2016). The adverse reactions directly attributable to atropine fully resolved shortly after discontinuation of the treatment, and included allergic conjunctivitis, which occurred in 13 children (4.1%) in the atropine 0.1% and 0.5% groups. In three children (1.2%), symptoms were severe enough to warrant ceasing trial medication. Four children in the 0.1% and 0.5% groups (1.3%) had allergy-related dermatitis of the eyelids. Six children had other eye symptoms; in five, these symptoms could be attributed to atropine, including one case of irritation and one case of blur in the atropine 0.01% group, and two cases of ocular irritation and one case of intolerable glare in the atropine 0.5% group.

Atropine 1% drops are also used as an alternative to occlusion therapy to treat childhood amblyopia. This method involves the instillation of 1% atropine sulfate, into the sound eye to prevent accommodation, blurring near vision, in this eye. Clinical experience has found that use of atropine to treat amblyopia was highly acceptable to children and parents, and consequently high rates of compliance are reported. In a trial comparing occlusion therapy versus 1% atropine eye drops for six months in 419 children younger than seven years (PEDIG group 2002), few side effects were observed; light sensitivity was reported in 18% of participants, lid or conjunctival irritation in 4% and eye pain or headache in 2%. Nearly all (194, 95%) of the 204 patients randomised to 1% atropine completed the treatment.

Cooper (2013) evaluated the maximum atropine concentration without clinical signs or symptoms and reported that atropine 0.02% was the highest concentration that does not produce any clinically significant symptoms from pupillary dilation or accommodation paresis. A recent study (Loughman 2015) in a young student population with myopia from Ireland found that atropine 0.01% was well tolerated and acceptable.

Atropine eye drops at a concentration of 0.01% are expected to be safe and well tolerated. This is supported by evidence from other trials that have employed the same and other more potent anti-muscarinic agents (e.g. 1% atropine; pirenzepine), and the well-established safety profile of atropine use in ophthalmology.

Accidental ingestion of a high dose of atropine sulfate may increase the risk of systemic side effects. Potential systemic side effects include gastrointestinal, respiratory, dermatological, cardiovascular, neurological and musculoskeletal effects. Each study bottle of atropine eye drops contains 10mls of a 0.01% solution meaning that the total volume contains 1mg of atropine. The bottles will be clearly labelled to advise that they should be kept out of the reach and sight of children and the study Parent Information Sheets will reinforce this information.

6.4 Rationale for a Comparator

The control group will receive placebo eye drops to minimise the risk of bias. A parent advisory group was consulted and it was agreed to include the placebo as comparator. In addition, in order to undertake a meta-analysis with the Dublin and Western Australia teams, the control group is required.

7 STUDY AIM AND OBJECTIVES

7.1 Research Hypothesis

Our hypothesis is that low dose atropine eye drops will reduce myopia progression in children compared with placebo.

7.2 Study Aim

The aim of the study is to evaluate the efficacy and safety of low dose atropine (0.01%) eye drops to reduce progression of myopia in UK children.

7.3 Study Objectives

The primary objective is:

- To evaluate the efficacy of 0.01% atropine eye drops to reduce the progression of myopia in children after 24 months of treatment

The secondary objectives are:

- To evaluate the safety and tolerability of low dose atropine eye drops
- To determine the mechanism of action of atropine eye drops

The exploratory objective is:

- To explore the influence of other factors in the progression of myopia, including hours of outdoor activity, iris colour, ethnicity, and family history

8 STUDY DESIGN

8.1 Study Design

This is a multicentre, randomised, double-masked, placebo-controlled, superiority trial, with 2:1 allocation of intervention and control (atropine:placebo).

