Template for comments and observations

Date: 2/12/18	Document: **Z80 Glaucoma**	Project: Z80.27

Initials	Line number	Clause/ Subclause	Paragraph/ Figure/ Table/	Type of comment[1]	Comments	Proposed change	Observations of the leader
GC	Pg 1	2	Paragraph 8,9	ed	ISO 14155 has been updated to 2011	"ISO 14155-1:2011, …" "ISO 14155-2:2011, …"	
MLG			various	ge, ed	Looks like everywhere there is a "NOTE" statement throughout the document, the font size of the note may be smaller than the font size of the body text	Check consistency in font sizes and increase to size of body text	
GC	Pg 2	3	Paragraph	ge	The definitions here could be updated to include "MIGS", and also the term, "stent", etc	Refer to the definition in the FDA MIGS guidance	
FDA		3 Definitions		ge	A definition is included in the MIGS Guidance: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM433165.pdf	Include definition for MIGS: A type of IOP lowering device used to lower IOP using an outflow mechanism with either an *ab interno* or *ab externo approach*, associated with little or no scleral dissection and minimal or no conjunctival manipulation.	
BJS		Physical and Mechanical Reqs	Page 3	Addition?	Not sure if this is the right section for this (perhaps Annex H instead?), but I believe that a short statement about MRI safety labelling for metallic implants, such as the majority of ab interno stents would be reasonable given the increased rates of patients receiving metallic stents currently.	Some sort of statement similar to that published on the Glaukos website: http://www.glaukos.com/dfu-mri-information/ Maybe this information should be required on the patient information cards that patients receive after surgery/implantation so they can present it if a MRI is ever needed in the future. This may be more appropriate for Annex H?	
AR		3.2		te	this definition of a bleb is incorrect as in a trabeculectomy a bleb does not have a fibrous capsule unless it is not functioning and encapsulated.		PL editorial: how do we need to distinguish encapsulated non-functioning device? Technically there will always be some fibrin around any externa device. Substitute "tissue" instead of "fibrin" for general case here? (cbt)
AR		3.3		ed	Drainage tube	"… device between the intra ocular…"	
AR		3.6		te		inserted within the eye or upon the eye	

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AR		3.8		te	Aqueous flow rates incorrect	where did this come from . Brubaker's 1.4 microliter/min to 2.6 ml/min	
FDA		4.2 General guidelines	2nd paragraph	ed	Biocompatibility of the device depends not only on the material but also on the manufacturing process. In addition, although the material has been used in prior ocular implants with same contact duration, it may be difficult to demonstrate that the same material, from the same supplier has been used. This is important because materials obtained from different supplier may have different specifications, different and/or novel impurities which ultimately may impact the performance and biocompatibility of the device. Consistence with FDA guidance "Use of international standard ISO 10993-1, Biological evaluation of medical devices- Part 1: Evaluation and testing within a risk management process." (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm348890.pdf)	Deletion of "The specific device and the historical use of the material in similar ophthalmic implants should be taken into consideration in determining if all of the preclinical requirements included in this standard are appropriate for a particular device."	
FDA		4.2 General guidelines	4th paragraph	ed	Same as above.	Revision of "…the material used in the tests may be a sample of the material fabricated and processed in a manner equivalent to that used for the implantable glaucoma device. The manufacturer shall establish and document equivalency in material and in test sensitivity, where appropriate, for the test sample and the sterile finished aqueous shunt." Proposed language: *…the material used in the tests may be a sample that is manufactured of the same materials using the same manufacturing procedures as the finished sterile*	

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						glaucoma device. The manufacturer should provide a discussion of why any differences between the test sample and the finished sterile device is acceptable and would not necessitate additional testing on the finished device.	
FDA		5.1 Scope		ge	For clarity.	Revise scope to include both aqueous shunts and MIGS	
FDA		5.2 Surface Quality		te	Surface imperfections not seen with the eye can potentially cause damage to tissue via abrasion. MIGS devices are often microscopic and should be inspected under appropriate magnification.	Remove “visible to a trained observer without magnification”; include recommended minimum magnification with caveat to use higher magnification as necessary	
FDA		5.3 Edge Quality		te	Edge imperfections not seen with the eye can potentially cause damage to tissue via abrasion. MIGS devices are often microscopic and should be inspected under appropriate magnification.	Include caveat to use higher magnification as necessary	
VR	Pg 4	5.5	Paragraph 1	te	Dimensional stability of the implant immersed in the BSS for 14 days. Is it necessary to define a longer test duration?	Define longer test duration as part of hydrolytic stability to demonstrate physical stability after the permanent implant	
AR		5.5		ed	stability	Add "as required by its specifications"	
VR	Pg 4	5.6	Paragraph 1	te	On certain devices the relationship between flow rate and pressure drop becomes non-linear at higher flow rates (1000 to 4000 µL/Min). Therefore, assumed linear relationship between pressure drop and flow rate is not applicable by using this method, especially when extrapolating to physiological flow rate.	Only require constant flow test method for certain devices. Make the gravity flow test optional or remove it.	
FDA		5.6 Pressure/ flow characteristics		te	Update to distinguish aqueous shunts from MIGS. Clarify applicability of Annex A.	Revise last sentence to state: “Annex A describes examples of test methods for determining the theoretical flow characteristics of *aqueous shunts*.” Clarify that the methods described in Annex A are applicable for constant	

