Ophthalmol Ther (2022) 11:15–34
https://doi.org/10.1007/s40123-021-00427-1

COMMENTARY

Intravitreal Corticosteroid Implantation in Diabetic Macular Edema: Updated European Consensus Guidance on Monitoring and Managing Intraocular Pressure

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Received: October 14, 2021 / Accepted: November 8, 2021 / Published online: January 5, 2022

ABSTRACT

Intravitreal therapy for diabetic macular edema can, in susceptible patients, increase intraocular pressure (IOP). As uncontrolled IOP can potentially be sight threatening, monitoring is an essential component of patient management. It can be challenging for retina specialists to ensure that monitoring is rigorous enough to detect and resolve any potential problems at the earliest opportunity without it also being overburdensome for patients who have the lowest risk of developing an IOP rise. We have developed dynamic algorithms that: (1) tailor the frequency and extent of monitoring according to individual susceptibility and current IOP and (2) assist retina specialists in deciding when they should consider a referral to a glaucoma specialist. One algorithm is for patients with a relatively low susceptibility to developing an IOP rise (those whose baseline IOP is < 22 mmHg and who do not have a history of IOP events). Depending on their first post-implantation IOP check, the algorithm classifies

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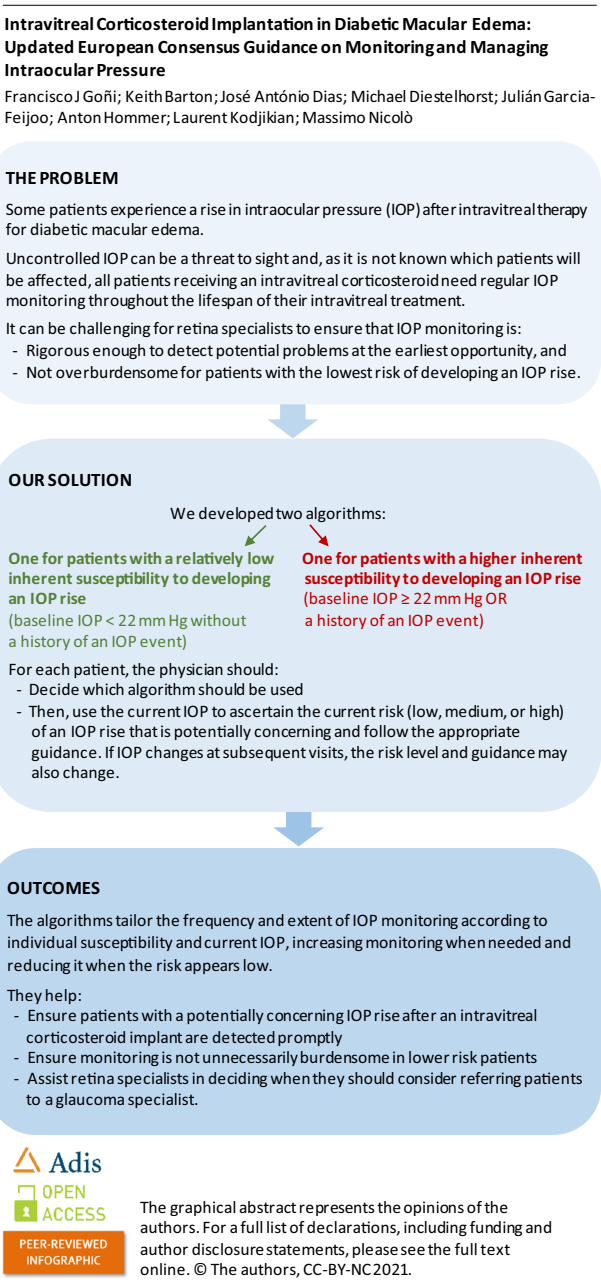
them as: low risk if IOP remains < 22 mmHg; medium risk if IOP is 22–25 mmHg and any rise from baseline is < 10 mmHg; or high risk if IOP is > 25 mmHg or any rise from baseline is ≥ 10 mmHg. Thereafter, the algorithm guides on the frequency and extent of monitoring required in each of these groups and, if IOP rises or falls during treatment, patients may move up or down the risk groups accordingly. A different algorithm is provided for patients who are more susceptible to developing an IOP rise (those with a baseline IOP of ≥ 22 mmHg or a prior history of an IOP event). These patients need monitoring more closely so this algorithm has only medium- or high-risk classifications. These algorithms update the previous monitoring guidance by Goñi et al. (Goñi et al. in Ophthalmol Ther 5:47–61, 2016).

Graphical Abstract:



PLAIN LANGUAGE SUMMARY

Some people with diabetes have macular edema, which is a swelling of the central part of the retina (the tissue that lines the back of the eye). This swelling can threaten eyesight if untreated.

Injecting a drug such as a corticosteroid into the eye can help treat the condition. Sometimes this has a side effect of increasing intraocular pressure (pressure within the eye). A small or short-lived rise in eye pressure should be no cause for concern, but it is very important to ensure the pressure is not too high for too long—because this could lead to the loss of eyesight. To prevent this happening, an eye doctor needs to check the eye pressure regularly.

Some people are more susceptible to this problem—for example, people who have had any problems related to eye pressure in the past or people whose eyes already have a higher than normal pressure even before treatment. People who are most susceptible may need more types of checks and more frequent checks to ensure that any problems are found and treated quickly.

We have developed flowcharts that help eye doctors decide which checks are needed and how often based on what the doctor knows about the person's eye before treatment and what they see at each check-up after treatment. They help doctors make sure that everyone has check-ups at the right time and they help doctors spot any problems early so that they can be resolved before long-lasting damage can occur.

Keywords: Consensus; Corticosteroid; Dexamethasone; Diabetic macular edema; Fluocinolone acetonide; Glaucoma; Implant; Intraocular pressure; Intravitreal; Triamcinolone acetonide

Key Summary Points

The intravitreal administration of treatments for diabetic macular edema can, in susceptible patients, increase intraocular pressure (IOP).

Increased IOP can threaten sight if not detected and treated promptly.

It is not possible to determine before treatment which patients will experience an IOP rise but those with a relatively high baseline IOP, a previous IOP rise, or a history of glaucoma may be more susceptible.

IOP should be monitored in all patients throughout the lifespan of their intravitreal treatment, with closer monitoring in those most at risk.

Algorithms are proposed that tailor the frequency and extent of monitoring depending on individual susceptibility and current IOP, with the aim of ensuring that any potentially problematic IOP rise is detected and treated promptly while allowing a lower level of monitoring in patients with a low risk.

