The Client-Consultant Relationship in Medical Research: The Role of a Professional Statistician in the Research Team

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Introduction

Serving on the Ethics Committee of King's College Hospital NHS Trust for the last six years has given the first author a unique perspective on the teaching of ethical practices in statistics. Moreover, current concern about the adequacy of certain clinical trials, highlighted by the withdrawal of some drugs and the curtailment of the use of others, has focused attention on the appropriate roles of statisticians and oversight agencies such as the U.S. Food and Drug Administration. Particularly significant is that training in the appropriate client-consultant relationship is key to the inculcation of ethical standards in all those disciplines where statistics is used and, in particular, in medical research.

In this paper we will discuss some issues arising in the applications of statistics to medical research projects. The main topics of our discussion are:

-The role of the medical statistician
-Some recurrent problems: type of design and size of the samples.

In the core of this paper (section 1.2) we discuss the second point in some detail and explain the background. At the end of the paper in, section 2, we draw some conclusions about the role of the statistician. We relate these issues to the training of doctors on the methodological aspects of their research and their view of the role of the medical statistician in their team.

The main principles in question will be illustrated by specific examples of the problems that have caused statisticians great difficulties in the provision of an objective and scientific input in research over the years. In spite of the fact that these concerns have been expressed countless number of times, bad practices persist [1] [2].

The first author took encouragement to voice these concerns from two sources. One source of encouragement is that she has been fortunate to be the statistician in a Research & Development department of a university hospital for the last six years. Research & Development was an initiative of the Department of Health, starting in 1997, to promote good research. The second source was from a meeting convened by the Royal Statistical Society (RSS) and the Central Office for Research and Ethics Committees (COREC) on statisticians working for Ethics Committees. (COREC works on behalf of the Department of Health in the UK, coordinating the development of operational systems for Local and Multi-Centre Research Ethics Committees (RECs), on behalf of the National Health Service (NHS).) This meeting took place at the RSS premises in London on the 31 st of March 31 2004. The

remit of the meeting was to touch on the Ethics Committees process and survey the thorny issues of the role of the statisticians on these committees.

We want to pass this encouragement to the statisticians attending this meeting.

1.1 BACKGROUND: THE PROCESS OF MEDICA L RESEARCH

Typically research projects are proposed by doctors, who apply for funding of a study involving the follow-up of a particular group of patients and the analysis of the observed outcomes. Statistics will be involved to some extent in all of these studies, although of course the sophistication of the methods and the particular problems that arise will vary from case to case. Of course achieving the correct analysis is a truly important matter because the treatment of patients, possible over a long period, may be determined by the findings. At the end of the study, the results are disseminated by publications in medical journals. There are various agreements on standard good practice on ethics and methodological issues (notably the Helsinki Declarat ion reference). The Consort statement, developed by t he Consolidated Standards for Reporting of Trials (CONSORT) Group, complements the existing codes of practice in terms of good science. The statement is regularly amended to try to cover all the methodological gaps that are detected in the practice of medical research, and has been extended to cover various kinds of trials. Full details of the current form of the Consort statement can be found in the web at http://www.consort statement.org. While the Hels inki declaration is carefully adhered to, the Consort statement is often either not known or simply ignored [3] [4] [5].

1.2 TYPE OF DESIGN AND SIZE OF THE SAMPLES.

The background here is that, obviously, in an ideal world all studies would be very large in order to get accurate results. The more patients we observe the more knowledge we have about a topic of interest, about the course of a disease, about the goodness of a treatment, etc. However, there are all sorts of natural constraints on the size of studies in reality. Recruitment of patients can be a very slow and expensive process particularly for rare diseases. On the other hand, if we want to know which of two treatments is better, how can we justify assigning subsequent patients to a treatment which we already suspect is inferior or even harming the patients? The tension caused by all of these different factors means that the issue of the type and size of a study is often contentious.

THE TYPE OF STUDY.