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						uniform flow (i.e., shunts with straight tube of uniform diameter). Devices of more complex design (with bends, tapered tubes, etc.) are more complex and the Hagen-Poiseuille Equation would not provide an accurate estimation of the pressure/flow characterization. Include reference to NEW annex for pressure/ flow characterization using computational modelling.	
FDA		5.7 Structural integrity		ed	Update to clarify testing expectations for devices with no junctions.	Modify to include statement: "*Manufacturer should provide evidence that the device can withstand surgical manipulations without failure.*"	
GC	Pg 4	5.7	Paragraph 1	te	This requirement does not work with single-piece implantable glaucoma devices. Should there be a different requirement for these types of designs?	Define criteria/requirement to test for the structural integrity after performing hydrolytic stability.	
MLG			5.7	ed	Structural Integrity section defines force requirements (eg, 0.5 N). N is not defined either at first use or in section 3	Define N	
FDA		6.2 General guidelines	1st paragraph	ed	Same as 4.2 above.	Revision of "…facsimile materials fabricated and processed in a manner equivalent to that used for the devices. The manufacturer shall establish and document equivalency in material and in test sensitivity, where appropriate, for the test sample and the sterile finished glaucoma device." Proposed language: *…facsimile materials manufactured of the same materials using the same manufacturing procedures as the finished sterile devices. The manufacturer should provide a discussion of why any differences between the test sample and the finished sterile device is acceptable and would not necessitate additional testing on the finished device.*	

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FDA		6.2 General guidelines	4th paragraph	ed	The proposed language clarifies that the material and manufacturing procedures should be the same as a marketed device that has the same contact and same duration with the patient.	Revision of "Some of the requirements may be waived if there is documented evidence that the glaucoma device material is identical to that used in another implantable device of an identical or equivalent application and which has been widely marketed for at least the last five years." Proposed language: *Some of the biocompatibility tests may not be needed if there is documented evidence that the glaucoma device material and manufacturing procedures are identical to those used in another implantable ophthalmic device with same type and contact duration with the patient which has been widely marketed in the US.*	
MLG			6.3.1	te	Section states that in tests that are conducted on material extracts, testing "shall be conducted with two different extractants", one of which is aqueous and the other is lipophilic or dipolar. It might be preferable to allow for flexibility to test more than two different extractants if desired.	Revise "shall be conducted with two different extractants" to "shall be conducted with *at least* two different extractants" to provide flexibility	
MLG			6.3.3	te, ed	Section requires demonstration of lack of genotoxicity. The note says: "Carcinogenicity testing can be considered to demonstrate biocompatibility if genotoxicity testing has demonstrated a genotoxic potential in the test material". From the context, it seems this is saying that you could choose to use carcinogenicity testing as a further test if your initial genotoxicity testing was suggestive of toxicity. But as written with "can be considered to demonstrate" it is unclear, because sometimes "considered" may mean "understood" and the statement could potentially be misunderstood as being contradictory to the main statement.	Consider revising note to clearer language. Eg, "if genotoxicity testing has demonstrated a genotoxic potential in the test material, consider using additional carcinogenicity testing to demonstrate biocompatibility". Or similar.	

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MLG			6.3.7	ed	As written, the text suggests that a device may be coated to evaluate the presence of any material-mediated pyrogen.	Recommend rewording the first sentence to "To evaluate the presence of any material-mediated pyrogen, the rabbit pyrogen test shall be performed… if the device is fabricated from a new material or if the device is coated."	
FDA		6.4 Physiochemical test requirements		te	Aligns with other ophthalmic standards.	Add evaluation for insoluble inorganics.	
FDA		6.4.1 Extractables by exhaustive extraction		te	Aligns with other ophthalmic standards.	Include determination of changes in mass and risk analysis justifying any changes in mass.	
FDA		6.4.3 Hydrolysis testing		te	Aligns with other ophthalmic standards.	Include qualitative and quantitative evaluation of exposure medium for any chemical entities at end of exposure.	
FDA		6.4.3 Hydrolysis testing		te	Aligns with other ophthalmic standards.	Modify last sentence to state: "The significance of any change to the physical and material properties of the device…"	
VR		6.4.3	Paragraph 1	te	No criteria to determine the structural integrity of the device after the hydrolytic stability. Define duration for the long term study beyond 5 years for permanent non degradable implants implanted in younger patients	Define duration criteria for the long term permanent implant beyond 5 years May apply similar criteria in ISO11979-5 for IOL device	
FDA		7.3 Validation of sterilization methods		ge	ISO 11134 is out of date and replaced by 17665	Update ISO 11134 to ISO 17665	
FDA		7.4 Ethylene oxide sterilant residues		te	The notice in which residuals were expressed in units of ppm was withdrawn in 2004; ISO 10993-7 recommends units of µg/device.	Update residual limits, to 1.25 µg/device for EO and 5.0 µg/device for ECH.	
FDA		7.5 Bacterial endotoxin		te	Recommendations regarding endotoxins for glaucoma devices are updated in FDA guidance, Endotoxin Testing Recommendations for Single-Use Intraocular	Reference the FDA guidance for single use ophthalmic devices.	

