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**ROP Safety Net:**

**Anti-VEGF for ROP**

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**OMIC policyholders who provide care must comply with the ROP Safety Net.**

OMIC’s ROP Safety Net is based on our claims experience. It is designed to address the causes of ROP lawsuits in order to protect the infant and the ophthalmologist. The ROP Safety Net Toolkit contains sample protocols, which may need to be customized, and refers to ROP clinical care guidelines. These protocols and guidelines are recommendations and do not constitute the standard of care. Ophthalmologists should use their professional judgment in determining the applicability of a given recommendation to their particular patients and practice situation.

The Toolkit does not provide legal advice. Consult an attorney if legal advice is desired or needed. Information contained here is not intended to be a modification of the terms and conditions of the OMIC professional and limited office premises liability insurance policy. Please refer to the OMIC policy for these terms and conditions.

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OMIC is committed to helping ophthalmologists provide safe care for infants at risk for retinopathy of prematurity (ROP). To that end, we have developed and published our ROP Safety Net, which includes an analysis of ROP malpractice claims, toolkits for both hospital- and office-based care, and sample consent forms for laser and anti-VEGF injection. To further reduce the risk and severity of ROP malpractice claims, OMIC conducts an underwriting review on a regular basis of all insured physicians who provide ROP care, and has mandated certain loss prevention actions that are summarized in “ROP conditions of coverage” (all documents available at <http://www.omic.com/rop-safety-net/>).

# **Treatment of ROP**

Ophthalmologists have been treating ROP with laser surgery for many years. Some babies are too sick to tolerate the anesthesia needed during the surgery. In others, the abnormal vessels are in an area that the laser cannot safely reach, or the view is obstructed by blood or a persistent tunica vasculosa lentis. Some infants have disease that persists despite laser. Other means of arresting ROP are thus needed.

Adult patients with retinal conditions due at least in part to VEGF have been successfully treated with intravitreal injections of anti-VEGF agents such as AvastinTM (bevacizumab), Macugen**TM** (pegaptanib), Lucentis**TM** (ranibizumab), and Eylea**TM** (aflibercept); intravitreal injection of anti-VEGF agents is hereafter referred to as **IVAV**. The similarity between ROP and adult retinal conditions prompted clinical trials on the use of IVAV in neonatal populations. Published reports from both clinical trials and “off-label” use of IVAV for ROP suggest that it can be effective and does not—so far—appear to produce many serious short or long-term side effects. **The efficacy, safety, and long-term consequences have not yet been proven.**

Concerns about IVAV both as primary or salvage therapy have been addressed in the literature and at eye society meetings. In addition, many questions are currently being studied and debated, such as agent, dosage amount, volume, timing of injections, length of follow-up, and contraindications. The 2018 ROP Screening Policy Statement (PS)[[1]](#footnote-1) addresses these issues. The PS recommends that infants treated with IVAV be followed closely until at least 65 weeks postmenstrual age (PMA).

Despite these uncertainties, when faced with aggressive or refractive ROP, ophthalmologists at times feel there is no other prudent choice but to treat ROP with IVAV. Given the extremely high indemnity payments often required to settle ROP malpractice claims, they are understandably concerned: they feel they are caught between the need to administer vision-preserving care and the risk of litigation—even decades later—for doing so. This document will address those concerns, and provide risk management recommendations specific to the use of anti-VEGF agents “off-label” for the treatment of ROP.

## **“Off-label” use of medications**

The federal Food and Drug Administration (FDA) approves and regulates the production, sale, and clinical research of medical drugs and devices. As a condition of approval, the manufacturer produces a “label” that summarizes the results of the research upon which the approval is based, as well as the indications, contraindications, known complications, and special warnings.

The FDA does not directly regulate the practice of medicine. Rather this oversight is provided by state legislatures, which pass medical practice acts generally granting the physician the right to use any and all means to diagnose and treat disease. Medical practice is further regulated by state medical boards, which issue licenses to practice medicine, and set conditions for license maintenance and renewal.

The FDA has explicitly addressed “off-label” use in an Information Sheet.[[2]](#footnote-2) The Sheet starts by declaring “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 judgment (emphasis added).” The FDA advises physicians who use approved products “off-label” to “be well-informed about the product, base its use on firm scientific method and sound medical evidence, and maintain records of its use andeffects.”

