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Mark A. Bullimore

Noel A. Brennan

Daniel I. Flintcroft

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ORIGINAL ARTICLE

The future of clinical trials of myopia control

 Mark A. Bullimore¹  | Noel A. Brennan²  | Daniel Ian Flitcroft^{3,4}
¹College of Optometry, University of Houston, Houston, Texas, USA

²Johnson & Johnson Vision, Jacksonville, Florida, USA

³Centre for Eye Research Ireland, Environmental Sustainability and Health Institute, Technological University Dublin, Dublin, Ireland

⁴Department of Ophthalmology, Children's University Hospital, Dublin, Ireland

Correspondence

 Mark A. Bullimore, College of Optometry, University of Houston, Houston, Texas, USA.
 Email: bullers2020@gmail.com

Abstract

In the field of myopia control, effective optical or pharmaceutical therapies are now available to patients in many markets. This creates challenges for the conduct of placebo-controlled, randomised clinical trials, including ethics, recruitment, retention, selective loss of faster progressors and non-protocol treatments:

1. Ethics: It is valid to question whether withholding treatment in control subjects is ethical.
2. Recruitment: Availability of treatments is making recruitment into clinical trials more difficult.
3. Retention: If masking is not possible, parents may immediately withdraw their child if randomised to no treatment.
4. Selective loss: Withdrawal of fast progressors in the control group leading to a control group biased towards low progression.
5. Non-protocol treatment: Parents may access other myopia treatments in addition to those within the trial.

We propose that future trials may adopt one of the following designs:

- A Non-inferiority trials using an approved drug or device as the control. The choice will depend on whether a regulatory agency has approved the drug or device.
- B Short conventional efficacy trials where data are subsequently entered into a model created from previous clinical trials, which allows robust prediction of long-term treatment efficacy from the initial efficacy.
- C Virtual control group trials based on data relating to axial elongation, myopia progression or both, accounting for subject's age and race.
- D Short-term control data from a cohort, for example, 1 year or less, and applying an appropriate, proportional annual reduction in axial elongation to that population and extrapolating to subsequent years.
- E Time-to-treatment-failure trials using survival analysis; once a treated or control subject progresses or elongates by a given amount, they exit the study and can be offered treatment.

In summary, the future development of new treatments in myopia control will be hampered if significant changes are not made to the design of clinical trials in this area.

KEYWORDS

clinical trials, myopia, myopia control, myopia progression

INTRODUCTION

In the field of myopia control, a range of optical or pharmaceutical therapies have proven efficacy.^{1,2} Practitioners in many countries can choose from several options for slowing progression in their young myopic patients, but with

no treatments completely arresting progression, the search for new therapies continues. In that regard, the length of myopia trials for regulatory approval can be challenging. The US Food and Drug Administration (FDA) currently requires 3 years of data,³ although the bar appears more reasonable in other markets, for example, the European Union

and Canada. This places a considerable burden on industry, researchers and participants. In contrast, clinical trials of refractive and glaucoma technologies can be considerably shorter.

As the regulatory pathway for myopia control therapies can be lengthy,³ some of these treatments have entered clinical practice prior to regulatory approval through investigator-led trials. This availability of proven therapies creates challenges for the conduct of conventional, placebo-controlled randomised clinical trials. Here we identify five specific obstacles for the successful execution of clinical trials in myopia control and propose potential solutions with examples from within and outside the field.

ONGOING AND EMERGING CHALLENGES FOR MYOPIA TRIALS

Ethics

The 2021 International Myopia Institute (IMI) Yearly Digest⁴ posed the question 'If the treatment is well enough established to slow or prevent myopia progression, is it ethical to randomly assign subjects to an ineffective sham/control group given their likelihood to develop myopia or have myopic progression?' In the absence of alternatives, the authors concluded 'at present, an appropriately selected concurrent control group is still ethical for myopia control trials'. As the evidence for the relation between the degree of myopia and visual impairment mounts,^{5,6} the withholding of treatment becomes less tenable. In the United States, developers of drugs and devices for myopia control may also be required to wash out or re-randomise subjects after 3 years, adding to the burden for all and raising additional ethical issues about withdrawing treatment from patients. Thus, in a rapidly evolving field, the question of both the feasibility and ethics of clinical trials in myopia management must be revisited periodically and often, as we do here.

