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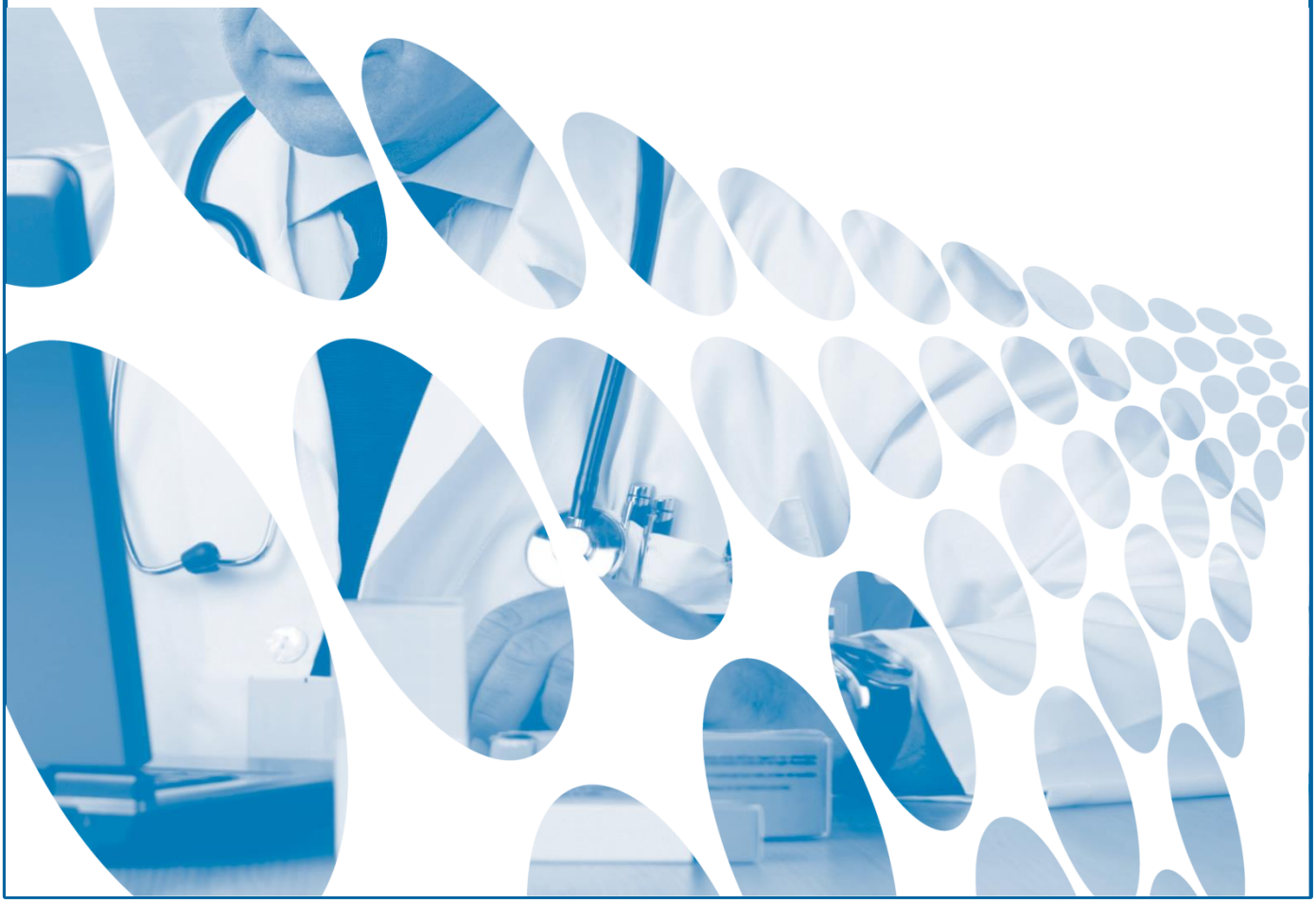
White Paper

Ophthalmic Study Endpoints



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1. Introduction

Ophthalmic studies rely on complex tests and assessments to meet clinical study endpoints. Each test may be time-consuming to administer, assess, and interpret. Consequently, it is important not to overcrowd a study with unnecessary assessments. Choosing endpoints that are clinically relevant is increasingly important in bringing new therapies to market more quickly.

