Clinical Research

A Primer for Ophthalmologists

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Clinical research is, and has always been, crucial to furthering our understanding of ophthalmic conditions - and their treatment and prevention. A basic understanding of the methods employed in clinical research, and the way it is conducted, is invaluable for understanding the scientific basis for existing clinical definitions, diagnostic and screening criteria, and treatment recommendations. It is absolutely essential to interpreting the results of new studies and contributing one's own insights to the body of ophthalmic knowledge.

This brief outline of critical steps in the design and reporting of clinical research was prepared in response to requests for guidance for ophthalmologists working in resource-poor settings, many of whom have not had the opportunity to obtain formal training in the conduct of clinical research. This primer cannot substitute for appropriate course work or personal mentoring in research methods. It is meant instead to introduce the subject, and perhaps more importantly, outline the rigor with which clinical research needs to be undertaken and its results communicated to others. Ophthalmologists interested in conducting their own clinical research are urged to pursue appropriate courses in epidemiology, statistics and study design where feasible, or participate in intensive two–three day courses often offered in conjunction with major ophthalmology meetings.

A short and frequently cited Oxford University Press publication, *"Epidemiology and Statistics for the Ophthalmologist"*, was designed to provide a basic understanding of core epidemiologic and statistical principles essential for meaningful clinical research. While the case studies might be dated, the principles are not. It is now freely available for use and downloading on the ICO Web site: http://www.icoph.org/research.

Why bother learning to conduct clinical research when working with poor populations? First, because it sharpens one's mind and stimulates one's analytic and deductive prowess. Second, because deprived populations often provide unique opportunities for investigation: the clinical conditions encountered may be unique to poor populations, or occur at far higher rates than in populations elsewhere (trachoma, onchocerciasis, xerophthalmia, loa-loa, agricultural injuries; open angle glaucoma in Sub-Saharan Africa or angle closure glaucoma in Mongolia). Larger numbers of subjects can make for more definitive diagnostic criteria and provide more accurate information about a condition's clinical course; populations in which a disease is more prevalent are more efficient for conducting treatment trials; and resource poor populations provide the only relevant opportunity for studying and testing simplified interventions appropriate to low-resource settings (alternative approaches to small incision manual cataract surgery in place of costlier phaco-emulsification).

Given the rich opportunities for making valuable contributions to ophthalmic knowledge, it is important that ophthalmologists in relatively unusual settings be prepared, and trained, to share the lessons of their clinical experiences in a manner that is sufficiently thoughtful and rigorous that the results are meaningful and coherent, and not merely "anecdotal". They should truly attempt to advance ophthalmic knowledge.

"Clinical research" includes the conduct of clinical trials, where one (or more) alternative treatments are compared with one another. But it also includes observations on the clinical appearance and evolution of an ocular condition, and its epidemiologic

characteristics (e.g. the frequency with which it occurs in different age groups, races and sexes; its seasonality; and other factors with which it is associated - that may or may not contribute to the occurrence of the disease or assist in its identification, diagnosis and management (intra-ocular pressure and cup-disc ratio in glaucoma, diabetes in the presence of retinopathy).

A. Formal Abstracts Provide a Useful Summary of Key Issues

Abstracts of clinical research papers published in major ophthalmology journals are rigorously structured summaries of the important issues one needs to consider in planning and reporting a research project. In essence, the reader needs to know, and the abstract needs to tell them, what was done, why it was done, and what the clinical implications of the findings might be. The rest is "commentary".

NOTE: the examples below are entirely hypothetical!

1. **Statement of the problem (and the question being addressed)**. The first section of an abstract generally includes two important statements (even if they are sometimes combined into a single sentence): "what is the specific question the research was meant to answer?" (e.g., the "purpose" of the study); and "why is it important?"

2. **Methods**. The second section briefly describes the methods used to collect the data upon which the report is based (e.g., "a randomized trial assigned 1,200 subjects to receive one drop of topical antibiotic either once or twice a day"; or, " 650 newly diagnosed diabetics presenting to a single urban hospital underwent detailed clinical examination including fluorescene angiography").