Recruitment

The availability of established treatments makes recruitment into clinical trials more difficult in many countries, although a recent Chinese study recruited and randomised 264 myopic children in 1 month.⁷ Parents of myopic children with knowledge of the public health issues and the availability of myopia control will be reluctant to enrol their child in a 3-year clinical trial where there is a 50–50 chance of being assigned to the control arm. Of course, the inability of some families to pay for treatment will likely mean that enrolling in a clinical trial is their only option, and thus the sample population in future trials may be skewed towards inclusion of a greater proportion of children from lower income families. This might introduce

Key points

- The availability of myopia control therapies creates challenges for the conduct of placebo-controlled, randomised clinical trials, including ethics, recruitment, retention, selective loss of faster progressors and non-protocol treatments.
- Potential solutions include non-inferiority trials, short-term conventional efficacy trials, use of a virtual control group, acquiring short-term control data and time-to-treatment-failure trials.
- Failure to rethink the design of clinical trials of myopia control may hamper the evolution of the field and, ultimately, patient care.

bias and affect generalisability. The prevailing evidence is that lower income and minority patients are less likely to enrol in clinical trials.^{8,9} But as a new therapeutic area, myopia control treatments are not yet reimbursable in most countries.

Randomising asymmetrically, for example, using a 2:1 treatment-to-control ratio is commonly used in drug trials, increasing the probability of a participant being assigned to active treatment and potentially improving recruitment at the expense of a small increase (12%) in overall sample size without compromising statistical integrity.¹⁰ The approach also provides more data on the safety of a new therapy, although its appropriateness in confirmatory trials has been questioned.¹¹

Long-term retention and immediate withdrawal

Retention of subjects participating in multiyear myopia clinical trials may approach 100%,^{12–14} or be as low as 50%.^{15,16} In randomised clinical trials, withdrawal is often greater in the placebo group than in the treatment group.¹⁷ This can occur over several years, or immediately.

If masking is not possible, for example, in orthokeratology,^{18,19} parents may immediately withdraw their child if randomised to no treatment. In a trial of bifocal and prism bifocal spectacles, 18% of children randomised to single-vision spectacles declined their allocation.²⁰ A similar trend appears to have occurred in a trial of overnight orthokeratology.¹⁹ In masked trials, parents being offered the certainty of known treatments outside the trial by other health professionals may not remain in the trial, although the cost of such alternatives outside a trial may limit such losses as most trials offer interventions without direct cost to the patient. As with recruitment, having a larger treatment than the control group increases the probability of receiving active intervention in a fully masked trial, which may motivate retention.

Differential loss to follow-up

Compared with many studies where the primary endpoint is not apparent to the trial subject, myopic progression will be easily apparent as loss of distance vision with the child's current correction. A parent of a child in a myopia clinical trial may also pay close attention to their child's rate of myopia progression and axial elongation. If their child's rate of progression is unacceptable to the parents or their regular eye care practitioner, they may withdraw their child or they may be offered an existing myopia control option by their regular eye care practitioner. Indeed in a recent clinical trial, 63% of the control group randomised to single-vision spectacles withdrew, mostly to 'seek myopia control interventions' compared with 19% in a treatment group randomised to overnight orthokeratology.²¹ Differential withdrawal of faster progressors in the control group can lead to a control group biased towards lower rates of progression, thus distorting the trial's findings.²² Likewise, if a treatment is poorly tolerated, there can be differential loss to follow-up, poor compliance or both.²³

Off-protocol treatment

If a child's rate of progression is unacceptable to a parent or if they believe that they have been assigned to the control group, they may be tempted to avail themselves of other myopia control options outside the trial. The annual rate of axial elongation in an untreated myopic child should, on average, be 15% slower than in the prior year.²⁴ In some clinical trials, axial elongation among control subjects in the second year was inexplicably 30%–40% slower than the first,^{19,20,25,26} suggesting the possibility of contamination by children receiving alternative therapy and thus reducing the observed treatment effect. Exaggerated slowing among control subjects later in a trial may also be due to differential withdrawal of faster progressing participants and has been reported in one recent trial.²²

POTENTIAL SOLUTIONS

These various issues threaten the successful completion of many ongoing intervention trials in myopia management and pose an even greater threat to future clinical trials of myopia control drugs or devices. We propose that the following designs may be more appropriate for myopia management trials in the coming years.