OMIC has analyzed the FDA guidance and its 31 years of ophthalmic claims, and concurs that it is not only legal but necessary for ophthalmologists to administer medications “off-label” when treating their patients.Moreover, OMIC feels that the ophthalmologist is in the best position to determine how to treat an individual patient. Accordingly, our professional liability policy provides coverage for such use.In the event of a lawsuit related to “off-label” use, ophthalmologists who are challenged will rely upon the expert witness testimony of ophthalmologists, peer-reviewed literature, and their well-documented efforts to provide quality care.

## **Obtaining informed consent for IVAV for ROP**

Intravitreal administration of anti-VEGF agents requires the informed consent of the infant’s parents or legal guardians. Informed consent discussions are often difficult, but rarely more so than in situations like this. Ophthalmologists who screen infants for ROP may not meet the parents during the screening process, and may thus be talking to the parents for the first time when they need to obtain consent. Once the need for treatment is identified, the eye surgeon needs to provide it within 72 hours to prevent progression to a retinal detachment; this timeline may make parents uncomfortable about making an informed choice. Premature infants run the risk of serious cardiac and respiratory complications with invasive treatment. In addition, the VEGF that causes ROP is vital for the development of the infant’s brain, lungs, and kidneys. When the treatment being proposed is relatively new and has unknown long-term risks, it is even more difficult for physicians to discuss and parents to consent.

OMIC has resources to help prepare parents for this discussion. In response to allegations made by plaintiffs in ROP malpractice lawsuits that they did not know that the infant was at risk for ROP, OMIC requires that insured physicians provide parents with a brief explanation of ROP prior to discharge from the hospital and at the first outpatient visit (the letters are in both toolkits).

Our sample protocols also advise educational efforts by the neonatologist and neonatal nurses. Neonatologists are a vital partner in the decision to use IVAV. Discuss the decision to use IVAV with the infant’s neonatologist to help determine the risk/benefit ratio in the particular child. Document the discussion, and relate it to the parents. Consider asking the neonatologist to be present during the informed consent discussion.

OMIC has also developed a sample consent form in English and Spanish for IVAV for ROP, which is in the hospital toolkit, and at the end of this document. As always, our sample forms need to be reviewed and may need to be revised. The hospital may need to have the form approved by its Forms Committee.

While the consent of the parent is legally required to treat a child, lack of consent may constitute child neglect if the proposed care is needed to prevent significant harm to the minor. Indeed, physicians must take action if there is a reasonable belief that there is child neglect or abuse. The consent form includes a paragraph that states that the surgeon must discuss the refusal with other physicians and Child Protective Services.

# **Managing parents who insist on IVAV**

While IVAV has an imprecise safety profile, it does not ablate the peripheral retina and may allow for better overall vision. Some parents prefer this treatment option. OMIC’s Risk Management Department has fielded calls from ophthalmologists who are uncomfortable with demands made by parents to use IVAV when laser surgery is, in the physician’s judgment, the best treatment. As in any case where the patient, or the patient’s legal representative, wants to engage upon a different course of treatment, clarify the reasons for the preference. Explain your reservations. Enlist the assistance of other members of the patient’s healthcare team, and document all discussions. If after careful discussion and consideration you feel you cannot provide the treatment that is requested, arrange for an ophthalmologist with current competency in ROP to assume care of the infant and provide treatment in the appropriate time interval before withdrawing from care. Conduct and document the transfer of care, and send the parent a letter confirming the end of the physician-patient relationship. OMIC has sample termination of care letters at [www.omic.com](http://www.omic.com).

# **Follow up**

Some studies and presentations have indicated that IVAV changes the natural history of ROP. Significantly, the disease may reoccur months later than expected. As a result, infants who receive IVAV need to be examined for longer periods. The need for longer and additional follow-up may increase the risk for noncompliance with some parents. Consider whether IVAV with laser or IVAV alone is the best choice in the setting of unreliable parents. Carefully monitor appointments and promptly involve Child Protective Services if needed. The office toolkit includes recommendations for tracking of appointments, and sample letters to parents that warn of the possible need to contact the authorities.