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					Ophthalmic Devices (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm393376.pdf).		
FDA		8 Shelf-life and transport stability requirements		ge	Currently only includes evaluation of package integrity. Evaluation of product for product stability should also be included for demonstration that following exposure to shipping and shelf-life, the device is free from damage.	Add specific clauses regarding device stability (i.e., testing the device itself for dimensions, surface quality, edge quality, pressure/flow characterization, insertion testing, coating stability, etc.) following exposure to shipping conditions and shelf-life.	
FDA		9 Additional requirements		te		Add section for metallic devices to include evaluation for MRI safety [FDA guidance, Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm107708.pdf)] and corrosion resistance (ASTM F2129 standard exists).	
FDA		9.1 Insertion Method		te	Mitigates risks associated with the injector damaging the surface/edge of the device, which can cause rough surfaces/edges that can damage tissue. Compromises in dimensions can compromise flow.	Currently it only says that the structural integrity shall be evaluated after simulated implantation. Revise to add surface quality, edge quality, dimensions and coating (if applicable…or include in 9.2 as recommended below).	
FDA		9.2 Surface Coating		te	Both devices and inserters can have coatings, and contact between the device/inserter (if any) can compromise the coating due to shear stresses. Coating that flakes off can result in a biological response or if large particles are found, a physical response can occur (i.e., elevated IOP).	Add "If the device is to be inserted with an inserter, then device and/or inserter coating stability should be assessed to demonstrate that the coating surface is not compromised. If the coating is compromised, then a risk analysis should be performed to justify the coating transfer into the eye."	
AR		10.2	2nd para	ed	Query on device utilization	should this be potential uses?	We can't specify clinical applications in ANSI standard
AR		10.2	3rd para	ed	poorly worded		Is this sentence necessary?
AR		10.2	6th para,	ed	Add "the" before "continuation"	acceptable prior to **the** continuation of the	

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			3rd line				
MLG			10.2	te	The 4th paragraph states: "the clinical protocol shall describe how subject visits in between reporting periods will be handled in the data analyses (eg, and interim report form will be used and the data reported separately". Is this referring to unscheduled visits (not predefined in the schedule of visits and procedures for the study)?	If yes, might be worthwhile to say, "how *unscheduled* subject visits in between reporting periods…"	
MLG			10.2	te, ge	Page 9, second paragraph. Requires that for a new device with a nonrefractory indication, enrolment shall occur in stages to minimize risk, and that enrolment will stop for data to be evaluated before the study enrolment can continue. Several years out from the last version of this document, we have seen many examples that the MIGS devices are generally safe and well tolerated. Is it still necessary to be this strict about this for MIGS studies?	If the interim data review must be done for MIGS, consider devising a way that a sponsor can continue to enrol while data review is underway. Eg, perhaps allow enrolment to continue at a reduced rate, so that study operations and progress do not have to stop and lose time, or interest of eligible patients and investigative sites. And/or, consider allowing the sponsor to use an external data review committee (firewalled from the study team) to review data and report recommendations to FDA on a rolling basis while full volume enrolment is allowed to continue. Etc.	
AR		11	7th bullet	ed	Add "a summary of"…..	A summary of clinical results…..	
BJS		Annex A	Page 10	Revision / Question	I wonder if "gravity flow testing" as described in Annex A applies for ab interno stents, such as the iStent and Cypass?	No change if these tests can be reasonably performed on stents of this size.	
BJS		Annex A	Page 11 and 12	Revision / Question	As above, does the "constant flow test" apply to ab interno stents? If such stents can be reasonably cannulated to test the above "gravity flow test" and "constant flow test" then I think it is reasonable to do so. Otherwise, it may be prudent to consider a different form of testing for these devices?	As above.	
MLG			B.2	te	Might there be ocular structural/anatomical considerations that would lead to the preference of one animal model over another?	Should ocular anatomy/structural compatibility requirement be added to the list?	
FDA		B.4 Test		ge	Same as 4.2 above.	Revision of "…the material used in the	