Non-inferiority trials

Randomising some patients to a placebo and thereby withholding treatment for sight-threatening diseases such as

neovascular age-related macular degeneration (AMD) and primary open-angle glaucoma would be considered unacceptable to patients, practitioners and regulators alike. The usual solution is to compare the new, experimental treatment to an established therapy. Forty years ago, early clinical trials of topical beta-blockers for the management of glaucoma, notably timolol, used pilocarpine as a control.²⁷ Timolol subsequently served as the control in the evaluation of a range of prostaglandin analogues,^{28,29} which in turn have served as the control for trials resulting in FDA approval of netarsudil, a novel Rho kinase inhibitor.³⁰ Likewise, the original intravitreal injection of ranibizumab, an anti-vascular endothelial growth factor, was compared with sham injections³¹ or verteporfin therapy.³² Ranibizumab then served as a control in the FDA approval of aflibercept,³³ which in turn was the control in the pivotal clinical trial of brodalumab.³⁴

There is also a precedent for this study design in contact lens trials. Silicone hydrogel contact lenses intended to be worn on a 30-day continuous wear schedule were compared with an existing, approved hydrogel lens worn on a 7-day extended wear schedule.³⁵ Once their longer term safety was established, the FDA allowed subsequent silicone hydrogel lenses to be compared with the initially approved silicone hydrogels. We are still in the early days of myopia control and, at the time of writing, no drugs are approved by the European Medicines Agency (EMA) or FDA for myopia control, and only one device, a dual-focus soft contact lens, is approved by the FDA.³⁶ Studies comparing two or more myopia control treatments are rare³⁷ and are yet to be used in regulatory-driven clinical trials. In the future, atropine could be used as a control for the evaluation of new myopia control drugs, following the established precedent from glaucoma and AMD. Nonetheless, stability issues associated with compounded low-concentration atropine would likely require the use of an approved formulation with documented stability.^{38,39} There is also uncertainty around the appropriate concentration of atropine.⁴⁰ A particular complication for myopia control is that both medical devices and pharmacological treatments appear to provide therapeutic benefits. It remains uncertain how the FDA will approach comparisons of myopic control devices and myopia control pharmacological interventions as they are currently reviewed by different groups within the FDA. Regardless, the margins needed to demonstrate non-inferiority and the sample size are both critical study design issues. Statistical non-inferiority may exist with an ineffective product if the confidence intervals are large.

Prior to any substantive non-inferiority trial, pilot data suggestive of efficacy are generally available. Such data make such a trial more ethical and more attractive to participants than a trial with a placebo, where no benefit is expected. Subject withdrawal rate is lower in trials with an active control group than those in which a new treatment is compared with a placebo.¹⁷ Thus, the ethics of withholding treatment and, in fact all five challenges listed