8.2 Study Schematic Diagram

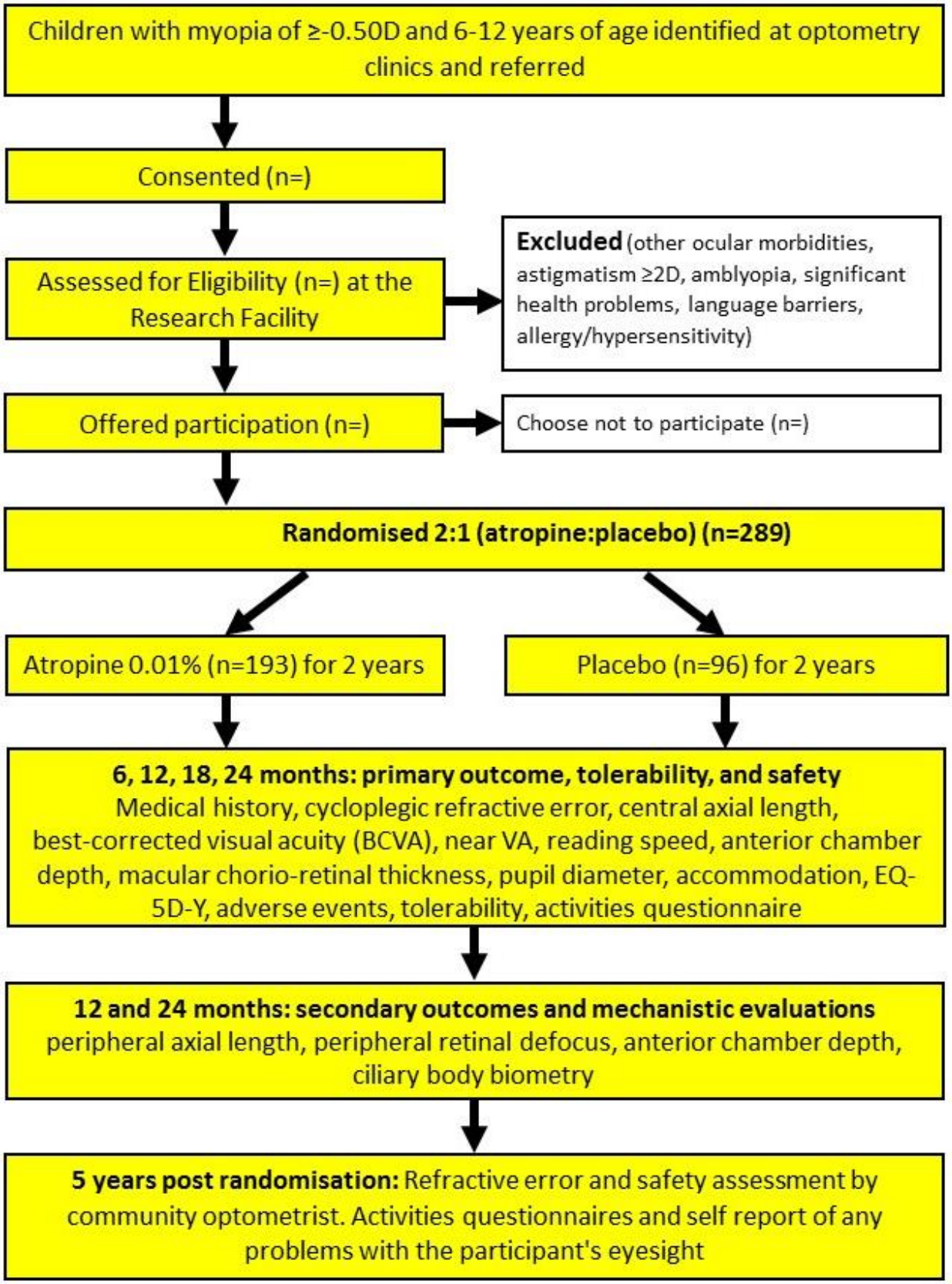

Figure 1: Flow Diagram; A multi-centre double masked placebo-controlled intervention trial evaluating low-dose atropine (0.01%) to reduce progression of myopia in children in the United Kingdom

9 Methods: participants, interventions, and outcomes

9.1 Study Setting

A minimum of four clinical research facilities from academic departments of medical or optometric schools and/or NHS Trusts from across the United Kingdom.

9.2 Eligibility Criteria

Children will be eligible to participate in the study if they fulfil the criteria below. Eligibility will be confirmed by a medically qualified doctor and documented on the eligibility checklist form.

9.2.1 Inclusion Criteria

1. Age 6-12 years (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

9.2.2 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. Previous use of atropine eye-drops, prior or current use of Ortho-K contact lenses or contact lenses with dual focus, multifocal or extended depth of focus lens design
11. Children or Parents / Guardians with latex allergy as the dropper used to administer the eye-drop contains latex.

*Children enrolled in observational studies are potential candidates for CHAMP UK. Whether or not children enrolled in CHAMP UK are also involved in other observational studies is at the discretion of the CHAMP UK local Principal Investigator (PI) and should be considered when the burden on participants is not expected to be onerous. Co-enrolment with other studies should be documented in the Case Report Form (CRF).

9.3 Interventions

9.3.1 Intervention Description

The intervention group will receive 0.01% atropine sulfate eye drops, administered once daily for 24 months. The control group will receive placebo eye drops, administered once daily for 24 months. Atropine and placebo bottles will be identical and thus participants and investigators will be masked.

Participants wearing contact lenses are eligible for the trial but should remove the contact lens at the time of drop instillation. Additional information on the drop instillation will be provided to each participant in the form of a guidance leaflet.

9.4 Concomitant Care

Participants will continue to attend their community optometrist for their routine eye health examinations and for the prescription of glasses or contact lenses. Soft contact lens wear will be allowed during the trial. It is not anticipated that children of this age group will use hard contact lenses, as this is not usual practice. If a participants wears hard contact lenses we will ask them to stop wearing these lenses and wear glasses for 24 hours before attending the research visit.

Participants will be provided with a study card, which will advise other healthcare professionals that they are participating on the CHAMP UK trial.

9.5 Outcomes

9.5.1 Primary Outcome

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.

Measuring the refractive error is most accurately and reliably done under cycloplegic conditions with an autorefractor. Spherical equivalent is the standard scale used to describe the severity of myopia and is calculated as sphere plus half cylinder power. A similar primary outcome has been used in other relevant studies (Chia 2012; Clark 2015; Walline 2011 (Cochrane Review); Chua 2006). Autorefraction is appropriate for refractive error studies because it is more repeatable than subjective refraction or retinoscopy (Zadnik 1992; Walline 1999). The autorefractor has been shown to be highly accurate and repeatable for on and off-axis measurement (Davies 2003), and has been used widely in studies of human refractive error (Logan 2011; McCullough 2016).

Five measurements will be taken and averaged; with the mean spherical equivalent refraction calculated as SER = sphere + cylinder/2.

