



DRAFT CONSENSUS STATEMENT FOR COMMENT
October 16 2015

This statement was developed as a result of breakout group recommendations from the March 24, 2014 Developing Novel Endpoints for Premium IOLs Workshop held in Silver Spring, Maryland. The primary goal of the workshop was to improve the regulatory science for evaluating premium IOLs, which in turn may enhance the efficiency with which safe and effective premium IOLs get to the market.

We are indebted to the Task Force on Developing Novel Endpoints for Premium IOLs formed after the Workshop for developing these statements based on the workshop discussions and recommendations, available peer-reviewed scientific literature, and other expert opinions. The Task Force includes the following : Jack Holladay, MD, Chair; Adrian Glasser, PhD, Scott MacRae, MD, Samuel Masket, MD, and Walter Stark, MD. The FDA liaisons to this Task Force include the following: Malvina Eydelman, MD, Don Calogero, MS, Gene Hilmantel, OD, MS, Tieuvi Nguyen, PhD, RAC, Eva Rorer, MD, and Michelle Tarver, MD, PhD.

We would like to solicit broad input from industry and other interested parties.

Please send your comments, your affiliation and contact information with the title of the referenced document to hoskinscenter@aao.org by the following deadline: **November 10, 2015**. Please note that comments received after close of the comment period will not be accepted.

**AMERICAN ACADEMY OF OPHTHALMOLOGY TASKFORCE CONSENSUS STATEMENT
FOR ACCOMMODATION CLINICAL STUDIES FOR ACCOMMODATIVE IOLS**

1. Measurement Methodology Calibration and Validation Protocol

1.1 Purpose

The purpose of this section is to provide guidance for clinical accommodation studies on the steps needed to provide validation for the objective measurement methods and protocol to be used.

1.2 Introduction

It is recommended that clinical accommodation studies for accommodative intraocular lenses (A-IOLs) include a sub-study in which objective methods are used to measure the accommodative changes, be they optical or biometric methods. Given the possible new and unique A-IOLs that may be investigated, it is impossible to dictate what instrumentation can or should be used for objective measurements in these clinical studies. If commercially available instruments that have been previously validated in peer-reviewed, published clinical studies are to be used, given the unique nature of the A-IOLs, it may still be necessary to validate the measurement methods on the specific A-IOL being investigated.

1.3 Calibration

Instruments to be used should include a calibration procedure. Many commercially available instruments include standard calibration procedures. For those commercially available instruments with standard calibration procedures, the instrument manufacturer recommended calibrations should be performed.

For those instruments without standardized calibration procedures, calibration procedures should be developed. Calibration curves should be generated for at least 5 standard samples that encompass the range of parameters expected to be measured in the clinical study. All quantitative metrics to be recorded in the clinical study should have such calibration curves. For example, if sphere and cylinder are to be measured with an optical instrument, then calibration curves for sphere and cylinder should be provided. These can be generated by, for example, placing trial lenses in front of model eyes.

If the measurement instruments generate images, such as Optical Coherence Tomography (OCT) or Ultrasound Biomicroscopy (UBM), and various ocular parameters are to be measured from the images, then calibrations should be provided for all the parameters to be measured, encompassing the range of values expected to be measured in the clinical study. For example, if lens surface curvatures are to be measured, then calibration surfaces or spheres should be imaged under the same conditions as they would be in the clinical study and measured from the images and the calibration curves shown. Imaging methods can suffer from image distortion, so image distortions will need to be corrected. The procedure whereby these distortion corrections are achieved should be explained. Optical instruments can suffer from optical distortions, so those optical distortions will need to be corrected. The procedure whereby the optical distortions are corrected should be explained. Optical instruments that image an ocular or optical surface through preceding optical surfaces also introduce optical distortions due to refraction from the preceding optical interfaces. Those optical distortions will need to be corrected. The procedure whereby these optical distortions are corrected should be explained.

1.4 Validation

Objective instruments to be used in a clinical study should be validated in a small pilot study. The protocol to be used in the clinical study should be developed and used for the pilot study.