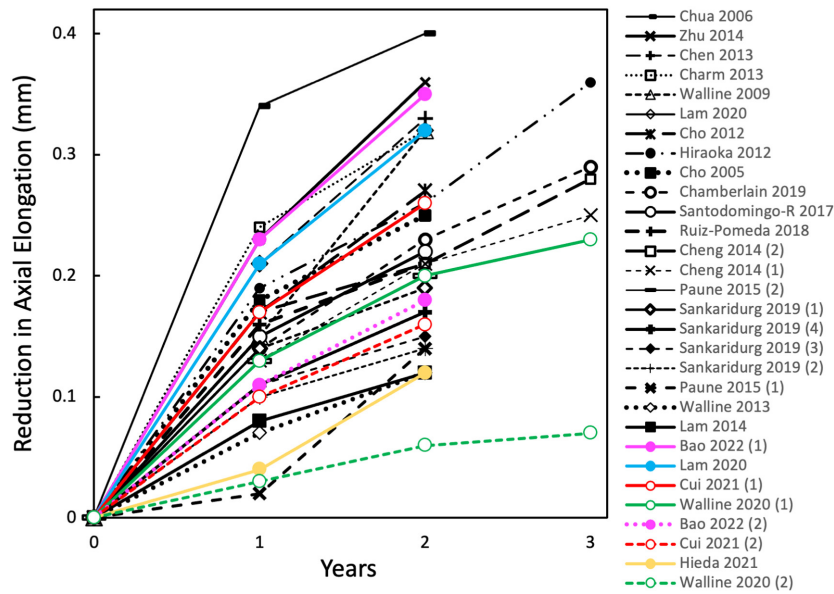


FIGURE 1 Cumulative absolute reduction in axial elongation at annual time points for myopia control treatments. Modified from Brennan et al.¹ to include recent clinical trials.

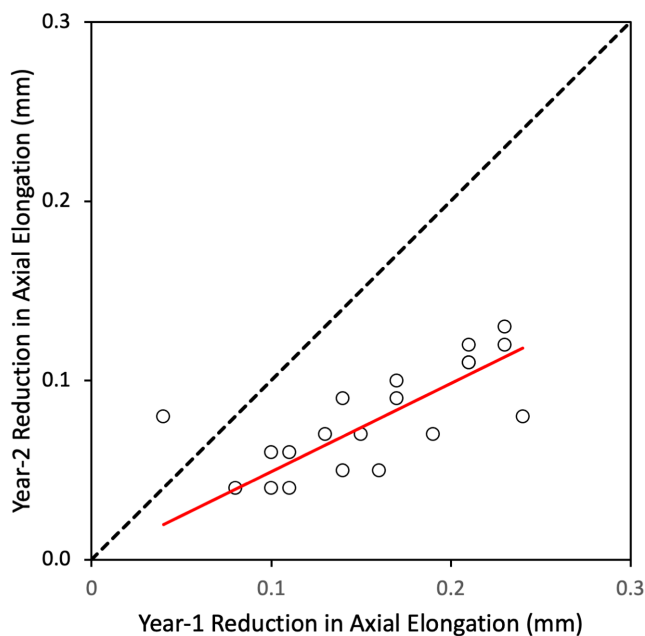


FIGURE 2 Year 2 reduction in axial elongation (mm) as a function of the Year 1 reduction in axial elongation (mm). Only measures in Figure 1 taken by optical biometry are plotted. A trend line anchored through zero is also shown. Not all of these are randomised clinical trials, and some used historical controls.

in the abstract above could be in part addressed by this approach. While an attractive option, this approach may not be tenable for several years until a clear ‘gold standard’ or reference treatment is accepted by regulatory authorities. If a pharmacological standard is adopted, this also creates issues with masking when evaluating non-pharmacological interventions such as contact lenses and spectacles.

Short conventional efficacy trials

Data from clinical trials clearly show that the treatment benefit is greater in the first year (or 6 months) than in subsequent years.¹ Nonetheless, the efficacy in Years 2 and 3 can generally be predicted from the Year 1 findings. Figure 1 is redrawn from a previous paper, and shows the cumulative absolute reduction in axial elongation at annual time points for myopia control treatments in trials of at least 2 years of duration.¹ Five recent randomised clinical trials are superimposed on the original figure.^{14,26,41–43} Note the divergence of effect size in the first year across treatments is largely maintained in subsequent years. Figure 2 plots the Year 2 absolute reduction in axial elongation as a function of the Year 1 effect. All data lie below the unit ratio line, indicating that while the treatment benefit continues in Year 2, it is nearly always less than in Year 1. The mean treatment effect in Year 2 is 52% of that in Year 1 (0.080 mm vs. 0.154 mm), similar to the slope of the trend line.

Adequately powered short-term trials with conventional control groups could therefore establish short-term efficacy of novel treatments. This would be an efficient method of differentiating effective versus ineffective treatments, without requiring 2- or 3-year trials initially. This may represent an efficient screening process, but it is likely that regulatory authorities would require definitive long-term efficacy data from subsequent full-length trials of those treatments with proven short-term efficacy. There is a small risk of false negatives in the first year, but as shown in Figure 1, only two studies in this analysis (7%) show low efficacy in Year 1 and much higher efficacy in Year 2. Of course, when considering this model, a new treatment, which has better long-term slowing of progression but does not show adequate 1-year efficacy, might be overlooked.