9.5.2 Secondary Outcomes

- Central axial length: measured using a laser biometer at central fixation conditions
- Best corrected distance visual acuity (BCdVA) (uniocular and binocular): assessed using the logMAR ETDRS chart. This is a standard letter chart used in research to ensure accuracy and validity of the acuity measurements and has been shown to be repeatable in children (Manny 2003)
- Near visual acuity (uniocular and binocular): tested using near logMAR ETDRS at 40 cm
- Reading speed: measured with the Wilkins Rate of Reading test
- Pupil diameter
- Spectacle correction
- Tolerability: using a 4-point scale to quantify, from the point of view of the participant, (1) local irritation/stinging associated with eye drop instillation; (2) photophobia; and (3) difficulties reading and writing
- Adverse event rates and allergic reactions rates
- Quality of Life: measured using the EQ-5D-Y

9.5.3 Exploratory Outcomes/Mechanistic Evaluations*

- Peripheral axial length: measured using a laser biometer at peripheral fixation conditions
- Peripheral retinal defocus: measured with the autorefractor at central and peripheral fixation conditions
- Anterior chamber depth: measured with a laser biometer
- Accommodation: using a near target and in accordance with the Clinical Assessment Guidelines

- Iris colour: measured using a visual grading scale of dark brown, light brown, blue, green, grey
- Height and weight to provide information about the links between the child's development and eye growth and potentially information about lifestyle
- Hours of outdoor activity: measured using an activities questionnaire
- Ciliary body biometry: measured using anterior-segment OCT (AS-OCT). This will enable changes in lens position and ciliary muscle changes resulting from atropine use to be compared with normal myopic growth
- Chorio-retinal thickness: measured using spectral domain OCT (SR-OCT). This will enable differences in choroidal thickness resulting from atropine use to be compared with normal myopic growth (Read 2009)

*Only to be carried out in sites with the relevant equipment. If measurements for exploratory outcomes cannot be collected this will not be recorded as a protocol deviation.

9.6 Sample Size

We anticipate that the effect of atropine eye drops in a UK population will be smaller than the reported effect in Chinese populations (Li 2014), but assuming that atropine reduces the progression of myopia by at least 40%, using SD=0.7, a correlation (ICC) between eyes of 0.9 and a variation inflation factor of 1.9, we will need 97 participants in each group. Considering a dropout rate of 15% and that 10% of the 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 population with 90% power.

Justification: in a study of 400 Chinese children evaluating the effect of 24 months of 1% atropine eye drops, myopia progression was -1.20 +/- 0.69 D in the placebo control group, and 0.28 +/- 0.92 D in the atropine group (Chua 2006).

We have assumed that progression of myopia and efficacy of atropine will be less in UK children than in Chinese children.

Progression of myopia of untreated children was estimated from the control groups of randomized trials for myopia. The following progression data have been reported:

- Katz 2003 (Chinese race): progression of -1.28D (SD 0.78) D after 2 years

- Edwards 2002 (Chinese race): progression of -1.26D (SD 0.74) D after 2 years

- Chua 2006, ATOM study (Chinese race): progression of -1.20D (SD 0.69) after 2 years

- Hyman 2005, COMET trial (children of mixed races, with whites being the most common ethnicity): progression of 1.32D after 3 years (standard error 0.04).

- In an observational study from the UK (Breslin 2013), myopia progression was 1.14D after 3 years.

9.7 Recruitment

9.7.1 Recruitment Strategy

Potential participants will be recruited through local optometric practices with which the investigators have strong links and who have confirmed willingness to collaborate. We have also received support from local optometric committees and the College of Optometrists. Researchers will provide local optometrists with information regarding the study, which they can pass on to parents of children meeting the inclusion criteria. If agreed, details of these parents will be passed to the local investigators and contact made. Potential participants will be invited to attend the research centre where consent will be obtained. We will also use local radio as a recruitment strategy. We will recruit five children per month in each of the four centres, a reasonable target based on our previous

experience. However, if required, contingency plans to boost recruitment have been identified, including approaching local schools to advertise the trial. Recruitment and assessments will be done at four academic units with previous clinical trial expertise in visual disorders and myopia. The NICTU will oversee statistics, randomisation, trial and data management and the NICRF will provide advice and support on appropriate methods for trial conduct, management and reporting.

We plan to undertake an internal "pilot" study to assess feasibility which will run until recruitment reaches a cumulative total of 15 months across the five sites. For example, as each site will have a target recruitment of six participants a month if all sites open at the same time this target will be reached following three months. At the end of the internal "pilot" study (15 cumulative months) we expect to recruit 90 participants during this time and will use standard recruitment feasibility milestones. If recruitment rates achieve 75-100% of the target, we will progress with the trial. If we achieve 50-75% recruitment, we will progress with the trial following review of screening logs and protocol and once barriers to achieve adequate recruitment are addressed. If we recruit 25-50% of the required number, the trial will be progressed only after screening logs and protocol are reviewed and once, following approval by NIHR-EME, additional sites are opened. Should projected recruitment be <25%, it is not expected the trial will progress; the decision will be made by the TSC and NIHR-EME.

9.7.2 Study Within A Trial

9.7.2.1. In order to assess the effects on recruitment of local media (radio) or social media advertisement, we will conduct a Study Within A Trial (SWAT) The primary outcome will be the change in recruitment after the radio or social media advertisement compared to before the advertisement. Secondary outcomes will be retention of participants in the trial, and changes in the number of potentially eligible participants who are assessed or approached for the trial.

9.7.2.2. An additional SWAT will be used to explore study drug adherence by comparing an inexpensive and pragmatic method of adherence assessment i.e. bottle weighing, with the electronic adherence monitoring data captured from a Medical Events Monitoring System (MEMS) described in section 11.6. At one site (Belfast), a sample of eye drop bottles will be weighed on calibrated scales in the pharmacy department.