**OMIC policyholders have specific obligations if an infant is treated with IVAV:**

* Follow infants closely until at least 65 weeks PMA.
* At 65 weeks PMA, may end screening if either of these endpoints has been reached:
	+ Full vascularization in close proximity to the ora serrata for 360° **OR**
	+ The avascular retina has been successfully treated with laser (e.g., no skip areas).
* Use professional judgment on continued monitoring in the following circumstances if no treatment endpoint has been reached at 65 weeks PMA:
	+ Low-grade disease that is clearly and slowly improving
	+ Stage 1 disease that is unchanged for 2 months
	+ No disease, no ROP, but incomplete vascularization
	+ Infant has a DNR order

# **Keep current and keep a file of resources**

Screening and treatment of ROP is a rapidly evolving discipline. Keep current by reviewing pertinent journals and attending talks. Keep a file containing such articles or notes from talks given at eye society meetings. Consider taking a course that provides advanced training in the diagnosis and treatment of ROP. OMIC has identified such a course, and will pay enrollment fees for insured physicians who provide ROP care. If you are interested, please contact Linda Nakamura at lnakamura@omic.com, or at 800.562-6642, extension 652.

If you have any concerns about the underwriting requirements for ROP, please contact your Underwriting representative. For questions about any other aspect of ROP care, please contact our Risk Management Hotline by calling 800.562-6642, option 4, or via email at riskmanagement@omic.com; the assistance is confidential.

# **Consent for injection to treat ROP (retinopathy of prematurity)**

Your baby has a condition of the retina (the back of the eye) called ROP.When a baby is born prematurely (too early), the retina has not had time to finish forming. After the premature birth, the blood vessels at the back of the eye stop growing. Soon the eye starts to make a chemical called VEGF (vascular endothelial growth factor). This chemical makes the blood vessels start growing again.

But these are not normal blood vessels. These abnormal blood vessels can bleed. They can also pull (detach) the retina away from its normal position. This is called an RD (retinal detachment), and it can cause blindness. This document gives information about the types of treatment. It also explains what happens if the baby does not get treatment for ROP.

**Ophthalmologists (eye surgeons) can treat ROP.**

Ophthalmologists have been treating ROP with laser surgery for many years. This type of laser surgery is called PRP (pan-retinal photocoagulation). The laser stops the eye from making more of the VEGF chemical. The abnormal blood vessels usually stop growing, the retina stays attached, and the central vision is good. Laser works for most babies.

But some babies are too sick to have surgery or anesthesia. In other babies, the abnormal blood vessels are too far back in the eye to use the laser safely. Other parts of the eye or blood in the eye may block the path to the abnormal blood vessels.

Ophthalmologists can inject a medicine in the baby’s eye to treat ROP.This is called an intravitreal injection. The medicine stops the eye from making the VEGF chemical. It is called an anti-VEGF medicine. There are three anti-VEGF medicines. They are called Avastin, Eylea, and Lucentis. The ophthalmologist will talk to you about which medicine will be injected.

**The baby may need more treatment.**

The goal of the injection is to keep the retina attached and save the baby’s vision. Some babies lose vision or go blind even if they have the injection. Sometimes, the abnormal vessels keep growing after the injection. The baby may need another injection or laser surgery to stop the abnormal blood vessels. These abnormal blood vessels can pull the retina off the eye and cause an RD. The baby will need other types of surgery to treat the RD. An ophthalmologist will need to keep examining the baby’s eyes for at least six months after the injection to make sure the ROP is gone. You will need to take the baby to the ophthalmologist’s office for these exams after the baby goes home.

Your baby could have very poor vision or go blind if the ROP is not treated. Your baby cannot choose whether to have treatment. You need to decide if your baby will get treatment for ROP. You have the legal right to choose for your baby. Because you are an adult, you can refuse (say no) to treatment to save your own vision or your own life.

Your ophthalmologist has a legal duty to treat the baby. If you decide not to treat the ROP, your ophthalmologist must talk to other doctors and child protective services about your choice.

**Anti-VEGF medicines have not been approved by the FDA to treat children. This is called off-label use.**

The VEGF chemical causes eye diseases in premature babies and adults. Some anti-VEGF medicines have been approved by the FDA (Food and Drug Administration) to treat eye conditions in adults. Ophthalmologists have given anti-VEGF injections to adults for many years. Ophthalmologists started to treat ROP with anti-VEGF medicine in 2006. Ophthalmologists are still studying how well the medicine works to treat ROP and how much medicine to give babies.