Prior to initiating the clinical study, it is recommended that a pilot study on 5 eyes be conducted. If the parameter to be measured can be measured in a phakic eye, then it would be appropriate that the eyes used for the pilot study are phakic eyes. If the parameter to be measured can be measured in a standard monofocal IOL pseudophakic eye, then it would be appropriate to use such eyes for the pilot study. For example, if the objective instrument to be used is a dynamic autorefractor, then the dynamic autorefractor could be used in a group of monofocal pseudophakic eyes to demonstrate that it measures refraction accurately in these eyes compared to an established instrument. To demonstrate that the dynamic instrument measures refractive changes accurately compared to an established instrument, trial lenses could be placed in front of the test eye to induce refractive changes to simulate accommodation. If the instrument to be used is an OCT instrument which would be used to, for example, measure changes in lens surface curvatures, then it can be used on monofocal IOL patients with monofocal IOLs of known curvatures to demonstrate that the IOL surface curvatures that are measured are accurate. If the parameter to be measured is something unique or exclusive to the A-IOL being tested, and a validation cannot be performed in control subjects, then the pilot study would need to be conducted on the eyes of study patients. The entire protocol should be run on these study subjects, including the data collection and data analysis and presentation of the data.

1.5 Measurement Protocol

For accommodation testing, the subjects need to be distance corrected. Any accommodation testing protocol should include measurements at distance (6 m; 0 D), intermediate (66 cm; 1.5 D) and near (40 cm; 2.5 D). A 4 m testing distance could be used with a near add, but this would depend on if testing is being done monocularly or binocularly. If binocular testing is performed, vergence comes into play. Further, proximity of a stimulus alone is a stimulus for accommodation. The best way to ensure that the starting point of an accommodative stimulus-response function is a truly unaccommodated state is to use a 6 m testing distance. Further, given that the accommodative response lags behind the stimulus amplitude, a 2.5 D stimulus may not be sufficient to produce the maximum response. Rigorous accommodation testing protocols would ideally include more stimulus amplitudes such as 0.0D, 1.0, 1.5, 2.0, 2.5, 3.0, etc.) to allow for a stimulus-response function to be plotted. If the stimulus amplitudes chosen are sufficient to achieve the maximum accommodative response amplitude, then the plotted stimulus-response function would show a plateau or an asymptote. This would provide sufficient data to identify the maximum objectively measured accommodative response amplitude. At least three, independent, repeated measures should be performed at each stimulus amplitude for reasons identified in the next section.

1.6 Measurement Precision

It is necessary to know and demonstrate the standard deviation of the chosen measurement method. Therefore, the protocol should include at least three repeated measures for each stimulus amplitude. This allows for calculation of a mean and standard deviation (SD). Due to instability of accommodation, particularly at higher stimulus amplitudes, it is possible that the standard deviations may increase with increasing stimulus amplitude. Therefore, to determine the precision of the chosen measurement

method, standard deviations from repeated measures to all the stimulus amplitudes tested should be calculated. The overall population mean standard deviation of the chosen measurement method should be determined from the pilot study. This could be obtained from an ANOVA or a regression model, for example.

2.0 Conversion of Accommodative Biometric Measurements to Accommodative Optical Changes

2.1 Purpose

The purpose of this section is to provide guidance for clinical accommodation studies that choose to use objectively measured accommodative biometric changes to demonstrate accommodation for A-IOLs.

2.2 Introduction

Clinical accommodation studies for A-IOLs should use objective measurements of accommodation as the primary effectiveness endpoint to unequivocally demonstrate an accommodative optical change in power of the eye. Normally, this is accomplished through the use of an autorefractor or aberrometer to measure the accommodative dioptric change in power of the eye. In some circumstances, there may be practical limitations on the ability to measure accommodative optical changes. In such cases, biometry measurements may be more suitable or desirable to demonstrate the presence of accommodation. Biometry measurements can include any measurement of the ocular biometry that may change with accommodation, including, but not limited to, changes in IOL thickness, anterior chamber depth, vitreous chamber depth or surface curvature of one or both surfaces of the cornea or the IOL. These kinds of ocular biometric changes are expected to lead to a change in the optical refractive power of the eye. However, if such biometric measurements are to be undertaken in clinical studies, the measured biometric changes will need to be converted into dioptric accommodative changes in power of the eye. This section is aimed at providing guidance on how this might be accomplished.