INTRODUCTION

Treating diabetic macular edema (DME) often necessitates the intravitreal administration of anti-VEGF products and/or corticosteroids, either of which can increase intraocular pressure (IOP) in susceptible patients [1–7]. Ocular hypertension is an important risk factor for primary open-angle glaucoma and, if untreated, can lead to optic nerve damage and vision loss [8, 9]. Transient ocular hypertension is not generally considered a problem providing that

the risk for glaucoma development is minimized [10], but early detection and treatment of an IOP rise are critical to ensuring that it remains transient. IOP monitoring is therefore an essential component of patient management after intravitreal therapy.

This commentary focuses on the issue of IOP monitoring after intravitreal administration of corticosteroid implants. Two such implants are approved for use in DME in Europe—a 700 μg dexamethasone implant (Ozurdex®; Allergan Ltd., Marlow, UK) that offers efficacy for up to approximately 6 months [6] and a longer-acting implant that offers continuous daily dosing of fluocinolone acetonide at 0.2 μg/day for up to 3 years (ILUVIEN®; Alimera Sciences Ltd., Aldershot, UK [7]). Some physicians also inject triamcinolone acetonide intravitreally for the treatment of DME. However, such usage is off-label in Europe, and this product is an injectable suspension rather than an implant (so provides a bolus dose rather than the slower release that is possible with an implant).

Corticosteroid-induced rises in IOP may be related to histological changes in the trabecular extracellular lamina increasing the trabecular resistance to the outflow of aqueous humour [11, 12] and possibly also trabecular fouling due to the repeated injection of silicone present in syringes and needles [13]. The development of corticosteroid-induced glaucoma may be related to environmental factors and gene locus interactions [12]. Although it is not possible to determine prior to treatment which patients will experience an IOP rise, several risk factors have been identified. These include: prior ocular hypertension or glaucoma [14–17], especially glaucoma treated with dual or triple therapy [18]; a history of an IOP rise or a prior or current need for IOP-lowering treatment [19–21]; a relatively high baseline IOP [14, 20, 22]; myopia [23]; axial length [24]; type 1 diabetes [18]; age [18, 24]; and Latino and South Asian ethnicity [25]. Furthermore, other factors such as implant positioning can also affect the risk post-implantation [26].

Although intravitreal corticosteroid implants are likely to be initiated by retina specialists, the potential complication of an IOP rise is an area in which glaucoma specialists have particular expertise. As a result, good communication between retina specialists and glaucoma specialists is needed for optimum patient outcomes. Guidance to assist retina specialists on the monitoring and management of IOP after intravitreal corticosteroid treatment of DME was published in 2016 [10]. This was 4 years after the first European license approval for the fluocinolone acetonide implant and at that time clinical data with this implant, and especially real-world clinical experience, were limited. Given the increase in clinical experience accumulated since then and the greater number of publications in the literature about corticosteroid implants—including, importantly, several long-term evaluations and numerous real-world evaluations (Table 1)—it is timely to revisit and update the guidance from 2016.

A group of six glaucoma specialists (FG, KB, JAD, MD, JGF, and AH) and two retina specialists (LK and MN) from across Europe gathered online in January and March 2021 to update the previous consensus guidance for retina specialists. Their recommendations are presented here and are designed to be suitable for implementation across Europe, subject to local adaptations in individual institutions and countries as needed. Key changes from the earlier guidance include:

- Closer monitoring in patients who are most susceptible to developing an IOP rise (i.e., those with a baseline IOP of $\geq$ 22 mmHg or a prior history of an IOP event)
- Closer monitoring in patients whose IOP increases $\geq$ 10 mmHg from baseline
- Greater clarity on the timing of monitoring visits
- Greater flexibility for retina specialists regarding when to initiate IOP-lowering medication and when to refer to a glaucoma

Table 1 Recent data on intraocular pressure (IOP) after intravitreal corticosteroid implantation (from key studies published since the guidance by Goñi et al. in 2016 [10])

Publication	Data type	Eyes (N)	Duration of follow up	Patients or eyes with IOP event (%)										Mean time (± SD) to first IOP-lowering medication (days)	Patients or eyes requiring IOP-lowering treatment (%)					
				Corticosteroid-induced ocular hypertension	IOP increased ≥ 10 mm Hg	≥ 21 mm Hg	> 21 mm Hg	≥ 25 mm Hg	> 25 mm Hg	≥ 30 mm Hg	> 30 mm Hg	≥ 35 mm Hg	> 35 mm Hg		Any treatment	Medication	Trabeculoplasty	Trabeculectomy	IOP-lowering surgery	Surgery or laser
DEXAMETHASONE																				
Maturi et al., 2016 [27]	Pooled data from multinational phase 3 MEAD studies in DME	347 [+350 sham]	≥ 36 months		27.7 [vs 3.7 with sham]			32.0 [vs 4.3 with sham]		15.3 [vs 1.4 with sham)		6.6 [vs 0.9 with sham]				41.5 [vs 9.1 with sham]				1.2
Callanan et al., 2017 [28]	Multicenter open-label randomized, parallel-group study in DME	181	12 months		34.3			36.5		16.6		5.5				39.2	0	0	0.6	
Maldès et al., 2017 [18]	French retrospective chart review in DME (Safodex study)	128	Mean 15.7 months		16.4			11				3				22.7				
Maldès et al., 2017 [29]	French retrospective chart review in DME (Reldex study)	128	Mean 16 months		19			10.2				2.3				21	0	0	0	0
Hemarat et al., 2018 [8]	US chart review in DME	52	≥ 2.2 months						25				8							
Iglicki et al., 2019 [30]	Multinational retrospective real-world study in DME	130	24 months													14.2			0	
Mello Filho et al., 2019 [31]	South American retrospective observational study in DME	329	Not specified		7.4			6.6				1.8							0	
Mathis et al., 2020 [32]	French retrospective evaluation of real-life data in DME	227	Mean 20.1 ± 15.8 months		20.3			14.1				3.1				18	0	0	0	
Rajesh et al., 2020 [33]	Multinational retrospective evaluation of real-life data in DME	1,434	Mean 18.05 ± 14.9 months						25.2 [a]							18	0.07		0.8	
Rosenblatt et al., 2020 [34]	European DME Registry Study (ARTES Study). Retrospective real-world data in DME	340	1.8 ± 0.8 years [b]		15.3			17.6				2.1				14.1				
Zarranz-Ventura et al., 2020 [35]	Spanish real-world evaluation in DME	203	24 months			50 at 12 mths 60 at 24 mths		23 at 12 mths 30 at 24 mths				6 at 12 mths 7 at 24 mths				21.8 at 12 mths 46.2 at 24 mths			0.5	
FLUOCINOLONE ACETONIDE																				
Currie et al., 2017 [36]	UK retrospective analysis of patients with DME comparing eye treated with implant vs fellow eye (ICE-UK study)	208 [+208 fellow eyes]	12 months													3 at months 0–3 [vs 1 in control] 7 at months 3– 6 [vs 1 in control] 11 at months 6– 12 [vs 4 incontrol]			0 at months 0–3 [vs 0 in control] 0 at months 3–6 [vs 1 in control] 1 at months 6– 12 [vs 1 in control]	
Eaton et al., 2019 [21]	US retrospective chart review in DME (USER study)	160	Post-implant mean 408 days [range 7–756] Pre-implant mean 903 days (35–4005]			30.6 [38.1 pre-implant; p=0.195]		15.0 [15.0 pre-implant; p=1.000]		5.0 [5.6 pre-implant; p=1.000]						24.4 [18.1 pre-implant; p=0.219]	1.3 [1.9 pre-implant; p=1.000]	0 [0 pre-implant]	1.3 [1.3 pre-implant; p=1.000]	