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		material				tests may be a sample of the material fabricated and processed in a manner equivalent to that used for the implantable glaucoma device. The manufacturer should establish and document equivalency in material and in test sensitivity, where appropriate, for the test sample and the sterile finished glaucoma device." Proposed language: *…the material used in the tests may be a sample that is manufactured of the same materials using the same manufacturing procedures as the finished sterile glaucoma device. The manufacturer should provide a discussion of why any differences between the test sample and the finished sterile device is acceptable and would not necessitate additional testing on the finished glaucoma device.*	
AR		B.5	3rd bullet	ed	Specify lenses used for indirect exam	Add "with appropriate lenses"	
AR		B.5	9th bullet	ed	Spelling of "anesthetic"		
GC, FZ, JH, TL	Pg 17	Annex C.1	Paragraph 1,2	te	The recent approval of the Xen device for refractory indication was based on the study that included a number of patients who had failed laser trabeculoplasty. Suggest align the definition for refractory glaucoma with recent FDA approved refractory indication, refer to XEN IFU below: The XEN Glaucoma Treatment System is indicated for the management of refractory glaucomas, including cases where previous surgical treatment has failed, cases of primary open angle glaucoma, and pseudoexfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy.	Recommend reconsideration of definition for what is "refractory" glaucoma. Recommend adding a criteria to include patients who failed laser trabeculoplasty (especially for devices functioning through non-TM pathway)	
FDA		C.1	Paragraph 1	Editorial	In 2018, there is a plethora of glaucoma surgeries to choose from. Failure of a minimally invasive procedure (i.e.,	Failed one or more conventional incisional intraocular glaucoma surgeries (e.g., glaucoma filtering surgery or tube	

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					Trabectome, iStent) that is conjunctiva-sparing does not seem to significantly limit surgical options and categorize a patient as refractory. Furthermore, the term “conventional” is consistent with the related regulation: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=886.3920	shunt);	
AR		C.1	Line 3	te	Inclusion of glaucoma types	Can we add "inflammatory glaucoma" along with neovascular?	
JH	Pg 17	Annex C.3	Paragraph 1	te	Is “5-year” a necessary requirement? Clinical studies are only recommended to follow up for 1-2 years.		
GC	Pg 17	Annex C.3	Paragraph 2	te	Should minimum be based on Sponsor's assessment of # of surgeries required to demonstrate proficiency?		
GC, JH	Pg 18	Annext C.3	Paragraph 2	te	Does this 10% only include LTFU patients or also include patients discontinue or miss at scheduled visit but seen Later	"to allow for 10% of subjects being lost over the course of the study..."	
GC	Pg 18	Annext C.3	Paragraph 4	te		Add “Considerations for evaluation of device position and steps to take if position is less than optimal.”	
FDA		C.3	Paragraph 4	Technical	To account for adjunctive drugs like Mitosol.	Specification of auxiliary surgical devices and/or on-label drugs to be used;	
MLG			C.3	te	Paragraph 1 states that expert help with study design and statistical analysis is essential. “expert” could be seen as vague without an example. Do we have a kind of expert in mind, eg a regulatory consultant, clinician in the field, etc.	Consider an eg.	
MLG			C.3	te	Page 18, states that the surgical procedure needs to be clearly delineated, with bulleted list of detailed instructions for several things. Patient preparation is not listed, only device preparation. Also, measures for	Consider adding to the list	

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					troubleshooting intraoperative complications unique to the device or implantation process is not listed.		
FDA		C.3	n/a	General	Consider developing performance goals for safety and effectiveness for "refractory" glaucoma indications	To improve consistency of study design for similar devices/indications for use and better define expectations for minimum acceptable clinical performance	
FDA		C.4	Paragraph 1	Technical	Potential subjects are more likely to read the ICD than protocol.	The investigational protocol and informed consent document should inform subjects and investigators that long-term follow-up (e.g., up to 60 months) may be necessary to evaluate the effect of the implantable glaucoma device on the eye adequately.	
AR		C.5	3rd para		Safety and efficacy The authors can claim safety or efficacy WithOUT at least 300 patients.		
FDA		C.5	Paragraph 1	Editorial	For adequate subject accountability.	Subjects should be considered enrolled upon signing informed consent.	
MLG			C.6.2	te	"eyes with NLP vision" are excluded. A sponsor wouldn't be able to follow vision changes in these eyes. But given that these eyes are at no risk for losing vision from complications of the device or implantation procedure, yet may still be in need of substantial IOP lowering to manage the disease, it might be reasonable to be flexible on NLP vision in the study eye only, as long as fellow eye meets the vision requirements listed.	Consider allowing a certain proportion of patients enrolled into refractory studies to have NLP vision in the study eye (only).	
AR		C.6.2	Para 5	te	Add OCT for evaluation of AC size?	determined by slit lamp examination and gonioscopy (and OCT)	
FDA		Annex C/D	n/a	General	Consider whether it is possible to better align criteria with current clinical standard of care for staging disease	Consider revising enrollment criteria to incorporate American Glaucoma Society (AGS) Glaucoma Stage Definitions, i.e., "refractory" for consistency with "Moderate Stage" to "Advanced, Late, Severe Stage" and "non-refractory" for consistency with "Mild or Early Stage" to "Moderate Stage" Glaucoma	