Biometric measurements of accommodative biometric changes can be accomplished with, for example, Ultrasound Biomicroscopy (UBM), A-scan ultrasound, Scheimpflug Photography, Partial Coherence Interferometry (PCI), Optical Coherence Tomography (OCT), Phakometry and Magnetic Resonance Imaging (MRI). In addition, other ocular components can be measured with corneal topographers, keratometers and corneal pachymeters. These are all objective measurement methods that provide quantitative data in the form of images or transit times that can be converted to represent physical measurements such as axial distances, thicknesses or surface curvatures of the component elements of the eye.

2.3 Validation and Calibration

If a biometric measurement is to be used in a clinical study, it needs to be a validated measurement method. Validation can come from using methods described in the peer-reviewed, published literature, or can entail a preliminary validation study. The measurements need to be calibrated to demonstrate that the measurements are accurate. Validation can come from, for example, measurement of known standards that encompass the range of values that are expected to be encountered in a clinical study. For example, if Ultrasound Biomicroscopy is to be used to measure lens surface curvatures, then measurements should be undertaken on calibration standards that span the range of surface curvatures expected to be measured in the clinical study population. Linear correlation calibration curves and mean versus difference plots should be provided to demonstrate the accuracy with which the calibration

standards can be measured. Many biometry instruments have inherent inaccuracies due to, for example, image distortion. Image distortion can come from optical refractive inaccuracies in the instruments or from optical refraction by optical interfaces preceding those being imaged. If such inaccuracies or distortions do exist in the measurement methods selected, then distortion correction algorithms will need to be developed or used from the published literature to correct the distortions and the accuracy of these distortion corrections on samples spanning the expected range will need to be demonstrated.

2.4 Schematic Eyes

A schematic eye is a simplified optical representation of an eye that includes the optical interfaces, distances and refractive indices that constitute the optical refractive components of a real eye. With the inclusion of these elements, optical calculations can be performed to either simulate the passage of light rays into the eye from an object in object space or out of the eye from the retinal plane into object space. These calculations can identify where an object should be in object space so that the image of that object falls on the retina, or conversely where in image space the image of an object in object space will fall with respect to the position of the retina. The refraction of a schematic eye can be calculated and the change in refraction of the schematic eye can be calculated as the eye undergoes accommodative biometric changes. Simple, paraxial schematic eye calculations can be used to translate biometric changes into dioptric changes. A paraxial schematic eye is a schematic eye that considers only the optical properties and the light rays very close to the optical axis. Using paraxial optics substantially simplifies the optical calculations required, avoids the need for measuring and considering aspheric surfaces and optical aberrations of the optical system and avoids the need to consider pupil diameter. Paraxial schematic eyes are well suited for calculating refraction and refractive changes. The values needed for simple paraxial schematic eyes are the radii of curvatures of the optical surfaces, the axial thicknesses and the refractive indices of the various elements of the optical system. For a normal phakic eye the following parameters are required to construct a simple paraxial schematic eye:

Axial distances:

- corneal thickness
- anterior chamber depth
- lens thickness
- vitreous chamber depth
- axial length (sum of corneal thickness, lens thickness and vitreous chamber depth)

Surface curvatures:

- anterior corneal surface
- posterior corneal surface
- anterior lens surface
- posterior lens surface

Refractive indices of the following:

- cornea
- aqueous humor
- lens
- vitreous humor

Any variation from the normal phakic eye would also need to be incorporated into the schematic eye calculations. For example, if a dual optic accommodative intraocular lens (A-IOL) were to be considered, then the additional surface curvatures, axial distances and refractive indices of the two optical elements of the dual optic AIOL would also need to be included in the schematic eye and schematic eye calculations.

