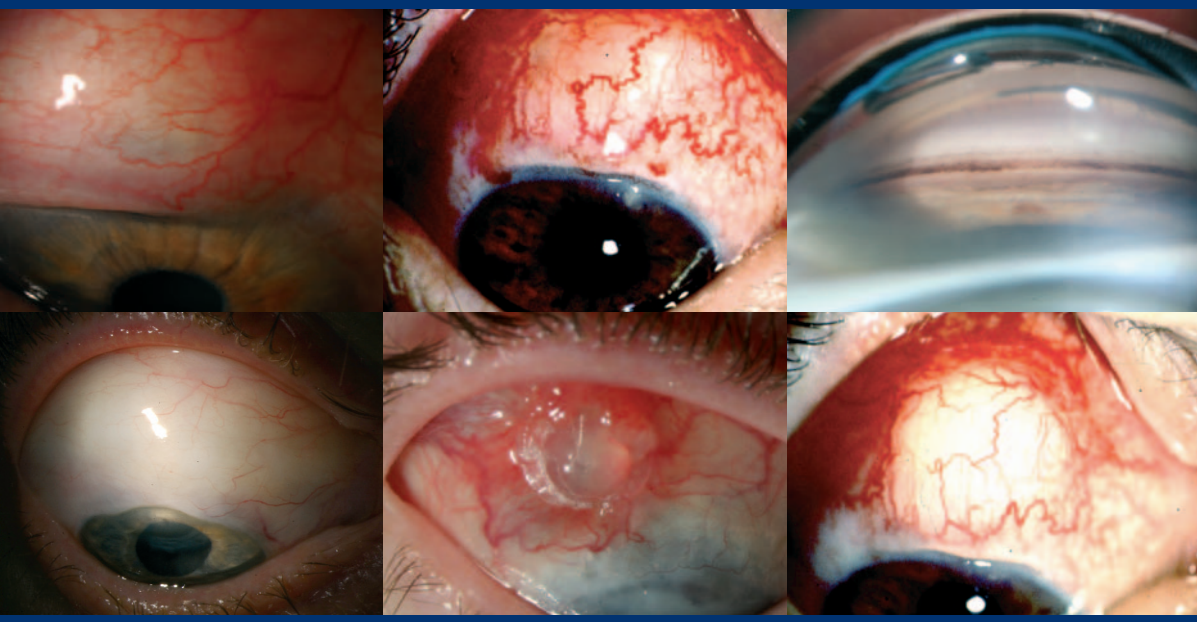
Guidelines on Design and Reporting of Glaucoma Surgical Trials

WORLD GLAUCOMA ASSOCIATION



Editors:

Tarek M Shaarawy, Mark B Sherwood, Franz Grehn

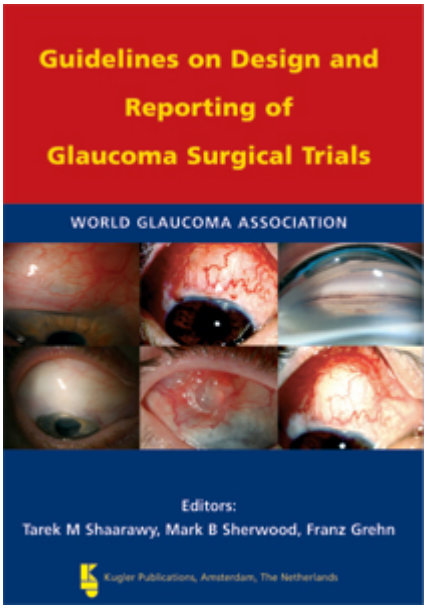
Kugler Publications, Amsterdam, The Netherlands

WGA GUIDELINES

KUGLER PUBLICATIONS

Guidelines on Design and Reporting of Glaucoma Surgical Trials

edited by: **T.M. Shaarawy** & **M.B. Sherwood** & **F. Grehn**



Price: € 25.00 / US $ 33.75 ***
ISBN 10: 90-6299-219-6
ISBN 13: 978-90-6299-219-5
Publisher: Kugler Publications
Publication date: 2009-03-30
Publication type: Book
Publication details: 2009. Book. vii and 83 pages. with 4 figures and 18 tables. Softbound.

*** *excl. 6% VAT and shipping and handling costs***

add to cart

WGA GUIDELINES ON DESIGN AND REPORTING OF GLAUCOMA SURGICAL TRIALS

Editorial Committee
T. Shaarawy, F. Grehn and M. Sherwood

Kugler Publications/The Hague/Amsterdam/The Netherlands

ISBN 10: 90 6299 219 6
ISBN 13: 978 90 6299 219 5

Distributors:

For the USA and Canada:
Pathway Book Service
4 White Brook Road
Gilsum, NH 03448
U.S.A.
email: pbs@pathwaybook.com

For all other countries:
Kugler Publications
P.O. Box 20538
1001 NM Amsterdam, The Netherlands
Telefax (+31.20) 68 47 788

website: www.kuglerpublications.com

Table of Contents

Introduction vii

Recommended Methodology for Glaucoma Surgical Trials, *R.K. Parrish II, D.S. Minckler, D. Lam, N. Pfeifffer and P. RojanaPongpun* 1
- Summary Points 1
- Introduction 2
- The Problem 2
- I. Clinical Interventional Studies (Clinical Trials) 3
- II. Observational Studies 4
- III. Other Study Types 5
- MSC Guidelines 5
- I. Study Design (Levels of Study) 5
- II. Baseline Pre-Operative Data 8
- III. Procedure Methodology 11
- IV. Post-Operative Assessment 11
- References 12

Consensus on definitions of success, *D.K. Heuer, K. Barton, F. Grehn, T. Shaarawy and M. Sherwood* 15
- Summary Points 15
- Introduction 15
- Report 16
- I. Intraocular Pressure Documentation 16
- II. General Data Presentation Requirements 18
- III. Other Possible IOP-Related Outcome Measures 21
- IV. Visual Fields 21
- V. Visual Acuity 22
- VI. Complications 22
- VII. Follow-up 22
- Conclusions 24
- Further Research Needed

The Ethics of Innovation, *A.V. Levin and G.L. Spaeth* 25
- Summary Points 25
- The Problem 25
- Report 26
- I. Clarifying the Objective 26
- II. Conflict of Interest 26
- III. Informed Consent 27
- IV. Other Research Ethics Principles 29
- Conclusions 31
- Further Research Needed 31
- References 31

Reporting post-operative complications in glaucoma surgical trials, *H.D. Jampel* 33
Summary Points 33
The Problem 33
Report 33
I. Intraoperative Complications 34
II. General Post-operative Complications 35
III. Complications Specific to Trabeculectomy (Bleb-related) 37
IV. Complications Specific to Drainage Device Surgery 38
V. Complications Specific to Non-penetrating Glaucoma Surgery 39
Conclusions 39
Overview 39

Guidelines for economic evaluation of glaucoma surgical trials, *S. Kymes and A. Azuara-Blanco* 41
Summary Points 41
Introduction 41
I. Methods of Economic Evaluation 42
II. Conducting Cost-effectiveness Analysis 43
III. Cost Utility Analysis 44
IV. Recommendations 45
Further Research 46
References 46

Statistical aspects of reporting glaucoma surgical studies, *W.J. Feuer* 49
Summary Points 49
Introduction 49
Report 50
I. Design Considerations 50
II. Analysis 55
III. Reporting 58
Conclusions 60
Further Research Needed 60
References 60
Overview 61

Appendix 63

Introduction

It is evident that in the last couple of years there has been a surge of interest in research in the field of glaucoma surgery. This includes research in the improvement of conventional glaucoma surgery; trabeculectomy, and glaucoma drainage devices, as well as research in more recently introduced surgical methods and their emplacement in our range of surgical therapeutic options. Modulation of wound healing, a factor of paramount importance, has also received its share of research interest. More recently, research has embarked on identifying different surgical approaches and alternative surgical strategies.

Clinical glaucoma surgical research is currently hindered by, among other things, the lack of uniform guidelines for clinical glaucoma surgical trials reporting. This has been clearly highlighted in the last ten years by the controversy that arose from the introduction of non-penetrating glaucoma surgery (NPGS). Despite a plethora of reports currently in the literature, it is quite difficult to make certain and accurate evaluation of the exact location of NPGS among our options. This is mainly because of the absence of a common platform (guidelines) on which studies can be reported and thus compared.

Currently such reports are reported with diverse, variable and inconsistent methodology. This is firstly because such guidelines do not exist, secondly because there is no general consensus, even among the experts in the field, and finally because basic knowledge pertaining to proper methodologies, ethical factors, and statistics are not readily available to all.

Seeing a pressing need for the creation and publication of clear and detailed guidelines for glaucoma surgical trials, the World Glaucoma Association (WGA) took the initiative to form a steering committee and to invite a working group of more than 70 leaders in the field of glaucoma research. The choice of invited scientists took into consideration all aspects related to glaucoma surgical research, spanning from clinical research to economic aspects, statistics, and ethical considerations. The choice of invited scientists was also based on a well-established and active track record of research in this domain.

What you have in your hands is the result of their combined efforts, their brainchild so to speak. After months of debate, controversy, and constructive discussion this group has achieved a consensus on a myriad of topics. These guidelines were validated by the Board of Governors of the WGA, and boards and members of all of its member societies. It can only be useful if it is well adopted by the majority, if not all researchers in this vital field.

The publication of these guidelines is seen by the steering committee as a first step, to be followed by many others aiming to promulgating and advocating its messages.

Tarek Shaarawy
Franz Grehn
Mark Sherwood

Recommended Methodology for Glaucoma Surgical Trials

Richard K. Parrish II, MD, Don S. Minckler, MD, Dennis Lam, MD, Norbert Pfeifffer, MD and Prin RojanaPongpun, MD

Summary Points

- The *Methodology Sub-Committee (MSC)* regards the randomized clinical trial as the most valid methodology to determine the safety and efficacy of new glaucoma surgical procedures and to compare their results and complications with those of established glaucoma surgical techniques.
- The *MSC* recommends investigators comply with the CONSORT checklist for reporting randomized clinical trials.
- The *MSC* understands that non-randomized studies may provide some information regarding outcomes and complications of new glaucoma surgical procedures; however, the non-randomized study design cannot assure the investigation of two comparable groups.
- The *MSC* recommends that investigators include broad-based study populations to develop widely applicable and generalizable new information about glaucoma surgical care.
- The *MSC* strongly supports and encourages the international collaboration of investigators to study new types of glaucoma surgery.
- The *MSC* believes that the benefits and risks of any new glaucoma surgical procedure should be compared with those of established and accepted interventions. The participation of concurrent controls, rather than previously collected information (historical controls) is strongly encouraged.
- The *MSC* recommends that investigators consider defining the nature of the glaucoma on the basis of anterior chamber angle anatomy; the structural state of the disease, based on quantitative assessment of the optic nerve or nerve fiber layer or both; and the functional status, as defined with standard automated perimetry.
- The *MSC* views the establishment of study endpoints before the initiation of any investigation as critical to the interpretation of the results.
- The *MSC* regards the comparison of two procedures to a single procedure as less valid than the comparison of single procedures.

Corresponding author: Richard Parrish II, MD, University of Miami Miller School of Medicine, Bascom Palmer Eye Institute, 900 NW 17th St, Miami, Fl 33136, USA.
E-mail: rparrish@med.miami.edu

WGA Guidelines, pp. 1-14
edited by T. Shaarawy, F. Grehn and M. Sherwood
2008 Kugler Publications, The Hague, Amsterdam, The Netherlands

- The *MSC* recognizes the importance of determining visual function before and after operative intervention to assess the outcomes of glaucoma surgery. Use of standard automated perimetry as described in several large randomized clinical trials may facilitate the comparison of results across different studies.
- The *MSC* recommends that investigators determine the best corrected visual acuity with the standard Snellen charts under standard conditions of distance and illumination or with previously published acuity charts, such as the Early Treatment of Diabetic Retinopathy Study.
- The *MSC* recognizes that several reports have identified the chronic use of specific topical ocular hypotensive medications as risk factors for failure with trabeculectomy. The investigators are encouraged to estimate the length of exposure to each class of medications, and examine for evidence of chronic inflammation.
- The *MSC* recommends masking of the surgeon and patient to the treatment being performed if this is practical; however, we also recognize that this is not possible for most glaucoma surgical procedures.
- The *MSC* recommends that the surgeon who performs the procedure should not evaluate the patient for the purpose of providing information that will be used to judge the success or failure of the procedure.
- When possible, the *MSC* strongly advocates the measurement of endpoints by skilled graders who have not been directly involved in patient care.

Introduction

The *Methodology Sub-Committee* (*MSC*) has been charged with developing guidelines for clinical studies to facilitate the acquisition of useful information to facilitate decision making in glaucoma surgery. Specific directives for the *MSC* state: The key discussion will be on how various elements in different surgical studies can be standardized so that clear comparisons can be made.

The Problem

Since currently no clear guidelines exist on methodology of design and reporting of glaucoma surgical trials, there is evident confusion as to how to draw conclusions and compare published trials.

The *MSC* Guidelines should assist investigators in the planning and reporting of studies that are used to evaluate glaucoma surgery, such as comparative trials, non-comparative case series, interventional case reports, and case control studies.

I. Clinical Interventional Studies (Clinical Trials)

I.1. Comparative Trials

I.1.1. Randomized controlled trial

The participation of patients in a human trial that involves at least one experimental treatment group and one control treatment group, concurrent enrollment, follow-up of the test and control groups, and assignment to experimental and control groups, should be determined by a randomization process. Neither the subjects nor the persons responsible for treatment can influence the assignments, and the assignments must remain unknown to the subjects and staff until eligibility has been determined. (Glaucoma Laser Trial,[2] Fluorouracil Filtering Surgery Study,[3] Collaborative Normal Tension Glaucoma Study,[4] goniotrabeculotomy versus mitomycin C trabeculectomy,[5] Collaborative Initial Glaucoma Treatment Study,[6,7] Advanced Glaucoma Intervention Study,[8] Early Manifest Glaucoma Trial,[9,10] Viscocanalostomy vs Trabeculectomy,[11] Tube versus Trabeculectomy[12,13]).

I.1.2. Non-randomized comparative trial

This study design includes two or more defined groups that are compared to another, to make a judgment about the influence of some factor or treatment. Types of studies to which the guidelines for comparative non-randomized interventional studies apply include:

I.1.2.a. Prospective study with concurrent comparison group; prospective collection of data by predetermined protocol, with assignment to treatment or non-treatment made by method other than randomization.

I.1.2.b. Prospective study with non-concurrent comparison group; prospective data collection for one group by predetermined protocol with a comparison made to data collected at an earlier time or to results in the literature.

I.1.2.c. Retrospective study with concurrent comparison group; retrospective data collection for both groups with the same time period of data collection for each group.

I.1.2.d. Retrospective study with non-concurrent comparison group; retrospective data collection with different time periods of data collection for the two groups, or comparison of a group assessed retrospectively with results in the literature.

I.2. Non-comparative Case Series

A retrospective or prospective report including three or more cases which may or may not be consecutive that describes the outcome of an intervention without a control group for comparison.[14,15]

I.3. Interventional Case Report

Report of one (or two) case(s) in which the outcome of an intervention is described.

II. Observational Studies

II.1. Case-Control Study

An observational (non-interventional, usually retrospective) study that begins by identifying individuals with a disease (cases) for comparison to individuals without a disease (controls). The research typically proceeds from effect to cause.[16,17]

II.2. Cross-Sectional (Prevalence) Study

An observational study that identifies individuals with and without the condition being studied in a defined population at the same point in time (synonymous with prevalence study); may or may not be population-based (Baltimore Eye Survey[18]).

II.3. Cohort Study

An observational study that begins by identifying individuals with (study group) and without (control group) a factor being investigated. Study and control groups may be concurrent or non-concurrent; are almost always prospective and longitudinal with regard to data collection; may or may not be population-based.

II.4. Case Series

A report of three or more consecutive or non-consecutive clinical cases or pathology samples in which the natural history or testing of a condition is described. The cases could be collected and studied prospectively or retrospectively over any time frame.

II.5. Observational Case Report

Report of one (or two) case(s) in which the natural history, testing or clinicopathological correlation is the main theme.

III. Other Study Types

III.1. Systematic Literature Review Study and analysis of previously published papers (Meta-analysis)

Data gathered entirely from existing literature, using statistical methodology to integrate and summarize the results of several studies. The data from individual studies may be weighted by the degree of variance to arrive at a pooled estimate of the outcome. This methodology is usually applied only to analysis of previously published randomized controlled trials (Cochrane Database Systematic Review,[19] 5-fluorouracil, Cochrane Database Systematic Review, Aqueous shunts for glaucoma[20]).

III.2. Experimental Study

Animal or non-human research describing surgical or medical interventions, testing, or devices. Often experimental studies involve changing a natural condition. Usually such a designation will apply to pre-planned (prospective) experiments using a defined protocol in which controls are included.[21,22]

MSC Guidelines

I. Study Design (Levels of Study)

I.1. Prospective or Retrospective

The *MSC* regards the **randomized clinical trial** as the most valid methodology to determine the safety and efficacy of new glaucoma surgical procedures and to compare their results and complications with those of established glaucoma surgical techniques. The international medical community has established a consensus regarding the hierarchy of evidence supporting clinical decision making for patient care: randomized clinical trials, controlled non-randomized trials, cohort studies, case control studies, interventional case series, and case reports.[23-25] The *MSC* recommends that investigators comply with the CONSORT checklist for reporting randomized clinical trials.[26] A modified CONSORT agreement modified published in a widely circulated ophthalmic journal, *Ophthalmology*, is available in the appendix to the Instructions for Authors in the January 2003[1] issue or available on the journal website as Study Design Worksheet #1.[1,26] A revised CONSORT guideline has been proposed by the European Glaucoma Society Standard for Reporting Glaucoma Surgical Trials (personal communication, Grehn F, Minckler DS, Lam D, November 2006). A revised CONSORT statement is available in the general medical literature.[27]

The *MSC* recognizes that the successful completion of randomized clinical trials requires a sufficient sample size of eligible patients, rigorous compliance to established methodology, and the expenditure of considerable effort and

money; however, the prospective study design minimizes selection bias and influence of the surgeon. For these reasons, the randomized clinical trial is the preferred methodology.

I.2. Randomized or Not

The *MSC* understands that non-randomized studies may provide some information regarding outcomes and complications of new glaucoma surgical procedures; however, the non-randomized study design cannot assure the investigation of two comparable groups. The unequal or unintentional assignment of patients or eyes with previously unidentified risk factors for failure may influence study results. Guidelines for reporting studies other than randomized clinical trials have been published and are available through the website of the journal *Ophthalmology*, as Study Design Worksheets #2 Non-randomized comparative trial, #3 Non-comparative Case Series, #4 Interventional Case Report, #5 Case-control Study, #6 Cross-sectional Study, #7 Cohort Study, #8 Observational Case Series, #9 Observational Case Report.[1,28] The *MSC* suggests that investigators use these worksheets to organize the methodology and presentation of results of nonrandomized trials.

I.3. Single versus Multiple Centers; Single Country versus Worldwide Enrollment

The *MSC* recommends that investigators include broad based study populations to develop widely applicable and generalizable new information about glaucoma surgical care. Multiple centers at international clinical sites and the participation of geographically distributed investigators may, in part, help to satisfy this recommendation. The *MSC* strongly supports and encourages the international collaboration of investigators to study new types of glaucoma surgery. This is of particular value in assuring the adequate enrollment of eligible patients with uncommon types of glaucoma.

I.4. Control Group

The *MSC* believes that the benefits and risks of any new glaucoma surgical procedure should be compared with those of established and accepted interventions. The participation of concurrent controls, rather than previously collected information (historical controls) is strongly encouraged. Currently trabeculectomy ab externo, the most widely performed filtering procedure worldwide, is the standard intervention against which newer procedures should be compared. If other types of glaucoma surgery that lower intraocular pressure (IOP) by reducing aqueous humor production are studied, such as newer cyclodestructive procedures, then their results should be compared with earlier cycloablative procedures or with concurrently performed trabeculectomy.