Virtual control group trials

A number of pilot studies have used historical controls.^{44,45} As a field matures, an increasing amount of control data is published or available in regulatory documents. A recent meta-analysis of axial elongation in childhood myopia identified over 40 randomised clinical trials with untreated control groups having a similar number of cohort or retrospective studies, and identified race and age as the primary determinant of annual elongation.²⁴ Thus, a virtual control group could be based on data relating to axial elongation, myopia progression or both, accounting for subject age, race and other factors known to influence myopia progression. The comparison data could be derived from the aforementioned meta-analysis,²⁴ progression or elongation derived from existing published data, or centile-based analysis⁴⁶ where each patient with intervention is benchmarked against an age- and gender-matched centile prediction on the assumption that, on average, patients track along their existing centile.

There is some precedent for this approach. The 1983 FDA report on intraocular lenses (IOLs) pooled data on 17 different IOLs from seven manufacturers representing over 45,000 patients.⁴⁷ This allowed precise estimates of adverse event rates, against which subsequent IOLs could be evaluated without the need for a concurrent control group. The safety and efficacy of corneal refractive technologies, including photorefractive keratectomy and laser-assisted in situ keratomileusis, have also been evaluated in the absence of a control group, with later devices expected to meet or exceed targets in a guidance document developed from early trials.*

There is also precedent in recent myopia research. Three-year results from a clinical trial were compared with those from previous cohort studies of emmetropes and untreated myopes.⁴⁸ Participants from a 2-year trial were followed up for a third year and compared with an age-matched control group selected from records in the investigators' clinic.⁴⁹ But using a small cohort or a single study may lead to erroneous conclusions. For example, preliminary studies of overnight orthokeratology⁴⁵ and multifocal contact lenses⁵⁰ used historical data from a previous clinical trial of 56 soft lens wearers.⁵¹ Unfortunately, 3-year progression in that particular control group (-2.19D)⁵¹ was markedly higher than that of subsequent 3-year trials of similar aged soft contact lens wearers conducted by the same investigators (-1.29D ¹³ and 1.05D ¹⁴). Thus, we recommend using control data from meta-analysis of extensive data to minimise the effect of control group outliers.

Short-term control data

While using a virtual control group is an attractive concept, the data indicate significant variance in progression for a

cohort of a given age and race.²⁴ To mitigate this problem, a control group could be recruited but only followed up for 1 year with previously modelled rates applied to estimate longer term progression. Meta-analysis shows that while East Asian children progress faster than non-East Asians, both groups show a 15% annual reduction in axial elongation with age.²⁴ This approach is superior to the virtual control group because it would establish a progression rate specific for the population under examination if the sample size is sufficient and randomisation is effective. An ideal example of this approach would be the Low-concentration Atropine for Myopia Progression (LAMP) study, where the control group was halted after 1 year because of ethical concerns but treated groups were continued for 3 years.⁵² One limitation of this approach is that beyond 1 year, or whatever duration the control group is evaluated, masking will not be possible as only treated patients would still be in the study.

Time-to-treatment-failure trials

Survival analysis or time-to-event analysis is an approach used to measure the association between an intervention and the rate at which an outcome of interest occurs over time.⁵³ This approach has been used in ophthalmology where the endpoint has been retinal detachment following either extracapsular cataract extraction or phacemulsification,⁵⁴ mortality following treatment of ocular melanoma by either brachytherapy or enucleation⁵⁵ or evaluating the risk factors for adverse events during contact lens wear.⁵⁶ The required binary outcome can also be based on a continuous scale and researchers have used a six-line loss in visual acuity⁵⁷ or a pre-specified degree of visual field loss.⁵⁸ The survival function models the probability of remaining event free over time and the hazard ratio is the ratio of the rate between the two groups. This approach has a number of advantages over comparing outcomes at a single time point—usually the end of the study. In this case, outcomes from participants who have not experienced the event of interest before being lost to follow-up must be treated as missing data, introducing a potential source of bias. Survival analysis uses data at all time points including those subjects lost to follow-up. Offering rescue treatment to children who progress by the threshold amount reduces ethical concerns and may address other challenges such as retention and recruitment.