Table 1 continued

Chakravarthy et al., 2019 [37]	ILUVIEN Registry Safety Study (IRISS) European multicenter open-label observational study in DME	593	Mean 471 days [range 1–1269]				33.6		19.1		8.3			244 ± 198		23.3 [10.5 had 1 med 5.1 had 2 meds 3.5 had 3 meds 4.2 had > 3 meds]	0.3	1.2	0.8	
Augustin et al., 2020 [38]	German Retro-IDEAL study Real-world data, mainly in DME	94	Mean 30.8 ± 11.3 months		22.2					12.3	7.4				27.2 post-implant				3.7	
Mansour et al., 2021 [39]	US PALADIN study Prospective real-world study in DME in patients without a clinically significant rise in IOP after prior corticosteroid	115	Post-implant 24 months Pre-implant up to 36 months						23.5 [12.1 pre-implant; p=0.007]		7.9 [4.0 pre-implant; p=0.132]					40.0 [9.6 pre-implant; p<0.001]	0.9 [0.0 pre-implant; p=NA]		3.5 [1.7 pre-implant; p=0.414]	
Bailey et al., 2021 [19]	Retrospective audit of UK Medisoft data in DME	256	Mean 4.28 years [3 years minimum]		28.9 [45.7 vs 19.1 with/without prior IOP event; p<0.001] at mean of 439 ± 332 days				33.6 [56.4 vs 20.4 with/without prior IOP event; p<0.001] at mean of 418 ± 324 days		18.0 [35.1 vs 8.0 with/without prior IOP event; p<0.001] at mean of 547 ± 324 days			476 ± 307		29.7 [50 vs 17.9 with/without prior IOP event; p<0.001]	0.8 [2.1 vs 0.0 with/without prior IOP event; p=0.062]		2.7 [5.3 vs 1.2 with/without prior IOP event; p=0.053]	
Fallico et al., 2021 [40]	Meta-analysis of real-world studies in DME[c]	1,283[d]	Mean of 14–36 months													27 (range 7–46)			3 (range 0–9.5)	
Kodjikian et al., 2021 [41]	Systematic review of real-world data in DME[c]	1,880	8.5–36 months	20.1												23.4			0.6	
OVERALL RANGE OF MAIN DATA QUOTED ABOVE				**20.1**	**7.4–34.3**	**30.6–60**	**33.6**	**6.6–36.5**	**19.1–33.6**	**5.0–16.6**	**7.4–18.0**	**1.8–7**	**8**	**244–476**	**27.2**	**3–46.2**	**0–1.3**	**0–1.2**	**0–3.7**	**0–1.2**

± signifies standard deviation

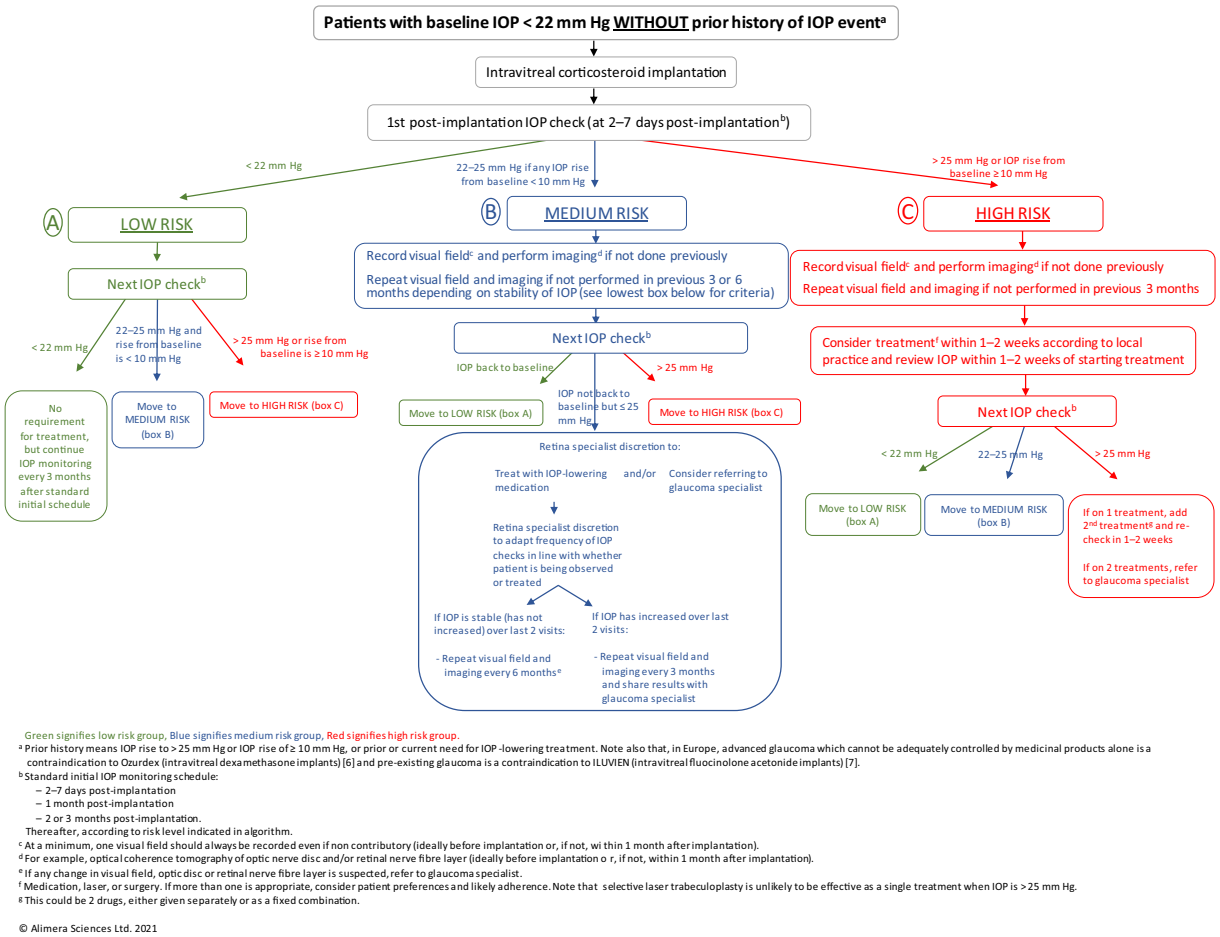
DME diabetic macular edema, *med* medication, *NA* not available, *SD* standard deviation