The process for calculating the optical power of simple schematic eyes is well documented in the literature and in book chapters and the equations for paraxial schematic eyes are available from these sources. The calculations can include calculation of the cardinal points of the eye such as principle planes, nodal points and focal points, or can be stepwise vergence calculations that allow for calculations of conjugate object and image positions. The refractive state (or refractive error) of a schematic eye can readily be calculated and therefore so can the change in refraction with accommodation, or the accommodative response. There are many different standard paraxial schematic eyes published, including, for example the Gullstrand schematic eye or the Le Grand schematic eye. The refraction of the schematic eye can be calculated when the eye is in an unaccommodated state and then again when the eye is in various progressively increasing accommodative states and the change in the refraction will represent the dioptric accommodative refractive change.

More complex, non-paraxial schematic eyes can also be used to calculate how biometric changes relate to accommodative optical changes. In addition to the parameters identified above, aspheric surface profiles, gradient refractive index elements and variations in pupil diameter can be considered in non-paraxial schematic eyes. Although the optical calculations for such schematic eyes are more involved, the process of calculating such schematic eye can be considerably simplified by using ray tracing software into which the various parameters of the eye can be entered and having the software calculate the refractive power of the eye. If such non-paraxial optical systems are considered, then consideration needs to be given for additional details such as how optical aberrations are to be considered, how a dioptric change in power of the non-paraxial eye can be calculated and what pupil diameter to consider or how changes in pupil diameter are to be dealt with.

2.5 A Population of Schematic Eyes

The efficiency of any optical system to undergo a change in optical power varies with variations in any one or a combination of some of or all of the optical elements. Obviously, a greater change in lens surface curvature within the eye will result in a greater accommodative change, but with a steepening in lens curvatures comes an increase in lens thickness and a decrease in anterior chamber depth. What might be less obvious is that an increase in lens thickness with no other change in the lens actually results in a decrease in lens power and therefore a decrease in overall optical power of an eye. Furthermore, the starting, unaccommodated, configuration for any eye also dictates the efficiency with which the eye can undergo accommodative changes. Because of this variation and because of the natural diversity of the eyes of human subjects, when schematic eyes are to be used for conversion of biometric changes into dioptric refractive changes, the schematic eyes used should also reflect the variation in natural eyes. Therefore, it is not suitable or appropriate to use a single schematic eye, but rather it becomes necessary to use a population of schematic eyes.

This population of schematic eyes should come from measurements on a population of actual eyes. This is the most effective way to represent the natural diversity in human eyes. A population of subjects should be selected that match the inclusion and exclusion criteria to be used in the clinical study. On each of those eyes in the selected population, all the schematic eye biometry parameters should be

measured using the methods and instrumentation selected for the clinical study. By way of an example we will consider a clinical study for an artificial accommodative intraocular lens that undergoes accommodation in a manner similar to that of the young phakic lens in which there is an increase in lens thickness and a steepening of both the lens anterior and posterior surfaces. If this is the anticipated mechanism of action of the AIOL, then it would be necessary to measure the lens thickness and the lens anterior and posterior surface curvatures as well as the anterior chamber depth and the vitreous chamber depth in the clinical study because some or all of these parameters would be expected to change with accommodation. These parameters would be measured in the unaccommodated eye and then again as the eyes accommodate to various increasing accommodative stimulus demands. In addition, the static biometry parameters such as corneal surface curvatures and thickness and axial length that would not be expected to change with accommodation would also have to be measured. These latter parameters which are not expected to change with accommodation can be measured only in the unaccommodated state and then the same parameters could be used for calculation of the refractive changes during accommodation.

All the measured (static and changing) parameters would be assembled to produce a schematic eye for each subject and for each accommodative stimulus demand. The schematic eye calculations could be performed in using formulas entered into an Excel Worksheet, in programmable code such as Matlab or using ray tracing software such as Zemax. The calculations would be used to demonstrate how much accommodative optical change in power of each schematic eye occurs with the measured biometric changes. Then for each schematic eye, a stimulus-response function would be calculated which would show on the y-axis the calculated accommodative refractive change from the schematic eyes for the increasing stimulus demands shown on the x-axis. Also, it is recommended that an analysis be performed to show how the dioptric response depends on corneal curvature, anterior chamber depth, IOL power, vitreous chamber depth and axial length. It is recommended that this kind of analysis be included with all dioptric conversions.