I.5. Single Disease Group or Several Types of Glaucoma

The classification of glaucoma has been defined in many glaucoma textbooks[29] and society publications.[30] The *MSC* recommends that investigators consider defining the nature of the glaucoma on the basis of anterior chamber angle anatomy; the structural state of the disease, such as quantitative assessment of optic nerve or nerve fiber layer or both; and the functional status, as defined with standard automated perimetry. At a minimum, studies should include the following description:

Primary Open Angle
Secondary Open Angle
  Pigmentary Dispersion
  Exfoliation Syndrome
Closed Angle
  Acute
  Chronic
  Neovascularization of the anterior segment
  Plateau Iris syndrome
  Iridocorneal endothelial syndrome
Associated with other ocular conditions
  Congenital glaucoma
    Not associated with ocular findings
    Associated with other ocular findings such as anterior segment dysgenesis
Previous ocular procedures involving the conjunctiva
  Filtering surgery
  Vitrectomy
  Scleral buckling surgery

I.6. Population Types Including Gender, Race, Age, Other Disease (such as Diabetes, Rheumatological Disease or Corneal Pathology)

The *MSC* recommends the inclusion of broad categories of patients or eyes or both, to assess the value and risk of newer glaucoma surgical procedures. Previously identified patient-specific risk factors for filtering surgery failure, such as youth and ancestral history, should be specified. Unless the study is designed to determine the outcome in previously unoperated eyes, eyes with specific risk factors for failure, such as aphakia, neovascularization of the iris, and failed filtering surgery, previous ocular surgery with conjunctival incision, should be included. The investigators should define the study population as total number of eligible patients who were offered participation in the study. The investigators should provide specific reasons why eligible patients did not elect to participate and explain any possible selection bias in establishing the study and control groups. If ineligible patients constituted a specific group based on characteristics, such as ancestral history, gender, age, socioeconomic background, or education, then they should be identified. The investigators should describe how the eligibility of patients selected for participation could limit the generalizability of the results.

I.7. Single Procedure versus Multiple (such as Combined Cataract/ Trabeculectomy or Penetrating Keratoplasty (PKP)/Trabeculectomy)

The *MSC* recognizes that the presence of two conditions, such as visually disabling cataract and medically uncontrolled glaucoma argues for the surgical intervention of both problems in a single setting, 'combined procedure'. Although the *MSC* finds some value in the comparison of the results of combined glaucoma and cataract procedures versus either cataract surgery or trabeculectomy alone, a statistically valid comparison cannot be made if justifications for both conditions require intervention for matters of patient safety. The decision to perform combined procedures should be based on patient needs. The possibility of comparing two types of combined procedures, such as phacoemulsification and trabeculectomy with phacoemulsification and cycloablative procedures, such as endocycophoto-coagulation should be based on uniform eligibility. The comparison is best achieved in the context of a randomized clinical trial.

I.8. Pre-Selection of Endpoints

The *MSC* views the establishment of study endpoints before the initiation of any investigation as critical to the interpretation of the results. This is particularly important when outcome assessment is based on information that has been previously recorded or historical controls. In randomized clinical trials, endpoints must be clearly stated and accepted by a data and safety monitoring committee for the purpose of defining conditions that demand that patient recruitment be discontinued (Stopping rules).

I.9. Comparison of Two Procedures versus Single Procedure Study

The *MSC* regards the comparison of two procedures to a single procedure as less valid than the comparison of single procedures. If two procedures are compared with a single intervention, then randomization is important to assure that selection bias did not cause the unintentional or unbalanced assignment of patients or eyes with risk factors for failure to one group.

II. Baseline Pre-Operative Data

II.1. How Many Data Points, Timing Before Surgery for Data Collection

II.1.1. Intraocular pressure measurement

Most studies compare the preoperative and postoperative intraocular pressure (IOP) values to determine the effectiveness of a glaucoma surgical procedure. The *MSC* recommends that preoperative intraocular pressure (IOP) be measured with a properly calibrated Goldmann Applanation Tonometer (GAT) by an individual who does not determine the success or failure of the

procedure or provide direct patient care. If methods other than GAT, such as pneumotometry, Tonopen, air puff, or dynamic contour tonometry are used to measure IOP, then the investigators should explain the rationale for their choice of instrumentation and provide GAT values for comparison. Optimally, the individual reading the tonometer dial and recording the numerical value should not be the same person who is viewing and aligning the mires of the Goldmann tonometer. This technique was used in the OHTS.[31,32] At least two measurements should be taken and averaged to determine the mean IOP as used in the OHTS, if the two values are within 2 mmHg.[31,32] Three measurements should be taken if the first two determinations are greater than 3 mmHg in difference. In this case, the median value should be used. The mean of at least three IOP readings taken at different hours of the day, on at least two separate days, not necessarily consecutive, but within a period of a month, should be employed to establish a preoperative or baseline value.

II.1.2. Central corneal thickness

To understand the IOP value as determined by GAT more completely, the *MSC* strongly recommends that the investigators measure the preoperative and postoperative central corneal thickness (CCT) with ultrasonic pachymetry. At least three values should be taken for each eye and averaged to define a preoperative and postoperative level. Differences in response to surgical intervention of various populations should be discussed in terms of central corneal thicknesss.

II.1.3. Preoperative ocular hypotensive medications

Since most patients use glaucoma IOP lowering therapy, the *MSC* recommends that the name, dose, and dosage of topical and oral ocular hypotensive medications, be specified before and after surgical intervention. Medications should be identified by class or generic name and not by brand name, for example, ‘alpha agonists, beta blockers, carbonic anhydrase inhibitors, prostaglandins, prostamides, adrenergic, cholinergic, guanethidine’ (Terminology and Guidelines for Glaucoma IInd Edition, Table IX, Monotherapy. Available free online at www.eugs.org after registration)[33] or ‘miotics, sympathomimetics, beta-adrenergic blocking agents, hyperosmotic agents, carbonic anhydrase inhibitors, alpha-2 selective agonists, prostaglandins’ (Physician Desk Reference).[34]

II.1.4. Visual field criteria

The *MSC* recognizes the importance of determining visual function before and after operative intervention. Use of standard automated perimetry as described in several large randomized clinical trials may facilitate the comparison of results across different studies. In The Advanced Glaucoma Intervention Study,[8] Collaborative Initial Glaucoma Treatment Study,[6,7] Collaborative Normal Tension Glaucoma Study[4] and Early Manifest Glaucoma

Trial,[9] visual field criteria have been widely published. The *MSC* recommends that investigators choose one of these previously published criteria, until an international consensus can be developed for the adoption of a single perimetric standard to be used in all future studies. The Glaucoma Progression Analysis software, based on the Glaucoma Change Probability Map that was used in the EMGT, may assist in determining progression.

II.1.5. Visual acuity

The *MSC* recommends that investigators determine the best corrected visual acuity with the standard Snellen charts under standard conditions of distance and illumination or with previously published acuity charts, such as the Early Treatment of Diabetic Retinopathy Study (ETDRS).

II.2. How to Randomize (Statistical Sub-committee)

The *MSC* recommends that investigators provide specific information to describe the precise method used to randomize eyes or patients. If random number tables or computer generated random number lists were used, then the specific type and methodology should be reported. The alternate assignment to one of two different treatments does not satisfy the requirements for randomization. When multiple clinical sites participate in the study, randomization in blocks should be performed to assure comparable randomization occurred at different clinical site locations throughout the course of the study.

If eyes, rather than patients were the units randomized, then the investigators should describe the rationale for this decision. Both eyes should not be included in the study except exceptionally, and the rationale for this decision should be clearly stated. If both eyes were included in the study, then the method of determining treatment for the first and second eye should be described in detail.

II.3. Effect on Tissues and Surgical Result of Therapy Given Before Surgery

The *MSC* recognizes that several reports have identified the chronic use of specific topical ocular hypotensive medications as risk factors for failure with trabeculectomy. The investigators are encouraged to estimate the length of exposure to each class of medications. The investigator should examine for signs of chronic ocular inflammation, such as follicular conjunctivitis, conjunctival hyperemia, and subconjunctival scarring, and attempt to quantitatively describe them. The description of these clinical findings may be of greater value than simply the identification of the duration and type of topical ocular hypotesive medication, since most patients receive multiple-drug therapy and are unaware of the exact length of exposure.

III. Procedure Methodology

III.1. Masking of surgeon if control group (for example, giving injections, use of implants)

The *MSC* recommends masking of the surgeon and patient to the treatment being performed if this is practical; however, we also recognize that this is not possible for most glaucoma surgical procedures. The scientific benefit of using sham intraocular or subconjunctival injections and conjunctival incisions that do not communicate with the anterior chamber must be weighed against the potential risk of causing harm, such as intraocular hemorrhage, infection, and subconjunctival scarring. Local Ethics Boards or Institutional Review Boards should determine which control procedures are appropriate and are consistent with the tenets of the Declaration of Helsinki.

III.2. Standardization of Study Procedure versus Real-world Surgeon Preference to Increase Generalizability

The *MSC* recommends that investigators describe the newer intervention for the readers, experienced glaucoma surgeons, so they can understand the rationale for the intervention and exactly how the procedure was performed. Ideally, the reader interested in learning more about the surgical procedure should be able to perform the technique after additional training. The inclusion of the results from skilled glaucoma surgeons who are not part of a small formal study group can provide information that may be generalizable to a larger group of patients. If the investigators use devices or drugs that are not commercially available, then they must provide identifying information regarding the manufacturer and location. Patients must provide appropriate informed consent that indicates they understand the investigational nature of the treatment.

III.3. Intraoperative Complications

The *MSC* recommends the reporting of intraoperative complications that accurately reflect the prevalence and severity of the unintended event. The analysis of results from patients who participate in prospective studies should be based on the initial randomization or assignment, (Intent to Treat Analysis), irrespective of the nature of the intraoperative complication. The effect of the intraoperative complication should be discussed in terms of effect on outcome measurement, such as visual acuity and visual field.

IV. Post-Operative Assessment

IV.1. Masking of Surgeon for Study Readings if Control Group

The *MSC* recommends that the surgeon who performs the procedure should not evaluate the patient for the purpose of providing information that will be

used to judge the success or failure of the procedure. The surgeons will record information that is used in customary patient care. This information may be evaluated by a separate group of individuals who assess the outcomes, the Data and Safety Monitoring Committee. The *MSC* recognizes that neither the personnel nor the funding may be available to provide the Data and Safety Monitoring Committee oversight for all studies. In these cases, the surgeon may record the data and forward the information to others to evaluate who are not involved in direct patient care.

IV.2. Measurements of End-points (Reading Centers versus Surgeon Review)

When possible, the *MSC* strongly advocates the measurement of endpoints by skilled graders who have not been directly involved in patient care. The *MSC* also recognizes that lack of adequately trained personnel and sufficient funding may prevent reading centers from being established for all studies. The *MSC* encourages the development of internationally based reading centers that could provide this service to international investigators.

IV.3. Masked End-point Committees

The assessment and interpretation of study results should be based on information that is masked to treatment assignment. Ultimately the determination of which group underwent safer or more effective surgery should be made after classification of results based on previously established endpoints.

References

1. Ophthalmology. Study Design Worksheets 1-11. Available at http://www.elsevier.com/framework_products/promis_misc/620418forms.htm. Accessed on January 19, 2007.
2. Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT) and Glaucoma Laser Trial Follow-up Study (GLTFS): VII. Results. Am J Ophthalmol 1995; 120: 718-731.
3. The Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the Fluorouracil Filtering Surgery Study. Am J Ophthalmol 1996; 121: 349-366.
4. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol 1998; 126: 498-505.
5. Quaranta L, Hitchings RA, Quaranta CA. Ab-Interno goniotrabeculotomy versus mitomycin C trabeculectomy for adult open-angle glaucoma. Ophthalmology 1999; 106: 1357-1362.
6. Musch DC, Lichter PR, Guire KE, Standardi CL; CIGTS Investigators. The Collaborative Initial Glaucoma Treatment Study (CIGTS): study design, methods, and baseline characteristics of enrolled patients. Ophthalmology 1999; 106: 653-662.
7. Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA, Mills RP, and the CIGTS Study Group. Interim clinical outcomes in The Collaborative Initial Glaucoma Treatment Study (CIGTS) comparing initial treatment randomized to medications or surgery. Ophthalmology 2001; 108: 1943-1953.

8. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000; 130: 429-440.
9. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002; 120: 1268-1279.
10. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. Arch Ophthalmol 2003: 121: 48-56.
11. Carassa RG, Bettin P, Fiori M, Brancato R. Viscocanalostomy vs Trabeculectomy in white adults affected by open-angle glaucoma: a 2-year randomized, controlled trial. Ophthalmology 2003; 110: 882-887.
12. Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL; The Tube Versus Trabeculectomy Study Group. Treatment Outcomes in the Tube Versus Trabeculectomy Study After One Year of Follow-up. Am J Ophthalmol. 2007; 143: 9-22.
13. Gedde SJ, Herndon LW, Brandt JD, Budenz DL, Feuer WJ, Schiffman JC; The Tube Versus Trabeculectomy Study Group. Surgical Complications in the Tube Versus Trabeculectomy Study During the First Year of Follow-up. Am J Ophthalmol 2007; 143: 23-31.
14. Fontana H, Nouri-Mahdavi K, Lumba J, Ralli M, Caprioli J. Trabeculectomy with mitomycin C in pseudophakic glaucomatous eyes: outcomes and risk factors for failure. Am J Ophthalmol 2006; 141: 652-659.
15. Gressel MG, Parrish RK II, Heuer DK: Delayed nonexpulsive suprachoroidal hemorrhage. Arch Ophthalmol 1984; 102: 1757-1760.
16. Jampel HD, Quigley HA, Kerrigan-Baumrind LA, Melia BM, Friedman D, Barron Y; Glaucoma Surgical Outcomes Study Group. Risk factors for late-onset infection following glaucoma filtration surgery. Arch Ophthalmol. 2001; 119: 1001-1008.
17. Soltau JB, Rothman RF, Budenz DL, Greenfield DS, Feuer W, Liebmann JM, Ritch R. Risk factors for glaucoma filtering bleb infections. Arch Ophthalmol 2000; 118: 338-342.
18. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javitt J, Singh K. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol 1991; 109: 1090-1095.
19. Wormald R, Wilkins MR, Bunce C. Post-operative 5-Fluorouracil for glaucoma surgery. Cochrane Database Syst Rev 2001; CD001132. Review.
20. Minckler DS, Vedula SS, Li TJ, Mathew MC, Ayyala RS, Francis BA. Aqueous shunts for glaucoma. Cochrane Database Syst Rev 2006; 19: CD004918. Review.
21. Gressel MG, Parrish RK II, Folberg R. 5-Fluorouracil and glaucoma filtering surgery. I. An animal model. Ophthalmology 1984; 91: 378-383.
22. Minckler DS, Shammas A, Wilcox M, Ogden TE. Experimental studies of aqueous filtration using the Molteno Implant. Trans Am Ophthalmol Soc 1987; 85: 368-392.
23. Guyatt G. Therapy and harm: why study results mislead – bias and random error. In: Guyatt G, Rennie D (eds.) Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. Chicago, IL: AMA Press 2002: 223-231.
24. Levine M, Haslam D, Walter S, et al. Harm. In: Guyatt G, Rennie D (eds.) Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. Chicago, IL: AMA Press 2002: 81-100.
25. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. JAMA 1996; 276: 637-639.
26. CONSORT agreement for a randomized controlled trial. Ophthalmol 2003: 110: 225-227.

27. Moher D, Schulz KF, Altman DG, for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Lancet 2001; 357: 1191-1194.
28. Guide for authors. Worksheets 2-11. Ophthalmology 2003; 110: 227-244.
29. Ritch R, Shields MB, Krupin T. Classifications of the glaucomas. In: Ritch R, Shields MB, Krupin T (eds.) The Glaucomas Basic Sciences. Volume II Clinical Science, 2nd Ed.St. Louis: Mosby 1996, 720-722.
30. European Glaucoma Society. Terminology and Guidelines for Glaucoma. IInd Edition. Chapter 2 – Classification and terminology. Savona, Italy 2003. Available at www.eugs.org (accessed on January 19, 2007; registration required for free download).
31. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: A randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002; 120: 701-713.
32. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: Baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol 2002: 120: 714-720.
33. European Glaucoma Society. Terminology and Guidelines for Glaucoma IInd Edition, Flowchart IX – Monotherapy. Savona, Italy. 2003 Available at www.eugs.org (accessed on January 19, 2007; registration required for free download).
34. Rhee DJ, Rapuano CJ, Weisbecker CA, Fraunfelder FW, Fraunfelder FT. Agents for treatment of glaucoma. In: Rhee DJ, Rapuano CJ, Weisbecker CA, Fraunfelder FW, Fraunfelder FT (eds.) PDR 32 Edition 2004, Physicians' Desk Reference for ophthalmic medicines. Montvale: Thomson PDR 2004,11.

Consensus on definitions of success

D.K. Heuer, K. Barton, F. Grehn, T. Shaarawy and M. Sherwood

Summary Points

- Although IOP is a surrogate end-point in the management of glaucoma, IOP reduction is the principle end-point of glaucoma surgical trials.
- Other end-points are important in certain circumstances (eg. angle width in treatment of angle closure).
- Robust baseline IOP documentation and consistent IOP recording is essential.
- Pre- and post-operative numbers of medications should be enumerated as the total number of classes of hypotensive drugs being used.
- Definitions of success should be clearly stated in trial design and should include an upper and lower limit. These may include more than one upper limit or a combination of an upper limit and a percentage reduction.
- Graphical representation of success should clearly illustrate the number of patients still in the trial at a particular time-point. The patients who have achieved a particular end-point without additional hypotensive medications, should be distinguishable from those who have required medications.
- A survival curve plus a scatter plot is the *minimum* requirement for presentation of trial outcomes data.
- Visual field data should be reported where possible, although the practicality of using visual field data as a primary outcome measure is limited in surgical trials for a number of reasons.

Introduction

A lack of consistency in reporting glaucoma surgical trials has hindered progress and communication among investigators and made comparison among studies difficult and sometimes, impossible. The development of reporting guidelines should facilitate trial design and outcome dissemination, without impeding innovation.

Recognizing that intraocular pressure (IOP) is currently the only modifiable risk factor for glaucoma, and that IOP reduction is the goal of current

Corresponding author: K. Barton, Moorfields Eye Hospital, 162 City Road, London EC1V 2PD, UK. E-mail: Keith.barton@moorfields.nhs.uk

WGA Guidelines, pp. 15-24
edited by T. Shaarawy, F. Grehn and M. Sherwood
2008 Kugler Publications, The Hague, Amsterdam, The Netherlands

glaucoma surgical approaches, variations of IOP reporting will inevitably be the cornerstone of success definitions; however, standardized presentation of other aspects of surgical outcome, should also be encouraged.

Report

I. Intraocular Pressure Documentation

I.1. Tonometry

Unless otherwise impossible, IOP measurement should be performed by Goldmann tonometry, the calibration accuracy of which has been confirmed periodically. Other tonometers may be used in certain situations in which Goldmann applanation tonometry (GAT) would be less accurate. Such situations include the presence of corneal edema and corneal scarring. However, other tonometers should not be used routinely, until a consensus regarding their accuracy has been established.

IOP should be measured at least twice in each eye, returning the tonometer dial to 10 mmHg (or another random position) between readings. If the first two measurements are within 2 mmHg, the mean IOP should be used, otherwise a third measurement should be obtained and the median recorded.

IOP readings should ideally be obtained on all subjects each day at the same time of the day before and after surgery at key postoperative windows (see below). IOP measurements at 08:00, 12:00, 16:00, and 20:00 are desirable to assess diurnal IOP variation. However, recognizing that few surgical trials are supported by external funding, diurnal measurement may be impractical.