[a]Calculated from the paper for the subgroup of patients with DME in the same manner as the authors used for the whole series of patients (i.e., 362 of 1,434 (25.2%) patients with DME had an IOP rise; 77/362 had a prior history of glaucoma and 285/362 had a new onset IOP rise). The authors state that "an IOP of > 25 mmHg was considered as significant ocular hypertension" so it has been assumed this definition applies to this calculation

[b]Patients received at least two injections, spaced 3–6 months apart, with the outcome analysed 3–6 months after the last injection

[c]Includes data from some of the studies already in this table

[d]Assumes the total number of eyes at baseline in the real-world studies (1283, as shown in Table 2 of Fallico et al., 2021 [40]) is also the same number of eyes evaluated for IOP drops and glaucoma surgery



Green signifies low risk group, Blue signifies medium risk group, Red signifies high risk group.

[a] Prior history means IOP rise to > 25 mm Hg or IOP rise of ≥ 10 mm Hg, or prior or current need for IOP-lowering treatment. Note also that, in Europe, advanced glaucoma which cannot be adequately controlled by medicinal products alone is a contraindication to Ozurdex (intravitreal dexamethasone implants) [6] and pre-existing glaucoma is a contraindication to ILUVIEN (intravitreal fluocinolone acetonide implants) [7].

[b] Standard initial IOP monitoring schedule:
- 2–7 days post-implantation
- 1 month post-implantation
- 2 or 3 months post-implantation.

Thereafter, according to risk level indicated in algorithm.

[c] At a minimum, one visual field should always be recorded even if non contributory (ideally before implantation or, if not, wi thin 1 month after implantation).

[d] For example, optical coherence tomography of optic nerve disc and/or retinal nerve fibre layer (ideally before implantation o r, if not, within 1 month after implantation).

[e] If any change in visual field, optic disc or retinal nerve fibre layer is suspected, refer to glaucoma specialist.

[f] Medication, laser, or surgery. If more than one is appropriate, consider patient preferences and likely adherence. Note that selective laser trabeculoplasty is unlikely to be effective as a single treatment when IOP is > 25 mm Hg.

[g] This could be 2 drugs, either given separately or as a fixed combination.

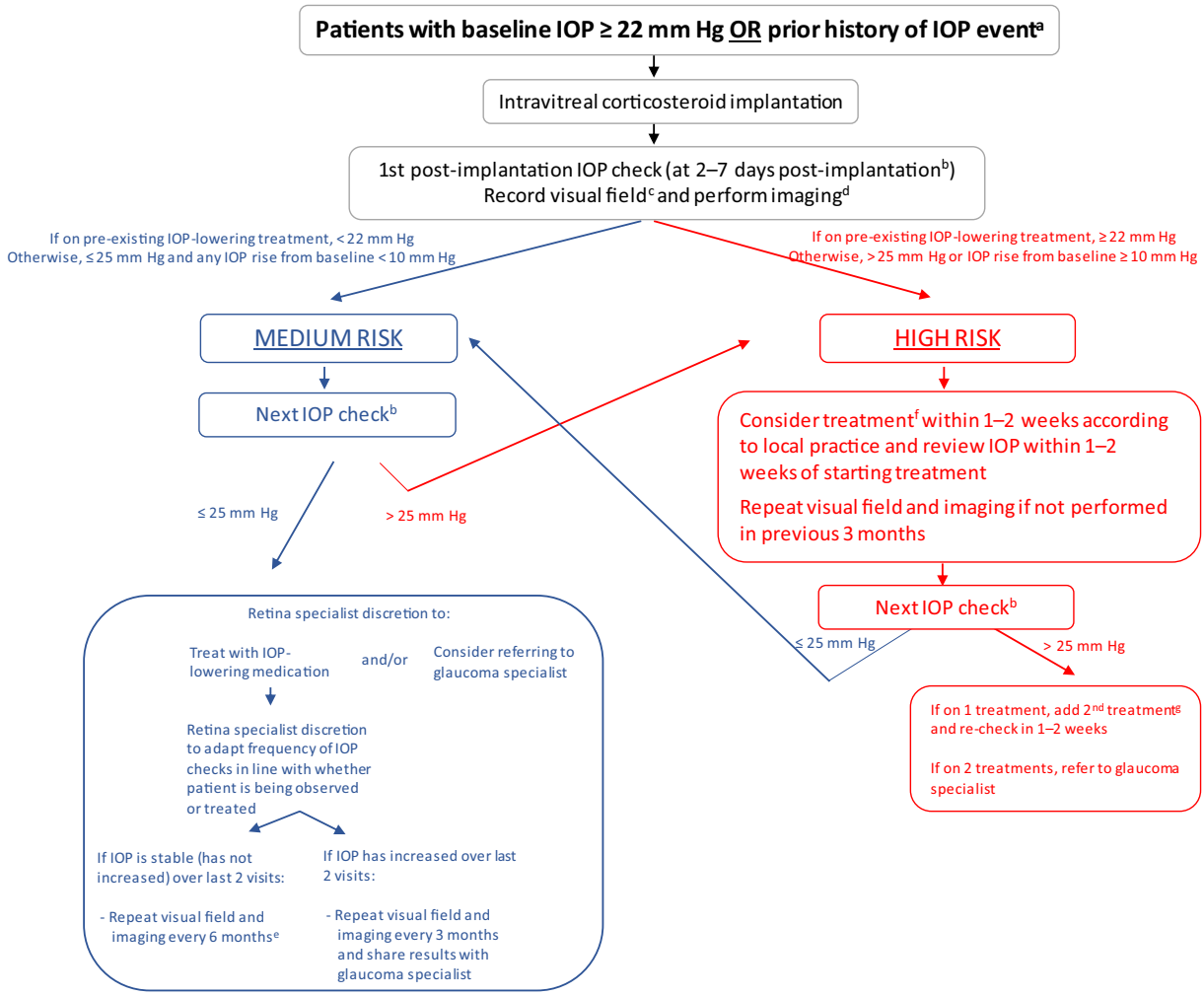
Fig. 1 Algorithm for monitoring and treating patients who are less susceptible to a rise in intraocular pressure (IOP) (i.e., patients with a baseline IOP of < 22 mmHg and no prior history of an IOP event). Guidance depends on whether the latest IOP measurement classifies patients as low risk, medium risk, or high risk for developing a potentially concerning IOP rise