9.7.2.3. A novel recruitment method will be investigated through embedding the TRECA (TRials Engagement in Children and Adolescents) study within the CHAMP UK trial. TRECA is investigating whether providing children and young people with information about a trial through a multimedia information resource (MMI) impacts on recruitment and retention rates as well as the quality of decision-making about trial participation.

TRECA is funded by the NIHR (HS&DR 14/21/21), with ethical and HRA approval already obtained. The MMIs are websites with text, images, animations and videos about the CHAMP UK trial. Phase one of TRECA saw the development of the MMIs, through participatory design and usability testing with children and adolescents with long-term health conditions, their parents and clinicians.

The MMIs will be based on information from the CHAMP UK PIS. The MMIs also include generic animations that cover elements about trials, including:

- what is a trial?
- why do we do trials?
- who is in a research team
- assent and consent

In addition, the CHAMP UK MMIs will have an explainer animation about the study on the front/home page of the MMI. The idea is that this explainer covers the main features of the trial in approximately 60 seconds of animation.

Patients approached to participate in CHAMP UK will be randomly allocated to receive either:

- the standard PIS, or
- the CHAMP UK MMI, developed by TRECA in conjunction with the CHAMP UK study team, or
- both the MMI and PIS

9.7.3 Screening Procedure

Community optometrists will be asked to inform potentially eligible participants of this study and give contact details of local investigators.

Screening will be conducted by research staff at the research facility. The NICTU will provide screening logs which must be completed by the local PI or designee to document all children screened for the study and all children recruited. Children screened and not recruited to the study should also be documented on the screening log, including the reason for not being enrolled. The local PI or designee will be required to submit screening logs to the NICTU on a monthly basis.

9.7.4 Informed Consent Procedure

As the clinical trial participants are minors under the age of 16, there are additional risks to be considered. Children are typically considered as vulnerable subjects and their participation therefore requires parental consent. We plan to conduct our research in an inclusive, child friendly manner, and will require child assent for participation.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Eligible children will only be included in the trial after written informed consent is obtained from at least one of their parents or guardians and written informed assent is obtained from the child.

Informed Consent Forms (ICF) approved by the Research Ethics Committee (REC) will be provided by the NICTU. The local PI or designee is responsible for ensuring that informed assent/consent for trial participation is given by each child and their parent(s) or guardian(s) prior to any trial procedure being performed. This requires that the ICF be signed and personally dated by the parent prior to any trial procedures being undertaken. If no consent is given, a child cannot be recruited into the trial. Two copies of the ICF must be signed and personally dated by the parent and the individual taking consent. Two copies of the Informed Assent Form will also be signed by the child and the person taking consent. The originals will be retained by the parent and by the local PI or designee in the Investigator Site File (ISF).

The NICTU will provide PIS approved by the REC. The local PI or designee is responsible for ensuring that all participants and parents/guardians allocated through the TRECA trial to receive a paper copy of the PIS, and are allowed adequate time to review this and the opportunity to ask any study related questions. Participants allocated to receive information via MMIs, through the TRECA trial will view explainer videos and animations detailing the information contained in the PIS. Participants and their parents/guardians will also be given adequate time to review the information provided and ask any questions they may have. This should be judged by the local PI or the designated member of the study team who will have the responsibility for taking consent.

9.7.5 Withdrawal of Consent

Participants have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason without any consequences. The investigator has the right to discontinue a participant from study treatment or withdraw a participant from the study at any time, if it is perceived to be in the best interest of the participant.

Participants must discontinue study treatment and be withdrawn from the study for any of the following reasons:

- Withdrawal of consent by the participant
- Loss to follow-up. At least three documented attempts will be made to contact any participant lost to follow-up
- Recommendation by the local PI, CI or Sponsor

If a participant is withdrawn before completing the trial, the reason for withdrawal (if known) must be entered on the appropriate CRF page. If data had been obtained and/or questionnaires been completed, then the data collected until the point of withdrawal will be used for the analysis of the trial, unless the participant specifically requests that the information not be used.

If a participant is withdrawn due to an adverse event, the following will apply: (1) if the participant wishes to finish involvement in the trial, the investigator will arrange for follow-up visits until the adverse event has resolved or stabilised, and acquired data will be used for analysis, if allowed by the participant; or (2) if the participant wishes to continue involvement in the trial, the research visits will continue as planned although the medication will not be used.

10 Methods: Assignment of interventions

10.1 Sequence Generation

All participants who agree to join the study will be assigned a unique Participant Identification Number. Randomisation will use the remote automated computer randomisation application, Sealed Envelope, ensuring allocation concealment. Randomisation will be computer-allocated using a minimisation algorithm to ensure balanced allocation of participants across the two treatment groups. Minimisation will be by centre, ethnic background (white/non-white), and severity of myopia (less than -3D in either eye / -3D or greater in the eye with more severe myopia). The unit of randomisation will be the participant (not the eye).

10.2 Allocation Concealment Mechanism

The randomisation list will be generated by Sealed Envelope and group allocation will only be visible to those with Administrator access in the Trial Management team in NICTU. The randomisation email generated by Sealed Envelope which is sent to the local researcher will provide the study drug kit number to be prescribed but will not reveal the group to which the participant has been assigned.

10.3 Allocation Implementation

The local researcher will access the automated randomisation system to obtain the kit number for each participant. Upon receipt of the randomisation email from Sealed Envelope, a prescription will be completed detailing the study drug kit number to be dispensed. A copy of the randomisation email will also be sent to the site pharmacist as a quality control check prior to dispensing.

10.4 Masking

The study will be conducted in a double-masked fashion. Study treatment assignment will be masked for both the investigators and the participant. The atropine and placebo eye drops will be packaged in identical bottles and labelled with a unique identification number so that the investigator and participants are unable to identify the contents.

