

IMI – Industry Guidelines and Ethical Considerations for Myopia Control Report

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PURPOSE. To discuss guidelines and ethical considerations associated with the development and prescription of treatments intended for myopia control (MC).

METHODS. Critical review of published papers and guidance documents was undertaken, with a view to carefully considering the ethical standards associated with the investigation, development, registration, marketing, prescription, and use of MC treatments.

RESULTS. The roles and responsibilities of regulatory bodies, manufacturers, academics, eye care practitioners, and patients in the use of MC treatments are explored. Particular attention is given to the ethical considerations for deciding whether to implement a MC strategy and how to implement this within a clinical trial or practice setting. Finally, the responsibilities in marketing, support, and education required to transfer required knowledge and skills to eye care practitioners and academics are discussed.

CONCLUSIONS. Undertaking MC treatment in minors creates an ethical challenge for a wide variety of stakeholders. Regulatory bodies, manufacturers, academics, and clinicians all share an ethical responsibility to ensure that the products used for MC are safe and efficacious and that patients understand the benefits and potential risks of such products. This International Myopia Institute report highlights these ethical challenges and provides stakeholders with recommendations and guidelines in the development, financial support, prescribing, and advertising of such treatments.

Keywords: conflict of interest, ethical prescribing, informed consent, medical device, myopia control

1. INTRODUCTION

Myopia currently affects approximately 30% of the global population and is predicted to affect 50% by 2050.¹ Of particular concern is the association of increasing levels of myopia with a higher risk of potentially blinding ocular

pathologies, such as myopic macular degeneration (MMD), glaucoma, cataract, and retinal detachment.^{2–9} Further details are provided in the accompanying International Myopia Institute (IMI) – Defining and Classifying Myopia Report.¹⁰ These complications mean that myopia is becoming one of the major causes of vision impairment and blindness in the



world,^{1,9,11} prompting interest in therapies to prevent myopia onset and progression.

Recently, a number of interventional studies have been conducted that attempt to prevent or retard the onset or slow the progression of myopia. Treatment options include increased time spent outdoors, pharmaceuticals, orthokeratology (OK), soft multizone contact lenses, and progressive addition and bifocal spectacle lenses.^{12–17} Further details can be found in the accompanying IMI – Interventions for Controlling Myopia Onset and Progression Report.¹⁸ These approaches raise a number of ethical concerns and challenges for the researchers and clinicians undertaking such treatments in vulnerable populations. What potential conflicts of interest (COI) require consideration? What are the regulatory considerations for the prescribing clinician? What part does industry play in the ethical conduct of myopia control (MC) studies? What are the roles and responsibilities of the various stakeholders that need consideration? How should the information from MC studies be appropriately disseminated? What are the relevant issues regarding education of prescribers of MC treatments, and how should such products be marketed to prescribers and patients?

In this paper, these questions are addressed by referring to best clinical practice and adherence to the guidelines for evidence-based practice.^{19–21}

2. ETHICAL CONSIDERATIONS IN IMPLEMENTING AN MC TREATMENT

From an ethical standpoint, deciding whether to implement an MC strategy represents the classical medical risk versus benefit ratio. A principal motivation for preventing myopia onset or slowing myopia progression is based on the unverified premise that limiting the extent of myopia progression reduces the risk of the development of vision-threatening disease. Conclusive evidence from appropriate clinical trials showing that preventing myopia onset and/or slowing myopia progression results in the prevention of myopia-related ocular pathology is unlikely to be available for decades. Nonetheless, if this assumption is correct, then the benefits to individuals and society could be substantial, given the clear relationship between myopia-related ocular pathology and the amount of myopia.²² Clearly, the risk-benefit analysis must take account of the outcomes arising from nonintervention.

Another motivation in the use of MC therapy is the avoidance of quality of life (QOL) problems arising from the use of corrective devices, such as the inconvenience of spectacle or contact lens wear, increasing reliance on corrective devices, cultural stereotyping associated with corrective eye devices, and the dysfunctionality and loss of QOL that comes with use of corrective devices with high prescriptions. Such influences may lead to introversion, anxiety, low self-esteem, and less perceived attractiveness.^{25–26} QOL assessments show that spectacle and contact lens-corrected myopes report increased concerns regarding the likelihood of injuring themselves, difficulties coping with normal demands of daily life, difficulties in fulfilling required roles, and less confidence joining in everyday activities compared to emmetropes.²⁷ Adults with pathologic myopia and associated visual impairment report experiencing significant social and emotional impacts and reduced life satisfaction.²⁸ The significant impact of myopia on visual function and QOL must be considered when making clinical decisions regarding treatments aimed to slow myopia progression in children, and these considerations must play into the decision concerning the appropriateness of intervening with a MC strategy.

Other factors that must be accounted for in the decision to undertake MC include the regulatory status of the treatment being considered, availability of the treatment, access to skilled eye care services, and pricing and convenience of the treatment, which are all potential barriers to accessing treatment.

These considerations place a burden of responsibility on the practitioner to be fully cognizant of the risks for the patient of developing different levels of myopia, the implications that progression to higher levels of myopia may have, the likely benefits of treatment, the side-effects of treatment, and other associated factors, so as to provide appropriate advice and care.²⁹ These issues are broadly addressed in the accompanying IMI – Defining and Classifying Myopia Report¹⁰ and the IMI – Interventions for Controlling Myopia Onset and Progression Report.¹⁸

All parties have an ethical responsibility to promote the patient's welfare³⁰ and to interact in an honest, open, and fair manner in questions related to the quality of, and access to, vision health care.³¹ Professions involved in delivery of eye care have developed codes of ethics,^{31–35} and these are particularly important to consider when making decisions concerning the management of children with myopia.

Providing efficient and effective health care is becoming more challenging, due to the increasing complexities of health care systems globally.^{36,37} Modern health care systems are often characterized by increasing demands for accountability.^{30,38} In this complex environment, it is critical that health care professionals (HCPs) remain focused on patient-centered clinical practice. In this mode of practice, HCPs help patients and their parents/guardians understand their clinical recommendations and make informed choices from the potential options for care. Ethical codes are general guiding principles that help HCPs in their clinical decision-making and in practicing in accordance with a set of expected standards.^{30,31,39,40} Clinical decisions must be targeted toward ensuring the individual patient's welfare. This includes referral to another HCP if the HCP has more expertise in the area and access to the best treatment for the patient in question.

As described in the American College of Physicians Ethics Manual,⁴¹ HCPs have a “primary role as a patient's trusted advocate, and he or she has a responsibility to use all health-related resources in a technically appropriate and efficient manner.” The Hippocratic Oath (above all to do no harm)⁴² refers to doing what is in the best interest of the patient. This requires balancing risks and benefits of any treatment under consideration and making decisions that optimize benefits and minimize risks for the patient. HCPs are expected to respect the informed choices that a patient makes about their own health. However, to make such informed decisions, patients (or their guardians in certain cases) require appropriate education based on the most up-to-date evidence-based health care practice for the disease or treatment being discussed.

2.1 Conflicts of Interest

COI arise when commercial or other private interests are at odds with the official and moral responsibilities of an individual or entity in a position of trust.^{43–49} All HCPs function in positions of trust and as a patient's advocate. Other professionals involved in the discussions around MC, such as researchers, are also placed in a position of trust and should appropriately present results of research without overstating their significance, so as not to unduly influence either a clinician or patient in deciding to undertake MC treatment. The Accreditation Council for Continuing Medical Education defines commercial interest as “any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients”.⁵⁰

COIs are common in medicine and almost impossible to avoid in research conducted in either university or other settings and that applies equally to MC research. Researchers and clinicians often partner with companies to conduct MC studies. However, there is a risk for these partnerships to introduce bias in clinical practice, and HCPs should be aware of the importance of evaluating any real or perceived COI when recommending a management plan for MC. These interactions between practitioners and producers and suppliers of devices or drugs should meet the highest possible standards of integrity and transparency. Relationships between clinicians and patients should not be compromised by commercial or other interests that could subvert the principle that the interests of patients are of primary concern.

COIs are created when HCPs:

- accept company gifts of various kinds, including meals and drug samples;
- act as promotional speakers or writers on behalf of companies;
- have a financial interest in a medical product company whose products they prescribe, use, or recommend.

All entities involved in MC practice or product development must disclose any potential COI, including any research funding sources. Various documents describe these COI that must be openly declared by researchers, educators, and company employees when discussing or presenting their findings, regardless of the medium being used.^{44,45,47-49,51-57}

2.2 Informed Consent

Unless treatments for MC are specifically approved for that purpose, their use is considered off-label and, therefore, adequate informed consent prior to their use should be obtained to minimize potential misinterpretations and/or legal claims.⁵⁸⁻⁶¹ For detailed information on the informed consent process, readers are referred to the US Office for Human Research Protection⁶² and for more specific information on informed consent for MC to the accompanying IMI – Clinical Management Guidelines Report.⁶³

Informed consent is not simply a signature on an informed consent form but, rather, it is a process of communication between the HCP and the patient. Each patient must be fully informed to balance the risks of no treatment against the risks of treatment. Eye care professionals (ECPs) are encouraged to rigorously apply informed consent processes whenever prescribing or recommending off-label treatments for MC. Providing full disclosure to patients and their families and encouraging them to participate in the decision-making process is vital to the value we place on patient autonomy.

The majority of MC treatments are currently off-label in most countries. Some organizations, such as the Food and Drug Administration (FDA), do not restrict HCP from discussing off-label treatment uses or distributing written materials concerning them. Given that patients and their families generally assume that a treatment prescribed by their clinician has been proven safe and effective and is supported by scientific evidence, we recommend all practitioners to follow the doctrine of informed consent, regardless of whether the treatment is prescribed on-label or off-label. Therefore, disclosing the nature, risks, benefits, and alternatives for each MC treatment is vitally important.

Most patients seeking MC treatments are children under the age of legal emancipation, and they are, therefore, accompanied by their parents or legal guardians. This population is categorized as a vulnerable population for clinical research and clinical care.^{64,65} It is recommended that practitioners provide documentation to vulnerable populations (specifically minors

in the case of MC) in the form of a written “assent” document. The assent document should at a minimum include the following (see Appendix for an example):⁶⁶⁻⁷⁰

- Text using developmentally appropriate language aimed to help the patient become aware of:
 - the nature of the condition (i.e., myopia);
 - what to expect with each of the recommended MC treatment(s).
- An assessment of the patients’ understanding and the factors influencing how they are responding, including whether there is inappropriate pressure to accept the MC therapy.
- Soliciting an expression of the patient’s willingness to accept the proposed MC treatment. If the patient will have to receive medical care despite their objection, the patient should be clearly told that fact.

As children develop, they should gradually become the primary guardians of personal health and the primary partners in medical decision-making, assuming responsibility from their parents. HCPs should give serious consideration to each patient’s developing capacities for participating in the decision-making process, including rationality and autonomy. The assent process empowers children to the extent of their capacity.⁷¹ In addition, HCPs must be aware of their country, region, or state’s regulatory laws on legal age of adulthood and whether minors have authority to make health care decisions, and whether they have legal obligation to obtain parental and/or minor’s consent. Just as is the case with informed consent, the emphasis on obtaining assent should be on the interactive process, in which information and values are shared and joint decisions are made.