**Doctors do not know if the anti-VEGF medicine injected in the eye harms other parts of the baby’s body.**

The medicine gets out of the eye and into the baby’s bloodstream. It reaches the brain, lungs, and kidneys. The brain, lungs, and kidneys need the VEGF chemical to grow. The medicine may harm the brain, lungs, and kidneys.

* Ophthalmologists and neonatologists (baby doctors) are studying babies who get this medicine to see if they have problems with the development of their brain, lungs, and kidneys.
* Premature babies often have problems with their brains, lungs, and kidneys that are caused by being born too soon. They can be very sick. Sick babies may have more problems after injections.
* It is also hard to know if problems that do show up are caused by being premature or from getting the medicine.
* The ophthalmologist will talk to the neonatologist about whether it is safe for your baby to have this medicine.

**This injection has risks and can cause problems.**

There are risks with all injections and with all medicines. These risks can cause vision loss or blindness. Here are some common or serious ones:

* The injection might not stop the ROP.
* The ROP can come back again. The baby may need another injection or laser surgery to treat the ROP.
* Your baby could lose vision or go blind.
* When ROP is treated with laser surgery, the ophthalmologist knows in a few weeks if the ROP will come back. The ophthalmologist may not know for months or years if the ROP will come back after an injection. The ophthalmologist will have to keep checking the eyes for ROP for a very long time after the injection. The baby may need laser surgery if the retina does not grow completely after the injection
* The injection can cause other eye problems:
	+ An eye infection that could cause blindness
	+ RD (detached retina)
	+ Cataracts (clouding of the eye’s lens)
	+ Glaucoma (high eye pressure)
	+ Hypotony (low eye pressure)
	+ Damage to the retina
	+ Damage to the cornea (clear covering of the front of the eye)
	+ Bleeding in the eye
	+ Bright redness in the white part of the eye
	+ Eye irritation and lots of tears
* Adult patients who had these anti-VEGF injections have had heart attack, stroke, or death. The FDA does not know if the medicine caused these problems.

**Consent**. By signing below, you consent (agree) that:

* You read this informed consent form, or someone read it to you.
* You understand the information in this form.
* The eye surgeon or staff offered you a copy of this form.
* You are aware that the baby may lose vision or go blind.
* You are aware that the baby may need another injection or surgery.
* You are aware that the FDA did not approve this medicine for ROP.
* The eye surgeon or staff answered your questions about the injection for ROP.
* You understand that it is your right to refuse (say no) this treatment for your baby. You also understand that if you do refuse the treatment, the ophthalmologist must ask other doctors or child protective services to talk to you about your decision.
* You agree to the injection.

**I want the ophthalmologist to give my baby an injection for ROP in:**

* **\_\_\_\_\_\_\_ the right eye**
* **\_\_\_\_\_\_\_ the left eye**
* **\_\_\_\_\_\_\_ both eyes.**

Patient (or person authorized to sign for patient) Date

# **Consentimiento para aplicación de la inyección como tratamiento de la ROP (retinopatía de la prematurez)**

Su bebé tiene una condición de la retina (la parte posterior del ojo) conocida como ROP.Cuando nace un bebé prematuro (antes de tiempo), la retina no ha tenido tiempo de acabar de formarse. Después de un nacimiento prematuro, los vasos sanguíneos en la parte posterior del ojo dejan de crecer. Muy pronto, el ojo comienza a producir una sustancia química conocida como VEGF (factor de crecimiento de la vasculatura endotelial). Esta sustancia química hace que los vasos sanguíneos comiencen a crecer de nuevo.

Sin embargo, estos no son vasos sanguíneos normales. Son vasos sanguíneos anormales que pueden sangrar. También pueden halar (desprender) la retina de su posición normal. Esto se conoce como DR (desprendimiento de retina) y puede producir ceguera. Este documento ofrece información acerca de los tipos de tratamiento. Explica también lo que ocurre si el (la) bebé no recibe tratamiento para la ROP.

**Los oftalmólogos (cirujanos de los ojos) pueden tratar la ROP.**

Los oftalmólogos han venido utilizando cirugía con láser para tratar la ROP desde hace muchos años. Este tipo de cirugía con láser se llama PRP (fotocoagulación panretiniana, por su abreviatura en inglés). El láser detiene la producción de la sustancia química VEGF en el ojo. En la mayoría de los casos, los vasos sanguíneos anormales dejan de crecer, la retina permanece adherida y la visión central es buena. El láser es un buen tratamiento para la mayoría de los bebés.