I.2. Definition of Baseline IOP

In order to quantify the IOP reduction after surgery, a consistent definition of the *baseline*, or *reference* IOP is essential. This may be recorded as the IOP before medication was started, the IOP after washout of medication, or the IOP on the patient's full medical regimen just before surgery (usually the maximum tolerated treatment).

No consensus was reached as to which of these was the most appropropriate. However, it was agreed that for practical purposes, the treated IOP just before surgery should be used, as this level is considered to be the best that medical treatment can achieve.

Single values are insufficient for documenting baseline IOP. The mean of at least three IOP readings taken at different hours of the day, on at least two separate days, not necessarily consecutive, but within a period of a month, should be employed to establish a preoperative or baseline value.

I.3. Success and Failure

There is a consensus that IOP *success* should be reported with a number of alternative upper limits (*i.e.*, ≤ 21, 18, 15, and 12 mmHg) and one lower limit (*i.e.*, 6 mmHg).

Failure would be defined as an IOP level measured above the upper limit or below the lower limit on *two* consecutive study visits.

Complete failure would be defined as loss of light perception attributable to glaucoma, or the necessity for further glaucoma surgical intervention (or recommendation thereof). Certain postoperative surgical *adjustments,* such as flap suturelysis, suture release, or Nd:YAG goniopuncture to the trabeculo-Descemet's window would be excluded from this category and would not be recorded as evidence of failure.

There is no consensus on whether late needling revision of a trabeculectomy bleb should be categorized as complete failure or simply as an additional measure to re-establish bleb function and promote ongoing success.

Success should be characterized according to whether or not this has been achieved without (complete success) or with ocular hypotensive medications (qualified success).

Furthermore, the number of ocular hypotensive medications should be reported before and after surgery. Fixed combination medications should be documented according to the number of active ingredients. Only one drug in each class of medication should be counted, *e.g.*, a topical, plus a systemic carbonic anhydrase inhibitor, should be counted as one medication.

Ideally, the numbers of patients requiring systemic carbonic anhydrase inhibitors before and after surgery should be identifiable separately. The reason is that, in contrast to topical medications, this medication is not usually a sustainable option after surgery and patients requiring systemic carbonic anydrase inhibitors in the long-term after surgery are usually classed as surgical failures.

I.4. Confounding Influences

In some patients, the baseline IOP may be within the normal range and therefore lower than some of the predefined upper limits of success. Under these circumstances it is important to judge success in terms of the percentage reduction in IOP achieved by surgery.

However, it is important to recognize that a patient with a preoperative IOP of 18 mmHg on 3-4 ocular hypotensive medications, whose postoperative IOP is 15 mmHg without medications, would be categorized as a 'failure' if a 20% reduction is required, even though such IOP in a patient with mild glaucoma might well be a successful outcome.

Others (CIGTS and EGS guidelines) have suggested various sliding scale targets based on the severity of visual field damage, perhaps classified into as many as the following five general loss categories: 0 to –5 dB; > –5 dB to –10 dB; > –10 dB to –15 dB; ≥ –15 dB (given common parlance of mild,

moderate, and advanced). With this approach, the following two suggestions were made for target IOP: ≤ 18 mmHg peak for mild glaucoma damage, ≤ 15 mmHg for moderate, and ≤ 12 mmHg for advanced damage.

OR in percentage terms: ≥ 20% IOP reduction and absolute IOP ≤ 21 mm Hg for mild glaucomatous damage; ≥ 30% IOP decrease and ≤ 18 mmHg for moderate glaucomatous damage; ≥ 40% and ≤ 15 mmHg for advanced damage.

While this degree of subcategorization is certainly possible, others emphasized that the purpose of glaucoma surgery is IOP reduction, so perhaps it is more important to be able to understand to what degree and quality (*i.e.*, need for supplemental ocular hypotensive medications and anticipated IOP fluctuation) the IOP can be expected after a specific surgical approach.

It is still difficult from the current evidence base to stipulate exact targets with any degree of certainty. These levels are guidelines.

II. General Data Presentation Requirements

Many important issues, such as sample size, study design, and specific statistical testing recommendations, will be discussed within the Statistics section of these guidelines.

However, it is important to emphasize that to understand the degree of variability within studies, the outcomes discussed should include mean and standard deviation or 95% confidence intervals for normally distributed data, while median and range should be used where the distribution of the data is less certain. The standard error should not be used.

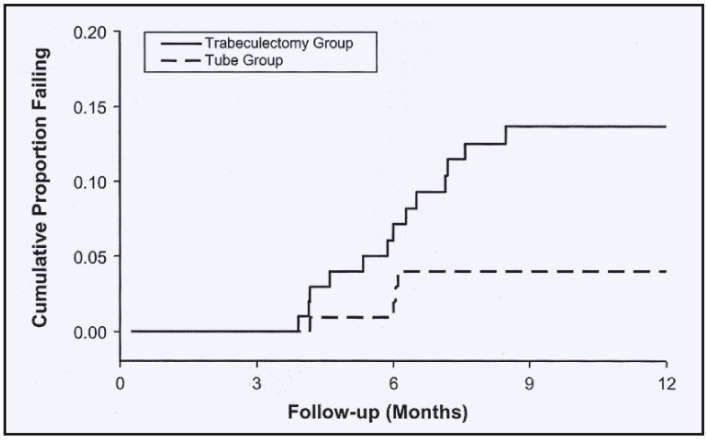


Fig. 1. Kaplan-Meier graph. In this graph, endpoints must be defined according to success criteria (21 mmHg, 18 mmHg, 15 mmHg, 30%, or combined). (From: Gedde SJ, et al., Am J Ophthalmol 2007; 143: 9-22)

Whenever possible, outcome data should be included for all patients and summarized according to the various criteria for success and failure. Survival curves (*e.g.*, Kaplan Meier) are considered mandatory for demonstrating surgical success. These should be displayed for the above success criteria. Survival should also be tabulated to document the numbers in each study group analyzed at each follow-up point. These should ideally be at annual intervals, but also including 6- and 18-month data (Fig. 1).

Specific IOP results should also be depicted graphically with scatter plots, as preoperative IOP (x-axis) versus postoperative IOP (y-axis); with distinctive symbols for postoperative IOPs with and without ocular hypotensive medications.

Scatter plots are particularly helpful at illustrating the proportions of study subjects who meet various criteria for success. A diagonal line at 45-degree (y = x) is especially helpful in illustrating those with an IOP reduction after surgery (right lower half) from those with an IOP increase (left upper half) or no change (Fig. 2).

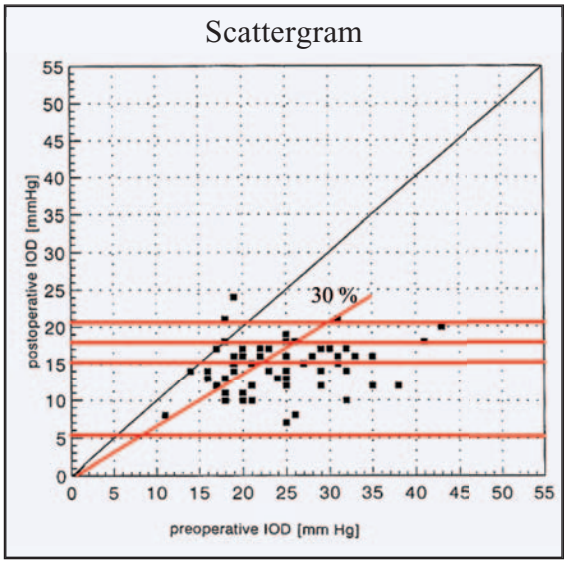


Fig. 2. Scattergram: (a) Preoperative IOP after 1 year: Each point represents one eye showing the preoperative IOP value on the abszissa, and the postoperative IOP values on the ordinate, respectively. Olique line indicates no change. (b) possible cut-off lines and percentage IOP decrease indicating defining 'success'. (From: Mutsch YA, Grehn F, et al., Graefe´s Arch Clin Exp Ophthalmol 2000; 238: 884-891.)

Other illustrative options include the percentage reductions, *e.g.,* 20%, 30%, 40%, which can also be included as appropriately sloped diagonal lines, or horizontal lines to represent absolute IOP targets (*e.g.*, 21 mmHg, 18 mmHg, and 16 mmHg, with an additional lower IOP-limit line drawn at 6 mmHg. These lines are, of course, for illustrative purposes and their selective use is encouraged.

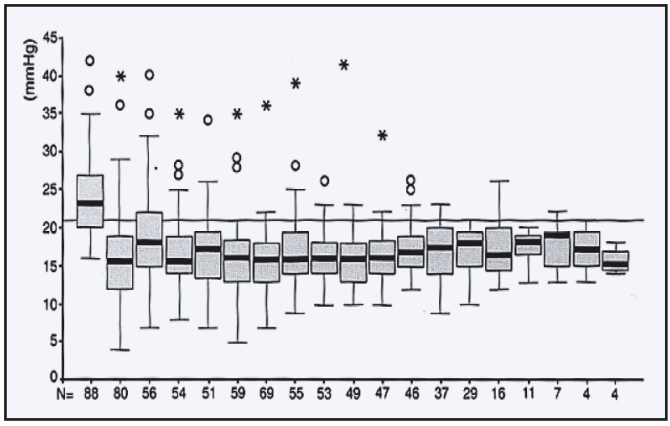


Fig. 3. Box-plot representation of IOP values over 18 months of follow-up: Median values (dark lines), 25/75 (boxes) and 5/95 percentiles (bars), and outliers (circles), respectively. Stars show significance ($p \leq 0.5$). The number of cases over the follow-up period is shown on the abszissa. Hence, a lot of information can be reproduced from this type of graphic representation. (From: Hoffmann E, et al.: Graefe´s Arch Clin Exp Ophthalmol 2002; 240: 2-6.)

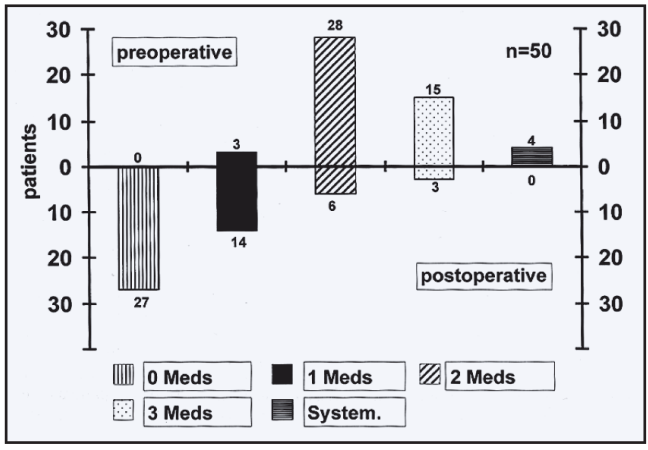


Fig. 4. This is a more condensed version of pre- versus post-operative medication: Upwards = preoperative, Downwards = postoperative. In this graph, topical and systemic medications are separated. (From: Borggrefe J, Grehn F, et al., Graefe´s Arch Clin Exp Ophthalmol 1999; 237: 887-892.)

If bar diagrams are used, it was agreed that box-plots should show median values, as well as 25/75 percentiles. 5/95 percentiles should be shown as bars. Outliers should also be added. Bars with mean values plus/minus standard deviation are not ideal as the distribution of study IOPs may not be normal. This graph has the advantage that it illustrates the change in IOP over time (Fig. 3).

Other illustrative options also include a graphic representation of pre- versus post-operative medications, in this graph topical versus systemic medications should be separated (Fig. 4).

In summary, a scatter plot plus a survival curve are considered to be the gold standard means of graphical representation of surgical success. A box-plot may also be helpful.

The evidence that circadian and long-term IOP fluctuation may be a risk factor for progression is controversial at the time of writing. Nevertheless, both provide useful extra information and should be reported if available.

III. Other Possible IOP-Related Outcome Measures

In studies designed to alter bleb morphology, this should be recorded by a masked evaluator using standardized photographs for comparison. The use of a reading center would be a good way of achieving this.

In studies examining symptomatology, quality of life, or patient function (*e.g.,* walking or driving) validated questionnaires or exercises should be administered by masked, trained individuals (or by telephone interview from centralized coordinating centers).

Although the assessment of primary angle closure and angle-closure glaucoma is outside the remit of this document, it is essential in surgical trials comparing treatments for angle closure, that end-points such as extent of iridotrabecular contact, peripheral anterior synechiae (PAS) and measures of angle width, before and after surgery, are documented, as well as IOP. These should be documented at each visit under identical lighting conditions (ideally with minimum slit-lamp illumination). If angle-width parameters are measured using anterior segment optical coherence tomography, this should be ideally performed on each occasion in a dark room.

Prophylactic procedures to prevent acute angle-closure glaucoma and/or progressive PAS should report the incidence of acute angle-closure episodes during the follow-up period.

IV. Visual Fields

Aside from the fundamental difficulty of defining visual field progression, the confounding influence of cataract, and the relatively short-term nature of most surgical studies, the incorporation of visual field status into the definition of success is problematic.

Preoperative and one year postoperative mean deviations should be reported. The baseline mean parameters recorded should be based on at least two field examinations before surgery. Likewise after surgery these should be reported at one and five years. If a change is detected this must be confirmed by a repeat visual field test. Ideally, visual field data should be reported in trial subjects with mean deviations better than –15 dB. Please also consider the recommendations from the methodology subcommittee (*MSC*) on visual field criteria (II.1.4)

In comparative studies, inter-group changes might be detectable even with such global reporting.

V. Visual Acuity

Best corrected visual acuity (BCVA) testing should be standardized (ideally with ETDRS charts). Beyond 20/400 (6/120), visual acuity should be measured in increments of at least 5/200 (≈ 1.5/60), 2-3/200 (≈ 0.75/60), 1/200 (≈ 0.3/60), hand movements (HM), light perception (LP), and no light perception (NLP). Visual acuity should be averaged by log(MAR) values only.

Visual acuity, like visual fields, has many potential confounders (*e.g.*, retinal diseases, corneal pathology, and pathologic intracranial processes, and limitations with individual patient reliability). Consequently, it should not be an integral part of the definition of failure, except in the case of loss of light perception, attributable to either glaucoma progression or surgical complications. Doubling of the minimal angle of resolution (MAR) (loss of approximately two Snellen lines) attributable to any cause should be reported and the reasons listed.

Specific BCVA results should also be depicted graphically on a log(MAR) scale, as preoperative BCVA (x-axis) versus postoperative BCVA (y-axis); with distinctive symbols for postoperative BCVA based on whether the individual patient represented by each point was categorized as a complete success, qualified success, or failure. For the purposes of statistical analysis and graphical representation, HM will be considered 1/800, LP 1/1600, and NLP 1/3200.

VI. Complications

A standardized menu of complications has been developed within these guidelines to facilitate reporting (please consider recommendations from the subcommittee on reporting complications). However, complications (even those for which surgical intervention is undertaken, such as anterior chamber reformation or choroidal effusion/hemorrhage drainage) should not constitute failure, unless they led to visual acuity (or visual field) decrement.

VII. Follow-up

Minimum follow-up should be one year with survival analysis indicating how many patients are still represented at each time point. Prospective data acquisition is strongly preferred.

It is important that trials reporting data at a particular follow-up time-point actually report the IOP of every patient still in the trial at that follow-up point. *E.g.*, IOP at one year should be reported as the IOP in the patients in whom IOP was measured at one year. This is very different from reporting the IOP at last follow-up in every patient in a study group of whom the average follow-up was one year.

The following are proposed reporting time windows:

	Pre-op	POD1	POW1	POM1	POM3	POM6	POY1	POM18	POY2	POY≥3
Ideal	1-7d	1d	7d	28-31d	90-92d	181-183d	Ann. date	547-548d	Ann. date	Ann. date
Preferred	0-21d	1-2d	4-11d	21-42d	77-106d	161-204d	334-387	486-609d	669-822d	±91d
Acceptable	0-42d	1-3d	4-14d	15-60d	61-122d	123-272d	273-456d	457-639d	640-913d	±181d

Preoperative: Ideal date = 1-7 days preoperatively; preferred range = 0-21 days preoperatively; acceptable range = 0-42 days preoperatively.

Postoperative day 1 (POD1): Ideal date = 1 day postoperatively; preferred range = 1-2 days postoperatively; acceptable range = 1-3 days postoperatively.

Postoperative week 1 (POW1): Ideal date = 7 days postoperatively; preferred range = 4-11 days postoperatively; acceptable range = 4-14 days postoperatively.

Postoperative month 1 (POM1): Ideal date = 28-31 days postoperatively; preferred range = 21-42 days postoperatively; acceptable range = 15-60 days postoperatively.

Postoperative month 3 (POM3): Ideal date = 90-92 days postoperatively; preferred range = 77-106 days postoperatively; acceptable range = 61-122 days postoperatively.

Postoperative month 6 (POM6): Ideal date = 181-183 days postoperatively; preferred range = 161-204 days postoperatively; acceptable range = 123-272 days postoperatively.

Postoperative year 1 (POY1): Ideal date = 365-366 days postoperatively; preferred range = 334-387 days postoperatively; acceptable range = 273-456 days.

Postoperative month 18 (POM18): Ideal date = 547-548 days postoperatively; preferred range = 486-609 days postoperatively; acceptable range = 457-639 days postoperatively.

Postoperative year 2 (POY2): Ideal date = surgery 2-year anniversary date; preferred range = 669-822; acceptable range 640-913.

Postoperative year 3 and beyond (POY $\geq$ 3): Ideal date = surgery anniversary date; preferred range ideal date ± 91 days; acceptable range ideal date ± 182 days.

Conclusions

Accurate and consistent IOP measurement is the cornerstone of glaucoma surgical trials. The accuracy of this primary outcome measure is critically dependent on the method of establishing an accurate baseline IOP and the method of IOP reporting.

Consistent postoperative time-points should be used, as recommended above and reported data should record the number of patients or eyes examined at that particular time-point.

Success rates may be defined in complete and qualified terms and there are a number of possible definitions of success that should be determined before surgery. These may include a combination of absolute and percentage reductions.

When reporting success, not only must survival be graphically represented, but the numbers of trial subjects who achieve a certain level of success should be clear as should the level of dependence of this success on ocular hypotensive medications. A scatter plot is the most useful way of documenting this.

Further Research Needed

While traditionally surgical trials have suffered from weaknesses such as case selection bias and variability in surgical technique, arguably the greatest weakness facing surgical trials in future will be the lack of a clear evidence base for many of our presumed thresholds for success.

Accepting the difficulties and limitations involved in visual field reporting in surgical trials, large long-term studies of visual field progression are essential to test the conventional wisdom that the setting of certain ‘targets’ is actually beneficial to the patient with glaucoma. Until the dose-response curve of IOP-lowering versus rate of glaucoma progression is absolutely clear, our current definitions of success are only educated guesses.

The Ethics of Innovation

Alex V. Levin, MD and George L. Spaeth, MD

Summary Points

- Innovation is a process which is fundamental to improved surgical and non-surgical care for all diseases including glaucoma.
- Innovation should be designed in the best interest of the patient with both patient and physician taking heed of the potential risks as weighed against the desired benefits.
- Innovating glaucoma specialists should begin by clarifying the purpose of the proposed innovation and the desired outcome. There should be a clear plan to monitor outcomes prospectively.
- Conflicts of interest may be financial, academic or personal. The potential or realized effect of conflicts of interest must be recognized, declared and managed.
- Informed consent is an integral and critical part of the innovation process.
- All studies, without regard to where studies are done, should be approved by an established Institutional Review Board (IRB)/Research Ethics Board (REB). In the situation in which the investigator is not associated with an institution that has an IRB available, the investigator should contact an established IRB (private or institutional) to ensure competent unbiased review before proceeding with the research.
- We encourage the use of an IRB/REB or equivalent, to provide consultation and oversight when considering innovation. In cases where the IRB/REB is not the group to provide this type of guidance, an alternate independent route should be in place to approve, monitor, and evaluate the innovation process.
- All sources of funding to support any aspects of the study, including but not limited to monetary or non monetary investigator support, should be declared to the IRB/REB, co-investigators, and study subjects.