A recent evaluation of myopia control with experimental soft contact lenses not only compared mean progression among lens designs but also converted progression to a binary outcome based on a cut-off value of -0.75D and compared time to this outcome and survival probabilities over 24 months using the Cox proportional hazard model.¹⁶ The authors did not give a hazard ratio, just a p -value of <0.005 , but reanalysis of their data yields a hazard ratio of 0.70 (95% CI: 0.55, 0.89), indicating that the test lenses reduce the likelihood of -0.75D progression by 30%. The value of this analysis is apparent given that only 234 of the

*<https://www.fda.gov/media/72224/download>

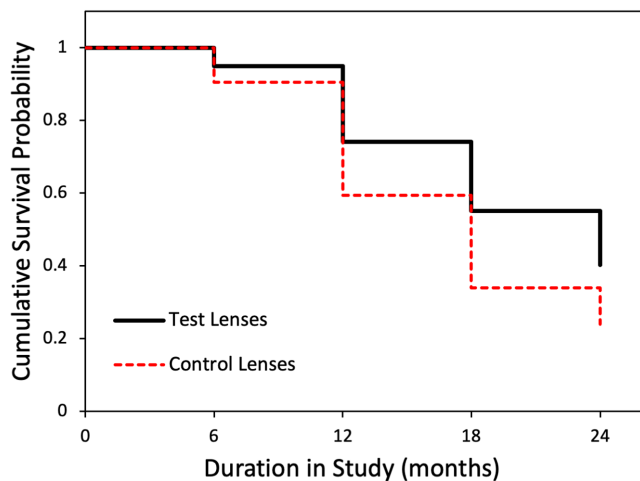


FIGURE 3 Probability of surviving progression of -0.75 D or more during a 12-month period. Redrawn from Sankaridurg et al.¹⁶

original 508 patients were available for analysis at 2 years, while data from 317 were available at 1 year, when 40% of the control subjects had already progressed by -0.75 D (Figure 3).

A number of ongoing myopia clinical trials use binary outcomes as their primary endpoints. For example, in 3-year FDA clinical trials of low-concentration atropine, the primary efficacy outcome is the overall between-treatment group difference (atropine vs. placebo) in the proportion of patients who show <0.50 or 0.75 D myopia progression over 3 years. Implicit in this statement is that only the proportions at 3 years will be analysed and the data from the five prior six-monthly visits will not be included. A modification to the protocol would allow any patient with 0.50 D progression to exit the clinical trial at an earlier juncture without affecting the primary endpoint, and in the case of control patients be offered a validated myopia control treatment. Exiting these patients would not impact the planned analysis of proportions at 3 years or an alternative survival analysis that would consider not only the proportion of patients progressing 0.50 D within 3 years but also how soon the endpoint was reached.

An initial limitation of this approach is that long-term data would not be available in all patients for other analyses, notably comparison of mean 2- or 3-year progression or elongation, but this might be addressed by modelling or comparison with published papers with both survival analysis and mean progression data. In addition, refraction measurement is relatively variable,¹ so there should be some concern over false-positive rates. This could be addressed by using more repeatable axial length measurements^{1,59} or by requiring a confirmatory repeated measurement.⁶⁰ The reduced follow-up of the fast progressing subjects also limits the amount of follow-up data available on safety and acceptability of the intervention.

Long-term progression and axial elongation thresholds for termination could be based on existing parametric

models,²⁴ centile models,⁴⁶ observational epidemiological studies⁶¹ or real-world evidence.

DISCUSSION

Of 45 active myopia control trials listed on [ClinicalTrials.gov](https://clinicaltrials.gov) (accessed 30 September 2022), 33 are conventional controlled trials with the control group receiving either no treatment or a placebo (73%). These may be at the mercy of some of the issues discussed above and could experience a high dropout rate or failure to reach completion. There is one trial using a non-randomised, matched control group, with the remaining comparing different modalities: mostly using atropine or orthokeratology as a control for an investigational device, comparing different atropine concentrations or dosing or comparing various orthokeratology designs.