10.5 Emergency Unmasking

To maintain the overall quality of the trial, unmasking should only occur in exceptional circumstances when knowledge of the group allocation is absolutely essential in a medical emergency for further management of the participant or where information is required for expedited reporting of a SUSAR. If time permits, the local PI should attempt to contact the CI prior to unmasking.

On the occurrence of any such event, the local PI will request for the participant to be unmasked through the Sealed Envelope system. If they experience any difficulties the PI should contact the NICTU to request emergency unmasking of the participant via the randomisation system (Sealed Envelope) during usual office hours. Where emergency unmasking is required out of hours, the local PI should contact the CI and if the CI is unavailable, the BHSCT Pharmacy Oncall Service as detailed in the study unmasking guideline. In the event that unmasking occurs, the participant may discontinue the study drug but will remain on the trial unless they decide to withdraw or the local PI feels that this is necessary. Where unmasking has occurred, this should be fully documented by the site and the NICTU informed.

11 STUDY DRUG

11.1 Study Drug Description

The eye drops to be used in the study are:

- Atropine sulfate 0.01% eye drops which consist of 10mls of a clear colourless solution of atropine sulfate 0.01% w/v and benzalkonium chloride 0.01% w/v in sterile water.
- Placebo eye drops which consist of 10mls of a clear colourless solution of benzalkonium chloride 0.01% w/v in sterile water.

Atropine sulfate and placebo eye drops are supplied in identical 15ml amber glass screwtop bottles and packed in boxes containing seven bottles. An eye dropper is provided separately for each bottle in the pack.

11.2 Study Drug Supply

Atropine sulfate 0.01% and corresponding placebo eye drops will be sourced, packed, labelled and distributed to each site pharmacy department by Victoria Pharmaceuticals, BHSCT. The study medication pack of seven bottles, provides a 24 week supply plus an extra four weeks. Each bottle of eye drops must only be used for 28 days after opening. Packs will be labelled in accordance with applicable regulatory requirements. Each pack will be labelled with a unique pack identification number determined by the study randomisation schedule.

On receipt of a prescription signed by an authorised member of the research team, the pharmacy department at each site will dispense a medication pack of seven bottles in accordance with the pack number specified in the assigned sealedenvelope.com email confirmation.

11.3 Study Drug Accountability

The site pharmacist will be responsible for maintaining complete records of all received, dispensed, unused and expired study drug. The NICTU will provide a drug accountability record form for this purpose. Parents will be instructed to return all used/unused bottles at the next study visit. Study medication may not be destroyed until the NICTU has completed stock reconciliation and issued a certificate of destruction. Study drug will then be destroyed locally in accordance with site policy.

11.4 Study Drug Storage

Study medication packs will be stored upright, protected from lightin a refrigerator at 2-8°C. On the first day of eye drop administration, one bottle of eye drops will be removed from the medication pack and placed in a MEMS device to monitor adherence as described in section 11.6. The MEMS device containing the eye drop bottle will be stored in the refrigerator at 2-8°C. Every 28 days, the eye drop bottle will be removed from the MEMS device and replaced with a new bottle from the medication pack.

11.5 Study Drug Administration

The parent or guardian of the participant will be instructed on technique of instillation and will also be provided with written instructions. The parent or guardian will administer one drop in each eye every day at the same time of day for 24 months as instructed. Participants and parents will be provided with information describing the clinical signs of potential side effects, and given instructions as to appropriate management in each case.

Drug administration will be recorded on the participant's CRF.

11.6 Study Drug Adherence

Compliance will be assessed using electronic monitoring with a MEMS device.

The MEMS Cap (AARDEX Group Ltd) is a plastic container with a screw top in which the eye drop bottle is stored until needed for drop instillation (Robin 2007, Sleath 2011, Sleath 2012, Barker 2015). An electronic record is made of the date and time that the top is unscrewed, and this is taken as a surrogate for administering the medication.

The research team will supply participants with a MEMS device at the start of the study to store their in-use bottle of eye drops.

Participants will be told how the MEMS works (including that it will record when the bottle is opened and that this is being taken as a measure of them taking their eye drops) and will be trained in how to use it correctly.

The MEMS device has previously been tested to measure adherence with eye drops in adults and children with glaucoma (Freeman 2012). A feasibility study on the use of MEMS container in an adult glaucoma population in the UK has been successful (Richardson 2013).

Participants will be telephoned after enrolment (within the first month) to assess whether and how they are using the provided medication bottle and MEMS Cap. After six months, participants will return the bottles and collect the new prescription.

The event logs will be extracted from the MEMS during visits (every six months) via a device connected to a computer. Adherence will be assessed as the percentage of days on which a dose was taken, and on which the correct number of doses was taken. Data will also be extracted on the time of day the MEMS Cap was opened to determine the time of drug administration, this information will then be used to examine the impact of the time of administration.

11.7 Study Drug Termination

The participant must discontinue study drug if any of the following occurs:

- Withdrawal of consent
- Any medical or ocular condition that the investigator or sponsor determines may jeopardise the participant's safety if she or he continues receiving the study treatment
- An adverse event which requires discontinuation of the study medication

As the trial will be conducted on an intention to treat basis, no participants will be required to discontinue the intervention on the basis of non-compliance with study visits. The level of compliance with eye drop use will be quantified by questionnaire (self-report), electronic monitoring and bottle weighing (BHSCT site only).