specialist (which helps overcome logistical difficulties where local facilities are lacking)
- Greater clarity on the stepwise introduction of treatments when IOP exceeds 25 mmHg and a de-emphasizing of the potential usefulness of selective laser trabeculoplasty as monotherapy in this scenario
- The incorporation of a dynamic feedback mechanism which means the guidance continually adapts in line with the latest IOP measurement (to ensure it accurately reflects the current risk level throughout what could be a lengthy period of monitoring).

This article is based on previously conducted studies and does not contain any new studies performed by any of the authors.

OVERVIEW OF RECENT KEY DATA

Key data published since the previous guidance in 2016 regarding IOP and IOP-lowering treatment following intravitreal corticosteroid implantation are detailed in Table 1, and an overview of the key findings are summarized in Table 2. Overall, these recent data confirm that intravitreal corticosteroid implantation can be associated with a risk of ocular hypertension in



Blue signifies medium risk group, Red signifies high risk group.

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[e] If any change in visual field, optic disc or retinal nerve fibre layer is suspected, refer to glaucoma specialist.

[f] Medication, laser, or surgery. If more than one is appropriate, consider patient preferences and likely adherence. Note that selective laser trabeculoplasty is unlikely to be effective as a single treatment when IOP is > 25 mm Hg.

[g] This could be 2 drugs, either given separately or as a fixed combination.

Fig. 2 Algorithm for monitoring and treating patients who may be more susceptible to a rise in intraocular pressure (IOP) (i.e., patients with a baseline IOP of ≥ 22 mmHg or a prior history of an IOP event). Guidance depends on whether the latest IOP measurement classifies patients as medium risk or high risk for developing a potentially concerning IOP rise

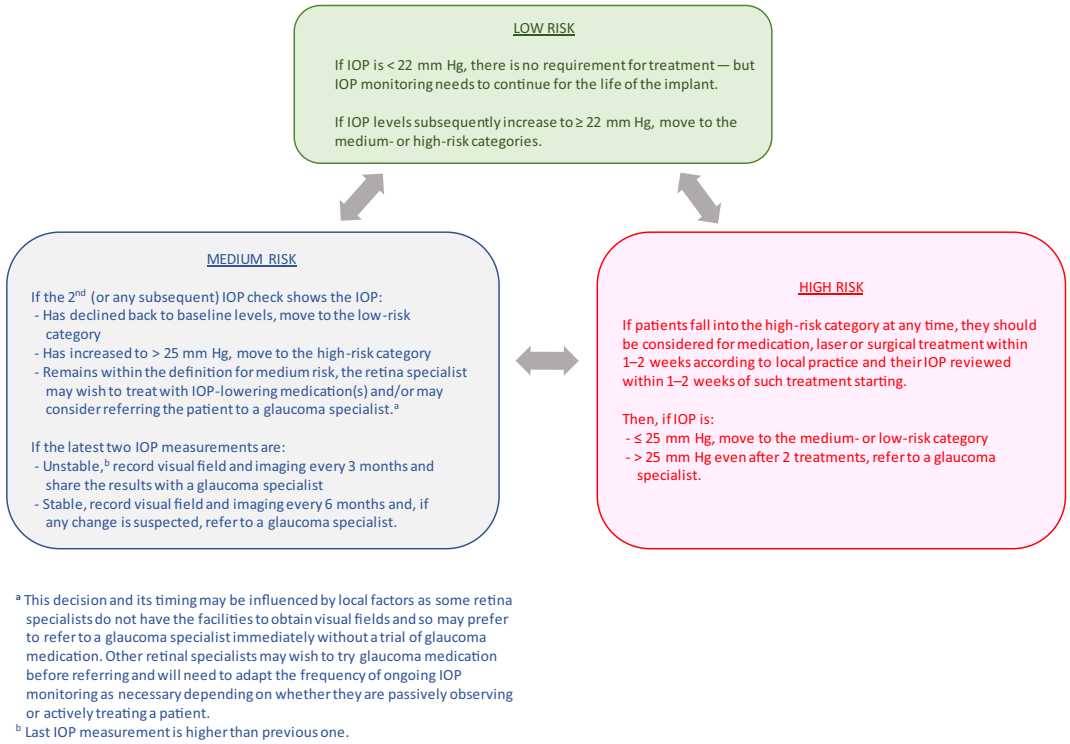

Fig. 3 Clarification of intraocular pressure (IOP) monitoring requirements in the different risk groups depicted in the algorithms of Figs. 1 and 2. Patients may move between the different risk groups at any time during monitoring depending on their latest IOP

some patients, with the risk being greater if patients have had a history of prior IOP events. In addition, the majority of IOP rises are managed with one or two IOP-lowering medications [37] (and so would generally be manageable by retina specialists), with only a small minority of eyes requiring additional medications, laser, or surgery.

PRE-IMPLANTATION CONSIDERATIONS

Patient selection is important for optimal efficacy and safety [39, 41]. From a safety perspective, it is critical to identify which eyes may be most susceptible to developing ocular hypertension so that their suitability for implantation can be considered carefully and their potential need for closer monitoring and additional interventions can be accommodated.