The future development of new treatments in myopia control will be hampered if significant changes are not made to the design of clinical trials in this area. In addition to the ethical issues, compromised data may be generated as bias is introduced to the control group by the factors mentioned earlier, including parents declining their child's allocation to the control group²⁰ and differential, higher withdrawal amongst the control group.^{21,22} Thus, a coordinated response from all stakeholders will be required to make such a transition. The potential benefits of different approaches must be balanced against their limitations. Offering complimentary treatment to all participants, be it following initial allocation or as rescue therapy, may assist with recruitment and retention, although it may also be viewed as coercion and any such offers must be approved by the relevant ethics body for the trial. In the light of the known possibility of rebound in myopia treatments, alternatives to the current 12-month washout can be incorporated into protocols to reduce the impact of withdrawal of treatment. One ongoing myopia trial is currently using the washout period to compare complete washout with a 9-month tapering regime of active drug in 50% of the subjects originally randomised to active treatment.[†]

While many regulatory bodies³ and other entities⁶² recommend 2- to 3-year clinical trials followed by a washout year, these place a considerable burden on patients and their families. With a conventional design, treatment will be withheld from a child for several years, and thus alternative designs need to be considered. A time-to-treatment-failure approach may be attractive as this allows initiation of treatment as soon as a child progresses or elongates by a prespecified amount. Unfortunately, such a design may limit the number of participants in whom rebound can be assessed, although they will represent those whose progression has been successfully slowed. But from an ethical

[†]<https://doi.org/10.1186/ISRCTN36732601>

perspective, this may be warranted anyway. With other study designs, including non-inferiority trials, assessment of rebound will require comparison with a virtual control group based on historical data.

If conventional trials are to continue, can they be shorter? Clearly, pilot, proof-of-concept trials will continue to be shorter in duration. Useful insights have been gained from unilateral treatments,^{63,64} contralateral-crossover studies^{65–67} and bilateral crossover trials.^{68,69} If pivotal trials were to be shorter, it is reasonable to consider what is more important: a third year of treatment-control comparison or a rebound year? Indeed, some may question whether there is a universal need to assess rebound as it has only been observed in trials of higher concentrations of atropine.^{52,70}

While we have mainly focussed on the US FDA, myopia is a global challenge. Regulatory bodies in East Asia are autonomous but may follow precedents set by the FDA, while requiring data on their own population. The US FDA has a tradition of being deliberate, with refractive surgery technologies being approved several years after other markets such as Europe, and myopia control is following this trend. Nonetheless, some countries such as China, Japan and South Korea look to US approval as a matter of course. The result can be a delay in approvals in those countries that need these therapies.

It should be noted that one area where no existing therapies have been shown to be effective is in preventing myopia onset, that is, preventing or delaying the conversion of premyopes⁷¹ to incident cases of myopia. At least for the time being, conventional placebo-controlled trials for myopia prevention may be achievable from both an ethical and practical perspective. Of course, there are many publications on incidence including large cohort studies,^{61,72} so comparison with historical controls from cohort or school-based studies of incidence may be feasible.

In summary, we have reviewed some of the challenges facing clinical trials of myopia control and proposed some potential solutions. The presented solutions cover short- and long-term options for this rapidly evolving field. Non-inferiority trials are likely to be the long-term solution, but there may not be sufficient comparator data available at present, so the other study designs should be considered in the short term. For ongoing trials, offering rescue treatments for fast progressors via substantial protocol amendments may provide a route to prevent trial failure or non-completion. For trials in the planning stage, without a viable referent against which to assess non-inferiority, some of the novel designs may be the best option. In the long term, as the field matures further with proven therapies, non-inferiority trials will likely become common. The timeline depends on approval of a critical mass of drugs and devices by the FDA, perhaps across several categories, and this may be several years away.

AUTHOR CONTRIBUTIONS

Mark A. Bullimore: Conceptualization (lead); formal analysis (lead); writing – original draft (lead). **Noel A. Brennan:**

Conceptualization (supporting); formal analysis (supporting); writing – review and editing (equal). **Daniel Ian Flitcroft:** Conceptualization (supporting); formal analysis (supporting); writing – review and editing (equal).

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ORCID

Mark A. Bullimore  <https://orcid.org/0000-0002-6315-3720>

Noel A. Brennan  <https://orcid.org/0000-0003-4635-6435>

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