The Problem

Innovation is a process fundamental to improved surgical and non-surgical care for all diseases, including glaucoma. Physicians have an obligation to seek the best outcomes for their patients. Particularly when available treatment options prove to be inadequate, whether it be in terms of outcome, cost, time, feasibility, efficacy, tolerability, or accessibility, physicians are likely

WGA Guidelines, pp. 25-31
edited by T. Shaarawy, F. Grehn and M. Sherwood
2008 Kugler Publications, The Hague, Amsterdam, The Netherlands

to propose and create alternative interventions designed to address these challenges. In so doing, patients and physicians have a mutual interest in protecting the patient from harm. Harm to patients may come in many forms including pain, undesirable outcomes, financial loss, time loss, or anxiety. Likewise, physicians may also experience harm, such as undesirable patient outcomes or litigation. Innovation should therefore be designed in the best interest of the patient, with both patient and physician taking heed of the potential risks as weighed against the desired benefits.

Report

I. Clarifying the Objective

The ultimate goals of treatment are restored, maintained, or, preferably, improved health. Glaucoma is a controllable, but currently incurable disorder, which has the potential to impair health. Patients require ongoing treatment to prevent visual loss or other problems that result in a decrease in health. Even with maximal medicinal and surgical intervention, some patients will still lose vision either due to the disease or the complications of treatment, or both. Patients may also experience a multitude of ocular, systemic, and psychological complications of glaucoma, even when vision is preserved and the intraocular pressure (IOP) controlled. Innovation should be designed to improve outcomes and/or reduce complications. Innovating glaucoma specialists should therefore begin by clarifying in their own minds as well as in writing or other public forums (*e.g.*, peer discussions, departmental meetings/rounds): 1) What is the purpose of the proposed innovation? and 2) What is the desired outcome?

II. Conflict of Interest

All human beings have conflicts of interest: a competition between interests which can not be equally satisfied. Some authors have suggested alternate terminology, such as ‘duality of interest’ in an attempt perhaps to remove the negative connotations that might be associated with the word ‘conflict’. But one need not characterize conflict in this setting as a positive or negative force. Rather it is the recognition of the potential or realized effect of this conflict that is relevant, and, importantly also, management of the conflicting interests.

Perhaps the most recognized conflict of interest is financial. If a physician stands to gain financially from an innovation, then there is the potential that his/her decision making could be influenced consciously or unconsciously by this financial lure, perhaps even to a degree that would compromise the primary objective of improving patient care. Perhaps the innovator would take excess risk without adequately protecting the patient from harm or be blinded to the downsides of the innovation while promoting its use.

But there are other conflicting interests as well. In the academic setting, physicians must 'publish or perish' and innovations become a tool for academic advancement. Additionally, personal gain or 'ego' may also be an interest that creates conflict: it feels good to be regarded as an innovator, to have an instrument or procedure named after you, to receive glowing attention in the media, or to be flown to exotic locations to present the innovative work at conferences where the applause of the crowd infuses one with a sense of pride and accomplishment.

Conflict is not 'bad' in of itself. Concerns arise when the mixed objectives bias or negatively impact the goal of innovation. Conflict of interest may also have an undesirable effect by the perception it creates, even when there is no adverse outcome. For example, when one reads an article in the peer-reviewed literature citing the benefits of a new glaucoma agent compared to another and then learns from the fine print that the study was sponsored and authored by the company that manufactures the allegedly better drug, is there not a feeling of skepticism? Some have suggested that disclosure is the tool by which we manage conflicts of interest. Indeed, that is an important starting point. However, disclosure does not remove the conflict or its potential impact. Other tools must also be used to manage potential conflicts such as masked study design, independent observer review of outcomes, peer discussions, funding from sources unrelated to the innovation (*i.e.*, non-medical industry), or independent review by a supposedly-neutral committee, such as an ethics review board or an institutional review board.

We suggest that innovators ask themselves the following questions:

1. Who is most likely to benefit from the project, and in what order will others benefit? If the order of expected benefit is, for example, industry, investigator, and lastly the patient, then the patient is probably at a greater risk of being harmed than if the order of benefit is first the patient, then the investigator, and finally industry.
2. What are the hidden as well as the apparent biases and conflicts of interest?
3. Is the issue being considered primarily from the patient's point of view?
4. Is the surgeon qualified and experienced to conduct the innovation or should the patient be referred elsewhere?
5. Is the surgeon ready to accept total responsibility for the outcome?
6. Is the innovation being conducted in a manner open to peer review? Is appropriate oversight and monitoring in place?
7. Where appropriate, has the innovation been adequately investigated in the laboratory or other *in-vitro* models, animal models, or less vulnerable populations (*vide infra*)?

III. Informed Consent

Patients (and the public in general) are drawn to what is new, to innovation and to innovators. New things have always been attractive, and many believe that if something is new it must automatically be better. Innovation is 'sexy',

exciting and promising and replaces feelings of desperation or hopelessness, which are feelings not uncommon in patients with glaucoma. A variety of studies have shown that loss of vision is the second most feared medical ailment, trumped only by cancer. Glaucoma can be a frustrating disease for patients as they watch their doctors struggle to prevent loss of vision. Especially when things look bleak, patients frequently welcome the idea of 'something new.' Some authors have recommended abandoning terms such as 'new,' or 'innovative,' because they are so seductive to patients, suggesting a promise which may not be realistic. These authors suggest replacing these terms with words such as 'unproven,' 'experimental,' or 'non-validated.' There is much to recommend in this idea. However, patients are far less likely, for example, to be receptive to a treatment which is called 'unproven,' in contrast to one qualified by the appealing adjective 'new' or 'innovative'. Many people want what is new, presuming it is better and ignoring the fact that new is by definition not known to be better. Ultimately, what both the doctor and patient want is a treatment which is superior, or at the least no worse than the standard, even if it is not necessarily new.

Informed consent involves a dialogue with the patient that includes discussion of the potential risks and benefits of any proposed treatment. What constitutes an adequate discussion is traditionally covered by saying that the content should be what a 'reasonable' person would want to know. Usually this would include an indication of the treatment's novelty, how many times it had been used, how many times the particular physician had employed it, what evidence there was to support it, and whether the person recommending the treatment had conflicts of interest, especially those that were financial. Alternatives, including standard interventions in previous use, also need to be discussed. Patients have a right and physicians a corresponding duty to engage in a dialogue which identifies in an understandable way a treatment as innovative and puts it in the proper context.

Some may argue that patients can never fully understand, but this is not an acceptable excuse for not involving the patient in decision-making. Every day we tailor our language to match the level of comprehension and the interests of all those people with whom we are speaking; this is an essential part of any meaningful communication. Of course one cannot expect meaningful dialogue when speaking English to an individual who only understands another language or when dealing with a frightened hysterical child. Meaningful communication must include words, grammar and tone that allow the communication to be understood, intellectually and emotionally. In discussing a proposed treatment, physicians must have a reasonable idea of the ability of the patient to understand, and a reasonable idea of what it is the patient wants and needs to know. Some have argued that detailed informed consent should be withheld in some circumstances for fear that it worries patients unnecessarily, a concept called 'therapeutic privilege.' This concept, or 'excuse', which leads to incomplete disclosure, has not been looked upon favorably by the courts. Although discussions with a patient, under the guise of informed consent, can be so frightening that they lead the patient in a direction which is not in the patient's best interest, it is the physician's duty to

shape those conversations and manage the patients fear so as a mutually agreeable and therapeutic plan is created. Numerous studies have demonstrated that patients want to know about their care. Patients deserve to have their condition and their treatment discussed with them honestly. Telling the truth need not be cruel. It is not the truth which is the concern, but the manner in which the truth is told, and how possibilities for the future are presented.

Appropriate informed consent is not only ethically mandatory, it also protects the physician. Thoughtful discussions lead to realistic expectations. Unrealistic expectations related to surgical treatments are the most common cause for disappointment, anger, and litigation. But it is not the informed consent form which protects the physician. Rather is it the meaningful dialogue. Indeed, some doctors and patients see the form as the means to avoid discussion, which may lead to a sense of distrust of the doctor and the doctor's staff.

Obtaining an informed consent properly enriches the entrustment which characterizes the supplicant patient who comes to the physician for help, and cements a trusting relationship.

IV. Other Research Ethics Principles

The field of research ethics teaches physicians other lessons that will facilitate effective innovation.

IV.1. Research Ethics Boards (REB)

Many cringe at the hurdle of the REB. The process is viewed as long, costly, time-consuming, frustrating, and obstructive by many. Yet the REB exists to protect the patient *and the researcher* from harm. For example, they may do so by a variety of means including review of language in consent forms to ensure they are understandable by the lay reader, examination of sample size and study feasibility to ensure that the study has the power to justify the use of patient and other resources, and oversight of financial relationships between the investigator and study sponsors to help reduce bias and improve study objectivity. We encourage the use an REB or equivalent to provide consultation and oversight whenever possible when investigating potential innovation. When innovation is not needed emergently, and there is time for thoughtful planning, application to an REB is indicated. In urgent scenarios, expedited approval for one time use of an innovation may also be sought through an REB. In an attempt to facilitate innovation, some institutions have established alternate means for obtaining pilot data prospectively without full REB review. However, the intention is for this data to be used to plan full research protocols for REB approval. In environments where there is no REB available we urge researchers to seek out consultation rather than proceed without oversight. Options include the use of a REB at a nearby or even remote hospital/university, a private REB many of which can be located via

web based resources, or the formation of an *ad hoc* local independent review committee specifically for the project. For example, the latter option could include non investigator colleagues, someone with training in bioethics, and a patient. Consultation with a bioethicist and/or REB chair via web based or telephone communication may also be helpful in exploring options.

IV.2. Vulnerable populations

Patients, by the very nature of their illness, are vulnerable. In the case of vulnerable patients it becomes perhaps even more important that full and clear disclosure without coercion be practiced. Financial incentives to participate in innovation research must be used with caution as vulnerable populations may be unduly motivated to participate and agree to do so with clouded judgment.

IV.3. Monitoring

There should be a clear plan to monitor outcomes prospectively. The degree of monitoring should be proportionate to the invasiveness of the innovation. Innovators should not cede postoperative to other parties but additional independent review is encouraged. Data analysis should be conducted by the research team and not by third parties such as medical industry. All co-investigators should be able to take responsibility for the outcomes, data analysis and interpretation. Peer review is desirable. Research results should be reported regardless of whether the results are 'positive' or 'negative'. We recommend that investigators carefully review contractual arrangements with medical industry and other sponsors to avoid 'suppression clauses' or other language which limits the investigators' ability to independently review and report their methods, results, and conclusions. Where applicable, registration may be required by the institution where the research is being done or the journal in which publication is desired (www.clinicaltrials.gov).

IV.4. Trainees

Although the participation of trainees in research is encouraged and we acknowledge that professional practices may vary depending on locale and culture, the introduction of innovative procedures requires a most skilled hand as the surgeon will not have had the opportunity to learn the new technique and requires a solid background experience. Proper research design demands precise control of variables wherever possible. Introduction of trainee error should be considered and at the very least be offset by intense supervision. When the primary objective of the research is to investigate a trainee's role, behavior, education and skills or to determine if a particular practice or procedure can be utilized by less experienced individuals, then the informed consent process must be explicit in reflecting this purpose.

Conclusions

Innovation is an integral part of advancing medical care. Innovators in the field of glaucoma must clearly identify to themselves and others the purpose of their proposed innovation with identification, disclosure and management of all potential or real conflicts of interest. We encourage the involvement of a Research Ethics Board and proper scientific method whenever possible. Proper informed consent and monitoring of outcomes while the innovation is in progress are cornerstones in preserving the best interest of patients.

Further Research Needed

Research in the field of innovation ethics will assist glaucoma specialists in identifying means by which innovation can be facilitated while maintaining the best interests to the patient. Examples might include the investigation of Research Ethics Board efficacy, or alternate pathways for expedited review of innovation proposals. Qualitative research will allow for a better understanding of the patient perspective. Randomized prospective trials of various approaches to informed consent, conflict of interest disclosure and management and other interventions will assist us in identifying the best means of ensuring that innovation proceeds in an ethical fashion.

References

1. The Ethics Committee of the American Academy of Ophthalmology, The Ethical Ophthalmologist: A Primer. American Academy of Ophthalmology, Inc., California, 1999.
2. Agich GJ. Ethics and innovation in medicine. J Med Ethics 2001; 27: 295-296.
   Bunch WH, Dvonch VM. Moral decisions regarding innovation. Clin Orthopaed Related Res 2000; 378: 44-49.
   Krieglstein GK. How new is new, and is it better? J Glaucoma 1999; 8: 279-280.
   Levin AV. The ethics of surgical innovation: more than one answer? Can J Ophthalmol 2005; 40: 685-686.
   Levin AV. IOL's, innovation and ethics in pediatric ophthalmology: let's be honest. J AAPOS 2002; 6: 133-135.
3. McKneally MF. Ethical problems in surgery: innovation leading to unforeseen complications. World J Surg 1999; 23: 786-788.
4. McKneally MF, Daar AS. Introducing new technologies: protecting subjects of surgical innovation and research. World J Surg 2003; 27: 930-935.
5. Parrish RK. Learning from surgical failures: an argument for clinical trials. Ophthalmology 2002; 109: 1045-1046.
6. Riopelle RJ. Bridging the gap between innovation and application: the essential role of the health services development unit. Ann RCPSC 2001; 34: 380-382.
7. Waring GO. Disclosure of potential conflict of interest. Refract Corneal Surg 1990; 6: 80-81.
8. Waring GO. Evaluating new refractive surgical procedures: free market madness versus regulatory rigor mortis. J Refract Surg 1995; 11: 335-339.
9. Waring GO. A cautionary tale of innovation in refractive surgery. Arch Ophthalmol 1999; 117: 1069-1073.

Reporting post-operative complications in glaucoma surgical trials

H.D. Jampel

Summary Points

- Standardized definitions for surgical complications and standardized reporting of complications in glaucoma surgical trials will allow for better comparison between trials.
- This report provides tables that can be used as templates for reporting complications and which can be modified to fit the particular trial.
- The tables in this report can be used to help design clinical trials so that the desired data on complications can be prospectively collected.
- This report does not mandate how to ascertain complications, but recommends that the methods by which complications are ascertained is reported.

The Problem

There is no standardized method for reporting complications arising in clinical trials of glaucoma surgery. This makes it difficult for readers to assess the safety of glaucoma surgery and to compare the frequency and severity of complications across clinical trials.

Report

We have chosen to present a standardized scheme for reporting complications in terms of a series of tables. The complications have been divided into those that could generally affect all glaucoma surgery, and those that are primarily specific to filtering surgery (Trabeculectomy/Non-penetrating surgery) or drainage device surgery. The idea is not to present a rigid template, but a guideline. Some tables may need to be modified to fit the particular study.

Corresponding author: Henry D. Jampel, MD, MHS, Odd Fellows and Rebekahs Professor of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

WGA Guidelines, pp. 33-39
edited by T. Shaarawy, F. Grehn and M. Sherwood
2008 Kugler Publications, The Hague, Amsterdam, The Netherlands

The tables allow for the categorization of complications in terms of their timing after surgery, according to the following, somewhat arbitrary, definitions:
Intraoperative: Occurring during the surgical procedure;
Early: Occurring within first postoperative month;
Late: Not present before one month, but occurring afterwards;
Early and Late: Present at some point both within first month and after first month;
Present at final visit: Self-explanatory.

In designing a surgical study, it is important for the investigator to determine what outcomes he/she will want to report. Hopefully these complication tables will help the investigator design the protocol to collect the desired information. For retrospective studies, they can serve as a guide for the clinical chart review.

We felt that mandating the 'correct' way to ascertain complications was beyond the scope of this chapter, and risked throwing away 'good' data because it was not 'perfect' data. For instance, the decision of when to look for a bleb leak, and then how to look for it, is debatable. As another example, the incidence of choroidal detachment is heavily dependent on how one looks. If B-scan ultrasonography were routinely performed one week after trabeculectomy, the incidence of choroidal detachment might be very high, but would all those choroidal detachments really represent complications? On the other hand, if the pupils were only dilated if the patient reported decreased vision, choroidal detachment would certainly be underreported. The critical point is that the investigator explicitly specify in the protocol the techniques that should be employed to ascertain complications and that the complications be defined ahead of time.

The cells in the Tables will usually include both a proportion and a percentage.

I. Intraoperative Complications

This table can be altered depending upon the surgical procedures under study. It can be modified to accommodate new surgical procedures that may have their own unique complications.

Complication	N (%)
Anesthetic or systemic complications	
Retrobulbar hemorrhage	
Subconjunctival hemorrhage	
Conjunctival buttonhole	
Severing of extraocular muscle tendon	
Scleral flap problems	
Iris prolapse	
Wound leak	
Anterior chamber bleeding	
Serous choroidal detachment	
Suprachoroidal hemorrhage	
Scleral perforation	
Vitreous prolapse	
Rupture of trabeculo-Descemet's membrane	

II. General Post-operative Complications

II.1. Loss of visual acuity

	Early	Late	Early and Late	Present at final visit	Total
Mild					
Moderate					
Severe					
Total					

Mild: 1-2 Snellen or ETDRS lines; Moderate: 3-4 lines; Severe: ≥ 5 lines

II.2. Non-physiological IOP and associated complications

	Early	Late	Early and Late	Present at final visit
IOP ≤ 5 mmHg				
Shallow or flat AC (all)				
Shallow AC (iridocorneal touch extending to within one mm of the pupil)				
Flat AC (lens or IOL touching cornea)				
Choroidal detachment (all)[1]				
Confined to anterior to the equator, without blood[2]				
Confined to anterior to the equator, with blood				
Extending posterior to the equator, without blood				
Extending posterior to the equator, with blood				
Obscuring disc or macula, but not kissing, without blood				
Obscuring disc or macula, but not kissing, with blood				
Choroidals touching in the center of the eye, without blood				
Choroidals touching in the center of the eye, with blood				
Hypotony maculopathy[3]				
Macular edema[3]				
Disc swelling[3]				

[1]Investigators must specify how hard they looked for choroidal detachment, *e.g.*, dilated exam every visit, B scan ultrasonography on every visit, dilated exam only when patient reported reduced vision, etc.
[2]Blood can be defined as a dark appearing choroidal with abrupt onset of pain, and/or blood present on b scan ultrasound.
[3]Methods of ascertainment must be specified, e.g.all patients underwent OCT on every visit; OCT was performed if there were a clinical suspicion of macular edema, etc.

II.3. Intraocular bleeding

	Early	Late	Early and Late	Present at final visit
Layered hyphema				
Layered hyphema covering the pupil				
Blood occluding the internal fistula (or tube lumen)				
Circulating blood in the AC and/or vitreous cavity decreasing vision				

II.4. Lens opacity

All studies should have some *a priori* method for addressing lens opacity.

Pseudophakic eyes at baseline	
Increased lens opacity	
Cataract extraction	

Baseline measure of cataract can include:
– Present or absent;
– Subjective grading as absent, mild, moderate, severe;
– Grading against LOCS photos;
– LOCS photos;
– Objective lens opacity measurement.

II.5. Corneal or graft decompensation

	Early	Late	Early and Late	Present at final visit
Number of eyes with decompensation at baseline				
With decreased acuity of ≥ 2 lines from baseline				
New onset painful bullous keratopathy				
Requiring corneal surgery				

Note: How the status of the cornea was determined at baseline, *e.g.*, CCT, presence of guttata, specular microscopy, etc., must be specified.

II.6. Inflammation

	Early	Late	Early and Late	Present at final visit
Requiring intraocular aspirate for diagnosis				
Requiring chronic topical corticosteroids				
Requiring systemic, periocular, or intraocular steroids				

Note: How inflammation was accessed: clinical exam, flare meter, etc., must be specified.