3. **Results**. The third section describes what the study revealed (e.g. "38 percent of newly diagnosed adult-onset diabetics were women aged 26 though 68 years of life. The frequency of "any retinopathy" on fluorescene angiography was 4 percent among those 25–34 years, 12 percent among those 35–49 years, and 24 percent among those 50 years and older. Males accounted for 62 percent of newly diagnosed cases, in whom the rate of retinopathy also increased with age").

4. **Conclusions**. The last section briefly recapitulates the results, in relation to their clinical relevance (e.g. "The risk of retinopathy among patients referred with newly diagnosed adult- onset diabetes increases with age in both sexes. It is important that all newly diagnosed type II diabetics receive a careful retinal examination, regardless of their age or sex").

B. An Expanded Description of Considerations Relevant to Human Research

All the important issues relevant to the design and interpretation of a well conceived and conducted clinical research project are detailed in the main body of articles published in high quality ophthalmic journals. Reading these reports ***carefully*** will

provide the new researcher with important insights, and a framework for planning his or her own work.

It is helpful to plan a research project with the eventual abstract, and the full report in mind. In fact, it is a useful exercise to write-up the project's report (except for its results and conclusions) **before** even beginning to collect data. This is an effective way to check that your plans really do meet your needs!

1. Introduction.

The introduction to every paper is, in many ways, the most important planning tool one has. Why? Because it indicates that the relevant literature on the topic has been reviewed and understood. If one hasn't adequately reviewed the literature, one has no way of knowing what the important questions are. Without knowing what the important questions are, one doesn't know what questions need to be answered.

The literature review also establishes the reason the clinical condition, and the question(s) being addressed, are important and worth the effort. A well-designed and conducted clinical research project takes considerable time, money and effort. These shouldn't be wasted on something of little importance—especially as there are likely to be many important questions, and clinical entities, that would benefit from the researcher's attention.

Finally, the literature review helps to inform the study's design and methods. Previous reports will reveal which study tools and approaches proved useful and which did not. There are few things more discouraging than discovering, after one has laboriously conducted a research project that failed to answer the question(s) posed, that others had experienced the same failed approach and had already reported it in the literature.

2. Methods.

The methods one employs flow directly from the introduction. The introduction will have contained the specific, primary question being addressed. That question is the primary end-point of the study. The methods employed to answer the question should be the most efficient and valid available. The more specific the question ("does lowering intraocular pressure by 25 percent or more slow the progression of glaucomatous optic nerve damage?"), the simpler the study design and the greater the likelihood it will actually be answered (as opposed, for example, to the diffuse and poorly considered question, "does treating glaucoma work?"). A study may also have many secondary end points. These too should be defined before initiating the study. Pre-specified endpoints (questions of interest) determine the methods that need to be employed, including the number of subjects to be studied.

Important aspects of the study's design can, and should be, precisely defined. These include the type and source of the study subjects (are they all referred to the hospital or office, or are they individuals randomly selected from the community; were they selected for their particular age, sex, or severity of the clinical condition under investigation?); the duration that the subjects will be followed, and the frequency with which they will be examined; every component of the examination (loupes or slit-lamp;

Goldmann or "puff tonometry; gonioscopy; examination of the retina with an direct or indirect ophthalmoscope; visual fields or not, and with which machine and protocol); the level of training of personnel conducting various aspects of the examination and the techniques employed to ensure standardization in recording and interpreting the results; clinical definitions ("an IOP equal to, or greater than 24 mm, with definable retinal nerve fiber layer defects and, or at least 3 adjacent points depressed 4 decibels or more on 'fast-threshold' perimetry"). Whatever the methods chosen, they must be carefully defined and the measurements repeatedly validated.
All policies and procedures used in a study should be compiled in a formal "manual of operations" that is available, and has been studied, by all personnel involved in the study.