2.6 Correlation Between Objective Measure and Subjectively Measured Accommodation

The choice to use objective biometric measures to demonstrate accommodation assumes that objective optical refractive measurements cannot be made. However, if accommodative biometric changes do occur, the expectation is that these are correlated with the accommodative optical changes in the eye. Therefore, a study should be performed in which the objectively measured biometric change can be shown to be reasonably correlated with subjectively measured accommodation. First the subjectively measured accommodative amplitude should be measured and the stimulus amplitude to achieve this response should also be recorded. Then the objective biometric changes should be measured in response to this same stimulus amplitude. Both the subjective and the objective measures should be repeated three times and the means and standard deviations calculated. This procedure should be repeated on one eye of each subject, and the data plotted and fitted with a linear regression line. Known covariates such as pupil size could be incorporated into the regression analysis, if desired. A similar separate analysis should be done on the control group.

2.7 Addressing Challenges

There are many possible challenges that may be encountered with objective accommodation measurements. One of the most significant challenges may be how the accommodative biometric parameters can be measured while at the same time stimulating accommodation in the same eye. By way of an example, if UBM were to be used to measure the biometry of the eye, UBM generally requires

the subjects to be lying on their back looking up with a fluid interface in front of the eye. In such cases, the instrument required to do the biometry measurement obscures vision in the eye being tested, so the accommodative stimulus would need to be presented to the contralateral unoccluded eye. If this is done, then under normal circumstances, the eye that is not viewing the accommodative stimulus (i.e., the eye being measured) undergoes all of the accommodative convergence change. This convergence response would make it difficult to measure the biometric change of the eye. Therefore, a stimulus system would have to be established to allow the unoccluded eye to view the near stimulus in an increasingly convergent posture so that the seeing eye takes up all of the convergence response and the eye being measured remains in the primary gaze posture throughout the testing.

Discussion of the acceptability and robustness of the protocol and method used should address the following:

- if the testing method depends on using the contralateral eye to respond to the accommodative stimulus, how might the accuracy of the measurement be affected if the two eyes are not equally effective in providing accommodation;
- if the testing method depends on using the contralateral eye to respond to the accommodative stimulus, how is the convergence response addressed;
- If the same eye is to be used for both stimulating and measuring the accommodative response, an explanation of the system or mechanism by which this is accomplished should be provided;
- the effects of possible artifacts or variations in the measured parameters due to eye movements or convergence responses should be addressed.

2.8 Accuracy

There is a question of how accurately measured biometric changes when converted to refractive dioptric changes using schematic eye calculations actually represents the true accommodative optical changes in power of the eye. The answer to this remains unknown because the definitive study on this has yet to be done. That study would entail doing simultaneous refractive and biometric measurements on the same eyes as they accommodate and the biometric measurements would have to simultaneously capture all the parameters required for the schematic eye calculations at one time. Even if this study had been performed, it would not have been performed in eyes with the specific A-IOL under investigation for the specific clinical study. There is tremendous variation in the accuracy with which any single parameter of the eye can be measured. There is even variation in the accuracy with which the accommodative optical refractive changes can be measured. If all these sources of inaccuracy are incorporated together into a single schematic eye calculation, the inaccuracies can multiply to cause either an over or an underestimation of the measured accommodative optical refractive change. So, any schematic eye calculation that is based off of actual biometric measurements could either over or underestimate the accommodative optical response of that given eye. These sources of inaccuracy in the measured biometry response and their potentially multiplicative effect on the calculated accommodative optical response would need to be addressed. This can be accomplished with an appropriate error analysis that considers the variation in the calculated accommodative optical response based on inaccuracies in the measured biometry parameters.