II.7. Retinal disease

	N (%)
Vein occlusion	
Artery occlusion	
Macular hole	
Macular edema	
Retinal tear	
With detachment requiring surgery	
With detachment that could not be repaired	

Note: Includes occurrences within three months of surgery (otherwise not attributable to the glaucoma surgery).

III. Complications Specific to Trabeculectomy (Bleb-related)

III.1. Dysesthesia or decreased uncorrected vision

	Early	Late	Early and Late	Present at final visit
Without obvious cause				
With large or exposed bleb				
With dellen				

Note: Recommend instrument such as the glaucoma symptom scale.

III.2. High bleb (Tenon's cyst)

Defined as taut, opalescent bleb with IOP $\geq$ 20 mmHg

	Early	Late	Early and Late	Present at final visit
High bleb				

III.3. Bleb leak

The authors should determine *a priori* how a bleb leak will be detected. For example, 'We defined bleb leak as a positive Seidel test. We performed the test using a fluorescein strip, whenever the IOP was equal to 6 or less, or when the anterior chamber was shallow, or when there is a suspicion of blebitis. We did not consider diffuse ooze from the entire bleb surface as bleb leaks.' Or, 'All eyes underwent Seidel testing on every visit, regardless of bleb appearance or intraocular pressure. Bleb leak was defined as a positive Seidel test'.

	Early	Late	Early and Late	Present at final visit
With discrete hole				
Without discrete hole				
Requiring slit lamp intervention				
Requiring operating room intervention				

III.4. Infection

	Early	Late	Early and Late	Present at final visit
Blebitis (all)				
With AC reaction				
With hypopyon				
Endophthalmitis				

Blebitis: defined as pus-like material in the bleb with surrounding hyperemia, no vitreous reaction; Endophthalmitis: vitreous reaction in the setting of blebitis. Details of each case of endophthalmitis (culture results, visual outcomes, IOP results) should be documented in a footnote to the table or in the text of the manuscript.

IV. Complications Specific to Drainage Device Surgery

	Early	Late	Early and Late	Present at final visit
Tube corneal touch (tip of tube in contact with cornea)				
Tube lenticular touch (all)				
Without laceration of anterior capsule				
With laceration of anterior capsule				
Tube occlusion (all)				
By iris				
By vitreous				
By other				
Tube retraction (lumen of tip is no longer visible in the anterior chamber gonioscopally)				
Tube exposure (transconjunctival)				
Plate exposure				
Plate displacement (symptomatic)				

V. Complications Specific to Non-penetrating Glaucoma Surgery

	Early	Late	Early and Late	Present at final visit
Descemet's membrane detachment				
Rupture of Trabeculo-Descemet's membrane				
Peripheral anterior synechia				
Scleral ectasia				

Conclusions

Surgical complications have historically been a deterrent to the more widespread use of incisional surgery to treat glaucoma. With many new surgical modalities on the horizon to treat glaucoma, it will be increasingly important to perform clinical trials and report them in such a way that valid comparisons concerning their safety can be made.

Overview

We present a series of tables that can be used as templates for both reporting complications in trials of glaucoma surgery as well as for designing protocols to adequate capture these complications. It is our hope that more standardized reporting of complications will allow for better comparisons of both established glaucoma surgery and the newer technologies on the horizon.

Guidelines for economic evaluation of glaucoma surgical trials

Steven Kymes and Augusto Azuara-Blanco

Committee members: Oscar Albis-Donado, Khaled BenAmor, Jennifer Burr, Paul Chew and Ravi Thomas

Summary Points

As the cost of care increases in all nations, it has become increasingly important for responsible clinicians and policy makers to consider the impact of their interventions on patients and the larger society. The purpose of economic evaluation in glaucoma surgical trials is to provide information to patients, physicians and policy makers to enable them to evaluate the balance between the cost of an intervention and its associated benefit. There are different types of economic analyses and perspective from which the analyses should be conducted. These will vary by the nation or jurisdiction in which the analysis is conducted.

Introduction

There have been a number of reports over the past two to three decades concerning the increasing share of the gross domestic product (GDP) devoted to provision of health care in many jurisdictions.[1] Certainly, with the share of GDP devoted to the health care sector approaching 16%, the problem in the U.S. is particularly acute, but focus on the U.S. has obscured the observation that over half of the Organization for Economic Cooperation and Development (OECD) countries have seen a 50% increase in health expenditures as a percentage of their GDP, and twelve nations were devoting in excess of 9.5% of their GDP towards health care in 2004.[2] This trend has spurred an explosion of cost-effectiveness research over the past in many nations, but in particularly Canada and the European Union where cost-effectiveness results

Corresponding authors: Steven Kymes, Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, 660 South Euclid Ave., Campus Box 8096, St. Louis, MO 63110, USA; Augusto Azuara-Blanco, Consultant Ophthalmologist and Honorary Senior Lecturer, Aberdeen Royal Infirmary and University of Aberdeen, The Eye Clinic, Aberdeen, AB25 2ZN, UK

WGA Guidelines, pp. 41-47
edited by T. Shaarawy, F. Grehn and M. Sherwood
2008 Kugler Publications, The Hague, Amsterdam, The Netherlands

play an integral role in the adoption of new drugs and technologies.[3-5] Economic evaluation has only been widely reported in the visual sciences in the past decade.[6-21] As with the introduction of any novel method to a new field, early cost-effectiveness work in ophthalmology has been highly variable in quality as investigators, editors, and readers grappled with unfamiliar methods. In the past, these limitations have been of little import as most ocular interventions are very cost-effective by their nature and place a relatively small claim on societal resources.

While much of this has concerned the role of cost-effectiveness research in developed nations, it must be recognized that this is also a problem in developing nations, and has a unique character in those settings. In these nations there is limited access to health insurance and limited governmental resources to pay for health services. Therefore, many patients must pay for interventions out of their own pocket. Under these conditions, cost-effectiveness studies have a very different meaning. Instead of the traditional purpose (*i.e.*, to provide a governmental or non-governmental agency the information necessary to support allocation of scarce resources), the investigator must find a way to provide *the patient* with information that can be used to evaluate the value of an intervention and support their decision making. In this report we will attempt to show the importance of rigorous methods of evaluation to obtain the appropriate data necessary to provide meaningfully interpretable economic studies in both developed and developing nations.

I. Methods of Economic Evaluation

Economic evaluation is the discipline of weighing the cost of an intervention (*e.g.*, a medical or surgical therapy, a diagnostic test, a health education program, etc.) against the benefit created by the intervention. Such analyses only have meaning in the context of a comparison (*i.e.*, 'cost-effective compared to what?'), therefore, it should only be conducted when there is some basis of comparison: a previously employed treatment (*i.e.*, glaucoma surgery versus medical management), or a characterizable consequence of non-treatment (*i.e.*, increased incidence of glaucoma among otherwise asymptomatic untreated ocular hypertensives). The evaluation itself may take a number of forms, including cost-minimization, cost-benefit, and cost-effectiveness. The methods differ primarily in the characterization and measurement of the benefit.

In cost-minimization analyses (often referred to as 'cost studies') the costs of competing interventions are compared to determine which is the least expensive. The implicit assumption is that all interventions yield equivalent benefits, this is of course rarely the case. Such studies are frequently seen in ophthalmology in the form of 'cost of illness' studies.[22,23] Such studies are inherently descriptive, and as such, their use is primarily limited to advising more comprehensive comparative analyses.

In cost-benefit analysis, the investigator directly compares costs and benefits of an intervention. Such a comparison requires that the cost and

benefit be characterized using the same metric. Cost is typically measured in monetary terms; therefore the investigator must monetize the value of an intervention's health benefit. While this method is commonplace in the United States' legal system and preferred by some classical economists,[24] ethical and methodological controversies surrounding have limited its application in the health sciences. However it should be noted that when the perspective of analysis is the provider or patient (see below) cost-minimization or cost-benefit analysis is typically the most appropriate method.

The most common form of economic evaluation in health care is cost-effectiveness analysis (CEA). We use the term to describe a specific type of economic evaluation, as opposed to the frequent generic application to all methods of health economics. In CEA, the benefit of the intervention is characterized by a tangible gain: a year of life saved, cases of amblyopia identified, line of vision preserved, etc. The incremental cost of the intervention (*i.e.*, the extra cost) is divided by the incremental benefit (described as the difference in effectiveness) to estimate the incremental cost-effectiveness ratio (ICER). The ICER represents the resources that must be expended to gain ('purchase') a unit of effectiveness. Cost-utility analysis is a particular form of cost-effectiveness analysis in which 'effectiveness' is characterized as utility, a measure of quality of life.[25] This metric considers not only disease, but its impact on quality of life. The utility characterizes a person's perception of quality of life on a scale of 0 to 1, which is then used as a weight to the persons life expectancy to create the quality-adjusted life year (QALY).[26] We will address utilities in a separate section.

II. Conducting Cost-effectiveness Analysis

CEA, as with all economic evaluation methods, must be conducted from a particular perspective: the provider (physician or hospital), payer (insurance company or government), patient (the recipient of care and/or their family), or entire community (society). The perspective of the analysis is based upon who must assume the cost of the care and it determines the costs and benefits considered. For instance, if the cost of care will be borne by the patient, that analysis will be from the patient's perspective would consider the patient's out of pocket costs and the reduction in consequences of disease, but would not consider costs incurred by government or social service agencies. Therefore, any study providing support for the patient in their decision making must extensively document the costs and benefits to the patient. Similarly, if the physician or hospital must pay for the intervention, the costs and benefit to the provider should be estimated. In most developed nations, it is the community that assumes the cost of care, therefore, expert panels have recommended conducting economic evaluations from the societal perspective to ensure the consideration of the widest range of costs and benefits.[27]

In all economic evaluations, 'cost' has a very particular meaning. While accountants might view 'costs' as the result of monetary transactions,

economists consider 'opportunity costs,' or the value forgone by not using the resource for its next best alternative use. For example, the closure of an operating room changes costs and revenue. Thus, the opportunity cost associated with that closure is the profit (not revenue) lost. A lack of competitive health care markets further complicates the measurement of costs as the market price is rarely the appropriate cost. Readers will often see detailed descriptions of how a treatment or intervention was costed that goes well beyond accounting-based costs. For instance, capital goods (*e.g.*, a new slit lamp microscope) often require calculations that include purchase cost, depreciation, maintenance and resale or scrap value.

Costs and benefits do not typically occur at a single point in time, *e.g.,* the new slit lamp may be paid for over time with a loan and will generate other costs and benefits over its useful life. Costs and benefits incurred in the future are not valued as highly as those at present – analysts 'discount' future costs and benefits, so that they are given an appropriate relative value. While recommendations generally suggest discounting both future costs and benefits, some decision makers find discounting health effects unpalatable – questioning why a year of life gained (or a line of sight saved) in the future should be valued any less than one gained in the present. While considered sub-optimal, it is acceptable practice not to discount health effects as long as costs are treated similarly.

III. Cost Utility Analysis

Often the answer to a cost-effectiveness investigation is not straightforward, even when it is properly conducted. Lairson and colleagues recently reported the results of an economic evaluation using a cost-effectiveness approach of the use of twice-daily oral acyclovir to prevent the recurrence of herpes simplex virus eye disease (HSV).[28] In the analysis, they characterized effectiveness as the prevention of a case of HSV and found that the treatment proposed cost $8,532 per case prevented.

The methods employed by these investigators were sound and received well-deserved plaudits in an accompanying editorial.[29] However, the results beg the question: is it cost-effective to use prophylactic antivirals to prevent recurrence of HSV? Interestingly, both the editorialist and the investigators suggest that it is not, which would imply that they believe that the value of preventing recurrence of a case of HSV would be less than $8,532. However, they present no empirical evidence to support this assertion. What is the value of preventing a recurrent case of HSV? If we are to take a societal perspective, we might assume the role of an 'average' person who has not yet contracted HSV, but properly understands his risk of doing so as well as the risk of recurrence. He also has good understanding of what impairment and pain HSV may cause and its impact on his quality of life. He (not his insurer) will fully bear the cost of treatment if he contracts HSV. Now, as someone who still has never had the disease, we ask him to decide whether it would be 'worth it' to pay $8,532 to prevent recurrence of HSV (if he were

to contract the disease). What would he decide?

Answering this question is the purpose of cost-utility analysis. In cost-utility analysis, 'benefit' considers not only prevention of disease, but the impact of the disease on quality of life by characterizing quality of life as *utility.* This is a measure of a person's perception of quality of life that is generally bounded by 0 and 1, with zero representing death and one, perfect health. (The methods used to estimate utility are beyond the scope of this report, but are discussed in detail elsewhere.[30]

Cost-utility analysis is used exclusively by health authorities considering the distribution of social resources, but its application for individual patient decision making has been somewhat limited. For health authorities, it is particularly well-suited to the evaluation of visual disease as most are chronic in nature and have significant impact on quality of life. It allows the length of time spent living with the disease (or without, in the case of prevention) as well as its impact on quality of life to be considered. This is addressed using a composite measure, the 'quality-adjusted life year' (QALY), calculated by weighing the patient's expected life span by the utility expected to be enjoyed during that period. When the difference in QALYs with and without the intervention is divided into the incremental cost of treatment, the result is incremental cost-effectiveness ratio (ICER), which provides an estimate of the additional cost of 'purchasing' an additional QALY (*i.e.*, a year of 'perfect' health). For instance, a recent cost-utility analysis of the treatment of ocular hypertension found that treatment of all people with ocular hypertension to prevent glaucoma had an ICER of $437,964.[31] (Kymes, 2006 #3080) This implies that employing such a treatment strategy would require the expenditure of over $400,000 for each QALY gained.

This approach requires that decision makers to consider how much 'society' is willing to 'spend' for a year of perfect health (*i.e.*, one QALY), but unfortunately there is little consensus on this question among policy makers, and there has been no research considering how much the willingness to pay might be in developing nations. For over 20 years, the informal standard was considered to be $50,000 in the developed world, but more recently, a approaching $100,000 has been frequently used.[32] Some authors have even provided compelling evidence that the true value society places on the QALY is over $200,000.[33]

IV. Recommendations

Any surgical development which anticipates adoption in any jurisdiction should include in its study design collection of the data necessary to conduct economic evaluation. As this will vary by jurisdiction the trial organizers should consult an experienced cost-effectiveness researcher in the process of their protocol development.

Where a trial shows that the surgical technique or device is efficacious, and if economic data is collected, the results of the economic analysis should be reported soon after the results of the report of efficacy.

In development of clinical trials and reporting the results of cost-effectiveness studies, attention should be made to the difference in information needs and decision making in developing nations versus developed nations. If separate reports are required, economic investigators and clinicians should seek out collaborators in the developed nations to insure that their reports are germane to patients and authorities in those settings.

Further Research

Further research should be focused in answering some fundamental questions such as:

Which is the best outcome measure in glaucoma from the patient's perspective? Does this vary across nations/cultures?

What is the best method for estimating the impact of glaucoma on quality of life? How does it vary across nations and cultures?

How relevant are changes in visual field to a patient's quality of life?

What are the direct (medical) costs and indirect (societal) costs of glaucoma? How do these differ across nations?

What is the rate of progression of glaucoma and how do interventions influence the rate of deterioration?

References

1. Anderson GF, et al. It's the Prices Stupid: Why the United States is so Different From Other Countries. Health Affairs 2003; 22: 89-105.
2. OECD Health Data 2006 – Frequently Requested Data (Health Expenditures). 2006, Organization for Economic Cooperation and Development.
3. Baladi JF, Menon D, Otten N. Use of economic evaluation guidelines: 2 years' experience in Canada. Health Economics 1998; 7: 221-227.
4. Drummond MF, et al. Methods for the Economic Evaluation of Health Care Programmes. 3rd ed. 2005, Oxford: Oxford University Press.
5. Oliver A, Mossialos E, Robinson R. Health technology assessment and its influence on health-care priority setting. International Journal of Technology Assessment in Health Care 2004; 20: 1-10.
6. Busbee BG, et al. Cost-utility analysis of cataract surgery in the second eye. Ophthalmology 2003; 110: 2310-2317.
7. Busbee BG, et al. Incremental cost-effectiveness of initial cataract surgery. Ophthalmology 2002; 109: 606-612.
8. Brown GC, et al. The cost-utility of photodynamic therapy in eyes with neovascular macular degeneration--a value-based reappraisal with 5-year data. American Journal of Ophthalmology 2005; 140: 679-687.
9. Brown GC, et al. Value-based medicine and ophthalmology: an appraisal of cost-utility analyses. Transactions of the American Ophthalmological Society 2004; 102: 177-185; discussion 185-188.
10. Busbee BG, Brown GC, Brown MM. Cost-effectiveness of ocular interventions. Current Opinion in Ophthalmology 2003; 14: 132-138.
11. Brown MM, et al. Health care economic analyses and value-based medicine. Survey of Ophthalmology 2003; 48: 204-223.

12. Membreno JH, et al. A cost-utility analysis of therapy for amblyopia. Ophthalmology 2002; 109: 2265-2271.
13. Kymes SM, et al. Management of ocular hypertension: a cost-effectiveness approach from the Ocular Hypertension Treatment Study. American Journal of Ophthalmology 2006; 141: 997-1008.
14. Brown MM, Brown GC, Sharma S. Value-based medicine and vitreoretinal diseases. Current Opinion in Ophthalmology 2004; 15: 167-172.
15. Busbee BG, et al. CME review: A cost-utility analysis of laser photocoagulation for extrafoveal choroidal neovascularization. Retina 2003; 23: 279-287; quiz 443-444.
16. Sharma S, et al. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration[see comment]. Ophthalmology 2001; 108: 2051-2059.
17. Sharma S, et al. The cost-effectiveness of early vitrectomy for the treatment of vitreous hemorrhage in diabetic retinopathy. Current Opinion in Ophthalmology 2001; 12: 230-234.
18. Sharma S, et al. The cost-effectiveness of grid laser photocoagulation for the treatment of diabetic macular edema: results of a patient-based cost-utility analysis. Current Opinion in Ophthalmology 2000; 11: 175-179.
19. Kymes SM, Frick KD. Value based medicine [comment]. British Journal of Ophthalmology 2005; 89: 643-644; author reply 644.
20. Brown GC, et al. A cost-utility analysis of interventions for severe proliferative vitreoretinopathy. American Journal of Ophthalmology 2002; 133: 365-372.
21. Brown GC. Vision and quality-of-life. Transactions of the American Ophthalmological Society 1999; 97: 473-511.
22. Chiang YP, Bassi LJ, Javitt JC. Federal Budgetary Costs of Blindness. Millbank Quarterly 1992; 70: 319-340.
23. Kobelt G, et al. Direct costs of glaucoma management following initiation of medical therapy. A simulation model based on an observational study of glaucoma treatment in Germany. Graefes Archive for Clinical & Experimental Ophthalmology 1998; 236: 811-821.
24. Kenkel D. On valuing morbidity, cost-effectiveness analysis, and being rude. Journal of Health Economics 1997; 16: 769-757.
25. Lee BS, et al. The impact of anchor point on utilities for 5 common ophthalmic diseases. Ophthalmology 2008; 115: 898-903.
26. Torrance GW, Feeny DH. Utilities and Quality Adjusted Life Years. International Journal of Technology Assessment in Health Care 1989; 5: 559-575.
27. Gold MR (ed.). Cost-Effectiveness in Health and Medicine. 1st ed. 1996, New York: Oxford University Press, p. 425.
28. Lairson DR, et al. Prevention of herpes simplex virus eye disease: a cost-effectiveness analysis [see comment]. Archives of Ophthalmology 2003; 121: 108-112.
29. Lee P, Zhang P. Economic Analysis in Eye Disease. Archives of Ophthalmology 2003; 121: 115-116.
30. Jampel HD, et al. Glaucoma Patients' Assessment of Their Visual Function and Quality of Life. Journal of Glaucoma 2002; 11: 154-163.
31. Kymes SM, et al. Management of ocular hypertension: a cost-effectiveness approach from the Ocular Hypertension Treatment Study. American Journal of Ophthalmology 2006; 141: 997-1008.
32. Gillick MR. Medicare Coverage for Technological Innovations – Time for New Criteria? New England Journal of Medicine 2004; 350: 2199-2203.
33. Ubel PA, et al. What is the Price of Life and Why Doesn't It Increase with the Rate of Inflation? Archives of Internal Medicine 2003; 163: 1637-141.