Two critical issues, that are closely related, deserve special mention: the choice of an appropriate number of subjects to study, and the protection of human research subjects. Far too many researchers fail to address these issues, and then discover, to their dismay, that they have wasted their time and effort. If too few subjects are studied to answer the specific question(s) being asked, then the answer(s) won't be found! By the same token, unless appropriate, formal and rigorous procedures for protecting human research subjects (that meet accepted international standards) are employed, no major journal will publish the results (indeed, no major meeting will even permit their presentation!).

Sample Size: A human research project needs to employ just the number of subjects required to answer the specific question(s) it proposes to address. No more and no fewer. This is not the place to explain the statistical principles and procedures for calculating sample size requirements, as these are thoroughly covered in appropriate textbooks (see "*Epidemiology and Statistics for the Ophthalmologist" at* http://www.icoph.org/research *for an introduction to the subject)*. Statistical techniques happily provide the mechanism for determining the number of subjects (sample size) needed to provide enough data to answer the question at hand—with an explicit probability that the sample might miss, purely by chance (bad luck), the real answer (the difference in frequency of diabetic retinopathy between males and females of the same age; the difference in the rate of progression of glaucomatous optic nerve damage in patients randomized to two different treatment regimens). One can choose a large sample, to reduce the probability of missing a difference that really exists, but at the cost of additional labor and expense; or a small sample, with the attendant increased probability of missing a true difference. The choice is up to the investigator; but statistical techniques define what those choices are and what probabilities they entail.

One complexity involved in choosing an appropriate sample size is nearly unique to ophthalmic research: because each patient has two eyes. If sample size calculations suggest the need for studying 100 eyes, does that require 50 subjects (using both eyes of each subject) or 100 subjects (using only one eye of each subject)? The answer is complex, and depends in large part, on what is being studied and how closely correlated the results for the two eyes of the same subject are likely to be. Since many ocular conditions are bilateral (e.g. glaucoma, age related macular degeneration, etc) the two eyes of the same subject are more likely to behave in similar fashion than the eyes of two unrelated subjects. For simplicity, and to insure adequate sample size, many researchers choose to include only one eye of each subject (e.g., all "left" or all "right"

eyes, or "the first eye to develop visual field loss" or "retinopathy"). This increases the probability that the sample size is sufficient to yield valid results.

Ethical Considerations and Protection of Human Subjects: The ethical appropriateness of a study and its protection of human research subjects are crucial. In most countries, every human research study requires prior review **and approval** by a formally constituted review board (often referred to as the "Committee on Human Research" or "the Institutional Review Board"). Such approval must be mentioned in any formal presentation and included in the written reports. Review boards have different procedures, but all require review of the study protocol(s), enumeration of the potential risks and benefits to the study subjects, and the exact manner in which study subjects will provide their informed consent to participate. While these involve issues beyond the scope of this brief outline, one aspect deserves mention: the definition of "research", since it is only "research" that requires formal approval.

The most commonly employed definition of "research", triggering the requirement for IRB approval, is an investigation undertaken to generate knowledge that might prove valuable in the care of similar subjects – hence results that the investigator plans to share with other clinicians (through lectures, courses or publications). This includes all forms of research involving humans, whether they are to be actively recruited as subjects for a treatment trial, or one is "merely" planning to review the charts of past patients (even with all personal identifiers removed!). An IRB may "exempt" a chart review from intensive oversight, because these generally pose little risk to the patients. But only a formally constituted IRB can make this determination, and exempt a study.

Information collected solely to treat a particular patient, whose outcome is of little interest to other clinicians (trying an alternative antibiotic to treat a recalcitrant corneal ulcer; needling a surgically induced bleb) is not considered "research" in this formal sense, and does not generally require IRB approval. If in doubt, check with your Human Research Committee.

Even when a study does not meet the formal definition of "research", basic ethical principles and concerns still apply!

A poorly designed (or conducted) study is never ethical. If the sample size is too small to answer the primary question, or if the measurements are poorly standardized or of indeterminate validity, then subjects have been exposed to unwarranted risks, no matter how small, to no purpose.

A brief description of ethical considerations and the need for suitable protection of human research subjects can be found on this ICO website http://www.icoph.org/research/regsandethics.html).