Decision-making involving the health care of older children and adolescents should include, to the greatest extent feasible, the assent of the patient as well as the participation of the parents/guardians and the HCP. Current literature suggests that adolescents, especially those age 14 and older, typically have well-developed decisional skills and are capable of making informed health care decisions.⁷²

2.3 Cost Considerations

Treatment for MC includes prescription of specially designed spectacles or contact lenses, or the use of pharmaceutical agents such as atropine, in addition to recommendations on various aspects of visual habits. The cost for these treatments may be higher than the cost of typical eye examinations and correction of myopia, due to the specialized equipment and extra time taken for their appropriate fitting and education on use.

In most countries (e.g., United States, United Kingdom, and Australia), a consultation fee for a comprehensive eye examination is required. In other countries (e.g., China, South Korea, and Cambodia), this consultation fee may be incorporated into the cost of the optical correction treatment. Given the wide variability in vision and eye health care costs, it is not possible to standardize a cost structure for MC treatment. In China, for example, patients visiting optical shops for refraction and vision correction would normally not pay a consultation fee and would only pay for the cost of the optical correction. However, those patients attending an eye clinic, hospital or optometric center for MC treatment are charged a fee for an annual “package treatment”. These packages typically include the original eye examination and follow-up visits as well as the treatment costs. Costs are often driven by the channels of service and public awareness.

One important aspect of MC to be considered when evaluating the cost of MC treatments is the availability of a number of treatments that may be beneficial for an individual

patient and the importance of not focusing on one specific product or treatment that the provider may be familiar with. Cost should not be considered in isolation but rather as the cost-to-benefit ratio for each individual patient. Benefits will be measured in terms of slowing the progression of myopia compared to what would be expected for that specific patient (considering the age of the patient, age of onset, number of parents with myopia, recent progression, amount of myopia, and visual environmental risks). Risks should include an evaluation of the risk of developing myopia progression and associated risk of developing pathology if left untreated. For example, an expensive treatment that has only shown benefit in a small subpopulation of patients, or if the effect found is not clinically significant, should not be considered cost effective. Similarly, if the patient's myopia has already ceased to progress, MC treatments should not be recommended if the treatment cost is greater than that associated with standard vision correction.

3. STAKEHOLDERS: ROLES AND RESPONSIBILITIES

ECPs have a responsibility to care for their patients by recommending MC treatments by using evidence-based practice and their informed clinical judgement. Evidence-based practice is a guiding principal used in making determinations about the most effective treatment to use for the diagnosed condition. It involves using both the current best evidence available (e.g., randomized masked clinical trials and systematic reviews) and replication of the findings by independent researchers, in addition to individual clinical experience.^{73,74} With a condition as multifactorial and individual as myopia, this means using published evidence along with clinical judgement to determine the best course of action for the young myopic patient. There is clearly a pressing need for the development and availability of clinically proven, effective methods to slow the progression of myopia. However, to date, few methods are available and those that are available are often used “off-label.” The rising incidence of myopia is driving off-label/unlicensed use of MC treatments in the absence or limited availability of licensed options. Whereas regulatory bodies have the essential role to ensure that medical products meet the highest standards of safety, efficacy, and quality before they become commercially available, the lack of approved treatment options for MC represents an unmet medical need and a challenge for all stakeholders concerned.

The following section provides information on a variety of aspects related to the role and responsibilities of various stakeholders in the prescription of treatments for MC in the pediatric population.

3.1 Regulatory Bodies

3.1.1 Regulatory Process for Marketing Medical Products. Marketing a medicinal product requires a marketing authorization (“product license”) for specified indications under specified conditions (e.g., target population, indication, and specific use), regulated by the country's medicines and health care products regulatory agency.^{75,76} The marketing authorization for the product includes the agreed terms of use (the “label”), described in the summary of product characteristics. This process is used to ensure that medical products meet the highest standards of safety, efficacy, and quality before issued a marketing authorization.

Prescribing a licensed product outside of the approved scope of use is called “off-label” prescribing, whereas prescribing a product that does not hold a marketing authorization is termed “unlicensed” prescribing. HCPs

sometimes practice off-label/unlicensed prescribing to address a deficit in effective products that are approved. Manufacturers are prohibited from marketing or promoting off-label/unlicensed uses of products to induce commercial sales (“mis-branding”). Regulatory bodies, however, do not normally regulate the way medicinal products are ultimately used in practice. The prescribing of a medicinal product, regardless of whether on-label, off-label, or unlicensed, is a decision taken within the relationship between the patient and the HCP.

a) On-Label Versus Off-Label Use. The term “off-label use” is widely used. The most common definition is the prescription of a medication or device that is available and marketed but for a different indication than it was approved for by the appropriate regulatory body. Off-label uses include giving an approved drug (or device) for a disease or indication other than the disease for which it is approved; at a different dose, frequency, or route of administration than specified in the label; or to treat a child when the product is approved to treat adults.⁷⁷ All of these instances could apply to the prescribing of MC products that are approved for other uses but not specifically approved for MC.

The FDA in the United States recommends that good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics, and devices according to their best knowledge and medical judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well-informed about the product, to base its use on firm scientific rationale and on sound medical evidence and to maintain records on the product's use and effects. Use of a marketed product in this manner when the intent is in the practice of medicine does not require the submission of an Investigational New Drug Application or review by an institutional review board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.

It is important to note that the FDA does not regulate medical practice in the treatment of an individual patient, but it plays other important roles, such as precluding pharmaceutical companies from marketing drugs to physicians, other HCPs, or patients for off-label use. It is, therefore, recommended that ECPs prescribe devices and medications only for indications they and their peers believe to be in the best interest of the patient. This will include MC treatments. In addition, it is the obligation of HCPs to educate themselves and their patients on the risks and benefits of each potential treatment to provide the best possible care for their patients. In the context of ECPs instigating MC therapies, the same requirements and responsibilities would apply.

Off-label and unlicensed prescribing use can occur due to a number of factors, including extended timelines in product development and/or the process of regulatory approval for authorized use, particularly in patient populations (e.g., pediatrics) or disorders (e.g., psychiatric) that are inherently difficult to study and, thus, are often excluded from clinical studies. If a product is discovered to be effective in treating a second indication, obtaining approval to treat the new indication often involves a second regulatory pathway that can be both lengthy and costly. Furthermore, even if the new indication eventually becomes approved, revenues for the new indication may not offset the expense and effort required to obtain approval.⁷⁸ In some countries, legislation may allow extended market protection time for a new indication that exhibits additional significant clinical benefits over existing therapies. This is provided that it is registered in the subsequent years after the initial marketing authorization has been granted.^{79,80} These regulatory hurdles, together with commercial risks such as low return on investment, particu-

larly with off-patent products, and challenges related to pricing and reimbursement, play a role in preventing wider availability of on-label options in specific patient groups. Additionally, the ongoing elevation of regulatory compliance obligations, which inevitably culminates in longer development and approval lead times, are likely to exacerbate the lack of availability of on-label products.

b) Frequency of Off-Label Use. The frequency of off-label use is generally high, covers a broad range of therapeutic areas, and is common practice for many prescribers all over the world, in particular in the areas of pediatrics, oncology, neurology, infection, and geriatrics.⁷⁵ In China, one survey revealed that off-label drug use accounts for up to 22% of all medicines prescribed, despite being prohibited.⁸¹ It has been reported that off-label prescriptions are significant in the United States, being greater than 50% in some groups of patients.⁸¹ Analysis of physician-prescribing habits in the United States revealed that overall, 21% of prescriptions were used off-label.⁸² For certain medications, off-label prescribing was as high as 83%. In certain cases, or with certain classes of patients, more than 50% of them may receive at least one off-label drug. A previous study found that 79% of children discharged from pediatric hospitals were taking at least one off-label medication.⁸³ In a pediatric emergency department, the rate of off-label drug prescribing was estimated to be 26%.⁸⁴ In Europe, up to 90% of treatment for infants in hospital intensive care units is understood to be off-label.⁸¹ A study by the European Union (EU) found a rate of off-label prescribing ranging from 13% to 69% of the prescriptions investigated in 32 studies, which took place in various pediatric populations within a hospital setting, covering data from 16 EU member states.⁸⁵ In 40 studies in the outpatient setting, covering data from 12 EU member states, there was a range of 2% to 100% of off-label prescribing.⁸⁵ A study performed in a mother-child tertiary care hospital in Canada found that 8% and 38% of prescriptions issued on a randomly selected day were unlicensed and off-label, respectively.⁸⁶

c) Advantages and Disadvantages. Advantages and disadvantages have been described with regard to off-label/unlicensed use of medical products.⁸⁵ A major advantage might be giving better access to relevant and innovative treatments and the fulfillment of the medical needs of patients, especially in cases where there are limited or no options available. It may also provide a level of health care that is not ordinarily available to the patient, due to cost- or time-related issues and, as such, may contribute to a positive medical outcome. Additionally, off-label/unlicensed use has significant economic implications in that it contributes to the sustainability of the health care system. In contrast, when economic justification is the prevailing rationale for off-label/unlicensed prescribing, friction between national authorities and industry might occur. Also, potential liability arising from unsuccessful off-label/unlicensed use is a concern for prescribing stakeholders.

3.1.2 Current Regulatory Status of MC Treatments. The majority of medical and surgical devices used in children do not have approval or clearance from regulatory bodies for use in pediatric populations.⁸⁷ For example, morphine has never been approved by the FDA for pain treatment in children, but it is widely used for this indication in hospitalized pediatric patients.⁸³ Similarly, many inhaled bronchodilators, antimicrobials, anticonvulsants, and proton pump inhibitors are used in pediatric patients, without FDA approval for use in this population.⁸⁸ There are many such examples of off-label use in ophthalmology. For example, antibiotic eyedrops, which are approved for specific forms of ocular infections, are used off-label for prophylaxis in ophthalmic surgery. In fact, antibiotic eyedrops are considered today the standard of care globally in

preventing ocular infections in the perioperative period. However, they are rarely approved for this use.