Statistical aspects of reporting glaucoma surgical studies

William J. Feuer, MS

Summary Points

- Glaucoma surgical trials should follow established design principles (randomized groups, sufficient sample sizes, stopping rules if necessary, data collection on standard study forms), include a Safety and Data Monitoring Committee, and document all study procedures in a Manual of Procedures.
- Efficacy endpoints should be prospectively determined and in be the form of dichotomous success versus failure criteria. Safety endpoints should be considered separately.
- Surgical trials are best conducted when enrolling one eye per patient.
- Analysis of the principal treatment outcome should be performed with time-to-failure methods such as Kaplan-Meier and Cox regression to account for follow-up time.
- Analyses should follow the 'intention to treat' paradigm.
- Significance tests should be supported by 95% confidence interval estimates.
- Ancillary hypothesis tests should be encouraged, but suitably labeled and not 'multiple comparison' adjusted.
- Reports should account for all patients and be clear about missing data.
- A customizable surgical trial Manual of Procedures is included in an appendix

Introduction

The randomized clinical trial is the 'definitive tool' for comparing the efficacy and safety of medical and/or surgical management strategies.[1] The principles underlying the design, conduct, analysis, and reporting of results for randomized clinical trials are well known.[1-3] Yet, surgical trials in glaucoma feature a number of specialized considerations. While management strategies

Address for correspondence: W.J. Feuer, MS, Senior Research Associate, Biostatistics Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA

WGA Guidelines, pp. 49-61
edited by T. Shaarawy, F. Grehn and M. Sherwood
2008 Kugler Publications, The Hague, Amsterdam, The Netherlands

for glaucoma patients have benefited from and been refined by a number of well-conducted medical and surgical multicenter randomized trials,[4-10] even these carefully thought-out studies may be controversial.[11] Well funded studies with large groups of investigators, in collaboration with their study statisticians and data and safety monitoring committees, will make their own decisions about the best ways to evaluate surgical treatments. Notwithstanding, this report provides a general framework and guidelines for statistical aspects of the design, analysis, and reporting of glaucoma surgical trials that aims to ensure that published trials use standard comparable methods and reporting strategies.

Report

I. Design Considerations

I.1. Organization and Registration

I.1.1. Investigators, coordinating center, safety and data monitoring committee

Whether a randomized glaucoma surgery clinical trial is conducted within a single clinic or in multiple clinical centers, it is useful to think of the organization of the trial as divided into: 1) The clinical investigators who will recruit patients, perform the study surgery, conduct follow-up evaluations, and record data; 2) The coordinating center which is responsible for supplying randomizations, data management, and statistical analysis; and 3) The Safety and Data Monitoring Committee (SDMC), which provides oversight of the conduct of the trial, ensures the safety of study patients, and may assess interim outcomes. The Principal Investigator (PI) is usually a clinical investigator who works with the coordinating center and the SDMC to maintain smooth running of the trial and solve operational problems, but is masked to the interim results of the trial and is not a voting member of the SDMC.

I.1.2. Trial registration

Many journals now require prior registration of clinical trials as a condition for publication. In the United States this may be done at clinicaltrials.gov.

I.2. Manual of Procedures and Study Forms

A sample manual of procedures that can serve as the basis for future glaucoma surgical trials is included in the appendix. This was developed from the Tube Versus Trabeculectomy Study manual of procedures, courtesy of S.J. Gedde.

I.2.1. Manual of Procedures

Prior to initiation of patient recruitment, the PI works with the coordinating center to develop the Manual of Procedures (MOP), a complete guide to all aspects of the study including a description of the hypothesis the trial is designed to test, the details of the study surgeries, eligibility criteria, examination procedures, visit schedules, sample size justification, primary outcome variables, stopping rules, etc. The MOP may be updated during the course of the trial. To the extent possible the study surgery is standardized among all clinical centers.

I.2.2. Study forms (Clinical report forms)

Clinical data should be collected prospectively on study forms designed for each visit. Within the constraint of capturing all important data (intraocular pressure, visual acuity, central corneal thickness, medication use, new adverse events, etc.), the simpler a form is, the more likely it is to be completed in a clinic setting. They should be clear enough that investigators need not refer to the Manual of Procedures to fill them out. To the extent possible, forms are designed with check boxes for the occurrence of any important events (*i.e.*, adverse events) to ensure prospective recording; dates of adverse events are always recorded when known. Efficacy for subsequent data entry is another important consideration. Within the foreseeable future real time web based data collection may replace paper forms, but the same principles apply.

I.3. Randomization

I.3.1. Methods

Balanced randomization lists constructed prior to the initiation of patient recruitment and administered by the study statistician (or coordinating center) ensure that both treatment groups are equally represented (unless the trial is designed with un-equal treatment allocation) and can be set up with varying block sizes so that clinical investigators remain masked to the next treatment assignment (*e.g.*, www.randomization.com). Use of 'coin-tossing' is discouraged. Envelopes containing randomizations for use with emergency surgeries, when the study statistician cannot be contacted, may be appropriate in some settings.

I.3.2. Stratification

Separate balanced randomizations lists should be created for each clinical center for multi-center studies. A frequent feature of the design of glaucoma surgical trials is additional stratification by important prognostic variables. In particular, consider stratifying for previous ocular surgery and the type of

glaucoma, to ensure balanced treatment assignment within these groups. It is not, however, necessary to stratify by all conceivably important variables as these can also be accounted for statistically in the analysis. Usually, simpler stratification is better. Separate randomization lists would then be constructed for all strata within each clinical center.

I.4. Follow-up Visit Windows

Follow-up visits are arranged in a standard schedule for patients in both (all) treatment arms. For glaucoma clinical trials, these will typically be day 1, week 1, month 1, month 3, month 6, month 12, and annually or semi-annually thereafter for as long as the trial lasts (please also see the report of the subcommittee on definitions of success). The ideally scheduled dates fall within windows which are adjacent for successive visits. For example the week-1 visit window might extend from 3 days to 14 days, and the month-1 visit window might extend from 15 days to six weeks. If more than one clinic visit occurs within a visit window, usually data from the visit closest to the ideal date is selected for the trial; however adverse events and the date they occurred will always be recorded at the next study visit.

I.5. Endpoints

I.5.1. Efficacy outcomes

I.5.1.1 Overview. Efficacy outcomes of glaucoma surgical treatment trials may be arranged in a rough hierarchical fashion. Clearly this list is not strictly hierarchical, but serves as a basis for a discussion of analyses.
– Intraocular pressure (IOP) control and associated reoperation ;
– Measures of structure and function which include but are not limited to visual acuity, visual field, disc characteristics
– Measures of patient quality of life quantified with questionnaires or utility assessments;
– Economic outcomes.

I.5.1.2. Surrogate outcomes. There is some debate on whether outcomes lower in the hierarchy (*e.g.,* pressure control) are in fact surrogates for outcomes later in the list (structure/function, quality of life). It is well known that treatments effective for biomarkers or surrogate outcome variables (say electrocardiogram abnormalities) may not, in fact, be effective treatments for the ultimate clinical outcome (say mortality). The consensus of this group is that the aim of glaucoma surgery is to control pressure and this should be the focus of the primary analysis. While IOP may be a biomarker for glaucomatous disease best measured by field loss or nerve fiber layer thinning, once a patient has been diagnosed with glaucoma clinicians feel ethically constrained to treat high pressure and would not be willing to participate in a trial in which uncontrolled pressure was allowed with the aim of demonstrating a treatment effect on structural or functional measures. Also, visual fields are often not

measurable in patients enrolling in glaucoma surgical clinical trials due to the severity of disease in many of these patients.

I.5.1.3. IOP endpoint definition. The advice of this group is to select a dichotomous definition of success/failure to allow comparison of failure rates between treatment groups. The definition of failure should be based on reoperation to control pressure, but also include a pressure criterion (*e.g.,* ≤ 21 mmHg, or < 30% decrease from baseline measurement; see report of definitions group) in case there is a bias in timing of reoperation between the treatments being evaluated. Investigators and the safety and data monitoring committees of individual studies should have discretion about whether or not to require consecutive high pressures as part of the failure definition or if pressure control with medications constitutes success, or to specifically account for changes in medications as part of the definition of success. This may depend on the severity of disease of eligible patients. Investigators may also wish to include a lower pressure indicative of hypotony as part of the definition of success.

I.5.2. Safety outcomes

Patient safety outcomes should be considered distinct from efficacy outcomes with the aim of assessing separately the benefits and risks of a surgical procedure, though analyses may be constructed that take both into account (*e.g.*, estimating incidence of all reoperations including those due to both treatment failures and the repair of complications). Investigators and the safety and data monitoring committee of individual studies should have discretion to propose trial-specific ocular and systemic safety outcomes, however these are likely to include incidence of complications (intra-operative, peri-operative, and short and long term post-operative), endothelial cell count loss, and loss of vision. Visual field progression is unlikely to be of use as a measure of treatment efficacy in short follow-up (≤ one year); however, it may be important for assessment of safety. Monitoring of major adverse events including mortality, an inpatient hospital stay, and loss of vision is mandatory and will be required to satisfy IRBs of participating centers.

I.5.3. Quality-of-life assessments

Investigators may also wish to include a validated questionnaire to assess the effect of the study treatments on participants' health related quality of life. For example, a functioning drainage implant that induces diplopia may successfully control intraocular pressure but have a devastating effect on a patient's vision-specific quality of life. Utility assessments are another option for collecting this information. At this time we do not feel that these measures should be considered the principal study outcome, but they may well provide useful ancillary information. The decision of whether or not to collect these data will likely depend on the availability of time and resources (*e.g.*, interviewers) in a given study.

I.6. Masking

Double masking of surgeons and patients to treatment assignment is the gold standard for treatment assignments in randomized trials, but this is frequently (almost always) impossible in glaucoma surgical trials. However, where possible, measurements of outcome variables (*e.g.*, IOP measurements) can be performed by personnel masked to the randomization or at least the study hypothesis. Legitimate disagreements exist about the importance, practicality, and role of masking and placebo controls in glaucoma trials.[11,12]

I.7. Sample Size Estimates

Most frequently, the trial's sample size estimate will be based on a desire to detect a specified, clinically relevant difference between the study surgery and the standard treatment in the primary efficacy outcome (*i.e.*, pressure control). However, studies may also be designed to detect differences in adverse event rates between treatment groups. Calculation of the sample size generally assumes a 0.05 alpha error and a statistical power of 80%, 90%, or 95%. Power less than 80% is unlikely to be acceptable. Survival analysis (Kaplan-Meier, Cox regression time to failure methods) provide more statistical power than a simple comparison between groups of proportions of cases failing at a given follow-up interval. PS, a useful power/sample size program, is available free from Vanderbilt University (www.mc.vanderbilt.edu/prevmed/ps/index). Another consideration is that one may desire a sample size large enough to create confidence intervals of a pre-specified width (say ± 5 or 10%) around expected complication rates.

I.8. Eyes Versus Patients

The last twenty years have seen a huge proliferation in methods for analysis of correlated data, such as the two eyes of a single patient. However, there is an ethical issue with the independent randomization of the two eyes of one patient into a surgical trial. Unless randomization of both eyes occurs at the same time, a clinical investigator may observe treatment failure or complications in the first eye of a patient and feel that for that particular patient the opposite treatment is the best choice for the second eye. This could lead to an unfixable bias because the investigator would be put into the position of not recruiting the second eligible eye of that patient into the study (and risking its randomization to the same treatment as the first eye). Therefore, we recommend enrolling only one eye per patient into glaucoma surgical trials.

I.9. Interim Analysis and Stopping Rules

A large statistics literature exists on the creation and application of stopping rules. The popular O'Brien-Fleming rule implemented in a program by Lan and DeMets (available at www.biostat.wisc.edu/landemets/) allows

computation of significance levels for planned interim analyses, while preserving the chosen overall alpha error (say, 0.05) of the study treatment comparison. The strategy of this method is to make it very difficult to stop a trial early (requires a very highly significant p-value) but easier as the study progresses. That said, however, a significant p-value from such an analysis should not be considered a 'trigger' to stop the trial, but rather one guide for the SDMC in making a decision.

If recruitment is expected to be completed prior to the time when outcomes become available a formal stopping rule may not be necessary. For example, if recruitment will be completed within six months of when the first patient is randomized and treatment failures are unlikely to be observed prior to six months follow-up, then the issue of stopping recruitment early is moot. Of course, planned recruitment goals are often overly optimistic and even in this setting stopping trial could become an issue because of safety outcomes occurring in early follow-up.

II. Analysis

II.1. Comparison of Treatment Groups by Baseline Variables

To evaluate if the randomization procedure successfully produced comparable treatment groups, they should be statistically compared with respect to all relevant demographic and clinical variables giving special attention to known risk factors for glaucomatous damage (*e.g.*, age, pre-operative IOP, race, central corneal thickness, etc).

Assuming the study compares a single new treatment versus standard treatment, significance testing can be performed with student's t-test for interval level variables; dichotomous and polychotomous variables can be compared with Fisher's exact test or the chi-squared test (with Yates correction for dichotomous variabes); and Mann-Whitney tests can be used for ordinal variables, as well as interval level variables if there are strong deviations from the assumptions of the t-test.

II.2. Principal Treatment Comparison

II.2.1. Univariate analysis with or without stratification

In keeping with our suggestion that the main outcome variable for the study be failure of pressure control, the principal treatment comparison will usually be a Kaplan-Meier analysis of time to failure accounting for randomization strata, and with a p-value based on the log-rank test (although other significance tests, such as Breslow's may be preferred by others). The cumulative proportions should be presented graphically with sample sizes of patients remaining at risk provided at regular follow-up intervals. Often, for graphical purposes, strata will be lumped, unless a test of treatment stratum interaction is significant. For manuscripts it is often wise to truncate these

graphs for long follow-up when sample sizes dwindle and standard errors become large. Including the standard errors in the graph is also an option.

Kaplan-Meier analysis can also be supplemented with a simple comparison of proportions failing in each treatment group, but these must be estimates of the true incidence of failure – that is, they must be rates which apply to a specific follow-up interval, for example one year. *Comparing proportions successful at 'last follow-up' is meaningless and unacceptable*. The Yates corrected Chi-squared test or Fisher's exact test should be used to calculate p-values for the significance of the difference between failure rates and the difference in failure rates should be presented with a confidence interval (usually 95%). StatXact (Cytel software) is good software for obtaining asymptotic or exact significance tests and confidence intervals.

II.1.2. Scatterplot analysis of pressure control

An excellent graphical means of conveying the effect of treatment on pressure control is to plot preoperative pressures against post-operative pressures at clinically meaningful follow-up times (for example 1 year post-op) in the form of an XY scatterplot. If the preoperative pressure is used as the X-variable then points below the diagonal represent eyes with lower postoperative pressures. A horizontal reference line can be used to show a success cut-off pressure of 21 or 18 mmHg post-operatively. Reference lines parallel to the diagonal can serve to highlight specific pressure reductions, such as 3 mmHg, or a line with a slope of 0.8 might illustrate a 20% percentage reduction from baseline IOP. Results for two treatments can be compared in a single graph by the use of different symbols, although with a large sample size these may become difficult to interpret, and separate graphs for each treatment, constructed on the same scale and presented side-by-side, may be preferable.

The advantage of this graphical method is its presentation of treatment effect data from all eyes in the study in an easily interpretable visual format for the reader of a study publication. The disadvantages are their lack of accounting for time to treatment failure, loss to follow-up of study participants, and the cumbersome nature of differentiating eyes with pressure controlled on medications or following reoperation (a treatment failure). Also, overlapping points become a problem in large studies. The two methods of analysis, Kaplan-Meier time to failure and scatterplot graphs, complement each other well and we recommend using both.

II.1.3. Risk ratios and multivariate analysis

If the proportional hazards assumption of Cox regression is valid (which can be assessed with SAS software), that is a useful, flexible method of analysis that provides risk ratios for treatment effects and 95% confidence intervals with and without controlling for important covariates. Cox regression models will also provide risk estimates for the effect of covariates. Even if the groups are similar and there are no statistically significant differences between group

means, the final model should adjust for known risk factors, since their distributions may be different between groups.

II.2. Intention to Treat

Not every patient randomized to a given surgery will receive that surgery. Due, for example, to errors in communication a patient may receive the opposite treatment of the one to which they were assigned. An important consideration for analysis is whether to classify these patients with the treatment they were randomized to or the treatment they received. The gold standard analysis in clinical trials is the intention to treat analysis; that is, a patient's data are included with the group to which they were originally randomized even if they did not receive that treatment. The aim of this paradigm is to prevent biases from creeping into the choice of surgery after the fact of randomization. In practice both analyses will usually be performed and the intention to treat analysis will have primacy; however, if the two analyses yield different conclusions, the reasons for this should be carefully considered by the investigators and the SDMC. Also in practice, patients may be withdrawn after randomization and before surgery is performed. W*ithdrawing patients after the study surgery is performed, either from efficacy or safety assessments, is dangerous and unacceptable.*

II.3. Subgroup Analyses, Tests of Interaction

We feel that investigators should refrain from reporting differential treatment effects within subgroups unless these are supported by a statistically significant test of interaction.[13] This holds true for randomization strata as well as groups defined by demographic characteristics such as race, gender, and age. For example if a significant treatment effect was found in women but not men, these two groups should not be presented separately unless there is a significant interaction between treatment and gender; that is, unless the difference between treatment groups in women is significantly greater than the difference between treatment groups in men.

II.4. Ancillary Hypotheses and Multiple Comparison Adjustment

Good clinical investigators provide a font of interesting hypotheses regarding differential treatment effects and risk factors, and the testing of these ancillary hypotheses are an excellent and important use of clinical trial data, especially when they are not 'data driven'. We encourage testing of these hypotheses without Bonferroni or other 'multiple comparison' adjustment, but it should be made clear in manuscripts that these are secondary hypotheses and an honest accounting should be provided of how many hypotheses were tested with non-significant results.[14] Exploratory analysis of trial data, not specified a priori, may best be viewed as 'hypothesis generating' and possibly spurious until confirmed by another study.

II.5. Secondary Outcome Analyses

For assessing both safety and efficacy, it is necessary to compare the treatment groups with respect to important secondary outcome variables. In glaucoma clinical trials these will include but may not be limited to changes from baseline in IOP, acuity, visual field (usually mean deviation and/or pattern standard deviation), medication use, and incidence of complications/adverse events. Measurements of cup/disc ratios and imaging of the disc or nerve fiber layer, for example by SLP or OCT may also be analyzed.

Analysis of visual acuity changes is best done as an interval level analysis of ETDRS letter score differences, providing acuity measurements were made with Baily-Lovie charts. An alternative is approximate LogMAR (-1 * log[Snellen Fraction]). Patient satisfaction or quality of life changes, measured with validated questionnaires such as the NEI-VFQ or SF-36 may be studied as well, and often are analyzed as interval level variables with covariate adjustment in multiple regression.

The statistical significance of differences from baseline to a particular follow-up point within each treatment group will be tested with paired t-tests or Wilcoxon tests if appropriate, and McNemar's test can be used for dichotomous variables. Statistical significance of differences from baseline between treatment groups can be assessed with student's t-test. Incidence of complications can be compared with the Chi-squared test or Fisher's exact test.

For glaucoma surgery in particular, assessment for a bias in re-operation should be conducted by comparing pre-re-operation IOP in both groups as well as IOPs of patients in both groups not undergoing re-operation.

Economic analyses receive consideration in a separate section.

III. Reporting

III.1. Statistical Methods

In addition to reporting all statistical methods employed in analyses of trial data, provide a brief description of data and safety monitoring procedures including any statistical stopping rule (if recruitment was terminated prior to completion of planned enrollment, that will be an important part of the trial results). For historical interest, the rationale for the sample size determination/power considerations may be included but are no substitute for reporting of confidence intervals around differences and risk estimates in the results.