Pero algunos bebés están demasiado enfermos para ser tratados con cirugía o para recibir anestesia. En otros bebés, los vasos sanguíneos anormales están demasiado atrás en el ojo para poder utilizar el láser con seguridad. Es posible que otras partes del ojo o la sangre que puede haber en el ojo bloqueen el paso del láser para alcanzar los vasos sanguíneos anormales.

Los oftalmólogos pueden inyectar un medicamento en el ojo de su bebé para tratar la ROP.Esta técnica se conoce como inyección intravítrea. El medicamento impide que el ojo siga produciendo la sustancia VEGF y se conoce como medicamento anti-VEGF. Hay tres medicamentos anti-VEGF. Se llaman Avastin, Eylea y Lucentis. Los oftalmólogos le explicarán cuál de estos medicamentos se inyectará.

**Su bebé puede necesitar más tratamiento.**

El objetivo de la inyección es mantener la retina adherida y salvar la visión de su bebé. Algunos bebés pierden visión o quedan ciegos aún si reciben la inyección. A veces, los vasos anormales siguen creciendo después de la inyección. El (la) bebé puede requerir otra inyección o una cirugía con láser para detener el desarrollo de los vasos sanguíneos anormales. Estos vasos sanguíneos anormales pueden halar de la retina y separarla del ojo ocasionando lo que se conoce como un DR. El (la) bebé requerirá otros tipos de cirugía para tratar el DR. Un oftalmólogo tendrá que examinar constantemente los ojos de su bebé durante al menos seis meses después de la aplicación de la inyección para asegurarse de que ya no haya ROP. Tendrá que llevar a su bebé al consultorio del oftalmólogo para estos exámenes después de que el (la) bebé haya salido del hospital para su casa.

Su bebé podría terminar con una visión muy baja o quedar totalmente ciego(a) si la ROP no se trata a tiempo. Su bebé no está en capacidad de decidir si quiere o no el tratamiento. Será usted quien decida si su bebé recibe o no el tratamiento para la ROP. Tiene el derecho legal de elegir a nombre de su bebé. Debido a que usted es una persona adulta, puede negarse (puede decir que no) al tratamiento para salvar su propia visión o su propia vida.

Su oftalmólogo tiene el deber legal de tratar a su bebé. Si usted decide no tratar la ROP de su bebé, su oftalmólogo deberá hablar con otros médicos y con los servicios de protección del menor, acerca de su decisión.

**Los medicamentos anti-VEGF no han sido aprobados por la FDA para ser utilizados en el tratamiento de los niños. Esto es lo que se conoce como un “uso no incluido en la etiqueta”.**

La sustancia química del VEGF produce enfermedades oculares en los bebés prematuros y en los adultos. Algunos medicamentos anti-VEGF han sido aprobados por la FDA (Administración de Alimentos y Drogas) para tratar afecciones oculares en adultos. Los oftalmólogos han administrado inyecciones anti-VEGF a adultos durante muchos años. Los oftalmólogos comenzaron a tratar la ROP con medicamento anti-VEGF en el 2006. Los oftalmólogos siguen estudiando qué tan bueno es el resultado del medicamento para tratar la ROP y qué cantidad de medicamento debe administrarse a los bebés.

**Los médicos no saben si el medicamento anti-VEGF inyectado en el ojo pueda dañar otras partes del organismo de su bebé.**

La medicina sale del ojo y entra a la circulación sanguínea de su bebé. Llega al cerebro, a los pulmones y a los riñones. El cerebro, los pulmones y los riñones necesitan la sustancia química del VEGF para crecer. El medicamento puede dañar el cerebro, los pulmones y los riñones.

* Los oftalmólogos y los neonatólogos (doctores de los bebés) están estudiando a los bebés que reciben este medicamento para ver si presentan problemas con el desarrollo de su cerebro, sus pulmones y sus riñones.
* Con frecuencia, los bebés prematuros tienen problemas con su cerebro, sus pulmones y sus riñones que son producidos por el nacimiento prematuro. Pueden estar muy enfermos. Los bebés enfermos pueden tener más problemas después de las inyecciones.
* También es difícil saber si los problemas que puedan presentarse sean causados por ser prematuros o por recibir el medicamento.
* EL oftalmólogo hablará con el neonatólogo para saber si es seguro administrar este medicamento a su bebé.