The clinical need for devices to diagnose and treat diseases or conditions occurring in children has led to the widespread use in pediatric medicine and surgery of approved devices that do not hold a marketing authorization to provide medical care to children but that are used “off-label.”⁷⁵ The latter has led to different professional associations reporting policy statements supporting off-label and unlicensed use, particularly whenever effective on-label options are not available. For example, the American Academy of Pediatrics has very recently provided a policy statement reporting:

“...off-label use is legal, is not regulated by regulatory bodies, and is considered by regulatory bodies to be the practice of medicine. Without such use, children may be left with no therapeutic options and, in fact, the off-label use of many devices has become the most common and appropriate practice in pediatrics, often supported by published data, professional guidelines, and expert opinions. The American Academy of Pediatrics recognizes that the use of off-label devices is not ideal, but often is necessary in children. For children, off-label approved devices are often the safest and most effective therapy available.”⁸⁷

Similarly, the American Society of Health-System Pharmacists recommends that off-label drug information undergo an evaluation process similar to that applied to materials for indicated uses. More specifically, the American Society of Health-System Pharmacists recommends before considering off-label use, supporting safety and efficacy evidence must be carefully evaluated and a risk-benefit determination made, especially when FDA-approved alternatives are available for the intended off-label use.⁸⁹ The American Medical Association has reported:

“...when the prescription of a drug or use of a device represents safe and effective therapy, third-party payers should consider the intervention as reasonable and necessary medical care, irrespective of labeling, and should fulfill their obligation to their beneficiaries by covering such therapy.”⁹⁰

Contact lenses, which typically have a marketing authorization for lens wear in adults only, are frequently fitted “off-label” to minors. The available documentation at the time of approval is usually sparser in children when compared with adults, and long-term data collection may be needed to support its safety profile; this is particularly relevant to detect any long-term or delayed complications in the child’s developing eye. Furthermore, concerns have been raised with regard to the possibility that children might be qualitatively and quantitatively at a higher risk than adults when exposed to the use of medical products approved for use in adults only.⁹¹ Although the latter may be theoretically possible with the off-label use of contact lenses in children, recent studies have shown that children do not have a higher risk than adults of suffering from contact lens-related complications with either OK^{92,93} or soft contact lens wear.⁹⁴ Based on their relative safety profile⁹²⁻⁹⁵ and significant levels of MC efficacy reported in the scientific literature,^{13,15,17,96} OK and multifocal soft contact lenses appear to represent a viable MC treatment option for children.

With regard to the use of spectacle lenses in children, there are no safety-related concerns. However, the use of progressive addition and bifocal spectacles typically produces more modest MC treatment effects than OK and multifocal soft contact lenses (see the accompanying IMI – Interventions for Controlling Myopia Onset and Progression Report).¹⁸ The

effects mainly occur in the first year of treatment; however, the treatment effect appears to be more significant in children with faster myopia progression, larger lags of accommodation, near esophoria, shorter reading distances, and/or lower baseline myopia.⁹⁷⁻¹⁰⁶ There are controversies with regard to the use of progressive addition and bifocal spectacles for MC, as some studies have found larger treatment effects occurring over a period of at least two years of lens wear,^{12,107} whereas others carried out with progressive addition lenses designed to reduce peripheral hyperopic defocus have found minimal impact on reducing myopia progression.^{108,109} Despite this, spectacle designs for MC are a necessary consideration, particularly in cases where other treatment options are not feasible (e.g., very young children, those unable to wear contact lenses due to access or cost, situations associated with poor hygiene conditions, or remote locations far from specialized eye care). Furthermore, a reserve pair of spectacles to the most recent prescription is always recommended for contact lens wearers. Therefore, the continued investigation and approval of optical designs for slowing the progression of myopia in children with spectacles lenses is warranted.

Well-designed studies using topical 0.5% and 1% atropine have demonstrated significant reductions in the progression of myopia.^{16,110-112} However, its use has been associated with side and rebound effects that many clinicians consider unacceptable for long-term therapy.¹¹³⁻¹¹⁶ Low-dose topical atropine has also shown promising effects in slowing myopia progression, and its use is associated with minimal adverse and rebound effects,¹¹³⁻¹¹⁶ thus representing a potentially viable therapeutic option for MC in children.^{16,112,117} Atropine is neither commercially available in adequate dosage nor approved for MC in children in the majority of countries today. This is mainly because atropine eyedrops, which have been used for many years, are not easily patentable for MC, resulting in industry reticence in pursuing formal drug approval with regulatory bodies, given the considerable financial outlay for long-term clinical trials in large groups of pediatric patients. However, at the time of writing this manuscript, several commercial preparations of low-dose atropine have been submitted for regulatory approval.

3.1.3 Efforts to Increase Approved Medical Products in Children. In view of the limited treatment options currently approved for MC in children, efforts and initiatives previously proposed in other medical disciplines as well as other possibilities to increase approved medical products in children at the governmental, regulatory, health care, and professional level are worthy of discussion, with a particular focus on how these initiatives could be potentially applied to speed up the approval of drugs and devices for MC in children.

a) Governmental. Due to a historic lack of scientific evidence available to substantiate submissions for devices that are indicated for use in the diagnosis or treatment of pediatric patients, several initiatives in the United States and Europe and at the World Health Organization have been introduced over the last two decades to promote the development of on-label products for children.¹¹⁸

In 1997, the FDA adopted the Modernization Act,¹¹⁹ followed in 2002 by the Best Pharmaceuticals for Children Act,¹²⁰ which provides an incentive for drug companies, including exclusive marketing and patent extension, to conduct FDA-requested pediatric studies.¹²¹ In 2003, the FDA also created the Pediatric Research Equity Act, which requires drug companies to study their products in children under certain circumstances.¹²² In 2004, the FDA published a guidance document entitled “Pre-market Assessment of Pediatric Medical Devices - Guidance for Industry and Food and Drug Administration Staff” to clarify the types of information needed to provide reasonable assurance of safety and effectiveness of

medical devices intended for use in pediatric patients and to promote the development of these devices, which was updated in 2014.¹²³ The latter version of the document indicates that data can be extrapolated to support effectiveness and, on a limited basis, safety for premarket approval (PMA) applications when consistent with scientific principles. More specifically, it provides criteria to be considered when evaluating the relevance and value of using nonspecific comparative data (such as that from adults or from a different pediatric subpopulation) and to determine if it can be extrapolated to support use in pediatric populations. It also addresses the premise of leveraging relevant available clinical data that may lead to more devices being granted marketing authorization for pediatric indications. This could result in an increase in the availability of medical devices, with appropriate labeling, to support safe and effective use in pediatric patients. Similarly, in 2006 the EU established incentives to conduct research and development of innovative products and to encourage the marketing authorization of medicinal products which fulfill a medical need.¹²⁴ In theory, such initiatives should incentivize the development of more on-label options and, in turn, reduce off-label and unlicensed use for the pediatric population within EU member states. In 1999, the Japanese Ministry of Health, Labour and Welfare introduced a program whereby, under certain conditions, it would approve a new supplement for a drug indication without clinical trials. This approval scheme involves an application based on evaluation of literature-based evidence. However, the type of indications and the kind of evidence used in practical applications remain to be clarified.¹²⁵

Despite the above government efforts, there has been no significant increase in the number of drugs that have supporting pediatric data at the time of their approval.¹²⁶ In fact, pediatric drug approvals and labeling revisions continue to lag behind their adult counterparts.¹²⁷ Nevertheless, companies pursuing marketing authorizations for MC in children should take the above initiatives into account and governments are encouraged to follow the growing movement toward harmonized regulatory systems. Proliferation of different national regulations increases costs, hinders access to health care technologies, and can even unwittingly jeopardize the safety and health of the patient.¹²⁸ Certainly, having to meet diverse regulatory requirements in different markets that are both lengthy and costly is going to prevent companies from pursuing marketing authorization for MC for products that might be already available in the market and could be used off-label.

b) Regulatory. Exploring possibilities of including alternate evidence to industry-funded randomized controlled trials for the marketing authorization of off-label indications and the conditions under which this would be possible have been proposed previously.⁸⁵ Evidence from peer-review clinical trials, monitoring of patient cohorts, data from routine patient registries, and data from reported adverse events are all examples of sources of evidence to support safety and efficacy. This option could be considered for MC, where a number of methodologies and their attendant devices have accumulated evidence for efficacy, from case reports, retrospective and prospective clinical studies, and meta-analyses, supporting their role as effective and relatively safe treatment options for MC.^{12,13,15-17,96,129} Furthermore, some optical devices have been available on the market for a number of years for use in a different patient population (i.e., adults) and can be referenced as supporting evidence for the safety and efficacy of such devices for MC in children.

Creating and/or enhancing incentives for companies to register new indications for existing products should also be considered and could include tax breaks, exclusive marketing

rights, increased time of market protection, and reduced application fees.^{75,85} These proposals, if successfully applied, are likely to incentivize optical companies in pursuing marketing authorizations for MC in children. Legal frameworks to issue temporary recommendations for use and permission to prescribe off-label could also be taken into consideration. Such a scheme of temporary recommendation is currently in use in France and Hungary, where prescribers or their organizations have to ask permission to prescribe a product off-label.⁸⁵

Providing guidance on off-label use in the form of treatment guidelines is another possible option to consider. A position paper by the European Society for Medical Oncology has argued for regulatory bodies to facilitate the production of compendia of anticancer drugs, enlisting those off-label uses judged to be legitimate.¹³⁰ According to this position paper:

“...this would not solve the whole problem at once, but it would at least clarify the situation and improve the physician’s position, particularly regarding the question of medical liability, when confronted with the described paradoxes of off-label drug use.”

The American Academy of Pediatrics has provided guidelines on a number of topics, including the off-label use of medical devices.^{87,131} Of greater relevance is that the scientific bureau of the World Society of Pediatric Ophthalmology and Strabismus has recently reported guidelines on current approaches for MC treatment.¹³² Additionally, a recent report by the American Academy of Ophthalmology concludes there is solid scientific evidence that supports the use of low-dose atropine to prevent myopic progression.¹¹²

c) Health Care. A policy option that could be considered is to develop a consensus list of accepted off-label/unlicensed uses of medical products for MC in children. The list could be based on solid scientific evidence or there could be a process, including, for example, evaluation by a subject-matter expert group, by which to approve such applications for promoting safer off-label and unlicensed use of medical products for MC in children.¹³³ This kind of process could be developed for ECPs to apply for permission to prescribe off-label/unlicensed products with the appropriate competent authority. The application could be evaluated with respect to its efficacy and safety, and an appropriate decision made. This would offer a balance between the benefits and risks of off-label/unlicensed use for patients. Additionally, implementing reimbursement measures to influence off-label/unlicensed use may also need to be considered. For example, France and Italy explicitly allow for reimbursement of off-label use when no alternative on-label options exist.⁸⁵ Such possibilities might help ECPs handle the ethical and legal paradoxes associated with the prescription of off-label and unlicensed treatment options for MC. At the same time, this may lead to a safer and more consistent prescription path for patients.

d) Professional. Safeguarding the safety, efficacy, and quality of MC treatments is, to a significant degree, related to the expertise of ECPs in the field. From such a perspective, the development of certified programs to ensure requisite competency standards of clinical practice in prescribing such treatments might be desirable. Although these programs may be developed in different forms and by different organizations, development by professional bodies at a national level might provide a better means of achieving higher and more consistent standards of practice. As an example of such a scheme, the United Kingdom College of Optometrists offers higher qualifications in a number of specialized areas (i.e., contact lens practice, glaucoma, independent prescribing, low vision, medical retina, and pediatric eye care) to enable optometrists to offer enhanced services. Similarly, US state

boards certify doctors of optometry on a variety of expanded therapeutic procedures (e.g. expanded therapeutic laser practice). In The Netherlands, off-label prescription is only allowed if the relevant professional body has developed protocols or professional standards with regard to that specific off-label use. The United Kingdom General Medical Council provides guidance on good practice in prescribing and managing medicines and devices.¹³⁴ These latter options might be particularly relevant considering it would be difficult for ECPs to independently maintain a level of relevant competency in the rapidly changing field of MC.