III.2. Results

III.2.1. Results of significance tests

The assessment of hypothesis tests with p-values is common practice and well understood, but estimates of the range of effect sizes presented as confidence intervals is equally, if not more important. A p-value of 0.049, while demonstrating the statistical significance of a treatment effect, also means that the trial data are consistent with a very small effect (and possibly a very large effect as well). This can only be appreciated by examination of 95% confidence intervals around differences in means, differences in proportions, and risk ratios. Confidence intervals around a non-significant treatment effect may reveal that trial data cannot exclude a clinically meaningful difference between treatments.

III.2.2. Table content

The comparison of randomized groups by important demographic characteristics and risk factors are best presented in tables, including Ns so the reader gets a clear idea of how much data is missing. Similar tables are usually the best method of presenting differences in means (of say IOP, number of medications, etc.) over a given follow-up interval. We suggest tabling differences rather than just baseline and follow-up statistics because missing data is virtually unavoidable, especially at longer follow-up intervals. There may be substantial or even statistically significant differences in the baseline measurements of cases with and without long follow-up; thus, the reader cannot infer the mean differences by subtraction. We encourage documenting Ns for each variable in a table.

III.2.3. Figure content

The reader of a clinical trial report should be able to understand how all patients randomized fit into analysis with respect to treatment group, stratification, and follow-up. This may usefully be conveyed in a flow diagram.

As above, a line graph of cumulative Kaplan-Meier proportions failing over time is usually the best way to convey the treatment effect. Similar line graphs may also communicate changes in IOP with time. Intraocular pressure reductions from baseline can be presented at specific follow-up visits in an XY scatterplot format, one including and one excluding those who have been reoperated.

Graphical displays of confidence intervals should be presented on a linear scale for differences in means and proportions, but on a logarithmic scale for risk ratios.

Conclusions

Following established, standard principles for design and analysis of glaucoma surgical trials should make future research reports comparable and easily interpretable. Of particular note, trials should include a Safety and Data Monitoring Committee and document all study procedures in a Manual of Procedures. Analysis should be performed with time to failure methods to account for follow-up. Significance tests should be supported by confidence interval estimates.

Further Research Needed

Research into design and analysis of clinical trials is ongoing and appears, for a wide range of topics, in journals such as Statistics in Medicine, Biometrics, Biometrika, and the Journal of the American Statistical Association. The real need is to focus attention on good application of existing and accepted methods in future glaucoma surgical trials.

Overview

A framework is presented for implementation of established principles regarding the design, analysis, and reporting of clinical trials with attention to outcomes relevant for glaucoma surgery. The aim of this report is to ensure that published glaucoma surgical trials will use standard, comparable methods and reporting strategies. A generalized manual of procedures is available in an appendix and may serve as a convenient model for new trials in the design phase.

References

1. Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials, 3rd ed. New York: Springer 1998, p. 368.
2. Meinert CL, Tonascia S. Clinical Trials: Design, Conduct, and Analysis. New York: Oxford University Press 1986, p. 469.
3. Fleiss, JL. The Design and Analysis of Clinical Experiments. New York: John Wiley & Sons 1986, p. 432.
4. The FFSS Study Group. Five year follow-up of the fluorouracil filtering surgery study. American Journal of Ophthalmology 1996; 121: 349-366.
5. The Advanced Glaucoma Intervention Study (AGIS): 4. Comparison of treatment outcomes within race. Seven-year results. Ophthalmol 1998; 105: 1146-1164.
6. Anderson DR, Drance SM, and Schulzer M, writing committee for Collaborative Normal-tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Amer Jour Ophthalmol 1998; 126: 487-497.

7. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002; 120: 1268-1279.
8. Musch DC, Gillespie BW, Niziol LM, Janz NK, Wren PA, Rockwood EJ, Lichter PR; Collaborative Initial Glaucoma Treatment Study Group. Cataract extraction in the collaborative initial glaucoma treatment study: incidence, risk factors, and the effect of cataract progression and extraction on clinical and quality-of-life outcomes. Arch Ophthalmol 2006; 124: 1694-1700.
9. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK, Wilson MR, Gordon MO. The Ocular Hypertension Treatment Study: A randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002; 120: 701-713.
10. The European Glaucoma Prevention Study Group. Results of the European Glaucoma Prevention Study. Ophthalmology 2005;112: 366-375.
11. Quigley H. European Glaucoma Prevention Study. Ophthalmology 2205; 112: 1642-1643.
12. Miglor S, Pfeiffer N, Zeyen T, Cunha-Vaz J, Torri V, Adamsons I. European Glaucoma Prevention Study. Ophthalmology 2005; 112: 1643-1645.
13. Ederer F. Refereeing clinical research papers for statistical content. Am J Ophthalmlol 1985; 100: 735-737.
14. Altman DG. Statistics in medical journals: some recent trends. Statist Med 2000; 19: 3275-3289.

Appendix
WGA Guidelines for Surgical Clinical Trials Manual of Procedures

Table of Contents

I. Introduction 65
I.1. Background and Significance 65
I.2. Objective 65
I.3. References 65

II. Study Design 65
II.1. Inclusion Criteria 65
II.2. Exclusion Criteria 66
II.3. Sample Size Calculations 66
II.4. Randomization 66
II.5. Masking 66
II.6. Timetable for the Study 67

III. Clinical Procedures 67
III.1. Visual Acuity 68
III.2. Slit Lamp Biomicroscopy 71
III.3. Seidel Testing 71
III.4. Tonometry 72
III.5. Motility Evaluation 73
III.6. Gonioscopy 73
III.7. Ophthalmoscopy 73
III.8. Perimetry 74
III.9. Optic Disc Assessment 74
III.10. Quality of Life Assessment 74

IV. Surgical Procedures 75
IV.1. Surgery A 75
IV.2. Surgery B 75

V. Study Organization 75
V.1. Introduction 75
V.2. Clinical Centers 75
V.3. Statistical Coordinating Center 76
V.4. Safety and Data Monitoring Committee (SDMC) 76
V.5. Steering Committee 77

VI. Policy Matters 77
VI.1. Patient Consent 77
VI.2. Publication and Presentation Policy 78
VI.3. Policy of Confidentiality 78

VII. Clinical Center Procedures 78
VII.1. Qualifying Assessment 78
VII.2. Assignment of Patient Identification Number 79
VII.3. Randomization Procedure 79
VII.4. Schedule of Visits 79

VIII. Statistical Coordinating Center Procedures 82
VIII.1. Data Management 82
VIII.2. Data Security 82
VIII.3. Data Forms 82
VIII.4. Data Analysis 82

I. Introduction

I.1. Background and Significance

It is felt that clinical glaucoma surgical research is currently hindered by, among other things, the lack of uniform guidelines for clinical glaucoma surgical trials reporting. The controversy that arose from the introduction of non-penetrating glaucoma filtering surgery and its position among our surgical treatment options is just one example. The reason is the lack of a common platform (guidelines) on which studies can be designed, reported and thus compared. It is envisioned that this document contains clear and detailed guidelines for designing and reporting on glaucoma surgical trials.

I.2. Objective

The objective of this study is to compare the long-term safety and efficacy of surgery A to surgery B in patients with (define type) glaucoma. Outcome discrimination between the two treatment groups will be made using measures of visual structure and function including intraocular pressure, glaucoma re-operations, visual field, visual acuity, optic disc, and economic quality-of-life assessment.

Safety will be assessed by monitoring complication rates during and after surgery, including suprachoroidal hemorrhage, endophthalmitis, and hypotony maculopathy. Other measures, such as visual field changes, optic disc progression, and changes in corneal endothelial cell counts, may be appropriate.

I.3. References

[Add appropriate references.]

II. Study Design

II.1. Inclusion Criteria

All of the criteria listed below must be present in the study eye in order for the patient to be eligible for enrollment in the study.

- Define age limits
- Define type(s) of glaucoma
- Specify other aspect of patient or eye necessary to be in study

II.2. Exclusion Criteria

If any of the following exclusion criteria are present in the study eye, the patient may not be entered into the study.

- Unwilling or unable to give consent, unwilling to accept randomization, or unable to return for scheduled protocol visits
- Other eye has been randomized into this study
- Is it appropriate to exclude pregnant or nursing women?
- Exclusion on basis of visual acuity, *e.g.*, 'No light perception'
- Specify other aspect of patient or eye which preclude enrollment

II.3. Sample Size Calculations

Sample size calculations were determined based on projected success rates in each treatment group and are shown in Table 1. Enrollment of ***XXX patients*** in each treatment group, or a total of ***YYY patients***, is required for the study to generate statistically valid conclusions. Some loss of patients to follow-up is anticipated. Therefore, enrollment in the study will be offered to a total of ***ZZZ patients*** in each treatment group.

II.4. Randomization

Since the purpose of this study is to compare the safety and efficacy of two surgical procedures used in the management of glaucoma, randomization techniques are used to assure an unbiased treatment assignment to patients. If patients in the study are expected to have different prognoses (*e.g.*, primary open angle, neovascular) it is appropriate to stratify patients before randomization. Randomization takes place at the time the patient is enrolled in the study. After the patient's eligibility is confirmed, the Statistical Coordinating Center assigns a treatment group. The randomization schedule is constructed using a computer pseudo-random number generator. The allocation ratio is equal between the two treatment groups. The randomization is blocked by clinic and study stratum using a scheme with small variable blocks. This procedure ensures that there is an equal number of patients in each treatment group even early in the trial, and that the Clinical Center is not able to predict the next treatment assignment. (Please note that in some studies, the number of patients may not be equal for each treatment group.)

II.5. Masking

The investigator and the patient will be masked as to which surgery they receive, if possible. If not possible, outcomes will be measured by personnel who are masked to the patient's surgery, if possible.

II.6. Timetable for the Study

Assign dates to the following tasks:

- Submit Reseach Protocol for Institutional Review Board which will include a Patient Consent Form.
- Write the Manual of Procedures
- Produce data collection forms
- Meet with investigators from selected Clinical Centers and members of the Safety and Data Monitoring Committee
- Certify participating Clinical Centers by:
  - Documenting number of patients who should be eligible
  - Identifying physicians at the Clinical Center who have performed requisite number of surgeries using both study treatments
  - Documenting IRB approval
  - Submission of completed 'dummy' data forms (through one year postoperative visit)
- Produce randomization schedules, stratified by Clinical Center and prognostic categories
- Recruit and randomize patients
- Monitor adverse events by treatment group
- Perform analyses to monitor for treatment differences and success rates on a routine basis
- Prepare manuscript(s)

Table 1. Sample size calculations*

Outcome Size	Success Rate		Required Sample in Each Group	
	Surg A	Surg B		
Success rate (cumulative rate after ***time t***)	***x%***		***y%***	***N***

*The sample size estimate is with a significance level of 0.05 and a power of 0.80 or 0.90 are acceptable levels.

This table can be extended to show various power and various success rates. A useful power/sample size program, PS, is available free from Vanderbilt University (www.mc.vanderbilt.edu/prevmed/ps/index).

III. Clinical Procedures

The following below were used in the Tube Versus Trabeculectomy Study. While they may not be applicable tp all glaucoma surgical trials, they are included as an example of the level of detail appropriate for a Manual of Procedures.

III.1. Visual Acuity

Visual acuity is an important outcome variable. Visual acuity is measured before pupil dilation, tonometry, gonioscopy, or any other technique that could affect vision. Two different techniques are used to measure visual acuity, including Snellen and ETDRS visual acuity testing. Refraction is performed prior to formal measurement of visual acuity by either technique at the Qualifying Assessment and at the annual follow-up visits. Snellen visual acuity is measured at the Qualifying Assessment and at every follow-up visit. ETDRS visual acuity is tested at the Qualifying Assessment and at the annual follow-up visits.

III.1.1. Subjective Refraction

Subjective refraction must be performed at the Qualifying Assessment and at the annual follow-up visits in order to determine best-corrected visual acuity. It is permissible to use a phoropter to determine best-corrected Snellen visual acuity. However, trial frames are required for testing best-corrected ETDRS visual acuity. The trial frame is placed and adjusted on the patient's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupil.

The left eye is occluded first. An approximate beginning refraction may be determined by retinoscopy, automated refraction, or a subjective refraction from a prior visit. The sphere is refined first. The cylinder is then refined, first the axis followed by the power. Finally, the sphere is rechecked. If a phoropter was used in the subjective refraction, the refraction is placed in a trial frame and the sphere is refined prior to ETDRS visual acuity testing. The right eye is then occluded, and the procedure is repeated for the left eye.

If the patient wears contact lenses and has glasses also, he or she is instructed not to wear the contact lenses on the day of the Qualifying Assessment. Patients unwilling to discontinue contact lens use after surgery will be excluded from the study. In the event that the patient either has no glasses or has forgotten the instructions and reported for the Qualifying Assessment wearing contact lenses, the contact lenses are removed and at least thirty minutes allowed to elapse before subjective refraction and visual acuity testing is performed.

III.1.2. ETDRS Visual Acuity

The logmar visual acuity testing has been adapted from the Early Treatment of Diabetic Retinopathy (ETDRS). The logmar visual acuity scale facilitates statistical analysis and simplifies quantification of acuity at various distances. The right eye is tested with ETDRS logmar chart 1, then the left eye is tested with ETDRS logmar chart 2. Each chart is hidden from view until the eye being examined is ready for testing. ETDRS visual acuity is measured after standardized refraction only during the Qualifying Assessment and at the annual follow-up examinations.

The room illumination should be at a level of 50 to 100 foot candles, and between 50 and 125 foot candles should illuminate the ETDRS visual acuity chart. The distance from the patient's eye to the visual acuity chart is exactly 4.0 meters. The patient may sit or stand, but he or she is not allowed to lean forward or backward so a constant testing distance is maintained. After proper instruction, refraction, and placement of the appropriate lenses in a trial frame, the left eye is occluded and testing is begun with the right eye. The patient is instructed that the chart has letters only and no numbers. If the patient forgets this information and reads a number, he or she is reminded that the chart contains only letters and the examiner requests a letter in lieu of the number. Each letter that is identified correctly is circled on the ETDRS Visual Acuity Worksheet. The patient is advised to read slowly, so as to achieve the best identification of each letter. When the patient says he or she cannot read a letter, he or she is encouraged to guess. The patient should be encouraged to fix eccentrically if this improves the visual acuity, but care must be taken to ensure that the fellow eye remains covered.

Eyes reading fewer than 20 letters correctly at a test distance of 4.0 meters are tested at 1.0 meter. Before testing at 1.0 meter, +0.75 sphere is added to the 4.0 meter correction already in the trial frame to compensate for the closer testing distance. The patient is asked to read only the first six lines at 1.0 meter, so the maximum score attainable at that distance is 30. Correctly identified letters are circled on the ETDRS Visual Acuity Worksheet. If the patient's visual acuity is so poor that he or she cannot read the largest letter at 1.0 meter, assess his or her ability to count fingers. After testing of the right eye is completed, chart 1 is replaced by chart 2 and the procedure is repeated for the left eye.

Each letter read correctly and circled on the ETDRS Visual Acuity Worksheet is scored as one point. The score for each line (which is zero if no letters were read correctly) and the total score is recorded after testing is completed. If testing at 1.0 meter is not required (*i.e.*, 20 or more letters were seen with testing at 4.0 meters), 30 points are automatically scored for the 1.0 meter test. The total score, equaling the sum of the 4.0 meter and 1.0 meter scores, is recorded on the data form. The ETDRS Visual Acuity Worksheet is for clinic use only and should not be sent to the Statistical Coordinating Center.

III.1.3. Snellen Visual Acuity

Snellen visual acuity may be measured using any standard visual acuity chart. The same type of chart must be used throughout the duration of the study. Snellen visual acuity is measured during the Qualifying Assessment and at all follow-up visits. Standardized refraction is performed prior to Snellen visual acuity testing at the Qualifying Assessment and annual follow-up examinations.

The patient is not allowed to lean forward or backward, so that a constant testing distance is maintained. After proper instruction and refraction, the left eye is occluded and testing is begun with the right eye. Progressively smaller

lines are presented to the patient until he or she makes two or more errors in a line. When a patient states he or she is unable to read a letter, he or she is encouraged to guess. If a patient misses only two letters on a line, a second chance is provided by asking the patient to read the line backwards. The patient is encouraged to fix eccentrically if this improves the visual acuity, but care must be taken to ensure that the fellow eye remains covered. The Snellen visual acuity is recorded as the smallest line in which the patient misses one or fewer optotypes. If the patient's visual acuity is so poor that he or she cannot read the 20/400 line, assess his or her ability to count fingers. After testing of the right eye is completed, the procedure is repeated for the left eye.

III.1.4. Testing for Finger Counting

After proper instruction and refraction, the examiner's hand is viewed at a distance of two feet from the patient's eye. The fellow eye is closed and completely occluded by the palm of the patient's or assistant's hand. The examiner presents a random number of fingers to the patient. The patient is asked to indicate the number of fingers seen. If the number of fingers shown is correctly identified on four or more of five presentations, vision is recorded as count fingers. If the number of fingers presented cannot be identified on four or more of five presentations, test for hand motions.

III.1.5. Testing for Hand Motions

In testing for hand motion, the examiner's hand is viewed with all fingers extended and separated at a distance of two feet from the patient's eye. The fellow eye is closed and completely occluded by the palm of the patient's or assistant's hand. The patient's glasses are not to be worn. The examiner's hand is presented in a random order under three conditions: stationary, moving back and forth horizontally, and moving up and down vertically. The speed of movement is approximately one complete cycle of movement (up and down or back and forth) per second. The patient is instructed that the examiner's hand will be presented in one of these conditions. He or she is asked to respond to the question, 'what is my hand doing now?' with either, 'still', 'back and forth', or 'up and down'. The process is repeated five times. It is considered a correct response if the patient states the hand is still or he or she cannot see it while it is stationary, and he or she is able to recognize movement and identify its direction. If hand motions are correctly identified on four or more of five presentations, vision is recorded as hand motions. If hand motions cannot be identified on four or more of five presentations, test for light perception.

III.1.6. Testing for Light Perception

Light perception is tested using the same complete occlusion of the fellow eye with no other bright lights visible from the patient's position. The patient's

glasses are not worn. The light of an indirect ophthalmoscope is directed into the eye from a distance of two feet for one or two seconds, then turned away. The patient is asked to report ‘on’ when he or she sees the light, and ‘off’ when it disappears. The process is repeated five times in a nonrhythmic fashion. The visual acuity is recorded as light perception if the patient responds correctly four or more out of five times.

III.1.7. Testing Visual Acuity in Illiterate Patients

Patients who are illiterate and cannot read standard letter charts have visual acuity tested using either a number chart, an illiterate E chart, a Landolt ring chart, or picture chart. The type of chart must be identified so that it can be used throughout the duration of the study. The smallest line in which one or fewer optotypes are missed is recorded as the Snellen visual acuity, and a notation is made that testing was performed in an illiterate patient. Because a method for ETDRS visual acuity testing has not yet been developed for illiterate patients, only Snellen visual acuity testing is performed.

III.2. Slit Lamp Biomicroscopy

Examination of the anterior segment using slit lamp biomicroscopy is performed at the Qualifying Assessment to document the preoperative status of the eye, and at all follow-up examinations to detect any changes in ocular status during the course of the study which may be attributable to the disease or treatment. Slit lamp biomicroscopy may be performed with any commercially available instrument, and it is used in a standard fashion starting anteriorly and working posteriorly. Standardizing subjective grading of bleb leaks and lenticular opacities is difficult, if not impossible. However, it is expected that subjective grading by each investigator is relatively reproducible. Attempts will be made to compare subjective gradings between investigators.

III.3. Seidel Testing

If relevant, we believe that if a bleb leak is a possible complication after either surgery then a strict protocol for Seidel testing be in place and testing should not be dependent on IOP or surgeon discretion.