**Esta inyección tiene riesgos y puede ocasionar problemas.**

Hay riesgos con todas las inyecciones y con todos los medicamentos. Estos riesgos pueden producir pérdida de visión o ceguera. Los siguientes son algunos de los problemas más comunes o más graves:

* La inyección podría no detener el desarrollo de la ROP.
* La ROP puede reaparecer más adelante. Es posible que el (la) bebé requiera otra inyección o una cirugía con láser para tratar la ROP.
* Su bebé podría perder visión o quedar ciego(a).
* Cuando se practica cirugía con láser para tratar la ROP, el oftalmólogo sabrá en unas pocas semanas si la ROP puede reactivarse o no. El oftalmólogo tendrá que seguir controlando y examinando periódicamente los ojos de su bebé para detectar la ROP durante mucho tiempo después de la inyección. El (la) bebé podría necesitar cirugía con láser si la retina no crece completamente después de la inyección.
* La inyección puede producir otros problemas oculares:
	+ Una infección ocular que puede causar ceguera
	+ Un RD (desprendimiento de retina)
	+ Cataratas (opacidad del cristalino)
	+ Glaucoma (alta presión dentro del ojo)
	+ Hipotonía (baja presión dentro del ojo)
	+ Daño a la retina
	+ Daño en la córnea (la superficie transparente que cubre el frente del ojo)
	+ Sangrado dentro del ojo
	+ Enrojecimiento intenso en la parte blanca del ojo
	+ Irritación ocular y abundante lagrimación
* Los pacientes adultos que han recibido estas inyecciones anti-VEGF han presentado infartos cardiacos, accidentes cerebrovasculares o muerte. La FDA no sabe si el medicamento ha sido la causa de estos problemas.

**Consentimiento**. Al firmar en la parte inferior de esta página, usted da su consentimiento y confirma que:

* Ha leído este formulario de consentimiento informado, o que alguien que se lo ha leído a usted.
* Entiende la información de este formulario.
* El cirujano o el personal del hospital le han entregado una copia de este formulario.
* Se da cuenta de que el (la) bebé puede perder visión o quedar ciego(a).
* Se da cuenta de que el (la) bebé puede requerir otra inyección o una cirugía.
* Se da cuenta de que la FDA no aprobó este medicamento para la ROP.
* El cirujano de los ojos o el personal del hospital han respondido a sus preguntas relacionadas con la inyección para la ROP.
* Entiende que tiene derecho a negarse a aceptar (a decir que no a) este tratamiento para su bebé. Además, entiende que si se niega a aceptar el tratamiento, el oftalmólogo deberá pedir a otros médicos o a personas que trabajen con los servicios de protección del menor que hablen con usted acerca de su decisión.
* Acepta la inyección.

**Deseo que el oftalmólogo le administre a mi bebé una inyección para la ROP en:**

* **\_\_\_\_\_\_\_ el ojo derecho**
* **\_\_\_\_\_\_\_ el ojo izquierdo**
* **\_\_\_\_\_\_\_ ambos ojos.**

Paciente (o persona autorizada para firmar por el paciente) Fecha

We welcome questions about the ROP Safety Net as well as suggestions on how to improve it. We can help OMIC policyholders to customize the procedures to their practice and hospitals. Please contact our Risk Management Hotline at 800-562-6642, option 4, or at riskmanagement@omic.com.

1. Fierson WM. “Screening Examination of Premature Infants for Retinopathy of Prematurity.” Policy Statement (PS) issued by the American Academy of Pediatrics (AAP) Section on Ophthalmology, the American Association of Pediatric Ophthalmology and Strabismus (AAPOS), and the American Association of Certified Orthoptists. Originally issued in 1997 and updated in 2001, 2005, 2006, and 2018; current version published in *Pediatrics* (Volume 142, Number 6, 2018, at <http://pediatrics.aappublications.org/content/early/2018/11/21/peds.20183061>. This document refers to recommendations based upon the numbers assigned to them in the PS. [↑](#footnote-ref-1)
2. Food and Drug Administration. Regulatory Information: “Off-Label” and Investigational Use of Marketed Drugs, Biologics, and Medical Devices—Information Sheet,” available at <https://www.fda.gov/regulatoryinformation/guidances/ucm126486.htm>. Accessed 8/17/18. [↑](#footnote-ref-2)