Nevertheless, safeguarding public health should always remain the primary goal over and above any economic considerations. As such, special care must be taken when designing or adopting any of the above suggestions to increase approved treatment options for MC in children, particularly bearing in mind that off-label and unlicensed promotion may challenge the integrity of the regulatory system by undermining the authority of regulators and discouraging companies from conducting trials for new medicines and devices as well as new indications.

3.2 Manufacturers

Manufacturers have a large part to play in the ethical decisions around the ECP prescribing of MC treatments.

3.2.1 Requirements for Advertising MC Treatments. To date, there are only two treatments that have been granted marketing authorization in certain markets for on-label prescribing in children for the purpose of MC (see the accompanying IMI – Interventions for Controlling Myopia Onset and Progression Report).¹⁸ Manufacturers cannot directly market other products for MC. In the United States, the FDA, through its division of drug, advertising, marketing, and communications, regulates off-label drug promotion. However, in practice, its capacity in such regulation is limited. Several reasons have been proposed in favor and against promoting off-label use of drugs and devices (Table 1).¹³⁵ Although the FDA prohibits the promotion of off-label use of drugs and devices, some sources of off-label use information are permitted (Table 2).¹³⁵

The FDA demands information regarding off-label use to be accurate, the relationship between the distribution of information and the sponsoring manufacturer be disclosed, and the published material not be edited or presented in an abridged form. Furthermore, such promotional materials must be submitted to the FDA at the time of dissemination to the public.¹³⁶ As a result of the increase in direct-to-consumer marketing by pharmaceutical manufacturers, the FDA introduced the Truthful Prescription Drug Advertising and Promotion (Bad Ad) Program in 2010. This program provides a mechanism by which the HCPs and patients can report illicit off-label promotion to the FDA. Despite regulations that prevent pharmaceutical and marketing companies from promoting off-label drug uses, off-label marketing by pharmaceutical companies has been reported to be one of the most common causes of Medicaid fraudulent claim investigations in the United States.^{84,137} Several pharmaceutical manufacturers have faced large settlements for illegal marketing of off-label uses.¹³⁸⁻¹⁴⁰

In Europe, EU law prohibits companies from marketing off-label/unlicensed drugs and devices. In some European countries, industry self-regulatory bodies monitor compliance with marketing rules. For example, the United Kingdom self-regulatory system for exposing marketing violations relies mostly on complaints from company outsiders, which may explain why most off-label promotion rulings relate to plainly visible promotional activities, such as advertising. This contrasts with the United States, where investigations by

TABLE 1. Reasons Proposed in Favor and Against Promoting Off-Label Use of Drugs and Devices in the United States. Text Quoted and Adapted From Ventola¹³⁵

| Reasons in Favor | Reasons Against |
|---|--|
| Can increase access to suitable off-label drugs for patients with rare and other diseases. | Can increase abuse and over-promotion of off-label when appropriate risk-to-benefit ratio has not been well established. |
| Off-label uses are important and even represent the recognized standard of care for some conditions. | Peer-review alone does not ensure that off-label information will be of a high quality. |
| Public health might be advanced if health care professionals were to receive journal articles and references that are truthful and not misleading about unapproved uses. | Strategic decisions made by industry sponsors might solely seek publication of positive trial results. |
| More data and better transparency to be readily available to physicians, enabling them to make better treatment decisions. | Misleading portrayal and interpretations of data in low quality studies. |
| Relaxing restrictions enables clinicians to become more knowledgeable about treatment alternatives as it is extremely difficult for them to independently keep up-to-date in reading all of the medical journals and compendia available. | Patients may still have to pay high treatment costs directly out of pocket for off-label products that their health professional has been encouraged to use. |
| The distribution of high-quality, focused information on off-label uses by manufacturers could therefore be seen as an important service if not abused. | Ghostwriting of journal articles sponsored by companies. |
| Supports innovation in clinical practice, which is particularly important when approved treatments have failed to deliver adequate care. | Limited ability of regulatory and medical journals to detect low quality studies. |
| Can keep medical practitioners informed about the treatment options available for patients afflicted with rare diseases where manufacturers have little economic incentive to conduct expensive clinical trials for drug or device to be used to treat small patient populations. | Peer-review is insufficient protection against corporate influence over the content of publications. |
| Because the regulatory approval process is complex, costly, and time-consuming, the distribution of off-label drug information provides physicians and patients with early notification about novel treatments. | Clinicians might rely solely on industry-distributed journal articles. |
| Gives patients opportunity to benefit from innovations that are continuously developed in clinical practice (e.g., aspirin was widely prescribed to reduce the risk of heart attacks long before the FDA approved it for this purpose). | Editors and manuscript reviewers might not be familiar with critical details of clinical study design and conduct and could unwittingly publish poor quality or biased data. |
| Valuable in updating treatment decisions because knowledge on off-label prescribing can play a key role in keeping up with rapidly changing prescribing practices. | Suppression of data on safety risks. |
| Reduction in resources and cost-saving for regulatory bodies. | |

the Department of Justice and whistleblower testimonies have alleged complex off-label marketing campaigns that remain concealed to company outsiders.¹⁴¹ European authorities might need to consider introducing increased incentives and protections for whistleblowers combined with United

States-style governmental investigations and meaningful sanctions.

Prescribing off-label and unlicensed MC treatments is being practiced worldwide,¹⁴² and it is likely to grow with the increasing levels of myopia worldwide.¹ As the interest in prescribing treatments for MC increases, having access to evidence supporting safety and efficacy, particularly for off-label/unlicensed treatments, is essential. From this perspective, industry should be encouraged to compile information from the literature and other reliable sources that are evidence-based to share with ECPs so they can make balanced, informed clinical decisions that are a public health benefit.¹⁴³ This is particularly important considering that medications are often prescribed for off-label use with absent or limited clinical evidence.⁸²

3.2.2 Efficacy Claims. MC efficacy relates to the reduction in axial elongation and/or increase in manifest myopia of the eye by the test device compared with a reference control device. Further information on this topic is provided in the accompanying IMI – Interventions for Controlling Myopia Onset and Progression Report¹⁸ and the IMI – Clinical Myopia Control Trials and Instrumentation Report.¹⁴⁴

There are two issues in assessing efficacy in this respect that warrant discussion. Firstly, ocular growth and refraction cannot be assessed simultaneously with the test and control devices in the same eye. Randomized, controlled clinical trials are the gold standard to minimize bias, but case-control trials are also a commonly accepted means of assessing efficacy. In both

TABLE 2. Sources of Off-Label Use Information Permitted by the FDA. Text Quoted and Adapted From Ventola¹³⁵

| Sources of Off-Label Use Information Permitted by the FDA |
|---|
| Compendia and drug/device information reference handbooks that are published by organizations or companies that are independent from manufacturers. |
| The presentation of scientific information in continuing medical education programs. |
| The dissemination of journal articles that discuss not yet approved product usages if FDA regulations are met. |
| Medical and graduate education in which off-label/unlicensed uses are discussed, although disclosures of significant financial relationships between program faculty and industry is requested. |
| Medical liaisons – companies are allowed to respond to unsolicited questions from HCP about off-label/unlicensed uses. |
| Sales representatives are allowed to provide copies of peer-reviewed journal articles to HCP, but are not permitted to use them to promote company products. |
| Off-label data may be freely posted in web sites that are not agents of the manufacturer. |

scenarios, changes in refractive error and/or axial length are compared between test and control devices to evaluate MC efficacy. The second issue is related to the metric used to assess efficacy. The measurement of refractive error, which should be ideally undertaken under cycloplegia and using automated refraction to minimize potential patient- and examiner-subjective bias, is the clinical standard used to assess myopia progression. However, some optical devices can impact the reliability and repeatability of refraction measurements. Optical biometry using low-coherence interferometry technology allows objective measurement of axial length with a resolution below 10 μm . Such technology¹⁴⁵ is considered the gold standard to quantify the axial elongation of the eye in myopia progression¹⁴⁶ and MC studies.^{147,148}

Changes in axial elongation for contact lens MC studies correlate reasonably well with changes in myopia progression.^{149,150} Results from 9 MC studies published over the last 8 years with OK^{147,148,151–154} and other contact lens types^{154–156} have reported mean increases in axial length in the experimental and control groups over a 2-year period of 0.33 mm and 0.55 mm, respectively, accounting for an average MC effect of 41%. However, it should be noted that calculation of MC efficacy based on refractive error measurements tends to be slightly higher than that calculated based on axial length,^{17,157} and thus, these two ways of calculating efficacy are not interchangeable. It has been reported that emmetropic eyes can remain emmetropic in spite of increases in axial length of the order of 0.1 mm/year, whereas eyes that eventually develop myopia have been reported to grow at a rate of 0.2 to 0.3 mm/year over a period of 10 years before and after myopia onset.¹⁵⁸

Studies on the use of atropine have shown a poorer correlation between axial elongation and refractive error, with refractive error reductions in myopia progression being greater than that determined for axial elongation (as outlined in the accompanying IMI – Interventions for Controlling Myopia Onset and Progression Report).¹⁸ Indeed, high-dose atropine not only limits the progression of myopia but also may even slightly reduce the refractive error in the first year.¹¹¹ This might reflect a suppression of the tonus of accommodation under the chronic effect of cycloplegia. This finding is relevant as it might justify the very high efficacy of this treatment in the first year or so and also help to explain the large rebound effect, part of which might be no more than the recovery of normal accommodation function. Thus, claims made for MC efficacy should not be limited to refractive error or axial length measurements in isolation but rather on both and the correlation between them reported. Rebound effects should also be reported and considered where such information is available.

3.2.3 Avoiding Non-Evidence-Based Claims/Recommendations. A number of animal studies carried out in different species have shown that peripheral refraction is important in the emmetropization process, such that relative peripheral hyperopic and myopic defocus can induce and inhibit myopia progression, respectively.^{159–167} Further details are provided in the accompanying IMI – Report on Experimental Models of Emmetropization and Myopia.¹⁶⁸ The latter has led to the assumption that inducing relative peripheral myopia through optical device use would reduce myopia progression in humans. Such an assumption has been applied in the development and marketing of devices for MC without, in many cases, confirmation that such devices are effective for MC in humans. It should be noted that myopic defocus induced in human subjects with optical devices^{105,169,170} can differ inherently from that produced by optically imposed defocus in animals, where exposure to defocus is generally substantial in terms of both magnitude and duration.^{159–167} Furthermore, large studies in humans have indicated that the effect of peripheral refraction appears to be design specific and

may not, in all cases, impact myopia progression.^{171,172} It is also common to find professional articles and presentations at conferences providing recommendations about customizing certain contact lens types to enhance MC efficacy, the evidence for which may be anecdotal rather than evidence-based.¹⁷³ Whereas some of the anecdotal information can be useful for the practicing ECPs, special care should be taken in adopting recommendations lacking robust scientific evidence.