12 METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

12.1 Data Quality

Data integrity and study credibility depend on factors such as ensuring adherence to the study protocol and using quality control measures to establish and maintain high standards for data quality.

On-site monitoring visits during the trial will check the accuracy of entries on CRFs against the source documents, the adherence to the protocol, procedures and Good Clinical Practice (GCP), as outlined in the trial monitoring plan.

Quality control is implemented by the NICTU in the form of Standard Operating Procedures (SOPs), which are defined to encompass aspects of the clinical data management process, and to ensure standardisation and adherence to International Conference of Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements.

Data quality control checks will be carried out by the Data Manager to ensure accuracy. Data errors will be documented in Quality Control Reports with corrective actions implemented.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify discrepancies such as out of range, inconsistencies or protocol deviations based on data validation checks programmed in the clinical trial database.

12.2 Data Collection

To ensure accurate, complete and reliable data are collected, the CI and NICTU will provide training to site staff on trial processes and procedures, including the completion of the CRF and data collection through investigator meetings and site initiation visits.

All data for an individual participant will be collected by the local 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 questionnaires by the local PI or designee.

Case report forms and questionnaires are to be submitted to the NICTU in a timely manner to facilitate query resolution.

12.2.1 Study Visits and Procedures

All children must be evaluated during the study according to the schedule of assessments and data will be collected at each of the following time-points as outlined in table 1 below.

Table 1. Schedule of Assessments

	Baseline	6 months	12 months	18 months	24 months
Consent	✓				
Randomisation	✓				
Medical history (including height*, weight*, concomitant medications and spectacle correction)	✓	✓	✓	✓	✓
Severity of parental myopia (self-report)	✓				
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	✓	✓	✓	✓	✓
Accommodation (in accordance with guideline)*	✓	✓	✓	✓	✓
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)*	✓	✓	✓	✓	✓
MEMS data		✓	✓	✓	✓
Study drug dispensing	✓	✓	✓	✓	

*: if instrumentation is available

12.3 End of Study Visits and Procedures

At five years after randomisation (approximately 7 years after the start of the study) we will post a questionnaire to participants and ask for details of any possible complications and adverse events. We will request information from their optometrist regarding their eye health, BCdVA, and refractive error data.

12.4 Participant Retention and Follow-up

The TMG will assure that participation in this trial will not represent a burden to participants and assure that retention during the 2-year intervention period of the study will be achieved.

Participants will be followed every six months for a total of five trial visits. In order to ensure adequate follow-up of children, participants' parents will be reminded by telephone or text the week prior to the study visit. This will be carried out either by research staff or by administrative staff at each of the participating centres.

12.5 Data Management

Study data, including the CRF and questionnaires, will be entered onto a web-based Clinical Trial Database (MACRO) and processed electronically as per NICTU SOPs and the study specific Data Management Plan (DMP). Data queries will be generated for site staff as required to clarify data or request missing information. The designated site staff will be required to respond to these queries within an agreed time period. All queries will be responded to/ resolved within the study database. Any amended information will then be entered in the study database.

All essential documentation and trial records will be stored securely and access will be restricted to authorised personnel. 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.

12.6 Data Analysis

12.6.1 Analysis population

Analysis will be based on both the intention to treat principle and per protocol analysis. 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.

12.6.2 Statistical methods

For the primary analysis, endpoints from both eyes will be pooled in combined analysis using generalised estimating equations (GEE) 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.

A detailed Statistical Analysis Plan (SAP) will be written by the trial statistician and approved by the CI and DMC prior to the final analysis.

12.6.3 Additional analyses

Exploratory subgroup analyses will 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 start of trial), ethnic background (white versus non-white), and severity of myopia (less than -3D in either eye versus -3D or greater myopia)

12.6.4 Missing data

Sensitivity analyses will assess the impact of missing data for the primary outcome by imputing extreme values (lowest and highest).

12.6.5 End of Study

For the purposes of submitting the end of trial notification to the Sponsor and the Research Ethics Committee (REC), the end of trial will be considered to be when the database lock occurs for the final analysis. The trial will be stopped prematurely if:

- Mandated by the REC
- Mandated by the Sponsor (e.g. following recommendations from the TSC
- Funding for the trial ceases

The REC that originally gave a favourable opinion of the trial will be notified in writing when the trial has been concluded or if it is terminated early.

13 PHARMACOVIGILANCE

13.1 Definition of Adverse Events

The European Clinical Trials Directive 2001/20/EC and applicable clinical trials regulations set out the legal requirements for adverse event recording, management and reporting of clinical trials.

Table 2. Terms and Definition for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences, which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product, which is related to any dose administered to that participant.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in: - The Summary of Product Characteristics (SPC) for that product (for products with a marketing authorisation) or - The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)
Serious Adverse Event (SAE)	A SAE is an adverse event that: - results in death - is life-threatening - requires hospitalisation or prolongation of existing hospitalisation* - results in persistent or significant disability or incapacity - consists of a congenital anomaly or birth defect - is any other important medical event (s) that carries a real, not hypothetical, risk of one of the outcomes above.

Serious Adverse Reaction (SAR)	A SAR is an adverse reaction that is classed as serious and which is consistent with the information about the investigational medicinal product in question set out in the: - SPC in the case of a licensed product. - IB for any other investigational product.
Suspected unexpected Serious Adverse Reaction (SUSAR)	A SUSAR is a serious adverse reaction which is unexpected i.e. the nature and severity of which is not consistent with the information about the medicinal product in question set out: - in the case of a product with a marketing authorisation, in the SPC for that product - in the case of any other investigational medicinal product, in the IB relating to the trial in question.