Let us consider this issue in somew hat more detail. First, t he choice of the type of study is crucial on many accounts. Obviously, in the case of a pilot study, a crossover study or a qualitative study, the requirements involving the size of the study are quite different. Unfortunately in medical research, too often these three approaches are taken as a route to get away with a small sample size, or simply to avoid computing the proper sample size. However, the serious implications of taking this action are ignored by many medical researcher s, journals and funding bodies. It is therefore important that researchers are required to make a very good case for their studies being considered in any of these categories.

Let us review the statistical issues of these options.

PILOT STUDIES

A pilot study is a small study often preparatory to a full scale one. First, it is very reasonable to question whether it is necessary to do a rigorous sample size computation in a pilot study where the only purpose is to check if a new treatment is not going to be inferior to an existing one or maybe even harm patients [6]. A pilot study that is run with this purpose should not use more than a dozen patients, and several experimental designs have been proposed to minimize any harm to patients [7]. In this category (of a small study) we could also consider those cases in which a pilot is run to check on the feasibility and logistics of the study; for example checking on the availability or recruitment rate of a target population, assessing the time and cost of obtaining a response or detecting problems in the wording of a survey questionnaire.

However, there are other reasons to run a pilot study. Very often a pilot study is needed to estimate the distribution of the outcome measure (generally the standard deviation) so that a proper sample size for a full scale study can be calculated. However, typically, to be useful for this purpose a pilot should have about 5% of the size of the corresponding full-scale study. The calculation of the full sample size and a statement on what proportion of it is used for the pilot study should be provided in applications and subsequent publications. But this is where we meet an obvious logical difficulty. If there is no information available to compute the sample size of the full scale study, how can we know what 5% of an unknown number is? Here the standard advice has been to base calculations on surrogate measures i.e. measures that have some degree of correlation with the one that we are interested in [6]. And, if all of this fails, sequential methods, as discussed below, will be very relevant.

"Although sample size estimation is useful in considering the feasibility of conducting a study (and protocol reviewers should discourage funding for studies that are plainly too small to be meaningful) attainment of the planned sample size does not seem to me to be a useful indicator by which journal reviewers should assess the validity of a completed research report in which clinically and statistically meaningful results have been obtained." [8].

We totally agree that small studies have a place in medical research, and that no study should be rejected solely on the grounds of the sample size. However, if the study is a pilot and the authors want to share the findings with the research community, the fact that it is a pilot and the reasons (objectives) for this must be clearly stated. As we all know, practitioners do not usually have time to read the whole of research papers, and may act on the basis of a quick glance at the results; so omitting the qualifier "A Pilot Study" in the title and abstract ---and failing to give the real reason why the study was conducted--- can be dangerously misleading. If the small study came about as a result of an interim analysis of a properly conducted prospective study, the title and the abstract should establish this as well and the researchers should ensure that the appropriate statistical methods have been used and are clearly stated. Only in this way will future researchers be able to include these small studies in their meta-analyses and exclude those pilot studies that were not designed to answer the main question of interest and which therefore most likely lack the appropriate features in the design, data collection and analysis.

CROSSOVER STUDIES.

A parallel design is a study in which we compare two independent groups, one receiving an intervention with and independent group of patients receiving a control. In contrast, a crossover study is one in which patients are given both treatments at two different times. In this manner, each patient serves as "her/his own control", and therefore the design is more efficient in terms of the sample size required. The validity of conclusions of crossover studies are extremely vulnerable to violations of the

model requirements. (The main requirements are random allocation of the order in which treatments are given and absence of a period-by-treatment interaction). For example, even if done in the proper way, the analysis of a crossover study might dictate that the second period of the crossover design is abandoned, and the analysis of the first period is done as if it had been a parallel study. The result of this is that you will end up with a sample that is a fraction of the size that you would have had if the crossover route had not been taken. For these reasons, the design and analysis of a crossover study requires a highly skillful statistician and it is recommended to restrict the use of the crossover design as much as possible [9] [10].

QUALITATIVE STUDIES

A qualitative study is a type of study, with origins in sociology and anthropology, in which narrative responses are examined to extract themes that may form the basis for a theory. Qualitative research does not deal with quantitative measurements but, as for any other area or method of research, it is a serious discipline. It is moving away from subjective representations to a more complex and objective "analysis of a narrative", where quantitative models and computer programs have an important role to play [11].