There is evidence in the literature for certain devices having a role as being effective^{12,13,17,96,129} and relatively safe^{92–95} in reducing myopia progression. Ultimately, MC efficacy should be demonstrated in controlled clinical studies on human participants and confirmed by regulatory bodies to obtain marketing authorization or by independent research laboratories in case of off-label/unlicensed treatments, rather than basing claims of MC on extrapolation of results from animal studies or presumption of equivalence. Until products obtain a marketing authorization for MC in children, manufacturers should consider compiling a list of selected, evidence-based, off-label/unlicensed MC use of their optical devices to share with those ECPs requesting such information, such that practitioners can make informed decisions regarding the use of such products.

3.3 Academics

Academics have an important role in disseminating scientific information related to the safety and efficacy of approved and nonapproved uses of MC treatments, which is typically undertaken in the form of peer-reviewed journal articles, in addition to abstracts and presentations at major scientific conferences. As myopia increasingly becomes a topic of discussion at the level of public health policymakers, it is timely for academicians to be cognizant of their duty to inform and continuously seek up-to-date resources in the field, so that accumulated knowledge on the topic becomes available in the public domain for advancing this important public health issue.¹⁴²

3.3.1 Examples of Public Health Initiatives. In the late 1990s, the National Committee on Myopia was developed in Singapore in response to the alarming increase in myopia prevalence that was being observed compared to the previous decade.¹⁷⁴ The threat of complications associated with the development of high myopia warranted disease prevention measures. The National Myopia Prevention Programme that ensued was an attempt by the Singaporean Health Promotion Board to decrease the prevalence of myopia in school children.¹⁷⁴ Despite myopia prevalence rates that remain among the highest worldwide, this program has proven to be a successful one. It continues to influence public health policies and, equally as important, has created invaluable public awareness on myopia at national levels, focusing on schools and educational institutions, which, in turn, have led to a much more informed patient population that recognizes the risks of high myopia and is more amenable to potential MC interventions.

In March 2015, a global scientific meeting on myopia was jointly held by the World Health Organization and the Brien Holden Vision Institute at the University of New South Wales in Sydney, Australia.¹⁷⁵ This meeting was held in light of concerns about the current and future impact of myopia within health care systems around the world. Important definitions were clarified, distinguishing “myopia” from “high-myopia” and agreeing upon characteristics of the clinical diagnosis of MMD.¹⁷⁵ Additional recommendations ranged from the use of cycloplegic drugs in myopia screenings to areas where further investigation would be beneficial to improve evidence-based

management of myopia, such as the need to have sound worldwide epidemiologic data.

In September 2016, the FDA held a public workshop titled “Controlling The Progression Of Myopia: Contact Lenses And Future Medical Devices.”¹⁷⁶ This meeting brought together prominent members of multiple interest groups who acknowledged the increasing prevalence of myopia and the need to act. The overall goal of this workshop was to reach a consensus for clinical trial design attributes for obtaining FDA marketing authorization of potential devices to control the progression of myopia. This event was the first of its kind to bring together interdisciplinary bodies that all see value in adopting MC practices and, to date, has seen the publication of two papers describing the meeting.^{177,178}

These are just a few examples of how the global increase in myopia prevalence and rates of myopia progression in the youngest patient population has caught the attention of global health agencies. The response of these agencies to supply public information, much of which resides on the internet and is not evidence-based, puts the onus on academics to ensure that accurate information is provided to both clinicians and the public.¹⁷⁹

3.3.2 Gathering and Building Sources of Information.

To inform others, there must be a reputable knowledge base. The growth in the scientific literature on the subject matter of myopia has accelerated in the last century. In 1957, when Robert Morrison reported on a case series of patients who had been steadily increasing in their myopia, he was cognizant of the potential pathologic consequences these individuals could face in their future.¹⁸⁰ A cohort of these myopic patients were fitted with rigid contact lenses flatter than their flattest keratometric measurement for daytime wear and they were followed for up to 2 years, in an attempt to prevent their myopia progressing. Fast forward 60 years and although we may appear to understand the dynamics of how a rigid lens can be designed to modify the physiologic growth of the eye, the field of MC is continuously evolving. Academics play an important role in ensuring that this evidence base continues to grow.

3.3.3 Bridging the Gap Between Academic Research and Clinical Practice.

Many academic institutions and professional organizations, in their commitment to providing lifelong learning, offer continuing education programs, courses, and workshop options. ECPs using these resources seek high-quality, evidence-based education to implement into their own clinical practices. Other potential sources of educating ECPs include professional (non-peer-reviewed) publications, presentations at national and international meetings, and direct peer-to-peer interactions.

3.3.4 Education Beyond the Field of Eye Care.

In the prevention of myopia progression, it is not solely professionals in the eye-related fields who should be well versed on the subject matter. School-based interventions are already in use in Taiwan and China, including mandatory outdoor time and reduced homework hours.¹⁸¹ Elementary school teachers need to be made aware of these new methods and be able to inform parents and students and provide access to appropriate resources. Pediatricians and other HCPs should also be well-informed and involved in MC programs. Resources should be regionally applicable and developed with input from scholars, with reference to the scientific literature that is currently in circulation.¹⁸²

3.4. Eye Care Practitioners

3.4.1 Ethical considerations for ECPs.

It is well-documented that increasing levels of myopia leads to a higher risk of potentially blinding ocular pathologies, such as

glaucoma, MMD, and retinal detachments.^{2,6,8,22,183} Therefore, not treating progressing myopia with some form of MC treatment is likely to expose patients to a higher risk of ocular complications in the future. However, it should be pointed out that although the reduction in myopia and axial length elongation of the eye has been proven with some MC therapies, there have yet to be long-term studies that demonstrate that MC treatment does lead to a significant reduction in the incidence of these potentially blinding ocular pathologies later in life. Thus, ECPs are faced with a dilemma. They do not want to leave the patient without treatment, as this can be interpreted as an omission of professional duties. However, they do not want to administer an insufficiently proven treatment and assume all the risks, which the regulatory approval process (as well as medical malpractice law) would normally avoid, for the patients' protection.¹³³ Some physicians have indeed been involved in legal claims related to adverse reactions occurring from the prescription of medications for off-label use.^{75,184,185}

To avoid potential prosecution for malpractice in the prescription of MC treatments, the ECP has to justify the professional rationale behind the prescription of such treatments. When prescribing an off-label/unlicensed MC treatment, an increased level of caution and monitoring must be demonstrated to monitor for any adverse events. The ECP should consider prescribing an off-label/unlicensed treatment option for MC if there is sufficient evidence supporting its safety and efficacy. When such proof exists, failure to prescribe an off-label/unlicensed MC treatment could, arguably, result in an ECP being liable for not following the appropriate standard of care for their patient. The patient should be adequately informed about the off-label/unlicensed nature and the possible existence of unknown risks for any prescribed treatment, although an ECP may not necessarily be subject to professional liability for nondisclosure of the off-label nature of the treatment.¹⁸⁶ Parents/guardians should be in a position to make a well-informed decision regarding whether a child should be treated with a conventional tested and approved treatment, if available, or with an off-label/unlicensed treatment, which might give the chance of a better result, but at the same time, may have unknown risks. Furthermore, the ECP is obliged to notify the patient when the health insurance provider could refuse reimbursement of costs, as well as the level of costs due to the off-label/unlicensed status of the treatment.

In some countries, off-label/unlicensed use of medicines is not reimbursed unless they are mentioned in HCP guidelines. Some physicians believe that providing patients with information about off-label use may afford greater protection from future liability suits.¹⁸⁶ However, no court in the United States has mandated that a physician must disclose the off-label use of a drug throughout the informed consent process.⁵⁸ Arguments against disclosure include that such process may “excessively frighten” patients and that constantly reviewing and providing extensive risk/benefit information may distract attention away from other more important patient care issues.⁵⁸ Nevertheless, from an ethical perspective, patients should be clearly informed about a drug or device's status of authorization, such that they are in a position to make informed decisions regarding treatment alternatives. It has been shown that patient's knowledge regarding a drug's status of authorization is frequently lacking and, when adequate information is provided, patients often refuse off-label treatments.¹⁸⁷

To help determine whether the standards of practice are being met when prescribing off-label treatments, authors have proposed that the HCP carefully consider five points:^{75,186,188}

1. Does the native drug or device have local regulatory approval?

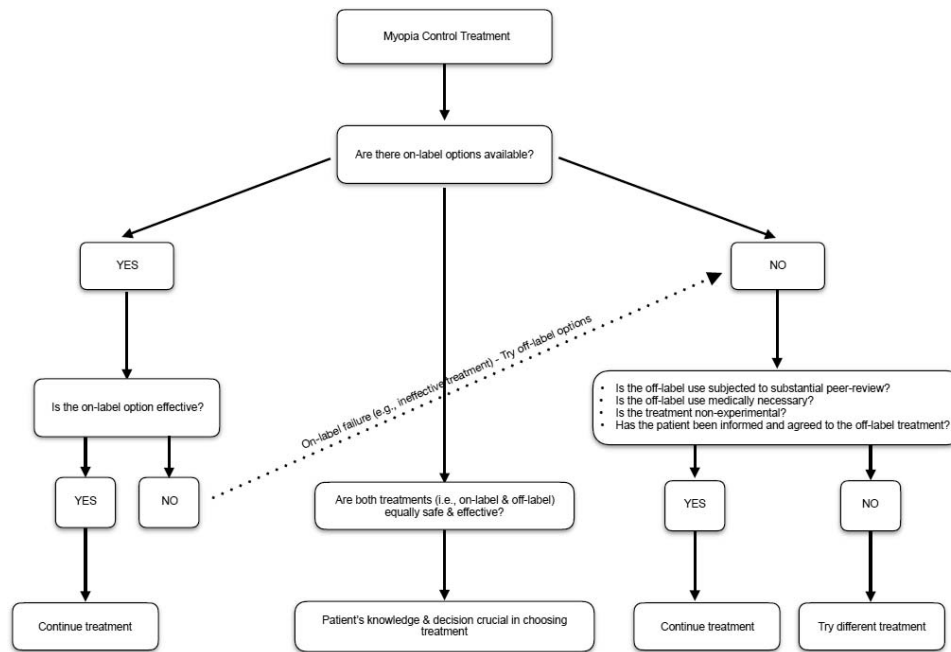


FIGURE. Flowchart describing the options for on-label versus off-label prescribing options for MC from a regulatory standpoint. Adapted from Wittich et al.⁷⁵

2. Has the off-label use been subjected to substantial peer review?
3. Is the off-label use medically necessary for treatment?
4. Is the use of the medication nonexperimental?
5. Has the patient been informed and agreed to off-label treatment?

To minimize liability risks, off-label drugs or devices should be prescribed in “good faith, in the best interest of the patient, and without fraudulent intent”.¹⁸⁸ Following this approach will ensure the FDA’s requirements are met, in that the HCP prescribing medications for off-label use should “be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects”.¹⁸⁹

A flowchart to aid with decision-making regarding the prescribing of off-label versus on-label options is described in the Figure.

3.4.2 Information Provided to Patients and Parents. In addition to information regarding off-label/unlicensed use of products, other information of clinical relevance should be provided. For instance, refractive surgeons offering corneal refractive surgical options (e.g., LASIK) to improve unaided vision should ensure that patients understand that such treatments do not, in any way, mitigate the risks of developing axial length-related myopic complications in later life. Likewise, patients informed about the benefit of overnight OK lens wear in temporarily correcting refractive error to enable good unaided visual acuity in the daytime, may confuse this aspect of visual correction with claims of reduced myopia progression and axial elongation, and this issue needs clarification.