Seidel testing must be performed at each postoperative follow-up examination. The Seidel test is performed using a fluorescein strip moistened with one or two drops of 0.5% proparacaine which is then applied to the conjunctiva. Alternatively, one drop of premixed fluorescein and anesthetic may be instilled. The area is closely observed using high magnification and a broad slit beam with maximal intensity illumination using a cobalt blue filter. Aqueous leakage is apparent as a light yellow stream and interrupts a dark green background of undiluted fluorescein. If the Seidel test is positive, the leak is graded as an ooze, frank leak, or brisk leak.

III.4. Tonometry

Goldmann applanation tonometry is used to measure the intraocular pressure, except when irregular corneal astigmatism, corneal scarring, or corneal edema precludes accurate readings. In these cases, alternative methoeds such as the Tono-Pen should used. The intraocular pressure is measured prior to pupillary dilation. Whenever possible, the intraocular pressure should be checked at the same time of the day as the Qualifying Assessment to minimize the effect of diurnal fluctuation of intraocular pressure.

III.4.1. Goldmann Applanation Tonometry

The calibration of the Goldmann applanation tonometer is checked every 3 months, as described in the Haag-Streit Goldmann Applanation Tonometer Operator's Manual. Clean the prism according to your institutional infection control policy. The right eye is always tested first. Following instillation of a drop of 0.5% proparacaine, a fluorescein strip is placed near the lateral canthus in the lower conjunctival sac. Once the lacrimal fluid has been sufficiently colored, the fluorescein strip is removed. Alternatively, one drop of premixed fluorescein and anesthetic may be instilled. The patient's head is properly positioned in the chin rest and against the forehead rest without leaning forward or straining. Any tight-fitting neckwear is loosened. The patient is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the investigator holds the eyelids open against the orbital rim taking care not to apply any pressure on the globe. The patient is instructed not to hold his or her breath. If corneal astigmatism is greater than 3.0 diopters, the prism is rotated so that the axis of the minus cylinder on the prism graduation corresponds to the red mark on the prism holder. The investigator looks through the slit lamp and gently brings the tip of the prism in contact with the center of the cornea. The mires should be well focused, centered horizontally, and positioned vertically so that they are of equal circumference above and below the horizontal dividing line. If the mires are narrower than approximately one tenth their diameter, the investigator instills additional fluorescein. The investigator adjusts the measuring drum until the inner borders of the two mires just touch each other. If pulsation is present, the measuring drum is adjusted until the mires separate a given distance during systole and overlap the same distance during diastole. The investigator removes the prism from the cornea and repeats the procedure in the right eye until two successive measurements are within 1 mm Hg. The investigator records the last two successive measurements. After testing of the right eye is complete, testing of the left eye follows the same technique.

III.4.2. Tono-Pen

The Tono-Pen (Mentor) is used in cases of corneal edema, corneal scarring, or irregular corneal astigmatism. The Tono-Pen probe tip is covered with a

new Ocu-Film Tip Cover. The instrument is calibrated immediately prior to use, as described in the Mentor Tono-Pen Instruction Manual. The right eye is always tested first. A drop of 0.5% proparacaine is instilled. The patient is positioned in the sitting position and instructed to fix on a distant object. Tight-fitting neckwear is loosened, and the patient is instructed not to hold his or her breath. The Tono-Pen is activated by depressing the activation switch momentarily. The Tono-Pen is brought in contact with the patient's cornea lightly and briefly while holding the instrument perpendicular to the cornea. A click will sound and a digital intraocular pressure measurement will be displayed each time a valid reading is obtained. After four valid readings, a final beep sounds and the averaged measurement appears on the display, along with a single line denoting statistical reliability. Measurements are repeated until two successive readings are obtained within 1 mm Hg and both have a statistical reliability of 5%, indicating that the standard deviation of the valid measurements is 5% or less of the number displayed. The investigator records the last two successive measurements. After testing of the right eye is complete, the same technique is applied to testing of the left eye.

III.5. Motility Evaluation (if relevant)

Diplopia is an important complication which may occur following glaucoma drainage implantation. The cover-uncover and alternate cover tests are performed with the patient looking in primary gaze, as well as in upgaze, downgaze, left gaze, and right gaze. Motility evaluation is performed with the patient looking in the distance and fixating at a near target. Any heterophorias or heterotropias are identified, and the deviation is measured with hand-held prisms. In patients who are unable to fixate for cover testing, the deviation may be measured by centering the corneal light reflexes with prism using the modified Krimsky method.

III.6. Gonioscopy (if relevant)

Gonioscopy is performed with the patient sitting at the slit lamp using either a Zeiss type four-mirror gonioprism or Goldmann single- or three-mirror lens to examine the anterior chamber angle for neovascularization, pigmentation and grading of depth.

III.7. Ophthalmoscopy

A dilated fundus examination is performed at the Qualifying Assessment to determine the preoperative status of the eye, and at all postoperative follow-up examinations to detect any changes in ocular status produced by the disease or treatment. After pupil dilation with appropriate mydriatics, the optic nerve and posterior pole are examined at the slit lamp using a Hruby lens, fundus contact lens, or Volk 90 diopter, 78 diopter, or 60 diopter lens. A head-mounted indirect ophthalmoscope and hand-held condensing lens

(20 diopter or 28 diopter Nikon aspheric lens) is used to evaluate the retinal periphery.

At the Qualifying Assessment, particular attention is paid for signs of proliferative retinopathy, including retinal neovascularization, neovascularization of the disc, vitreous hemorrhage, or preretinal hemorrhage. Patients with active proliferative retinopathy are excluded from the study. The presence of a scleral buckling element also makes the eye ineligible for the study. At all postoperative follow-up visits, ophthalmoscopy is performed to evaluate for posterior segment complications, such as serous choroidal effusions, suprachoroidal hemorrhage, or hypotony maculopathy.

III.8. Perimetry (please adjust criteria for individual study)

In surgical clinical trials, patients are often unable to perform perimetry due to the advanced state of their disease. However, visual field assessment is an important outcome and safety measure. Quantitative automated perimetry is performed using autmotaed Field Analyzers. Visual field testing is performed before tonometry, gonioscopy, or any other technique that could affect vision. A visual field should be attempted in any eye that has sufficient vision to permit finger counting at two feet. Eyes with poor central vision may have an intact, off-center island of vision which may be measured with perimetry.

A threshold test is performed in all patients using a size III white stimulus. Visual field testing may be performed with Interactive Thresholding Algorithm or full threshold strategy, but the same testing strategy must be used throughout the duration of the study. The pupil diameter should be 3 mm or greater before visual field testing is undertaken, and this may require pharmacologic dilation. Standardized refraction is performed to determine the patient's distance refraction and best-corrected visual acuity prior to visual field testing. The age appropriate plus lens is added to the distance refraction. Patient education is provided, and the instrument is set up for the test. The technician should monitor the patient during testing. Visual fields are performed preoperatively (within one month of enrollment in the study) and annually
thereafter.

III.9. Optic Disc Assessment

Optic disc photographs or other structural imaging may be necessary to follow as an outcome or as a safety measure in those patients whose discs can be followed for glaucomatous progression.

III.10. Quality of Life Assessment (QOL)

There has been a growing interest within the medical community to determine the impact of different medical interventions on a patient's functional status and quality of life. The NEI-VFQ is a quality of life instrument that was designed to evaluate visual disability and its impact on daily functioning in

ophthalmic patients. The NEI-VFQ is administered to all patients via telephone interview by the Statistical Coordinating Center at the Qualifying Assessment and annual follow-up visits. A telephone interview format serves to prevent bias which could be introduced by a clinical care provider administering the questionnaire.

IV. Surgical Procedures

IV.1. Surgery A

Please provide detailed description of surgical procedure.

IV.2. Surgery B

Please provide detailed description of surgical procedure.

V. Study Organization

V.1. Introduction

Multicenter clinical trials require an organizational structure that provides efficient operations and facilitates communication. The following resource centers work together in this study:
– Clinical Centers (CC)
– Statistical Coordinating Center (SCC)
– Safety and Data Monitoring Committee (SDMC)
– Steering Committee (SC)

V.2. Clinical Centers

Each Clinical Center is responsible for screening potential study patients, enrolling an adequate number of eligible patients, and following the patients according to the protocol until the termination of the study. Each CC has one principal investigator. The responsibilities of the Clinical Centers are as follows:

- To assess the eligibility of patients for the Study
- To enroll an adequate number of patients in the study through informed consent
- To manage each patient in accordance with the randomized assignment provided by the SCC
- To examine patients using the techniques and schedules established for the study
- To complete the proper forms and obtain prescribed assessments at the appropriate follow-up visits

- To respond promptly to requests made by the SCC
- To maintain patient records for the Study in an easily accessible and confidential manner
- To obtain approval for the study and consent form from the local Institutional Review Board
- To promote patient satisfaction and commitment to the trial
- To provide representation at all meetings of the SC

V.3. Statistical Coordinating Center

The SCC receives, edits, processes, analyzes, and stores all study data. The SCC coordinates the activities at the Clinical Centers and monitors adherence to the study protocol. The responsibilities of the SCC are listed below:

- To provide guidance in the development and implementation of the design of the primary study and ancillary studies
- To confirm local IRB approval of the study and consent form before initiating participation of a CC
- To verify eligibility of the patient and completion of the consent form prior to randomization
- To randomize study patients
- To review data received, process, and store all study data
- To produce monitoring reports for the SC and SDMC every six months and upon request
- To analyze data
- To assist in the preparation of manuscripts

V.4. Safety and Data Monitoring Committee (SDMC)

The Safety and Data Monitoring Committee is responsible for the ethical conduct of the study. This committee oversees the informed consent process and major changes in the protocol. The SDMC reviews the accumulating data for evidence of adverse and beneficial treatment effects. This committee meets twice each year for the duration of the study. Telephone conferences will occur as needed. The responsibilities of the SDMC are as follows:

- To review the study design and study documents before the start of the study to identify any problems that may affect future data analysis or patient safety.
- To monitor adherence to the study protocol at each CC.
- To review treatment reports prepared by the SCC for evidence of adverse and beneficial treatment effects.
- To terminate the study if treatment benefits or treatment risks are so high for one treatment group that continuation of the trial is deemed unethical.
- To advise the SC on interpretation of study data.
- To recommend to the SC changes in study protocol based on periodic data analysis.

- To review and approve all publications and presentations.
- To determine when data collected in the study should be released to study investigators, study patients, the medical community, and the public.

The SDMC may want to adopt the O'Brien-Fleming rule, implemented in a program by Lan and DeMets (available at www.biostat.wisc.edu/landemets/), which allows computation of significance levels for planned interim analyses, while preserving the chosen overall alpha error (say, 0.05) of the study treatment comparison. The strategy of this method is to make it very difficult to stop a trial early (requires a very highly significant p-value) but easier as the study progresses. That said however, a significant p-value from such an analysis should not be considered a 'trigger' to stop the trial, but rather one guide for the SDMC in making a decision. The SDMC also has a responsibility to monitor adverse events, and they may decide to stop the trial because of the occurrence of an unexpected adverse event, or a worrisome incidence in one treatment group, without a statistically significant difference between treatment groups.

V.5. Steering Committee

The Steering Committee is composed of the principal investigator from each Clinical Center and the Study Chairmen. The SC provides leadership for the trial. This committee has overall responsibility for directing activities and formulating policy for the study. This committee meets twice each year for the duration of the study. Telephone conferences will occur as needed. The specific functions of the SC are as follows:

- To evaluate and approve operational procedures in the study, including the Manual of Procedures and data forms
- To change procedures and resolve technical issues during the course of the trial
- To review study progress and take steps to correct deficiencies, such as patient recruitment, adherence to protocol, or data collection procedures
- To appoint and disband subcommittees needed for execution of the study
- To review and approve ancillary studies
- To collaborate in preparing manuscripts of study findings for publication
- To review and approve all publications and presentations

VI. Policy Matters

VI.1. Patient Consent

This surgical clinical trial for glaucoma patients requires that written consent be obtained from each patient enrolled in the study. The patient is requested to sign the consent form only after patient education is completed. The signed consent form is kept with the study records at the Clinical Center. A copy of

the signed consent is given to the patient, and a second copy is sent to the Statistical Coordinating Center.

The principal investigator of each Clinical Center is responsible for obtaining approval for the study and consent form from the local Institutional Review Board. A copy of each Clinical Center's approved consent and documentation of IRB approval must be submitted to the Statistical Coordinating Center prior to beginning patient enrollment in the study.

VI.2. Publication and Presentation Policy

A Study paper or publication is one which contains details of the design, methods, or results of the study, and is written by investigators. Any Study paper classified must be approved by the Steering Committee and Safety and Data Monitoring Committee prior to submission for publication. Similarly, any presentation made on behalf of the Study must be approved by the Steering Committee and Safety and Data Monitoring Committee. No Clinical Center will publish its own results, except with explicit and written permission of the steering committee, and with clear acknowledgement of this work being part of a larger trial.

VI.2.1. Ancillary studies policy

An ancillary study is defined as any investigation which is carried out at one or more, but not all, of the participating Clinical Centers and which utilizes the resources of the Study. The resources may involve the participants themselves (through collection of added items of data for special analyses) or the database of one or more of the Clinical Centers. All ancillary studies require review and approval from the Steering Committee and Safety and Data Monitoring Committee before they are implemented. No ancillary study will be approved which interferes with the data collection, treatment, or recruitment process of the study.

VI.3. Policy of Confidentiality

Materials distributed for Steering Committee and Safety and Data Monitoring Committee meetings are confidential. Minutes from all study meetings are confidential. Access to a participant's record by any unauthorized individual is prohibited. Tabulations or listings which reveal the identity of individual study participants are confidential.

VII. Clinical Center Procedures

VII.1. Qualifying Assessment

The Qualifying Assessment establishes whether the patient satisfies eligibility criteria. It is vital to the scientific validity of the study that every eligible patient be offered enrollment.

VII.2. Assignment of Patient Identification Number

Any patient who is confirmed by the Statistical Coordinating Center to meet the eligibility criteria and is enrolled in the study is assigned a patient identification number.

VII.3. Randomization Procedure

Randomization takes place at the time the patient is enrolled in the study. After patient eligibility is confirmed and a patient identification number is provided, the Statistical Coordinating Center assigns treatment. The randomization schedule is constructed using a computer pseudo-random number generator. The allocation ratio is equal between the two treatment groups. The randomization is blocked by clinic and study stratum using a scheme with small variable blocks. This procedure ensures that there is an equal number of patients in each treatment group even early in the trial, and that the CC is not able to predict the next treatment assignment.

VII.4. Schedule of Visits

All study investigators must be familiar with the schedule of visits to ensure that required data is collected and that future visits are scheduled within the appropriate time windows. The need for continued follow-up and timely visits should be stressed to the patient during the informed consent process and throughout the study. An appointment schedule is generated for each patient by the Statistical Coordinating Center and sent to the patient's Clinical Center. An example of possible time windows for follow-up visits is shown in Table 2. Table 3 presents an example of the data to be obtained at each of the scheduled visits.

Table 2. Time windows for follow-up visits

Number of Days After Surgery			
Follow-Up Visit	Ideal Time	Preferred Time	Acceptable Time
1 Day	1 day	1 day	1–3 days
1 Week	7 days	6–8 days	4–14 days
1 Month	30 days	23–37 days	15–59 days
3 Month	90 days	76–104 days	60–120 days
6 Month	182 days	161–203 days	121–270 days
12 Month	365 days	305–425 days	271–455 days

Follow-Up Visit	Ideal Time	Preferred Time	Acceptable Time
18 Month	547 days	487–607 days	456–637 days
2 Year	730 days	670–790 days	638–912 days
3 Year	1095 days	1005–1185 days	913–1277 days
4 Year	1460 days	1370–1550 days	1278–1642 days
5 Year	1825 days	1735–1915 days	1643–2007 days

Table 3. Schedule of visits

Preoperative	1 Day	1 Week	1 Month	3 Month	6 Month	1 Year
Refraction	X					
Snellen VA	X	X	X	X	X	X
ETDRS VA	X					
Slit Lamp Biomicroscopy	X	X	X	X	X	X
Seidel Testing		X	X	X	X	X
Tonometry	X	X	X	X	X	X
Motility Evaluation	X					If diplopia
Gonioscopy	X					
Ophthalmoscopy	X	X	X	X	X	X
Automated perimetry	X					
Optic disc exam/photos	X					
NEI-VFQ	X					
Informed Consent	X					

	18 Months	2 Years	30 Months	3 Years	42 Months	4 Years
Refraction	X		X	X	X	X
Snellen VA	X	X	X	X	X	X
ETDRS VA	X		X	X	X	X
Slit Lamp Biomicroscopy	X	X	X	X	X	X
Seidel Testing	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X
Motility Evaluation	If diplopia	If diplopia	If diplopia	If diplopia	If diplopia	If diplopia
Gonioscopy						
Ophthalmoscopy	X	X	X	X	X	X
Automated perimetry	X		X	X	X	X
Optic disc exam/photos	X		X	X	X	X
NEI-VFQ	X		X	X	X	X
Informed Consent						

VIII. Statistical Coordinating Center Procedures

VIII.1. Data Management

A master log is kept of each patient randomized. An appointment schedule is made for each patient and sent to the patient's Clinical Center. When a data form is received at the Statistical Coordinating Center, it is processed for filing and data entry. Each form is data entered by a data entry clerk and then verified by double entry by the SCC Research Coordinator. Edit checks, such as missing data and out-of-range values, will be clarified within the CC.

VIII.2. Data Security

Description of how data are kept confidential.

Description of how data are backed up.

VIII.3. Data Forms

The data forms were designed to be self-explanatory. Their completion should not require reference to separate information manuals. The data forms contain information to be collected at a given point in time during the study. Information collected at another date is incorporated into a separate form.

VIII.4. Data Analysis

The primary analysis will be done with Kaplan-Meier analysis or Cox regression, if the proportional hazards assumption holds. The dichotomous variable success, as defined earlier (as reoperation for glaucoma, and IOP over a designated value, and possibly a vision requirement) will be compared between surgery A and surgery B, and adjusted for appropriate variables. Bias in reoperation rates needs to be assessed, especially if the decision to reoperate is not made in a masked fashion. This entails comparing the IOPs of those reoperated in the two treatment groups, and also comparing the IOPs of those not reoperated between the two treatment groups.
A table comparing baseline factors by treatment group should be included in manuscript. Even if the groups are similar and there are no statistically significant differences between group means, the final model should adjust for known risk factors, since their distributions may be different between groups.

Intraocular pressure (IOP) analysis can be presented at each follow-up visit, including those who have been reoperated, and also excluding those who have been reoperated. Graphical displays for each treatment group of pressure changes from baseline to specific follow-up visits in the form of XY scatterplots are also useful in this regard.

Visual-field parameters, such as change from baseline in mean deviation or pattern standard deviation are important measures of glaucomatous progression. Another potentially powerful analysis is to determine each

patient's slope over time, and test treatment differences with a test of slope. Visual field should also be monitored as a safety measure.

Optic disc measurements such as cup/disc ratio or imaging of the disc or nerve fiber layer, and progression determined by masked evaluation of follow-up versus baseline can be an outcome measure and also monitored as a safety measure.

Snellen visual acuity at each follow-up (or change in number of lines from baseline) can be analyzed with Mann-Whitney tests. LogMar acuity or ETDRS letters (or change in logMAR acuity or ETDRS letters) can be compared between treatment groups with t-tests.

Quality-of-life scores and subscores (and change in scores from baseline) can be assessed with validated questionnaires such as the NEI-VFQ.

Interval level variables (IOP, ETDRS acuity letters, number of meds, visual field parameters, quality of life scores, etc) are compared between groups with t-tests or Mann-Whitney tests, and can be adjusted for the effects of covariates with multiple regression. Analyses to evaluate change from baseline to follow-up within group are performed with the paired t-test or Wilcoxon test. Incidence of complications or progression (or proportions constructed from other dichotomous variables) are analyzed with Yates corrected chi-squared or Fisher's exact test. Changes in dichotomous variables within group can be assessed with McNemar's test.