Glaucoma can be a contraindication for intravitreal corticosteroid implantation [6, 7] as it is known to increase the risk of an IOP rise [8, 18]. (In Europe, advanced glaucoma which cannot be adequately controlled by medicinal products alone is a contraindication to intravitreal dexamethasone implantation [6] and pre-existing glaucoma is a contraindication to intravitreal fluocinolone acetonide implantation [7].) Nevertheless, anecdotal reports from glaucoma specialists and the literature [11, 18, 38] show that patients with glaucoma have been successfully treated with intravitreal corticosteroid implants. Such patients could include, for example, those with glaucoma whose IOP is well controlled by medication [42] or stents and those with uveitis and glaucoma who are in great need of corticosteroid treatment and have no suitable alternatives. In such scenarios, the risk-to-benefit equation can be in favour of the need for disease control through the use of intravitreal corticosteroid

Table 2 Summary of key findings from Table 1. Note that the numerous methodological differences between the analyses (especially affecting patient characteristics at baseline, treatment given, and duration of follow-up) preclude cross comparisons

Key findings from evaluations of one or more intravitreal corticosteroid implants	Conclusion
•The incidence of patients with diabetic macular edema (DME) whose intraocular pressure (IOP) increased by $\geq$ 10 mmHg—or whose IOP was $\geq$ 25 mmHg, $\geq$ 30 mmHg, or $\geq$ 35 mmHg—was greater after injection of an intravitreal dexamethasone implant than after a sham injection procedure (a needleless applicator pressed against the conjunctiva) [27]	Implantation of an intravitreal corticosteroid may increase the likelihood of a clinically significant rise in IOP or ocular hypertension
•The incidence of eyes with DME having an IOP > 25 mmHg was significantly greater *after* injection of an intravitreal fluocinolone acetonide implant than *before* implantation [39]	Implantation of an intravitreal corticosteroid may increase the likelihood of ocular hypertension
•During the various follow-up periods after injection of an intravitreal corticosteroid implant, IOP was: 21 mmHg or greater in 31–60% of patients or eyes [21, 35, 37] 25 mmHg or greater in 7–37% of patients or eyes [8, 18, 19, 21, 27–29, 31–35, 37, 39] 30 mmHg or greater in 5–18% of patients or eyes [19, 21, 27, 28, 37–39] 35 mmHg or greater in 2–8% of patients or eyes [8, 18, 27–29, 31, 32, 34, 35] Increased by $\geq$ 10 mmHg in 7–34% of patients or eyes [18, 27–29, 31, 32, 34]	A proportion of eyes may develop clinically significant IOP after implantation of an intravitreal corticosteroid
•Relative to eyes *without* a history of prior IOP events, eyes *with* a history of prior IOP events that received an intravitreal fluocinolone acetonide implant for DME had a significantly higher incidence of [19]: IOP rising by $\geq$ 10 mmHg (45.7% vs 19.1%; $p < 0.001$) IOP > 25 mmHg (56.4% vs 20.4%; $p < 0.001$) IOP > 30 mmHg (35.1% vs 8.0%; $p < 0.001$) Needing IOP-lowering medication (50.0% vs 17.9%; $p < 0.001$)	A history of a prior IOP event significantly ($p < 0.001$) increases the likelihood of an intravitreal corticosteroid implant resulting in: IOP rising by $\geq$ 10 mmHg IOP exceeding 25 mmHg or 30 mmHg IOP-lowering medication being needed

Table 2 continued

Key findings from evaluations of one or more intravitreal corticosteroid implants	Conclusion
•The incidence of patients or eyes with DME reported to receive IOP-lowering treatments after injection of an intravitreal corticosteroid implant was: Up to 46% for medication[a] 0–1.3% for trabeculoplasty[a] 0–1.2% for trabeculectomy 0–3.7% for IOP-lowering surgery[a]	The vast majority of eyes requiring IOP-lowering therapy after intravitreal corticosteroid implantation are managed with glaucoma medication. Only a small minority of eyes are treated with laser or surgery

[a]At least some of these were also required pre-implantation so these data are not necessarily solely attributable to implantation [21, 39]

treatment—although, consequent to this, there will need to be collaboration with a glaucoma specialist to ensure adequate monitoring so that risks are minimized and potential problems are detected and addressed at the earliest opportunity.

Non-glaucomatous patients who may have higher than average susceptibility to a rise in IOP include those with higher IOP at baseline or a history of a prior rise in IOP (including a history of needing IOP-lowering treatment) [19, 21]. It is logical that monitoring may need to be more frequent and/or extensive in these more susceptible patients and, as a result, we advise closer monitoring for patients with a:

- Baseline IOP of $\geq$ 22 mmHg (ocular hypertension according to the European Glaucoma Society [43]).
- History of an IOP rise to > 25 mmHg or an IOP rise of $\geq$ 10 mmHg.
- Prior or current need for IOP-lowering treatment.

We recommend monitoring less susceptible patients (i.e., those *without* these criteria) according to the algorithm in Fig. 1 and those who have greater susceptibility (i.e., those *with* these criteria) according to the modified algorithm in Fig. 2.

POST-IMPLANTATION RECOMMENDATIONS

IOP should be checked within the first week after implantation [7]. Figure 1 shows that the latest IOP reading and the degree of change in IOP from baseline are used to classify whether a patient has a low, medium, or high risk of developing a potentially concerning IOP rise. The algorithm in Fig. 2 omits the lower risk classifications because patients following this algorithm have inherent risk factors that could remain for the lifetime of any implant—so their monitoring needs to retain a consistently higher level of alertness.

Each risk category is associated with different monitoring and/or treatment recommendations in line with the level of surveillance and intervention that is appropriate (Figs. 1, 2, 3). With each subsequent IOP check, the level of risk is re-evaluated based on the latest IOP level. Therefore, if a patient's IOP rises and falls during the post-implantation follow-up, then the patient's risk category may also rise and fall—triggering adaptations to monitoring and/or treatment as necessary. In this way, the algorithms offer a dynamic reflection of a changing clinical situation (Fig. 3).

Both algorithms recommend assessing IOP at 2–7 days after implantation [7], 1 month after implantation, and 2 or 3 months after implantation. Thereafter, the frequency of subsequent

monitoring depends on the risk category (every 3 months in the low-risk category, at the retina specialist's discretion in the medium-risk category, and at the glaucoma specialist's discretion in the high-risk category). The 1-month check has been shown to have value in identifying an increased risk for subsequent ocular hypertension [24] but an increase in IOP can occur at any time during the life of the implant and not only in the weeks and months immediately following implantation. Indeed, with the fluocinolone acetonide implant, it has been reported that the first observation of an IOP > 25 mmHg occurred a mean (± SD) of 418 ± 324 days post-implantation [19]. This wide variability in possible timing underscores the need for regular monitoring throughout the lifespan of the implant. It is similarly important to maintain monitoring throughout the total duration of treatment with repeated dexamethasone implants because, at least in patients with uveitis or retinal vein occlusion, a need for glaucoma surgery has been reported to have arisen after anywhere from one to ten implants—thus, it cannot be assumed that a lack of IOP rise early in treatment precludes the risk of a rise occurring later [8].