*Hospitalisation is defined as an inpatient admission regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

13.2 Eliciting Adverse Event Information

The local PI or designee will record directly observed AEs and all AEs spontaneously reported by the participant. In addition, the participant will be asked about AEs at each visit following initiation of treatment. It is expected that this paediatric population may experience a range of AEs over 24 months of trial participation such as sore throats, common colds or other common childhood illnesses and falls/accidents through play and sport. Such events will not be considered as reportable adverse events unless the event is considered by the investigator to be associated with the study drug or unexpectedly severe or frequent.

The CI will assess all AEs for seriousness, causality, severity and if the adverse event is related to the study drug, for expectedness.

13.3 Assessment of Seriousness

The CI or designee will make an assessment of seriousness i.e. whether it is an adverse event, adverse reaction or suspected unexpected adverse reaction that:

- Resulted in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

13.4 Assessment of Causality

The CI or designee will make an assessment of causality, i.e. the extent to which it is believed that the event may be related to the study drug:

- **Not Related:** Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.
- **Unlikely:** Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
- **Possibly*:** Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.

- **Probably*:** Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause.
- **Definitely*:** Temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

* Where an event is assessed as possibly, probably or definitely related, the event is an AR.

13.5 Assessment of Severity

The CI or designee will make an assessment of severity for each AE according to the following categories:

- **Mild (Grade 1):** A reaction that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.
- **Moderate (Grade 2):** A reaction that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe (Grade 3):** A reaction that prevents normal everyday activities.
- **Life Threatening (Grade 4):** A reaction that has life threatening consequences; urgent intervention indicated.
- **Death (Grade 5):** A reaction that results in death.

13.6 Assessment of Expectedness

If the event is possibly, probably or definitely related to the study drug, the CI or designee will make an assessment of expectedness based on any relevant product information as documented in the summary of product characteristics (SPC) for atropine sulfate 1% eye drops approved by the MHRA as the reference safety information. Adverse reactions or serious adverse reactions may be classed as either:

- **Expected:** The AR is consistent with the undesirable effects of the atropine sulfate eye drops listed in the SPC.
- **Unexpected:** The AR is not consistent with the undesirable effects listed in the SPC.

An AR may be described as 'unexpected' if it has occurred with greater frequency or severity than might otherwise have been expected.

13.7 Adverse Event Reporting Period

The AE reporting period begins upon enrolment of the participant into the trial and ends 30 days after the last administration of study drug. All AEs assessed by the CI as possibly, probably or definitely related to the study drug and all SAEs that occur during this time will be followed until they are resolved or are clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es). The CRF should be updated with the date and time of resolution or confirmation that the event is due to the participant's illness as soon as this information becomes available.

13.8 Adverse Event Reporting

All AEs should be reported on the AE form within the CRF. An adverse reaction (AR) is an AE which is related to the administration of the study drug. An unexpected adverse reaction (UAR) is an AE which is related to the administration of the study drug and that is unexpected, in that it has not been previously reported in the current SPC.

These events will be included as part of the safety analysis for the trial and do not require expedited reporting to the NICTU.

13.9 Serious Adverse Event Reporting

A SAE is defined as an AE that fulfils one or more of the criteria for seriousness outlined in Table 2. SAEs that are related to the administration of the study drug are SARs. SUSARs are SAEs that are considered to be caused by the study drug and are unexpected i.e. their nature or severity is not consistent with the SPC. All SAEs, SARs and SUSARs must be reported to the NICTU.

If a SAE occurs, reporting will follow the regulatory requirements as appropriate and all SUSARs will be the subject of expedited reporting. SAEs will be evaluated by the CI for causality (i.e. their relationship to study drug) and expectedness (if related). SAEs will be reported using the SAE Form and must be reported to the NICTU within 24 hours of becoming aware of the event. The CI should not wait until all information about the event is available before notifying the NICTU of the SAE. The NICTU will acknowledge receipt of the SAE Form within two working days by email to the site. Information not available at the time of the initial report must be documented on a follow up SAE Form. Follow up information should be sought and submitted as it becomes available. The follow up information should describe whether the event has resolved or persists, if and how it was treated and whether the participant continues on the study or has been withdrawn from treatment.

The NICTU is responsible for reporting SAEs to the Sponsor, ethics committee, and MHRA within the required timelines as per the regulatory requirements. A fatal or life threatening SUSAR must be reported within 7 days after the NICTU has first knowledge of such an event. Relevant follow up information will be sought and communicated within an additional 8 days. All other SUSARs will be reported to the relevant competent authorities and research ethics committees within 15 days after the knowledge of such an event.

13.10 Recording and Reporting of Urgent Safety Measures

If the local PI or designee becomes aware of information that necessitates an immediate change in study procedure to protect clinical trial participants from any immediate hazard, they can implement this immediately prior to approval by REC/MHRA.

They should phone the clinical trials unit at the MHRA and discuss the issue with a medical assessor once an urgent safety measure was taken. They should also report the urgent safety measure within one working day to the NICTU who will notify the Sponsor.

The local PI or designee should respond to queries from the Sponsor immediately to ensure the adherence to reporting requirements to REC and Competent Authority (CA).

13.11 Pregnancy Reporting

The local PI or designee must collect pregnancy information for female participants participating in the trial.

The pregnancy reporting period for the trial is from the commencement of the study drug until 30 days post admin of the final dose of study drug. The local PI or designee should complete and submit the Pregnancy Reporting Form to the NICTU by email within 14 days of being made aware of the pregnancy. The CTU will acknowledge receipt of the Pregnancy Reporting Form within two working days by email to the site.