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						http://www.americanglaucomasociety.net/client_data/files/2015/433_15289.codingcheetsheet.lowres2.pdf	
MLG			Annex D	ge	Section G.3.1 refers to studies done in conjunction with cataract surgery regarding BCVA loss safety reporting. Annex D and the FDA Guidance document on MIGS studies both do not appear to explicitly state that nonrefractory MIGS studies must be done in patients undergoing cataract surgery. However, as I understand it all (most?) non-refractory MIGS studies so far have been expected by the agency to be done in patients undergoing concurrent cataract surgery (please correct me if I am mistaken?). Cataract surgery has an effect on IOP that can have an extended duration, thus implantation in the setting of cataract surgery is not “clean” IOP-lowering data. Also, comparing that to cataract surgery without device may not show much differentiation if the comparator cataract surgery effect is very robust and long-lived. It makes sense from a safety perspective to do it with cataract surgery because the eye is being opened anyway, and the lens is being removed. But from a study perspective, it limits what the sponsor can compare the MIGs device to. Given that we have several more years’ worth of experience with various MIGS now, we should consider whether we can/should clearly state that a nonrefractory MIGS study implantation could be done as stand-alone procedure. And consider the requirements in which we would recommend doing it.	Recommend adding clear language to Annex D confirming that a non-refractory MIGS procedure that is expected to be low-risk could be done as a stand-alone implantation, to increase flexibility in designing MIGS studies and “cleanliness” of data. Discuss patient and study design parameters in which it would be acceptable. Eg, -pseudophakes only? - Studies in which the hard stop for interim data review as described in section 10.2 will be a strict requirement? - Data review committee required? - Only parallel group studies and no paired eye comparisons? - More strict requirements in non-study eye? - different/more robust risk analysis or monitoring? - Etc.	
AR		Table C.1			Diurnal IOP assessment	must be defined as to the minimal for variation perhaps four times at 8, 10, 2 and 4/?	

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AR		Table C.1			Slit lamp exam	How, LOCS grading?	
FDA		Table C.1	n/a	Technical	The latter was recommended by George Spaeth at the FDA-AGS MIGS Workshop. Dependent on device design, intended implantation site, and/or risk analysis. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm391542.pdf	Operative visit could include gonioscopy, post-op IOP check as needed. Add adverse event assessment for each visit.	
FDA		Table D.2	n/a	Technical	Same as Table C.1.	Operative visit could include gonioscopy, post-op IOP check as needed. Add adverse event assessment for each visit.	
AR		D.2	First para	te	safety and effectiveness needs to be in terms of the following: Ophthalmology 2003; 110 (11)2073-2074		
AR		D.3	10th para		should the protocol be based on some studies such as OHTS		
GC	Pg 21	Annex D.3	Paragraph 2	ge	This session should be updated to take into consideration the approvals of certain non-refractory devices; e.g., how can previous PMA data be leveraged for new studies of same device/different indication?		
GC	Pg 22	Annex D.3	Paragraph 6	te		Add “Considerations for evaluation of device position and steps to take if position is less than optimal.”	
CH, GC	Pg 22	Annex D.3	Paragraph 6	ed	This is the one place in the guidance where 10% lost to follow up PER YEAR is allowed. In other sections of the guidance, 10% LTFU OVERALL is permitted (e.g. Annex G.2).	Clarify if LTFU should be less than 10% overall or per year throughout the guidance. Change the requirement on Page 18 (Paragraph 2) to "... to allow for 10% of subjects being lost over the course of the study..."	
MLG			D.3	te	Same comment as for C.3, page 22 bulleted list regarding list of required instructions to	Consider adding to the list	

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					the surgeon. Patient preparation is not listed, only device preparation. Also, measures for troubleshooting intraoperative complications unique to the device or implantation process is not listed.		
AR		D.4			Long term followup-- this raises the issues of age and general health and the ability to return for repeated follow up visits		
FDA		D.4	Paragraph 1	Technical	Same as C.4	The investigational protocol and informed consent document should inform subjects and investigators that long-term follow-up (e.g., up to 60 months) may be necessary to evaluate the effect of the implantable glaucoma device on the eye adequately.	
MLG			D.5	te	The enrolment section recommends sample size calculation should account for dropout of patients for screen failing and exiting the study prior to treatment in order to have a sufficient number of patients for primary endpoint analysis. It does not address accounting for study dropout after treatment is administered. In a sample size calculation, it would make sense to calculate the number needed to receive treatment in order to reach X number of patients completed, assuming a dropout rate of Y%. You could also calculate the number needed to screen to reach that X enrolled, assuming a screen fail rate of Y%. But it seems incomplete to focus only on screen fails and not on dropout rate once actually treated in the study.	Consider revising the text to address dropouts across the study period, not just screen fails that don't make it to treatment.	
FDA		D.5	Paragraph 1	Technical	Same as D.5	Subjects should be considered enrolled upon signing informed consent.	
MLG			D.6	te	Hexagonality (% of cells that are hexagonal) is often also collected along with CV	Do we need to consider adding hexagonality to the list?	