And, of course, there is a place for qualitative studies in epidemiology and medical research. For example, qualitative research would help doctors understand the quality of life and positivity of MND (motor-neurone disease) patients at the stage when they are too disabled to communicate. Perhaps, in the first visit to the patient, the researcher would be able to form an understanding, through the patient's surroundings and demeanour ---using the researcher's own impressions and interpretations---so as to identify the patient's different constructs and continue evaluating the evolution of those constructs over the next follow-up visits. Qualitative research will also help to detect repetitive themes from patients diagnosed with a new disease such as fibromyalgia, in order to start a process of definition of a set of symptoms for that disease. For example, the early stages of the process of identifying the factors responsible for the "non-progressors or "exposed-uninfecteds" in HIV medicine started with qualitative data from the patients themselves [12], although we may now be at the stage where genetics statistics can step in.

However, in common with quantitative studies, qualitative studies should be properly planned and conducted. At an early stage in qualitative research there will be the need to conduct pilot studies, perhaps using unstructured or semi-structure interviews, opening informal chat rooms around this topic, etc. Such pilot studies will feed into more structured interviews and questionnaires when issues of a quantitative nature, like validity and reliability, will arise. It is at this point when an integration of quantitative and qualitative methods will be necessary. So, if adopted in medical research, qualitative studies have to be treated with the same statistical rigour as any other methodology [13] [14] [15] [16].

It often happens that the justification given for the sample size of a study is "this is a qualitative study and therefore statistics and a formal sample size calculation do not apply". In many of these instances the studies are really quantitative in nature. (Many of them for example are surveys aimed at finding out attitudes or auditing the provision of a service, generally of healthcare in a hospital setting.). This careless approach is both a symptom and a cause of the often low esteem in which qualitative methods are held; wrongly in view of their important role, as we have described above. (In rather the same way and for the same reasons as statistics is held in low esteem by some scientists.)

II. SAMPLE SIZE

A study with a small sample size is very likely not going to reach statistical significance and may produce biased results. What sometimes motivates researchers to take the route of a pilot or crossover design is that they may be concerned that the required sample size may not materialize within their allocation of time or funding. They want to get their study approved, and many times the funding bodies or research committees reject applications for perfectly good research on the grounds that there will not be enough time or resources to acquire the sample size that is needed to complete the research in the timeframe proposed. But this is bad practice and there must be clear reasons for a pilot or a crossover design being chosen.

The good news is that statistics is there to cater for these problems as well. A rather modern branch of statistics called Sequential Analysis [7] would allow them to conduct their prospective studies in a scientific manner, with the possibility of analysing and publishing interim findings and leaving the study open to future research if no conclusive result is reached by the end of their resources. A good understanding of sequential methods will sort out many of the problems so frequently encountered in medical research.

When a comparative study is conducted sequentially, interim analyses are performed with the intention of stopping recruitment of patients as soon as a significant effect detected. In this way we avoid randomising patients to treatments that have shown already to be inferior, and, as a consequence, the sample size at termination of a sequential clinical trial is generally much lower than for a clinical trial that has been conducted in the conventional way. As calculations of sample size are often based on guesses concerning distributional properties (standard deviations, prevalences, etc.) of the outcome of interest and recruitment patterns, they should not be viewed as a gold standard or as an automatic default design. It is no longer ethically acceptable to collect long-term follow-up data without periodic assessments of the accumulating results, preferably by an independent Data and Safety Monitoring Committee. Such assessments could lead to design modifications or to termination of the study, and therefore allowance for these interim analyses should be made. Interim analyses are becoming steadily more widely used in the design of clinical trials [17].