This paper provides a brief overview of some common endpoints in ophthalmology research, and issues to take into account when considering endpoints for ophthalmic studies.

2. Overview

The primary endpoint should address the study objectives and answer the most important questions being asked. As such, the primary endpoint should be the variable that can provide the most clinically relevant evidence. Scientific quantification of the primary endpoint needs to be translated into clinical benefit to the patient. Few objective endpoints are available in ophthalmology studies. Functional or subjective endpoints include visual acuity, visual field, colour vision, and contrast sensitivity.

Visual acuity and visual field tests are subjective and rely on patient understanding and cooperation. Surrogate endpoints may be valuable if direct assessment of clinical benefit is not feasible. A surrogate outcome should be able to change with an intervention and should be standardized and reproducible across study sites. In ophthalmic studies, surrogate outcomes should correlate with vision.

As the most important factor to the patient, visual acuity is the 'gold standard' primary outcome measure.

3. Visual Acuity Endpoints

Visual acuity data points are usually collected at specific follow-up intervals that should be pre-specified and consistent. Treatment differences are detected by calculating mean visual acuity or mean change in visual acuity. A minimum clinically relevant improvement should be defined. This should be based on a minimal clinically relevant improvement in terms of number of 'lines lost' or 'lines gained' in the specific disease or condition.

Analyses of 'final' or 'best corrected' visual acuity (BCVA) outcomes should consider whether the condition being studied continues to improve or deteriorate beyond the time

at which the 'final' or 'best corrected' outcome was measured. Clinically relevant treatment effects should be pre-specified and justified in terms of 'change in BCVA from baseline' when comparing active and placebo groups.

4. Patient Reported Outcomes

Patient reported outcomes (PRO) are increasingly important, particularly in studies related to vision. These are not often primary endpoints, but serve an important role in providing a better understanding of outcome measures. A PRO measures factors such as symptoms and their impact on functioning, adverse events or treatment tolerability. They can be difficult to quantify and validate, as there needs to be a connection between what the patient reports and a functional assessment. The most common PRO in ophthalmology studies is the 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ 25). Questionnaire length plays a critical role in study cost, patient adherence and data quality.

5. Endpoints in Glaucoma Studies

Defining endpoints for studies in slow progression disease such as glaucoma can be challenging. There is the common problem of lack of early patient symptoms which makes functional assessment of improvement difficult.

Standard measurements generally accepted are visual field assessment and measurement of intraocular pressure (as a surrogate outcome). Visual field measurement uses the 'gold standard' standard automated perimetry (SAP) test. As visual field testing can be subjective, the SAP has the advantage of standardization from test to test. Measurement of intraocular pressure uses the applanation tonometer to measure corneal resistance. This test should be conducted at a set time as the parameter varies during the day.

Structural endpoints may be more consistent than functional endpoints as they are not subjective or affected by a learning curve. It is important to understand how structural changes relate to clinically significant functional changes, for example when using OCT to detect changes related to glaucoma. The extent of optic nerve damage in glaucoma is assessed by testing optic nerve function. The standard structural efficacy endpoint in glaucoma studies is a reproducible change in optic disc appearance using stereoscopic optic disc photography. There are limitations in using this as the sole structural outcome endpoint as glaucoma slow disease progression means that subtle changes can easily be missed.

6. Statistical Considerations: One Eye or Two?

A fundamental assumption of standard statistical analysis is that data are independent of each other. However, if there is a correlation between eyes, this will not be the case. The study design should consider whether the condition, response or treatment occur at the patient level or the eye level. Will there be similarities or differences between the eyes? Will data be available for both eyes for all patients? Any correlation must be accounted for or there may be statistical error and inappropriate conclusions.

Statistical ramifications of the study design should be considered and specialist statistical help may be required if more complex analyses are appropriate.

7. About CROMSOURCE

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