Both algorithms show that all patients in the medium- or high-risk groups should have their visual field recorded at least once. This is good clinical practice and important for legal defence reasons, so is valuable even if it is non-contributory.

Imaging of the optic head and/or retinal nerve fibre layer is also advised as soon as a patient is classified as medium or high risk. In the medium-risk group, it should be repeated every 3 months if IOP increases (i.e., is unstable) or every 6 months if IOP has not increased (i.e., is stable). In the high-risk group, it should be monitored every 3 months.

Regarding treatment, in the low-risk group no IOP-lowering treatment is necessary if the IOP remains < 22 mmHg but IOP monitoring should continue at least quarterly for the life of the implant. In the medium-risk group, IOP-lowering treatment may be advised at the discretion of the retina specialist or glaucoma specialist. In the high-risk group, IOP-lowering treatment is usually necessary—initially one treatment and, if this is not sufficiently effective within 1–2 weeks, then two treatments. If these fail to maintain the IOP < 25 mmHg within another 1–2 weeks, the patient should be referred to a glaucoma specialist.

The results of a recent study evaluating referrals to glaucoma specialists from optometric practitioners that were based on IOP alone suggest that limiting referrals to patients who are at least 45 years of age (in addition to having an IOP of at least 25 mmHg) may improve the effectiveness of referrals without missing any patients who have glaucoma or who require IOP-lowering treatment [44]. Currently, we do not know if this might also be the case with referrals from retina specialists.

HYPOTHETICAL PATIENT SCENARIOS ILLUSTRATING THE GUIDELINES IN ACTION

JOHN	
History	No prior history of intravitreal corticosteroid treatment or raised IOP or glaucoma
Baseline IOP	14 mmHg
Pre-implantation assessment	John does not have any of the above-mentioned factors that might make him more susceptible to an IOP rise and so his retina specialist can consider him for an intravitreal corticosteroid implant without needing to consult glaucoma colleagues
Post-implantation monitoring	John is treated with the intravitreal corticosteroid implant. As he does not have any of the key factors increasing his susceptibility to an IOP rise, his monitoring follows the algorithm for less susceptible patients (Fig. 1). His IOP monitoring starts on the standard schedule (i.e., 2–7 days, 1 month, and 2–3 months after implantation and, thereafter, depending on the relevant risk classification) as follows:
7 days post-implantation:	IOP is 19 mmHg, so he is in the low-risk group
1 month post-implantation:	IOP is 24 mmHg and, because this is $\geq$ 10 mmHg higher than his baseline IOP, he moves to the high-risk group. His visual field is recorded, imaging is performed, and he is treated with one topical IOP-lowering medication within 1–2 weeks. He is followed up again 1–2 weeks after starting the medication
1.5 months post-implantation:	IOP is 26 mmHg, so a second topical IOP-lowering medication is added to his treatment
2 months post-implantation:	IOP is still 26 mmHg, so he is referred to a glaucoma specialist

WILLIAM	
History	No prior history of intravitreal corticosteroid treatment or raised IOP or glaucoma
Baseline IOP	21 mmHg
Pre-implantation assessment	William does not have any of the above-mentioned factors that might make him more susceptible to an IOP rise and so his retina specialist can consider him for an intravitreal corticosteroid implant without needing to consult glaucoma colleagues
Post-implantation monitoring	William is treated with an intravitreal fluocinolone acetonide implant. As he does not have any of the key factors that could increase his susceptibility to an IOP rise, his monitoring follows the algorithm for less susceptible patients (Fig. 1). His IOP monitoring starts on the standard schedule (i.e., 2–7 days, 1 month, and 2–3 months after implantation and, thereafter, depending on the relevant risk classification) as follows:

continued

5 days post-implantation:	IOP remains at 21 mmHg, so he remains in the low-risk group
1 month post-implantation:	IOP is 22 mmHg, so he moves to the medium-risk group and has his visual field recorded and imaging performed for the first time
2 months post-implantation:	IOP returns to baseline level of 21 mmHg, so he returns to the low-risk group and his next IOP check will be in 3 months
5 months post-implantation:	IOP is 21 mmHg, so he remains in the low-risk group and continues with IOP checks quarterly
8 months post-implantation:	IOP is 20 mmHg
11 months post-implantation:	IOP is 28 mmHg, so he moves to the high-risk group, is treated within 2 weeks with a single topical IOP-lowering drug and, as he has not had his visual field recorded and imaging performed within the last 3 months, these are repeated. His next IOP check is scheduled for 2 weeks after starting the medication
12 months post-implantation:	IOP is 22 mmHg, so he moves to the medium-risk group and continues the medication. His retina specialist decides to schedule the next IOP check for 4 weeks later
13 months post-implantation:	IOP is 21 mmHg, so has returned to the baseline level. He returns to the low-risk group and continues the medication. His IOP continues to be monitored every 3 months for the 36-month lifespan of the fluocinolone acetonide implant
16 months post-implantation:	IOP is 21 mmHg
19 months post-implantation:	IOP is 21 mmHg. In this low-risk scenario, a washout of the topical medication can be considered to determine whether or not the medication needs to be continued
22 months post-implantation:	IOP is 21 mmHg
25 months post-implantation:	IOP is 21 mmHg
28 months post-implantation:	IOP is 20 mmHg
31 months post-implantation:	IOP is 20 mmHg
34 months post-implantation:	IOP is 21 mmHg