The rigour of the design and analysis in a sequentially conducted clinical trial is of paramount importance. When a sequential approach is taken, there is a need to adjust the p-values for the multiple testing that takes place and for the bias incurred by stopping at the precise time when a treatment difference is observed. In addition, the conclusions of any study are dependent on the nature of the assumptions and models used in the analysis, and the influence of such assumptions may be most important at early interim analyses of a sequential trial: precisely when there is the least data available to test them. In order to reduce the potential of interim analyses to mislead, there are several tools which can be employed: delay the first look at the data so that its conclusions have some credibility; adjust for prognostic factors which might affect outcome; and choose a model which is resistant to anticipated departures from assumptions. Likewise, there is considerable variation in the expected sample size at termination among the different sequential stopping rules, and concern over stopping inappropriately (either too early or too late) could be addressed by the appropriate choice of the sequential design. Sequential analysis therefore requires the use of a sound statistical methodology that allows for the required stopping rules, and for necessary mathematical adjustments to be made. Frequentist [18] and Bayesian [19] statistical methodologies and computer software are now available for the implementation of these approaches. Several authors have shown how sequential methodology can be applied to clinical trials collecting long-term data, and the benefits of such an approach [20] [21] [22].

FORMAL REQUIREMENTS

The issues that we have discussed above arise in relation to the requirements stated by the application forms for funding or approval of protocols and by formats for published papers in the medical journals. Leading medical (BMJ, Lancet and JAMA) or biochemistry journals (Clinical Chemistry in the US and Annals of Clinical Biochemistry in the UK) require authors of clinical studies to conform to the reporting guidelines set in the Consort statement. Nevertheless, many medical journals and grant - funding institutions, research and ethics committees do not explicitly impose any requirement on applicants to provide the crucial statistical input, a proper calculation of the size of the study based upon a power requirement of the main outcome examined.

To mention an example, a question in the COREC application form of the UK Department of Health is "Has the size of the study been informed by a formal statistical power calculation ?". We have seen instances in which medical researchers have answered "No" to this question and have challenged arguments against accepting such an answer on the grounds that a negative answe r "was admissible" or "correct for the stated question". What this means is that many applicants do not interpret the form as requiring any real methodological rigour in their plans. Unfortunately, some members of the review committees (maybe as a result o f these committees not being independent or external), and some journal editors, condone this view. This has the effect, perhaps unintentional, of exploiting the wording of the form or the lack of a formal policy with regard to statistics to promote unscientific practices. Independent scientific review is not necessarily independent at present and local research & ethics committees or data monitoring committees, when they exist, are often internal to the institutions.

By modeling on the requirements of the Consort Statement, researchers would not be tempted to trivialize methodological issues such as the type of study proposed, the justification of the proposed sample size (with appropriate references to backup the statistical summaries used in this calculation) and the statistical methods planned for the analysis of the data that will follow in their research. Not compromising the rigour that these three issues require will promote good practice, and avoid all sorts of difficulties.

The second issue, closely related to the first, is that there should be a formal involvement of a professional statistician in the research team. A professional statistician will serve as a filter for errors and misconceptions earlier in the review process, speeding up that process and the progress of the scientific research. For example, the section on statistical analysis will be written at a high level, with a succinct yet proper indication of the methodology that will be applied, without going into lengthy discussion of standard material, many times just mere quotations from elementary textbooks.

Thus we feel that these are the questions that must be asked by a funding body or a journal considering the results for publication. (Here we are just spelling out –only asking for more detail - the requirements that are implicit in the Consort Statement and the guideline for authors of the BMJ).

For types of study:

What type of study is proposed/was carried out? Qualitative / Clinical Trial (RCT/Crossover/CRT) / Observation al (Prospective/Retrospective).

Is this study Pilot / Full -Scale.

If this is a pilot or a crossover study, give the reasons why it has been classified as such and not as a full-scale study.

If this is a qualitative study, give the reasons why it has been classified as such and not as a quantitative study.

The title of the paper should always start with the identification of the type of study. For example, "A pilot study to determine the efficacy and safety of treatment A in children with leukemia ". The letter of ethical permission for the study should also be required.

For sample size:

If this is crossover study, give the power that the study would achieve if carryover effects force the analysis to be confined to the first period only.

For interim analysis:

Are interim analyses intended/ Were interim analyses carried out?
How many or how often? What is/was the stopping rule?
Constitution (affiliation, contact details) of the Study Monitoring Committee or Working Party set up to monitor these interim analyses.