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MLG			D.6.1	ed	Second bulleted list of items that should be specified in the protocol- first bullet, “the criteria for confirming a diagnosis if glaucoma” is indented after the bullet and the rest are not	Recommend correct formatting error	
GC	Pg 23	Annex D.6.1	Paragraph 2	te	CV<=0.45 needs a reference		
JH	Pg 23	Annex D.6.1	Paragraph 3	ed	Extra indentation for the first bullet point	Adjust the indent	
JH	Pg 23	Annex D.6.1	Paragraph 3	te	VF criteria is also needed for study eye to define disease severity (non-refractory)	May refer to the criteria in the FDA MIGS guidance	
JH	Pg 24	Annex D.6.2	Paragraph 2	ed	Extra indentation for the last two bullet points; non-study eye criteria should be separated	Adjust the indent	
MLG			D.6.2	ed	List of exclusion criteria. Why are “conditions that meet the definition of refractory glaucoma” and “subjects with BCVA worse than 20/80 in NSE” both listed as sub bullets of “known corticosteroid responder”?	Recommend correct typo	
AR		D.6.2		te	Complex cataract surgery definition- specify-	needs to be better defined as iris stretch, or using dye are CMS defined complicated cataract surgery.	Do we mean vitreous loss or any technical issues?
JH	Pg 26	Annex D.7	Table D.2	te	Footnote for “Motility Evaluation” to be consistent with Table C.1	Add “For designs that potentially affect motility as determined by the risk analysis”	
MLG			Table D.2 and Section E.2	te	Two questions/comments about VA testing. 1. Table shows BCVA (ETDRS). Text in E.2 suggests use of ETDRS style chart, but does not mention use of ETDRS light box or recording number of letters versus Snellen equivalents. Is full ETDRS methodology and recording required, or can ETDRS style chart (eg, as a wall chart, not with a lighted box) be used for Snellen equivalents instead of number of	Consider clarifying ETRDs methods used, and if Snellen equivalents are allowed. Consider clarifying the “best” nature of BCVA, eg if refraction is required to assess “best”.	

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					letters read? 2. Says that all corrective lenses should be recorded. Should the BCVA collected at study beginning be based on manifest refraction or just BSCVA using habitual correction? Habitual correction worn may not be the best possible corrected visual acuity.		
MLG			E.3	te	Asks that IOP measurements be taken at 4 hour intervals over an 8-hour period between sunrise and sunset. If for some reason there is a medication component to the scenario, (eg, a comparison to something that involves drug) or some other reason that flexibility in when the diurnal measurements are collected, it may be preferable to allow flexibility in collection times. Eg, if a medication were involved as comparator for some reason, peak and trough effect times might be of interest.	Consider adding flexibility to the language in this section for collection times. For example, consider revising to something like "taken at 4 hour intervals (+/- 30 minutes) over an 8-hour period between sunrise and sunset; *following a different pattern of IOP collection timepoints within that same time frame may be considered with sufficient justification*"	
MLG			E.4	te	Consistent grading system for gonio should be used within each site, *and* across the study. All sites should be using a standardized grading system for gonioscopy. Exams should be standardized across all sites as much as possible.	Consider revising to be clear about standardization of gonioscopy. Eg, "a gonioscopic exam using a consistent grading system *across each site in the study* should also be conducted"	
MLG			E.5	te	Two questions about lens exams. Should it be recommended that patients be dilated for the lens examination regardless of which grading method they choose? And, would AREDS grading be acceptable?	Consider whether revisions need to be made to clarify methodology of lens evaluation, and/or expand examples of lens grading systems	
FDA		E.5	Paragraph 2	Technical	ASC opacities are anticipated with MIGS procedures and not included with LOCS III.	For any type of lens opacities (e.g., anterior subcapsular opacities) not characterized by standardized grading systems, a qualitative description should be made.	
JH	Pg 29	Annex E.7	Paragraph 1	te	Visit schedule should be annul after 24 months	Change to "… every six months up to 24 months postoperative and annually thereafter to evaluate …"	