ANN	
History	Ann hates injections but is very motivated to do everything possible to protect her eyesight. She once had an IOP of 28 mmHg a few weeks after a previous intravitreal dexamethasone implant but this was controlled with a single glaucoma medication
Baseline IOP	20 mmHg
Pre-implantation assessment	Because of her prior history of an IOP rise beyond 25 mmHg after intravitreal corticosteroid treatment, Ann is more susceptible than most patients to developing another rise in IOP. As a result, her retina specialist should discuss protocols with the local glaucoma team to help determine Ann's potential suitability for an intravitreal corticosteroid implant. The glaucoma team can also advise on monitoring and a plan of action if she has another rise in IOP
Post-implantation monitoring	Ann receives a fluocinolone acetonide implant because she can only tolerate the thought of a single injection every 3 years and not more frequently. Because of her prior history of an IOP event, her monitoring starts by following the algorithm for more susceptible patients (Fig. 2). Her visual field is recorded and imaging is performed. Her IOP monitoring starts on the standard schedule (i.e., 2–7 days, 1 month, and 2–3 months after implantation and, thereafter, depending on the relevant risk classification) as follows:
5 days post-implantation:	IOP is 20 mmHg, so she is in the medium-risk group
1 month post-implantation:	IOP is 21 mmHg, so she stays in the medium-risk group
3 months post-implantation:	IOP is 27 mmHg, so she moves to the high-risk group and within 1–2 weeks is treated with a single IOP-lowering medication. Her visual field and imaging are repeated and her IOP is scheduled for review within 1–2 weeks of starting treatment
3.5 months post-implantation:	IOP is 25 mmHg, so she moves back to the medium-risk group. Her retina specialist schedules her next IOP check for 4 weeks later
4.5 months post-implantation:	IOP remains at 25 mmHg and her retina specialist adds a second topical IOP-lowering medication to reduce IOP further and schedules another IOP check for 6 weeks later
6 months post-implantation:	IOP is 25 mmHg. Ann continues with the medication and stays in the medium-risk group. Her retina specialist decides to continue monitoring IOP every 2 months. Because IOP has not increased over the last two visits, visual field and imaging only need to be repeated within 6 months of the last check (which was at 3 months post-implantation), so these are scheduled for the next visit
8 months post-implantation:	IOP is 22 mmHg, visual field and imaging are repeated
10 months post-implantation:	IOP is 22 mmHg

continued

	12 months post-implantation	IOP is 21 mmHg
	14 months post-implantation:	IOP is 21 mmHg, visual field and imaging are repeated
	16 months post-implantation:	IOP is 21 mmHg
	18 months post-implantation:	IOP is 21 mmHg
	20 months post-implantation:	IOP is 21 mmHg, visual field and imaging are repeated. Her retina specialist has concerns over a possible change in the retinal nerve fibre layer so refers Ann to a glaucoma specialist

ELSIE		
History	Elsie has no prior exposure to intravitreal corticosteroids but has been on IOP-lowering medication for several months	
Baseline IOP	19 mmHg	
Pre-implantation assessment	Because of her existing need for IOP-lowering medication, Elsie is more susceptible than most patients to experiencing a corticosteroid-induced rise in IOP. Her retina specialist should discuss protocols with the local glaucoma team to help determine the potential suitability of an intravitreal corticosteroid implant. The glaucoma team can also advise on monitoring and a plan of action should a further rise in IOP occur	
Post-implantation monitoring	Elsie receives an intravitreal corticosteroid implant and, because she is already on IOP-lowering treatment, her monitoring starts by following the algorithm for more susceptible patients (Fig. 2). Her visual field is recorded and imaging is performed. Her IOP monitoring starts on the standard schedule (i.e., 2–7 days, 1 month, and 2–3 months after implantation and, thereafter, depending on the relevant risk classification) as follows:	
	7 days post-implantation:	IOP is 19 mmHg, so she is in the medium-risk group
	1 month post-implantation:	IOP is 21 mmHg, so she remains in the medium-risk group. As her IOP values over the last 2 visits have been unstable (i.e., have increased), her visual field and imaging are flagged to be repeated every 3 months and the results are to be shared with a glaucoma specialist
	3 months post-implantation:	IOP is 22 mmHg and, as indicated previously, visual field and imaging results are repeated and the results shared with a glaucoma specialist for advice on ongoing management

ACKNOWLEDGEMENTS

Funding. Alimera Sciences, Ltd. (Aldershot, UK) provided funding for the meetings, the development of this manuscript, and the journal's Rapid Service Fees.

Medical Writing Assistance. Medical writing services were provided by Gill Shears PhD (Write on Target Ltd., Leighton Buzzard, UK).

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. FG facilitated the online meetings, reviewed the first draft manuscript, and approved the final manuscript. KB reviewed the first draft manuscript and approved the final manuscript. JAD reviewed the first draft manuscript and approved the final manuscript. MD reviewed the first draft manuscript and approved the final manuscript. JGF reviewed the first draft manuscript and approved the final manuscript. AH reviewed the first draft manuscript and approved the final manuscript. LK reviewed the first draft manuscript and approved the final manuscript. MN reviewed the first draft manuscript and approved the final manuscript.

Disclosures. All authors received honoraria from Alimera Sciences Ltd. Francisco Goñi also declares that he is/has been a consultant in the last 2 years for Aerie Pharmaceuticals, Allergan-AbbVie, Esteve, Horus Pharma, Omikron, and Thea. Keith Barton also declares that he has been a consultant to Alcon, Allergan, Ivantis, Carl Zeiss Meditec, Santen Pharmaceutical Co. Ltd., Radiance Therapeutics, pH Pharma, Kowa, Glaukos, iStar, EyeD Pharma, Laboratoires Théa, Advanced Ophthalmic Innovations, ELT Sight, Sight Sciences, Alimera Sciences, C-Mer Holdings, and Shifamed/Myra Medical. He has received honoraria from Alcon, Allergan, Laboratoires Théa, Eye Tech Care, Jamjoom Pharma, Santen Pharmaceutical Co. Ltd., and Carl Zeiss Meditec. In addition, he holds a patent with the National University of Singapore and holds stock in Vision Futures Ltd., Vision Medical Events Ltd., Aquesys, MedEther Ophthalmology (Hong Kong) Ltd., and International Glaucoma Surgery Registry Ltd. José António Dias has nothing additional to declare. Michael Diestelhorst also declares that he has utility patents. Julián Garcia-Feijoo also declares that he has been a consultant or advisory board member for Alcon, Allergan, Glaukos Corporation, iSTAR, Alimera, and Santen, Inc. He has received honoraria from Alcon, Allergan, iSTAR, Thea, and Santen, Inc. and has performed research for Alcon, Allergan, Glaukos Corporation, iSTAR, Ivantis, Inc., AJL Ophthalmic, Santen Inc., ZEISS, Heidelberg, Johnson & Johnson, Bausch & Lomb, Thea, and Pfizer. Anton Hommer also declares that he has been a speaker for Aerie, Allergan, Nidek, Santen, and Thea. Laurent Kodjikian also declares financial associations with AbbVie-Allergan, Bayer, Horus, Roche, Thea, and Novartis. Massimo Nicolò also declares that he is/has been a consultant in the last 2 years for Alimera, Allergan, Bayer, Novartis, and Roche.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. All data analysed during this study are included in this published article.

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