*Draft Guidance – Not for Implementation*

Guidance for Industry and for FDA Reviewers

# Accountability Analysis for Clinical Studies for Ophthalmic Devices

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**This guidance document is being distributed for comment purposes only.**
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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Devices and Radiological Health**

**Division of Ophthalmic Devices**
**Office of Device Evaluation**

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# Preface

## Public Comment:

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852. For questions regarding the use or interpretation of this guidance contact Donna Lochner at (301) 594-2053 or by electronic mail at DRL@CDRH.FDA.GOV

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## I. Introduction

This guidance is intended to provide general information about the analysis of accountability in ophthalmic device investigational and marketing applications and notifications. It is a suggested format only, and other methods of reporting accountability are acceptable. By providing a reference point for the reporting of accountability information, it is hoped that terminology and methods of presentation can be standardized so that the Division and sponsors can more effectively analyze these data. We believe this may be particularly helpful for devices that are presented to FDA's Ophthalmic Devices Panel and that a common understanding of accountability may result.

This guidance document represents the agency's current thinking on the analysis of accountability in ophthalmic device investigational and marketing applications and notifications. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

We note that for some devices, for example contact lenses, sponsors may have used other terms and presentation styles than those presented in this guidance. Where previous convention has been established, we recommend that those established methods be retained.

## II. Definitions

The following definitions are used in this guidance. Recommended terms are **bolded** and synonymous terms are [bracketed]. Depending upon the study, the total number of subjects may or may not be the total number of eyes. For the purposes of this guidance, it is assumed that treatment is unilateral and total number of subjects is equivalent to the total number of eyes.

**Active**, [not yet eligible for the interval] - total number of subjects that have not yet reached the postoperative interval being reported prior to the accountability analysis. For PMA filing purposes, active subjects refers to those that have not yet reached the final form required for filing of the PMA.

**Available for analysis,** [completed], [cohort] - total number of subjects for whom data is available that have reached the postoperative interval being reported. This analysis may be performed at any postoperative interval and/or at the final visit.

**Discontinued** - total number of subjects that have discontinued treatment prior to completion of the prescribed investigational period for any reason (e.g., death, replacement of an implanted device). This category does not include "lost to follow-up" subjects, who are presumed to have continued treatment.

**Enrolled,** [intent-to-treat] - total number of subjects enrolled in the investigational study. For contact lenses, **enrolled dispensed** refers to all patients who signed an informed consent document prior to trial lens fitting and had lenses dispensed to them; **enrolled but not dispensed** refers to eyes considered enrolled because the patient had signed an informed consent document, but for

which lenses had not been dispensed. For devices that entail two step procedures (e.g., LASIK), subjects are considered enrolled as soon as the first procedure is attempted.

**Lost to follow-up,** [incomplete] - total number of subjects for whom a visit at the prescribed post-operative visit or later has not been obtained but are not considered to be active or discontinued. **Percentage lost to follow-up** is the total number of subjects for whom a visit at the prescribed post-operative visit or later has not been obtained but are not considered active or discontinued divided by the total number of subjects enrolled. For PMA purposes, total lost-to-follow-up is defined at the last [final] visit.

**Missed visit**, [accounted for] - total number of subjects that missed the visit being reported upon, but were otherwise accounted for. Missed visit includes those subjects that missed the visit being report upon but were seen at a later visit, the discontinued subgroup, those subjects that were not seen but their status was obtained (e.g., by telephone interview), and the lost to follow-up subgroup. Note that a telephone interview is not sufficient for all devices; sponsors should contact the Branch for guidance on this issue.

**Percent Accountability** - total number of subjects available for analysis divided by (the total enrolled less total discontinued less total active)

## III. Loss to follow-up

The number of subjects lost to follow-up is always critical in determining whether the data upon which conclusions are being drawn are unbiased. Historically, the Division of Ophthalmic Devices has aimed for review of studies with loss to follow-up of 10% or less. There are some assumptions inherent in acceptance of a certain level of loss to follow-up.

First, it is understood that few studies result in no loss to follow-up, so sponsors will typically enroll more subjects than the sample size required to document a particular effect size. Some studies (e.g., intraocular lens studies) enroll approximately 143% of the sample size required so that the number of subjects expected to become lost to follow-up is built into the study design.

Second, most studies call for a particular post-operative visit schedule. The minimum sample size required to document a particular effect size should be obtained at each post-operative visit.

Last, while summary data for all subsets of subjects within the overall accountability (i.e., available for analysis, discontinued, missing) should be presented, the lost to follow-up analysis is particularly critical. Sometimes called a worst case analysis, last visit carried forward analysis, or extrapolation analysis; the analysis on the lost to follow-up subjects should be performed to demonstrate whether or not this population data is different from those subjects available for analysis.

One should understand that adding the percentage accountability for a study with the percentage of lost-to-follow-up at a particular postoperative time interval will not equal 100%. This is because discontinued and active subjects are not included in the total lost to follow-up.

## IV. Recommended Analyses

### A. Overall Accountability

A table showing the overall accountability should always be presented. The overall accountability generally refers to either the accountability at the last visit or at the visit that is required for filing of a PMA or 510(k). For example, if a two-year study is being conducted but filing of a PMA / 510(k) is acceptable at one year, a sponsor would present at the time of submission of the PMA/ 510(k) an overall accountability table at one year. Usually, the total number of subjects available for analysis at the time of PMA / 510(k) submission is a population that will remain throughout the PMA as the sample size for analysis. Later amendments would report upon the active subjects separately.

In the example above, as subjects completed the two year visit, updated data would be presented with a separate two year accountability analysis. *In any accountability analysis, it is important to specify the timeperiod upon which the analysis is based (e.g., accountability at one year, accountability by postoperative visit, etc).*

### A.1. Suggested Format for Overall Accountability

Overall Accountability at {final visit}

| | Total | Percentage n/N |
|---|---|---|
| Enrolled (N) | | |
| Available for Analysis | | |
| Form 1 (post-op visit at time period) | | |
| Form 2 | | |
| . | | |
| . | | |
| . | | |
| Missing subjects at {final visit} | | |
| Discontinued | | |
| Missing {final visit} but seen at a later visit | | |
| Not seen but status obtained (e.g., by phone) | | |
| Lost to follow-up | | |
| Active | | |

### A.2. Suggested Format for Accountability by Post-Operative Visit

Accountability by Post-Operative Visit

| | (a) Month | (b) Months | (c) Months | (d) Months | (e) Months |
|---|---|---|---|---|---|
| Available for Analysis n/N* (%) | | | | | |
| Discontinued n/N (%) | | | | | |
| Active n/N (%) | | | | | |
| Lost to follow-up n/N (%) | | | | | |
| % Accountability = <br><br> Available for Analysis <br> (Enrolled - Discontinued - Active) | | | | | |

*N = total eyes enrolled