3.4.3 Guidelines for Treatment. As discussed previously, having access to guidelines on MC treatment developed by professional bodies would be ethically and legally desirable. However, following such guidelines will not exempt ECPs from professional responsibilities and liability in the prescription of off-label/unlicensed MC treatments. When considering prescribing a treatment for MC, the ECP should ideally begin by considering any on-label products that may be available and

contemplate off-label/unlicensed prescribing only if no on-label options are available or if these options would be inappropriate for the patient. It has been reported to be common practice by HCPs in Europe to switch to off-label medicines when there is a lack of effectiveness with on-label products.⁸⁵ In case of treatment alternatives where one product is off-label/unlicensed and the other is licensed, but from the HCP’s point of view both alternatives are equivalent, the patient’s contribution in the decision-making process is critical.^{58,133}

3.5 Patients

The need for patient compliance is of key importance with any treatment, but it is of particular relevance for off-label/unlicensed treatments. In the latter case, higher levels of monitoring than normal are required to warrant both safety and efficacy with the treatment. Therefore, the patient needs to fully agree to any extra measures of precaution indicated by the ECP.

A further aspect of compliance relates to patient compliance with the MC treatment prescribed, as only occasional use of the prescribed MC contact lenses or spectacles, or failure to use atropine as prescribed, will inevitably impact the treatment efficacy. Indeed, longer wearing times exerted a greater MC effect with a soft contact lens, confirming that wearing compliance does indeed impact treatment efficacy.¹⁵⁶ Finally, compliance with issues such as contact lens storage, replacement, and case hygiene can all impact safety of the prescribed device and patients must understand their role in this to ensure maximal chances of contact lens success.^{190–195}

3.6 Impact on MC Therapies

The increasing prevalence of myopia is driving off-label and unlicensed use of treatments options for MC in the absence of on-label therapies. Several incentives at governmental, regulatory, health care, and professional level have been implemented in the past and some others have been suggested, but they

have had little impact on the number of products approved for pediatric indications. Regulatory bodies do not normally regulate the way medicinal products are ultimately used in practice. The prescription of a product, regardless of whether on-label, off-label, or unlicensed, is a decision taken within the relationship between a patient and the treating HCP.

Companies are not typically permitted to promote treatments for MC that are not approved for that purpose, although the dissemination of scientific information that is truthful and not misleading about unapproved uses is allowed. Academics have an important role in disseminating scientific information related to the safety and efficacy of potential MC treatments. The latter is likely to help ECPs make balanced informed clinical decisions about unapproved use of drugs and devices that might help advancing public health, particularly until approved clinical guidelines for MC treatment became available. Nevertheless, the treating ECP can be trapped in the difficult dilemma of whether or not to treat progressing myopia in children. ECPs involved in prescribing MC treatments should show an increased level of caution and monitoring with off-label or unlicensed therapies. The option to prescribe off-label/unlicensed MC treatment options based on the most credible available evidence, rather than restricting prescriptions to indications only approved by regulatory bodies, is likely to work in the best interest of the patient.

Patients should be well-informed about the nature of the product's marketing authorization status for the intended use and in case of off-label/unlicensed treatments that the risks associated with the treatment might be unknown and that there might be possible difficulties in connection with the reimbursement of the treatment costs by health insurance companies. Such information should be provided in a neutral, balanced, and nonbiased way and be accompanied by easily accessible online and printed information. The use of informed consent and assent forms are strongly recommended. Additionally, until more on-label options become available, ECPs should continually educate themselves about off-label/unlicensed uses of MC treatments to weigh the risks and benefits and provide the best possible care for their patients.

4. REGULATORY CONSIDERATIONS

Regulation of drugs and devices helps to protect the health and safety of communities, improves patient access to high quality products, increases confidence in the health system, and creates stable conditions for manufacturers to pursue novel therapies. However, drug and device regulations vary significantly from country to country (see Table 3 for some examples of regulatory agencies). Furthermore, in most countries, drugs and devices will be regulated by different governmental offices. As countries advance economically and socially, there is considerable flux in regulations, with a strong tendency to greater formality. MC treatment is a relatively recent concept and, therefore, regulatory guidelines on this topic are yet to be clearly established. Similarly, legal authorization for practitioners and commercial bodies to deliver and advertise treatments to the public or practitioners vary substantially between countries. Addressing all of these regulatory topics comprehensively by country is beyond the scope of this document. Therefore, the following discussion presents a general overview, highlighting some of the relevant principles appropriate for regulation of MC treatments. Because of its prominence, influence, and well-established procedures, the US FDA is referenced to provide examples of regulatory processes. The two main areas addressed are (1) clearance for use of a product

TABLE 3. Examples of Regulatory Bodies

| Market | Regulatory Body |
|----------------|--|
| Australia | Therapeutic Goods Administration |
| Canada | Health Canada |
| China | Chinese FDA |
| Europe | European Medicines Agency |
| Hong Kong | Medical Device Control Office and Drug Office |
| Japan | Pharmaceuticals and Medical Devices Agency (PMDA, or Koseisho) |
| Singapore | Health and Science Authority |
| South Korea | Ministry of Food and Drug Safety |
| Taiwan | Taiwan FDA |
| United Kingdom | Medicines and Healthcare Products Regulatory Agency (MHRA) of Department of Health |
| United States | Food and Drug Administration |

from governmental authorities and (2) licensing of practitioners to implement MC treatments.

4.1 Product Registration

4.1.1 Classification and Approval. Approval of a drug by a regulatory body naturally relies on the risk-benefit assessment and is informed by science, medicine, policy, and judgment, in accordance with applicable legal and regulatory standards. Different regulatory pathways may be used to enhance efficiency and shorten timelines for the development and approval of novel drugs or to expand indications for existing drugs. For example, the Center for Drug Evaluation and Research of the US FDA has applied different designations for novel drugs, such as first-in-class, orphan, fast track, breakthrough, priority, and accelerated approval, often with drugs falling into multiple designations. It does not appear that there are novel drugs on the immediate horizon for MC, although this may change in the future.¹⁹⁶

Drugs under consideration for MC would most likely fall under the banner of new uses for previously approved drugs (termed “efficacy supplement” by the US FDA), with new indications and labeling required to address the new indication. The approval of such drugs for new use may be facilitated, in part, by existing data, but often will need to undergo stringent efficacy and safety testing similar to new drugs. Pathways for development and approval are best explored using documents such as International Organization for Standardization standards, guidance documents, and manual of policies and procedures, in addition to discussion of specific requirements with regional authorities. Some indication of the requirements for obtaining approval for a MC drug may be obtained from the transcripts of the Dermatologic and Ophthalmic Drugs Advisory Committee meeting of the FDA from 2003¹⁹⁷ and in a recent paper by Novack.¹⁹⁶

Further requirements for some jurisdictions may also be obtained by considering the experimental designs of phase 3 studies for MC drugs, as may be found in clinical trial registries. Some countries may rely on approvals obtained in lead regions (e.g., United States or Europe) to assist in regulatory decision-making. Considerations for experimental designs in submissions for approval of drugs may be found in the accompanying IMI – Clinical Myopia Control Trials and Instrumentation Report.¹⁴⁴

Devices are commonly classified according to risk for the purposes of providing guidance as to the type of testing that will be required. Different jurisdictions take different approaches but, by way of example, the US FDA divides devices

into three classes. Class I devices are low-risk medical devices. These will generally be exempt from the need for regulatory approval (premarket notification) but are not exempt from other general controls, such as the need to be manufactured under a quality assurance program, be suitable for the intended use, be adequately packaged and properly labeled, and have appropriate registration with the FDA. Spectacle lenses (and frames) for myopia correction currently fall into this category.

FDA Class 2 devices are more complex devices entailing a higher risk profile than Class 1 devices. Such devices generally require a 510(k) premarket notification to demonstrate that they are at least as safe and effective as an existing product or PMA where no predicate device exists. Submissions are reviewed prior to marketing clearance. Class 2 (and 3) products are also subject to design controls, a set of quality practices and procedures that control the design process to ensure that a product meets user needs, intended use, and specified requirements. Daily wear soft contact lenses for myopia correction are currently classified as Class 2 devices.

FDA Class 3 devices are the most complex devices and carry the highest risk profile. Soft and OK contact lenses for refractive correction and overnight use are classified as Class 3 devices. These products require a PMA, the most stringent regulatory device category. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use.

To our knowledge, there are only two products (both multizone soft contact lenses) that currently have general regulatory clearance anywhere in the world (low-dose atropine has limited regulatory status in Singapore and Malaysia). Both contact lenses are Conformité Européenne (CE)-marked, which is the manufacturer's self-certification that the products conform to the health, safety, and environmental protection standards within Europe. Because the dossiers for CE marking are not public, there is no information available about the standards or evidence used by the manufacturers for self-certification with respect to safety and efficacy.

Because no MC devices have FDA clearance, regulatory requirements remain unclear. The FDA held a public workshop, cosponsored with other professional bodies, with the purpose of discussing “clinical trial design attributes for studies using contact lenses or other medical devices to control the progression of myopia”.¹⁷⁶ Two papers have been published in relation to this meeting, one reviewing previous key studies and a second discussing study design and regulatory issues relevant to future clinical trials.^{177,178} Further discussion of experimental design considerations is presented in the accompanying IMI – Clinical Myopia Control Trials and Instrumentation Report.¹⁴⁴

For both drugs and devices, regulatory bodies may impose post-approval requirements, such as postmarket surveillance. Again, information about what might be required in this regard is speculative at this time.

4.1.2 Practitioner Licensing. The matter of practitioner licensing to prescribe MC devices or drugs is complex due to the fact that the scope of practice and levels of training of ECPs vary markedly from country to country. In many developed countries (e.g., United Kingdom, United States, Australia, and Canada), the profession of optometry has matured to that of an independent primary eye care level (Category 4 in the “Global Competency-based Model of Scope of Practice in Optometry” of the World Council of Optometry).¹⁹⁸ In these countries, optometrists are qualified to prescribe most of the typically available MC treatments (in some, to prescribe drugs such as atropine, a higher qualification is required). However, in many countries, optometrists may only be allowed to prescribe spectacles lenses or contact lenses but not drugs. In certain

countries, contact lenses can only be prescribed for minors by ophthalmologists and not optometrists. Furthermore, in some countries, there is no specific legislation on the practice of optometry and there is no regulatory control of the prescribing of optical devices, including contact lenses.

This makes the regulations around the prescribing of optical devices for MC somewhat complicated. For example, once a soft contact lens or OK product receives FDA approval or a European CE mark, ECPs in these markets may prescribe these products without any limitation. However, in China, once these same products are approved by the Chinese FDA, soft lenses can be fitted by practitioners in local hospitals, eye clinics or optical retail premises, but only practitioners with a medical license or those working in a hospital, eye clinic, or optometry practice that has received a practicing medical license can prescribe OK devices. Optical retail premises in China without a practicing medical license would not be able to prescribe OK lenses, although they can prescribe soft contact lenses.