3. Results.

Now the fun begins! This is the first part of a paper (or presentation) that cannot be written before the study has been conducted. (It is still helpful to design the analytic

procedures one expects to employ, including "dummy" tables [e.g. as yet devoid of data], before beginning a study.)

The first data presented define the population studied (how many subjects were asked to participate, and how many actually did; baseline demographic and clinical characteristics of those studied, and the ways in which two groups in a treatment trial differed at baseline). This is important as it establishes the characteristics of the subjects included in the study, and therefore the characteristics of individuals outside the study to whom the results might reasonably be expected to apply.

The next set of data address the question(s) the study sought to answer. All quantitative data, whether prevalence rates (the proportion of diabetics with retinopathy) or comparisons between treatment groups (did one medication lower IOP more than another) should employ basic statistical techniques, like "confidence limits" within which the "true" prevalence, or the "true" difference in the outcome between treatment regimens, are likely to lie.

Thoughtful investigators will conduct additional analyses, including some that had never originally occurred to them, but which, given the actual data in hand, now appear to have potential value and interest. These so called "fishing expeditions" are often the source of new, groundbreaking insights not previously considered or encountered. Since all quantitative results have a finite probability of occurring by pure chance alone, large numbers of comparisons will inevitably uncover apparent associations that are simply chance events, unlikely to recur when another group of subjects are studied in similar fashion. For this reason, potentially important new insights almost always require confirmation by subsequent studies.

Any well-analyzed study will generate far more data than is of interest to anyone but the investigator. In preparing manuscripts and presentations, it is the job of the investigator to include only those data that are critical to answering the question(s) of greatest interest, or are needed to understand the potential validity and ability to generalize the results.

It is worth recalling that most readers (and those in the audience at oral presentations) cannot absorb more than one or two important new concepts at a time; it is rarely a good idea to overwhelm the audience.

4. Discussion and Conclusions.

This section should not mindlessly repeat the results already detailed. Instead, its best to summarize and integrate the important findings in ways that assist the average reader in grasping the answer(s) to the question(s) the study was meant to provide.

These "answers" then need to be placed in context. How do they compare with other studies and other data available in the literature, and what might account for any differences observed? This is the "nugget" of the research: what has it added to our knowledge and how does this support, contradict, refine or otherwise modify existing knowledge and beliefs? Is this now so definitive, either because of the quality and representativeness of the study, or by its confirmation of previous work, that it signals

the need for a change in clinical practice? If so, what is the clinical "take home" message?

If the results are new, contradictory or tantalizing, it is customary to suggest "additional work is needed to "confirm"…"refine"… or "explain" the results.

Be exceedingly careful not to claim more for the data than the data deserve! If only patients "over 65 years" were studied, there may be need for studying younger patients before extrapolating the results to all age groups. If the short-term (2 month) effects of a medication for treating glaucoma, or trachoma were studied, it is dangerous to predict what the results imply for 6 months—or two years of therapy.

It is always helpful to define, and describe, the potential limitations of a study ("28 percent of subjects were lost to follow-up"; "we only studied patients with advanced retinopathy referred to our practice").

5. Other.

In addition to a list of relevant references, at least two other issues require attention: "acknowledgements" and the "disclosure" of potential conflicts of interest.

Never fail to "acknowledge" those individuals who have contributed to the successful completion of the research. It gives them a sense of "ownership" in the report and pride in the work. Both will increase the likelihood they will collaborate again, in the future. If someone has made truly original and substantive contributions to the research and its publication (in the design or analysis of the study, or preparation of the manuscript) they should be offered authorship. No one (that I know of) has ever gotten angry by being offered authorship—of course no one should be an "author" who has not genuinely contributed to a study in a substantial way. Most journals require that every author signify their approval of the manuscript as submitted; many also require that each author indicate the manner in which they contributed substantively to the work.

Almost all presentations, and publications, require that author(s) state their potential conflicts of interest. In most instances this is accomplished by listing any financial interests, as for example, receiving remuneration from the company that makes the product that was studied, or having an equity interest in that product.