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JH	Pg 29	Annex E.8	Paragraph 1	te	Can HRT/OCT been used as surrogate to evaluate ONH or RNFL?	Add “RNFL”; Refer to FDA MIGS guidance	
JH	Pg 29	Annex E.9	Paragraph 1	te	Perimetry needs a reliability criteria	Add a reliability criteria (ref. Yohannan et al, 2017); Refer to the definition in the FDA MIGS guidance	
FDA		E.9	Paragraph 1	Technical	MIGS Guidance criteria is based on Humphrey outputs. https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM433165.pdf	Humphrey visual field 24-2 SITA-Standard or equivalent is recommended.	
JH	Pg 29	Annex E.10	Paragraph 1	te	Months 30 is not a regular visit as in the Table D.2	Remove “Months 30”	
FDA		E.10	n/a	General	To protect subject safety. Low endothelial cell count may affect patient management.	Subjects with endothelial cell loss ≥30% from baseline should be identified promptly after specular microscopy and investigators should be notified about the subjects’ condition promptly. For ex. of this type of recommendation, see Special Report: American Academy of Ophthalmology Task Force Recommendations for Specular Microscopy for Phakic Intraocular Lenses http://www.aaojournal.org/article/S0161-6420(16)31335-5/pdf	
GC	Pg 31	Annex E.11	Paragraph 1	ge	Need to discuss Patient Questionnaire. What is the status of the questionnaire FDA is working on with Stanford, Johns Hopkins, etc.? Also, how to make sure the questionnaire identifies glaucoma-related improvements in patient condition (rather than cataract-related improvements, if device is implanted in a combo procedure)		
FDA		E.11	Title	Editorial	Patient-Reported Outcomes (PROs) is any outcome that comes directly from the patient without interpretation by others. It is a commonly used term that could apply to	Change title from “Patient Questionnaire” to “Patient-Reported Outcomes and Patient Preference Information”	

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					formats other than a questionnaire (e.g., diary, etc).		
FDA		E.11	Paragraph 1	Editorial	A PRO is designed to measure an effectiveness outcome and/or a safety outcome. Hence, the purpose and context of use of the PRO measure in a given study should be specified in the protocol.	A patient-reported outcome (PRO) measure should be administered to all subjects to assess the safety outcomes of visual and ocular surface symptoms.	
FDA		E.11	Paragraph 1	Editorial	The language was modified to allow for additional items depending on the device. Health-related quality of life is too broad and often not truly measured by most of the questionnaires. Visual function is often what is measured instead. While health-related quality of life could be measured, it is not necessary for these clinical studies.	The PROs should include but are not limited to ~~questions regarding~~ pain/discomfort, foreign body sensation, droopy eyelid, dry eye, tearing, red eye, and the device's impact ~~on health-related quality of life~~ visual function.	
FDA		E.11	Paragraph 1	Editorial	The change would allow for device manufacturers to develop their own PRO measures and clarifies that the amount of needed development work would be influenced by the context of use. https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf	The PRO measure ~~should have previously been referenced in the peer-reviewed literature and their~~ should be developed using patient input and evaluated (at a minimum) for its interpretability and the appropriateness of the recall period and response options. ~~reliability and validity undergone some degree of evaluation.~~ FDA's Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims should be consulted for further guidance on developing PRO measures and, ~~particularly for~~ evaluating the adequacy of a ~~patient-reported outcome (PRO) instrument~~ measure.~~as a measure to support device claims, if the manufacturer wishes to make such claims.~~	
FDA		E.11	Paragraph 2	Editorial	Examples of symptoms which should be included to assess safety are included on the list. While visual function could potentially be a safety outcome (e.g., show no worsening of visual function after the device is implanted), it is unlikely to be a meaningful effectiveness endpoint.	Examples of ~~existing questionnaires that measure~~ PRO measures that assess some of the ~~parameters~~ symptoms listed above are the short form ~~of the National Eye Institute's Visual Function Questionnaire (VFQ-25) (impact on quality of life), the~~ of the Symptom and	

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					Related reference: DC Musch, ME Tarver, MJ Goren, NK Janz. Development of an 18-Item Measure of Symptom Burden in Patients With Glaucoma From the Collaborative Initial Glaucoma Treatment Study's Symptom and Health Problem Checklist. JAMA Ophthalmol 2017 Dec 1; 135(12):1345-51.	Health Problem Chart from the Collaborative Initial Glaucoma Treatment Study (CIGTS) ~~and , Quality of Life Assessment Instrument (symptoms),~~ the Ocular Surface Disease Index (OSDI) (dry eye symptoms).	
FDA		E.11	Paragraph 2	Editorial	Patient preference information is increasingly being used in medical device benefit-risk determinations for other device areas. It is possible that this study approach could also be useful for MIGS devices as well as other implantable glaucoma devices.	Patient preference information may also be considered to help inform benefit-risk determinations, determine thresholds for outcome measures, and to help support clinically meaningful endpoints. The Patient Preference Information—Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and de novo Requests, and Inclusion in Decision Summaries and Device Labeling provides additional information about the use of these studies to inform device clinical studies.	
FDA		E.11	Paragraph 3	Editorial	Depression is not a clinical outcome of the studies and is unlikely to be directly related to the device.	Delete sentences related to depression	
JH	Pg 31	Annex E.12	Paragraph 2	te	Hypotony should be classified as early/late, w/wo clinical sequela	Refer to the "clinically significant hypotony" defined in the FDA MIGS guidance	
AR		E.12		te	Hypotony- should this be persistent? Over two or mre study visits? Not sure this is a good criteria...perhaps low IOP less than 8 mm Hg with chorioidal folds, hypotony maculopathy or presistent serous choroidal detachments?		Should we define hypotony with clinical AE secondary to low IOP, rather than just assign a number?
FDA		E.12	Paragraph 1	Technical	Comprehensive list of relevant intraoperative versus post-operative AE's. Reconciliation with MIGS Guidance and Aqueous Shunt Guidance.	Recommend separating intra-operative and post-operative adverse events (AE). Currently, intraoperative AE's are not specified, such as: "device malfunction identified prior to implantation,"	