It is, thus, a complex matter to review and/or standardize an “indication of treatment,” when both product registration and practitioner legislation in different countries/territories are taken into consideration.

4.2 Relevant Regulatory Requirements

It is clear that the complexity of regulatory frameworks pose a challenge in standardizing the indications for the use of MC treatments in different countries or regions. This, however, does not prevent the global industry from adopting a standard protocol and good practice guidance to meet “general” regulatory requirements, including even the most stringent ones such as FDA in the United States and Pharmaceuticals and Medical Devices Agency in Japan.

4.2.1 Good Laboratory Practice and Good Manufacturing Practice. In the optical, pharmaceutical, and ophthalmic industries, Good Laboratory Practice and Good Manufacturing Practice require clear protocols to be established before a prototype or a finished product is produced.

A number of global standards, such as British Standard, European Standard, or International Organization for Standardization, are available and used globally in the development and licensing of ophthalmic medical devices. For example, British Standard, European Standard, International Organization for Standardization 11981:2009 on “Ophthalmic optics, contact lenses and contact lens care products. Determination of physical compatibility of contact lens care products with contact lenses” is a relevant standard for many MC devices.

4.2.2 Good Clinical Practice (GCP). GCP involves standards and guidelines required for designing, planning, conducting, monitoring, documenting, analyzing, and reporting of clinical trials. This ensures that the conduct of clinical trials follow internationally acceptable ethical and scientific standards. Optical, pharmaceutical, or ophthalmic industry involved in MC should adopt GCP for their clinical trials and is a requirement from most IRBs. This will facilitate the recognition of the clinical results by regulatory authorities, with potential to establish a recognized norm in MC studies.

4.3 Industry Accreditation of Prescribers

A point worthy of consideration relates to the potential accreditation or training of ECPs in the prescribing of devices or pharmaceutical agents for MC. In unregulated markets, this is difficult to achieve, but in those in which a company has control over whom has provided the MC product then it would be worthwhile for companies to consider what is required to access and prescribe the product. Industry should effectively

communicate and participate in advocating the importance of early intervention in MC and in providing high-quality training and education for practitioners to support their implementation.

One such example relates to the recent commercial release of a soft multizone contact lens that has received regulatory approval for MC in several countries. To have access to a fitting set of lenses and be permitted to order the lens, prescribing practitioners were required to undergo a 1 hour web-based educational program that discussed the growing problem of myopia, the pathologic implications of high myopia, expected clinical results, and how to fit and problem-solve issues with the device in pediatric patients.

4.3.1 Educational Materials. There is an urgent need to create standardized educational materials on myopia risk and MC treatments. Such educational materials should cover areas such as epidemiology, the public health burden due to myopia, contemporary research in MC, interventional options, and best clinical practices for MC. Currently, there are many different groups of researchers, clinicians, and scientists across the globe expending efforts to provide information on MC treatments, and these efforts often overlap across groups.

For practitioners to appropriately prescribe MC treatments in their clinical practice, it is important that materials used for educational purposes meet the following criteria as a minimum standard:

- Present evidence-based information on the efficacy, safety, and benefit/risk ratios for each treatment when applied to different population groups (e.g., different ages, races, and educational levels);
- Present this information in a clinically oriented manner that the practitioner may relate to.

Independent stakeholders such as the IMI could play a key role in the development of such educational materials, which would need to be developed for ECPs and other related professionals (pediatricians, general practitioners, and school teachers) with widely varying educational backgrounds. These materials would be beneficial for all stakeholders, including industry and regulatory bodies, as well as providing a global approach for MC by practitioners across the world.

4.3.2 Ongoing Educational Requirements. To acquire and maintain standardized minimum clinical competencies, knowledge, and skills in providing MC treatment and management, continuous training is essential. It is recommended that MC treatment and management training incorporates current best practice principles used in continuing professional development (CPD) courses. CPD is a mandatory requirement in many countries where optometry and ophthalmology are mature professions (e.g., Canada, United Kingdom, United States, Australia, and Singapore) but is voluntary for optometry in others (e.g., Hong Kong). Therefore, standardizing MC education based on CPD requirements is a complex, yet important, principle to apply where possible.

Initially, it is recommended that stakeholders consider establishing a standardized global CPD credit system that is aligned with the different tiers of education or training worldwide. To achieve these standardized programs, open communication and close collaboration with local professional and regulatory bodies worldwide is important. Once “accredited” following such a period of training, regulatory bodies (both government and professional) and/or industry could develop and make available a database of “approved” prescribers of the device or pharmaceutical agent intended to provide MC. This would ensure that patients would understand that the prescribing ECP has obtained the appropriate training to use the device or pharmaceutical agent in an appropriate manner.

In countries where graduating optometric competencies include MC management and there is already a well-developed

CPD program, an official extra CPD system is probably not needed. In these places, ECPs might prefer to be involved in a fellowship process involving the myopia specialty or membership of a Myopia Association as proof of interest in staying current with changes in the myopia field.

5. RESPONSIBILITIES IN THE DISSEMINATION OF INFORMATION

The volume of information available regarding MC efficacy is increasing rapidly, and assessing the quality of publications claiming potential benefits from these treatments may prove difficult for both patients and practitioners. One major issue relates to the fact that MC treatments do not impart an immediate effect but rather an expected outcome that is several years in the future. Potential outcomes should be explained in a non-biased way and realistic expectations provided.

Potential sources of bias in information presented to the public include:

- Claims on efficacy of the treatments from limited-term clinical trials;
- Claims on efficacy of treatment based from animal studies;
- Claims on efficacy of treatment based solely on presumption of device equivalence;
- Claims on mechanisms of action of treatments;
- Claims on cumulative efficacy in the long-term;
- Claims on long-term reduction of comorbidities related to myopia progression.

To filter out potential “exaggerations” of the impact of MC treatments, the information presented must rely on robust scientific evidence. Such information is typically available in scientific journals, and it is important that clinicians have access to the sources supporting the claims made and evaluate the publications appropriately. Additionally, scientific publications are not easily assimilated by patients (children) undergoing MC treatment or their parents/guardians, and thus, efforts should be considered to present such information in formats that they can more easily comprehend. Finally, as MC treatments become more popular and their use expands, it is necessary to update the information on the post-market experience such that clinicians and patients are made aware of the longer term efficacy and safety of such treatments.

This section will address these topics from the standpoint of the stakeholders participating in marketing medical devices and treatments for MC to both clinicians and their patients.

5.1 Peer-Reviewed Scientific Journals Versus Clinical Journals

Evidence-based clinical practice is supported by the body of literature published on the topic of interest. The evidence used should use the highest standards of research design, methodology, and conduct. In a general sense, the highest standards for evidence supporting new devices or treatments are derived from the conduct of randomized, controlled, masked clinical trials published in peer-reviewed scientific journals.

Although the open access regime of publication is becoming more common, most scientific journals are still available through scientific or professional organizations and subject to subscription-based access. Clinicians not involved in research activities may be more familiar with clinical journals that are not always peer-reviewed and, therefore, are potentially subject to bias. There are multiple examples of misuse of scientific evidence in clinical recommendations published in

both peer-reviewed and non-peer-reviewed journals. Dissemination of information with suboptimal levels of scientific evidence is an increasingly relevant issue¹⁹⁹ and given the importance of this issue to the clinical decision to undertake MC treatment in a vulnerable population, it is vitally important that the utmost care is taken in the reporting of MC studies and their outcomes and conclusions.

5.2 Public Dissemination of Information for Patients and Their Families

Patients rarely have access to or consult scientific literature. Even if access is available, the increasing trend of using technical information makes the scientific literature incomprehensible to most people. Therefore, scientists, practitioners, industry, and organizations with expertise in MC should direct efforts to provide the public with trustworthy and transparent information in an effective manner so that parents can understand the available treatments and their potential short-term and long-term benefits as well as risks. To be truly effective, the challenge is to provide the information in a way that is understood by the lay person, allowing them to judge the efficacy and safety of the treatments for themselves.

5.3 Confidentiality Versus Transparency

There is increasing pressure on researchers and industry to provide a detailed database of their research results. Some peer-review journals and funding agencies are driving this change to expand the concept of Open Access not only to the contents published but also to the source data to increase transparency. This could create potential conflicts with the confidentiality of the participant's data, which must be protected by adequate anonymization of any databases.

Another serious risk for transparency in dissemination of information from clinical trials is publication bias, which tends to lead to the more frequent publication of positive results rather than negative results.^{200,201} The need to publish negative and positive results is very important to build up an unbiased body of evidence around the efficacy and safety of medical devices and treatments. In the MC context, negative results might not be disclosed due to an effect contrary to the one expected or because the clinical benefit found is not enough to make the device or treatment appealing for stakeholders. Of note is that there are several publications of nonclinically significant results in the MC arena and several other studies that have published negative results.^{98,104,109,202–204} This increases confidence that publication bias in this domain as of now might not be a problem, but this issue must be considered, as the number of publications in this field continues to rise.

5.4 Handling and Reporting of Discontinuations in Clinical Trials

Clinical trials on MC involve several years of follow-up and, thus, participant drop-out is common, varying from less than 10% to over 25%. There are several reasons that justify early discontinuation from a clinical study. Some of them (e.g., loss of interest due to nonobservable effect of the treatment) might have an impact on the overall efficacy, whereas others (e.g. complications) might have an impact on the final safety outcomes. High levels of early withdrawal, particularly when this is asymmetric in different treatment groups, might also negatively impact the comparability of the results between treatment arms. The statistical power may also be at risk when modest samples are initially recruited and/or high rates of withdrawal are observed, which may limit the ability to estimate the treatment effect. To understand the impact of this factor, the discontinuation rate in

each group and subgroup should be reported, as well as the reasons and the impact on the randomization process and final statistical power.

5.5 Subgroup Results from Clinical Trials

Our understanding of the potential factors impacting myopia progression has increased over the past decade and so has the number of factors that can potentially influence the efficacy of MC devices and treatments.^{104,205} Authors reporting on clinical trials frequently discuss their findings in light of this knowledge to find a mechanistic explanation for their results. Unfortunately, study design and results analysis do not always allow testing of the hypothesis to confirm the cause and effect relationship between the results and the proposed mechanism. Therefore, future clinical trial design should anticipate the inclusion of subgroups (e.g. phoria status, relative peripheral refraction, and accommodative lag) that might help to test the hypothesis of working principles involved in the design of the treatment device. This will undoubtedly have an impact on the complexity and costs involved in the clinical trial recruitment.

When different subgroups are included in the analysis, their results should be communicated separately to help practitioners decide the clinical scenarios where a given device or treatment might be more effective. Similarly, when different treatment or control groups are included in the same trial, reporting should specify the results on all groups. Providing such data will allow the stakeholders to evaluate the absolute efficacy of the treatment and not only the percentage efficacy compared to the control group. When more than one treatment group is involved, the outcomes of all groups should be reported and not only the results of the treatment of interest.