Any pregnancy that occurs in a participant during the trial should be followed to outcome. Follow up/outcome information should be provided to the CTU as soon as it becomes available.

14 DATA MONITORING

14.1 Data Access

Prior to commencement of the study, the local PI will give permission for trial related monitoring, audits, ethics committee review and regulatory inspections, by providing direct access to source data and trial related documentation. Consent from the parent/guardian of participants for direct access to their child's data will also be obtained. Participants' confidentiality will be maintained and their identity and data will not be made publicly available to the extent permitted by the applicable laws and regulations.

Following the publication of the primary and secondary outcomes, data will be shared with the Dublin Institute of Technology and Lions eye Institute, Western Australia to facilitate prospective individual data meta-analysis. The data transferred to the Western Australia team will be anonymised, and will comply with Chapter 5 of the General Data Protection Regulation (GDPR).

There may be scope to conduct additional analyses on the data collected. In such instances, formal requests for data will need to be made in writing to the CI who will discuss this with the TMG.

14.2 Record Retention

The local PI at each site will be provided with an Investigator Site File (ISF) by the NICTU and will maintain all trial records according to GCP and the applicable regulatory requirements. The TMF will be held by the NICTU within the BHSCT and the essential documents that make up the file will be listed in an SOP. On completion of the trial, the TMF and study data will be archived by the NICTU according to the applicable regulatory requirements and as required by the Sponsor. Following confirmation from the Sponsor, the NICTU will notify the local PI when they are no longer required to maintain the files. If the local PI withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept responsibility and this must be documented in writing to the NICTU and Sponsor.

14.3 Monitoring Arrangements

The NICTU will be responsible for trial monitoring. The frequency and type of monitoring will be detailed in the monitoring plan and agreed by the trial Sponsor. On-site monitoring visits and central monitoring activities will be conducted in accordance with the trial monitoring plan. On-site monitoring will be an on-going activity from the time of initiation until trial closeout and will comply with the principles of 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 (SDV) will be documented in the monitoring plan.

15 REGULATIONS, 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.

15.1 Regulatory and Ethical Approvals

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol will be approved by a Research Ethics Committee.

A Clinical Trial Authorisation (CTA) will be obtained from the Medicines for Human Use Regulatory Authority (MHRA) before the start of the trial.

15.2 Protocol Amendments

The investigators will conduct the study in compliance with the protocol given approval/favourable opinion by the Ethics Committee and the Regulatory Authority. Changes to the protocol may require regulatory authority/ethics committee approval/favourable opinion prior to implementation, except when modification is needed to eliminate an immediate hazard(s) to participants. The NICTU in collaboration with the sponsor will submit all protocol modifications to the competent authority/research ethics committees for review in accordance with the governing regulations.

15.3 Good Clinical Practice

The trial will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org). All members of the trial team will be required to have completed GCP training.

15.4 Protocol Compliance

A protocol deviation is defined as an incident which 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

The local PI or designee is responsible for ensuring that serious breaches are reported directly to the Sponsor within one working day of becoming aware of the breach.

Protocol compliance will be monitored by the NICTU who will undertake site visits to ensure that the trial protocol is adhered to and that necessary paperwork (e.g. CRFs, patient consent) is being completed appropriately.

15.5 Participant Confidentiality

In order to maintain 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 will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.6 Post-trial Care

Administration of study eye drops will stop after 24 months of trial participation. Management of the participant's myopia at the end of the trial will be in accordance with normal clinical practice.

15.7 Indemnity

The BHSCT will provide indemnity for any negligent harm caused to participants by the design of the research protocol through the Clinical Negligence Fund in Northern Ireland.

Queen's University Belfast shall be liable for its employees' negligence in connection with research-related activities, and BHSCT shall be liable for the negligence of any employee of Queen's University Belfast who is jointly appointed by BHSCT, and whose negligence relates to clinical activities.

15.8 Competing Interests

The research costs are funded by NIHR EME Programme. The CI and members of the TMG have no financial or non-financial competing interests and the members of the TSC and the DMC will be asked to confirm that they have no conflict of interest. In the event that a DMC member reports a conflict of interest, advice will be sought from the Sponsor.

16 DISSEMINATION/PUBLICATIONS

16.1 Publication Policy

The final study data report will be provided by the Trial Statistician. It is anticipated that the study findings will be published in national and international peer reviewed journals and these articles will be led by the CI. This will secure a searchable compendium of these publications and make the results readily accessible to the public and health-care professionals. In addition, study findings may be presented at both national and international meetings and to appropriate patient groups.

16.2 Authorship Policy

We will follow International Committee of Medical Journal Editors (ICMJE) guidelines to decide authorship. In brief, an author will be considered to be someone who has made a substantive intellectual contribution to the study and the relevant report. All investigators, Trial Statistician and relevant members of the TMG can potentially be co-authors. Collaborators will be acknowledged.

16.3 Trial Registration

The trial will be registered with the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database, the International Standard Randomised Controlled Trial Number (ISRCTN) registry and Clinicaltrials.gov.

16.4 Data Sharing Statement

Requests for data sharing will be reviewed on a case by case basis by the CI and TMG. We will share data with The Dublin Institute of Technology (Prof James Loughman) and Lions Eye Institute, Western Australia (Prof David Mackey) to facilitate prospective individual participant data meta-analysis with the MOSAIC trial (ISRCTN36732601) and the WA ATOM trial (ACTRN12617000598381) once the results of the CHAMP UK trial are accepted for publication.

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