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					Addition of AE's reported in relevant device trials. https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM433165.pdf https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073806.pdf	"inadvertent perforation of sclera," "inadvertent loss of vitreous," "and "choroidal hemorrhage or effusion." Postoperative AE's missing are: "visual acuity loss," "tube malposition," "loss of eye," "chronic pain," "ptosis," and "atrophy/phthisis." Instead of "hypotony (IOP<6 mmHg)," specify early and late clinically significant hypotony as outlined in the MIGS guidance (D.1.a). Similarly, specify early and late IOP spikes. Instead of "chronic iritis," include definition of chronic anterior uveitis as specified in the MIGS guidance (D.1.b) Expanding corneal adverse events to include dellen, pannus, opacity, shunt/corneal touch. Recommend addition of "failure to implant," "Implant fracture," "IOL decentration," "IOL anterior-posterior movement" or refractive surprise, "blebitis," "loss of light perception," "inadvertent bleb," "BCVA loss of ≥2 lines (early and late)," "cyclodialysis," "iridodialysis," "device malposition" (such that device is not in the supraciliary space or there is clinical sequelae, including but not limited to secondary surgical intervention to modify device position, corneal endothelial touch, corneal edema, progressive endothelial cell loss (i.e., ≥30% from baseline), device obstruction), "device movement," "ciliary body edema," "choroidal folds." Recommending specifying secondary surgical intervention categories (i.e., glaucoma re-operation (e.g., tube revision, tube explant, tube repositioning, SLT/ALT, ECP, diode laser, bleb revision), secondary procedures (e.g.,	

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						laser to clear obstruction, subconjunctival injection, bleb needling, etc.), other procedures (e.g., CE/IOL, YAG for PCO).	
CH	Pg 35	Annex G.1	Paragraph 1	ed	Safety and effectiveness are both included in Annex G.3 – there is no Annex G.4	Create Annex G.4 with effectiveness analysis details or align Annex G.1 with the current structure of Annex G.	
CH	Pg 35	Annex G.2	Table G.1	te	Accountability is based on number of enrolled. Should it not be based on the number treated? A subject that enrolled but never received treatment should not be included in the table of follow up accountability as these subjects are expected to be exited from the study without further follow up.	Replace 'Enrolled' with 'Treated' in the table title. Remove footnote for 'Enrolled' and replace with 'Treated – represents the total number of subjects who entered into the study, i.e., by undergoing informed consent and signing the informed consent document, AND received treatment.'	
GC	Pg 35	Annex G.2	Table G.1	te	Miss surgery/operative visit	Add surgery visit to this table	
JH	Pg 36	Annex G.3.1	Paragraph 1	te	Visit schedule should be annul after 24 months	Change to "… every six months up to 24 months postoperative and annually thereafter to evaluate …"	
FDA		G.3.1	Paragraph 1	Technical	Additional safety analysis	• Percentage of eyes that lose 2 lines or more BCVA (10 or more ETDRS letters) at the final visit compared to baseline; report etiology (i.e., macula, glaucoma, cataract, unknown, etc.)	
CH	Pg 36	Annex G.3.2	Paragraph	ge	Title of G.3.2. should say 'effectiveness' instead of 'efficacy' for consistency with the rest of the document (see use of 'effectiveness' in the rest of this section).	Change 'Efficacy' to 'Effectiveness.'	
JH	Pg 37	Annex G.3.2	Paragraph	te	Lack guidance on how to handle imputation of treatment failures such as IOP-lowering SSIs	Add a paragraph to describe conditions that should be imputed as treatment failures	
FDA		H.4	Paragraph 1	Technical	To standardize confirmation of movement or malposition.	Physician labelling (directions for use) should specify proper device position and instruction on how to confirm appropriate placement.	
FDA		NEW,		te	Suggest literature models that could be	Include a new informative annex to	New Annex??

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		Computational modelling of fluid flow			applied to the specific new device type. One example: BS Gardiner et al. Computational Modeling of Fluid Flow and Intraocular Pressure following Glaucoma Surgery, PLos ONE 5(10) e13178 doi:10.1371/journal.pone.0013178 2010 Also, Adler's Physiology of the Eye, WM Hart ed, 1992	recommend a mathematical model to predict the device performance (pressure/flow characterization, finite element analysis, etc.) and interactions with the human eye to rule out adverse events with IOP before a device is clinically evaluated. This type of analysis should be considered only for new device designs. The analysis is not recommended for modifications of existing devices that have known performance characteristics.	

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