5.6 Sample Sizes

Sample size calculations must be conducted a priori to warrant sufficient statistical power to test the hypothesis being investigated, (e.g., difference between treatment groups in axial elongation and/or myopia progression over a certain period of time). This estimation may be challenged by the early drop-out of participants during the study, which may have an impact on the statistical power of the final outcomes. The publication of research results should include details on the statistical power for the sample size that was initially intended and the power for the sample that finished the study. This will provide the stakeholders with a sense of the risk of erroneously accepting the null hypothesis (Type II error). Similarly, the report should include the statistical significance used in the statistical analysis to provide a sense of the risk to erroneous rejection of the null hypothesis (Type I error).

5.7 Consideration of Location of Studies

Previous studies have shown that a given treatment (e.g., OK) might not present the same efficacy in clinical trials conducted in different countries and ethnic groups.^{147,148,151,152,157} However, this information was collected from a variety of studies that did not permit the exclusion of other factors apart from ethnicity and geographic location. In clinical trials where different ethnicities were involved, no significant differences were reported regarding the ethnicity of the participants enrolled,^{98,206} although accounting for this factor would require larger populations than those studied. A recent multicenter clinical trial conducted in Europe, Asia, and North America showed that ethnicity was not a determinant factor in the efficacy of a dual focus soft contact lens (Chamberlain P, et al. *IOVS* 2017;94:ARVO E-Abstract 170075). Although further information is produced on the potential differences in efficacy

of treatments between ethnicities and/or geographic location of the myopic patients, efficacy data should be accompanied by information regarding the sites and ethnicity of the participants enrolled, as this may differ between geographic locations and ethnicities.

5.8 Rebound Effects

Rebound is a well-known effect in pharmacology and is observed as a manifestation of the symptoms or signs when medication is discontinued or reduced, once the medical condition was appropriately treated. Rebound effect in the context of MC represents a faster axial elongation and increase in refractive error than that expected in a matched group, upon cessation of the MC treatment. This has been shown to various degrees with cessation of both atropine and OK.^{115,207} A potential rebound effect following the use of bifocal/multifocal soft contact lenses for MC has not been studied and warrants investigation.

Significant rebound in MC is particularly relevant, as this is a treatment intended to reduce the long-term myopic changes that occur in later life. If the potential benefit gained during treatment is lost after treatment discontinuation, then this obviously compromises the goal of the treatment. As the biological mechanisms involved in MC with optic devices are still relatively unknown, the same reasons that drive atropine rebound effect might not apply to contact lenses or spectacles used for MC.

It is desirable to evaluate the rebound effect after MC discontinuation to provide practitioners, parents, and patients with realistic expectations on the long term benefits of MC treatments and the ideal duration of the treatment to overcome a potential faster progression after early discontinuation.²⁰⁷ Ideally, such studies should incorporate a control group, as it is expected that the axial elongation will slow down naturally with age. Communication of these outcomes should be reported in comparison to a randomly assigned, age-matched control population. It should also be noted that investigation of potential rebound effects is subject to difficulties in study design and ethical committee approval, as such testing would naturally involve exposing participants to potential increased rates of myopia progression.

5.9 Postmarketing Surveillance Studies

Contact lenses are medical devices, which are cleared for marketing in relatively small clinical trials, based on showing equivalence to currently marketed predicate devices. These studies cannot usually assess the safety of these devices, considering the relatively low incidence of adverse events with such optical devices. However, once the products are commercialized, sales increase and the likelihood of detecting any complications increase.

Most of the treatments currently in use for MC involve medical devices that have a degree of risk that ranges from low to moderate.²⁰⁸ Given that these devices are being used on vulnerable populations, it is suggested that postmarketing surveillance studies postapproval should be undertaken, as these may provide valuable data on such devices in the context of misuse or safety.²⁰⁹⁻²¹¹

6. RESPONSIBILITIES IN MARKETING, SUPPORT AND EDUCATION

6.1 Marketing and Guidelines

MC cannot be implemented widely without a strategy for transferring the required knowledge and skills to ECPs, who

are in the front line of servicing the public, and to academics who are key in nurturing the forthcoming generations of clinicians.

Although there are many scientific conferences that include information on MC through scientific papers or continuing education lectures, these are typically annual or biannual events that many practitioners will not have an opportunity to attend. Many other scientific conferences involving medical practitioners, pediatricians, and ophthalmologists may also have MC sessions in the future. Structured and locally delivered CPD in MC is critical to equip clinicians and academics with the knowledge and skills required to best manage their patients. Section 4.3.2 has already discussed the need for CPD programs for HCP and the need to establish standardized educational materials to cater for the varying levels of training required in various countries or regions.

Key stakeholders in the development of this educational material includes:

- ECPs
- Optic, ophthalmic, and pharmaceutical industries
- Regulatory bodies (for products)
- Legislative bodies (for practitioners)
- Health care agencies
- Academic institutions
- Vision and eye health institutions
- Professional bodies or associations
- Patient groups

In addition, it may be worthwhile to explore other channels for partnership to secure financial support to market and advocate for MC programs. This may include nongovernmental organizations, nonoptic industries, or high net worth individuals or firms. There is an increasing trend among commercial companies to allocate revenue streams for corporate social responsibility projects. Some are directed toward activities that improve children's lives (i.e., skill development, building of schools, and learning capabilities), whereas others are targeted in health-related areas. The possibility of developing projects that cross-fertilize these areas should be explored with regard to MC programs.

Industry partners are likely a key source of funding, and any MC programs will directly or indirectly benefit industry through increased sales and/or the access to new markets. Sponsorship for such programs needs to be managed ethically and professionally to avoid any potential COI and to fulfill the ultimate aim of benefitting patients.

7. CONCLUSIONS

Undertaking MC treatments on vulnerable populations creates an ethical challenge for a wide variety of stakeholders. Regulatory bodies, manufacturers, academics, and ECPs all share an ethical responsibility to ensure that the products used for MC are safe and efficacious and that the wearers understand the benefits and risks of such products. For ECPs, it is essential to provide appropriate information to patients who are at risk of developing myopia or for whom myopia-related pathology could occur due to rapidly progressing myopia. This IMI report highlights these ethical challenges and provides stakeholders with a framework to consider such issues in the development, financial support, prescribing, and advertising of products for MC.

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APPENDIX

Example of a consent and assent form for signing ahead of undertaking MC treatment.

MYOPIA CONTROL

Information and Consent

YOUR BUSINESS INFORMATION HERE

What is myopia? Myopia (also called near-sightedness) occurs when images focus in front of the retina, resulting in blurred vision. Vision is made clearer by putting a spectacle lens or a contact lens at the front of the eye to focus light onto the retina so that the image is clear and in focus.

What causes myopia? We are not 100% sure why some children become myopic and others do not. We do know that there is most likely a genetic component, and if a child has myopic parents, then they are more likely to become myopic. There is also some evidence to suggest that excessive near work could contribute to the onset of myopia. There is also evidence to suggest that spending more time outside in daylight could be a preventative measure to protect against the onset of myopia.

What can I do now that my child is myopic? It is important that your child have clear distance vision, which is most easily achieved initially with spectacles or contact lenses. There are several options available that may slow down the progression of myopia.

Why should myopia progression be slowed down? Myopia control treatments have been shown to slow down the progression rate of myopia by up to 60%. This would mean that, although your child's prescription may continue to change, it would hopefully change more slowly than if they were wearing a normal refractive correction, ultimately resulting in a lower prescription. It is well-documented that high prescriptions result in an increase in myopia-related ocular complications, such as retinal detachment, glaucoma, and myopic macular degeneration.

What options are available for controlling the progression of myopia? There are various options available that have been shown to slow down the rate at which myopia increases:

- **Progressive and bifocal spectacle lenses:** your child would wear their regular spectacle prescription in a “bifocal” design, with less power in the lower portion of the spectacle lens. It is thought that by reducing the demand on focusing for near work, myopia may not progress as quickly.
- **Enhanced Single Vision spectacle lenses:** your child would wear their regular spectacle prescription in a “multifocal” design. It is thought that by adjusting the peripheral vision, myopia may not progress as quickly.
- **Orthokeratology (Ortho-K):** your child would wear specially designed rigid contact lenses overnight and

remove them in the morning. The lenses are designed to alter the shape of the front of the eye so that your child has clear vision without correction during the day. This type of treatment has also been shown to slow down the progression of myopia.

- **Multifocal/Dual focus soft contact lenses:** your child would wear soft lenses during the day that are designed to change the way that images focus on the peripheral retina. These types of lenses have been shown to slow down the progression of myopia.
- **Atropine eye drops:** low doses of atropine (0.01%) have been shown to slow down the progression of myopia. Your child would insert one drop of the atropine drug into their eye once per day.

Are the treatment options safe?

- **Spectacles:** Typically wearing spectacles poses very little risk to patients.
- **Contact Lenses:** Children are commonly fit with contact lenses and are able to wear them successfully. The (low) rate of complications related to contact lens wear is similar in children and adults. There is a higher risk of contact lens-related complications (including corneal infection) in patients who wear contact lenses overnight than those who wear contact lenses during the day.
- **Atropine:** Low-dose atropine is considered to be safe for children and has been shown to have a small effect on pupil size and focusing ability compared to full strength (1%) atropine.

Are these treatment options approved by (insert your country's regulatory body, e.g., FDA, Health Canada, etc.)? At the moment, there are only two products that have regulatory approval as a product for myopia control. What this means is that the other treatment options are being used “off-label” or in a nonapproved manner. It should be noted that there are many occasions when medications or treatment modalities are prescribed in an “off-label” way by qualified practitioners.

As examples:

- Orthokeratology is indicated for the management of a myopic prescription and happens to have an added benefit of slowing down progression.
- A regular soft multifocal contact lens has an indication for vision correction for patients over 40 who are experienc-

ing reading difficulties, and fitting this approved lens to a child would be using it in an “off-label” modality.

- Atropine 0.01% is not commercially available and has to be specially formulated by a pharmacist. It does not have an indication for myopia control and therefore would be used in an “off-label” modality.

What complications or side-effects can my child expect? Complications with any of the myopia control options available are rare. Your child may notice the following:

- Orthokeratology—discomfort on lens insertion, difficulty handling the lenses, or blurred vision during the day if the corneal reshaping has not fully eliminated the prescription.
- Multifocal contact lenses—difficulty handling lenses, or ghosting of images under certain lighting conditions.
- Atropine—larger pupils leading to light sensitivity and a slightly reduced ability to focus at near.

Complications other than these are very rare; however, should your child experience any symptoms or signs related to their myopia control treatment, you should contact the clinic immediately.

There are four ways to potentially slow down the progression of myopia in children. Each treatment has its own risks and those have been explained to you. After consideration of your child's prescription and visual needs we have decided that the best option to slow the progression of your child's myopia will be:

- Orthokeratology
- Soft multifocal contact lens
- Atropine
- Progressive and bifocal spectacle lenses
- Enhanced single vision spectacle lenses

Parents declaration: I understand the risks as explained to me and indicated above. I also understand that some of the treatment options maybe being used in an “off-label” modality.

I understand that there is no guarantee of the treatment outcome for my child with the chosen modality.

Child's name (print) _____
 Child's name (sign) _____
 Parent's name (print) _____
 Parent's name (signed) _____
 Date _____
 ECP name _____
 ECP signature _____