And this precisely brings us to the most crucial issue and, no doubt, the root of the problem. Is there a professionally qualified statistician in the working party or the team of scientists conducting this piece of research? Is the statistician's presence required in the periodical meetings of the working party and in the meetings of the Data Monitoring Committee that oversees the conduct of the said research project, if there is a DMC at all? An informal involvement of a statistician is as unethical for science as is not involving one.

2. CONCLUSIONS. THE ROLE OF THE PROFESSIONAL STATISTICIAN AND ISSUES RELATING TO TRAINING.

There are two aspects of education relevant to this paper: training future generations of professional statisticians, and training physicians to give them an overall vision of the methodology involved. Some physicians try to learn statistics, and a few have developed to the extent that they are very good statisticians. Some leading figures in the application and methods of statistics are physicians, but typically physicians receive minimal training in statistics, if any. Typically there is one statistician in each hospital providing general advice, or engaging in collaborative research, with a large number of research teams. The research fellows who are directly involved with the medical research teams are often social scientists with inadequate or inappropriate statistical training. From what we have already said, it is clear that there can be serious pressures on the interactions between phsycians and statisticians.

Doing a short course in statistical methods can make newly qualified physicians understand the general principles and modes of study design and ethics, and make them aware of many of the problems we have illustrated above. This will allow physicians to communicate better with a professional statistician, but the course must not give the erroneous impression that it is in itself a qualification to do statistics. Intensive short courses in statistics, aimed at doctors or specialists in other disciplines, has taught us that "a little learning is a dangerous thing". Many of the problems in published research result from an inadequate understanding of basic statistical methodology. Just as you cannot expect a statistician to perform surgery on a human body after a quick module on the subject, so you cannot expect a surgeon or a natural or social scientist adequately to deal with the statistics of research after exposure to a module on the subject, no matter how well taught. Statistics is a branch of science that

uses an intricate combination of mathematical techniques, and logical reasoning. In order to apply statistics to the science that it is serving, the statistician needs in addition to a scholarly kn owledge of the subject three additional talents: common sense, vision and creativity. In the case of a medical statistician, a good understanding of the core of biomedical sciences, including medical ethics, and the systemic constraints of the research process are also essential. Unfortunately, none of these ingredients can be injected in sporadic, one -off, courses. We therefore advise a statistician to have at hand a list of references, with appropriate indications of the level of difficulty and topic, ready to provide on request, for those who want to learn more about the statistical aspects of the research. This will discourage the notion that statistical expertise can be achieved through bed time reading or in a short introductory course. (We would reco mmend Pisani [23] as a starting point.)

We turn now to the training of medical statisticians. Part of their training should be to make them aware of the pressures that they will encounter and to emphasise that they must resist certain unethical modes of practice that can cause their careers severe damage. Medical Statisticians: be aware! It is a very dangerous exercise for a statistician to get informally involved in a research project. Most statisticians have encountered cases where their name has been acknowledged in a publication when in actual fact they have had no control over what version of their comments and opinions was used, and worse, when they disagree with the stated version. Many statisticians have encountered cases where their analysis has b een left out of the report because it does not support the desired sensational conclusions. So, providing the name of a statistician in a marginal way, or in a mere acknowledgement, is meaningless in certifying the correctness of the methodology and is una cceptable. Obviously, statisticians need to be alerted to their ethical responsibility to adhere to sound statistical analysis even when their client may exert pressure to influence their conclusions. A more difficult issue is whether they have the addi tional obligation of “whistle blowing” if the work is published without their agreement, with or without the acquiescence of a more compliant statistician.

Crucially, as an ethical and scientific matter, statisticians should be encouraged to define their involvement with their clients. On the one hand, a help desk consultancy should be limited to a period of 15-30 minutes. If the consultancy session is to take any longer, the statistician should most likely be recommending formal involvement of a statistic ian, or enrollment of the client in a formal course in statistics. If the statistician him/herself is invited to be a member of the research project, a formal letter of invitation should be sought, defining the co -authorship/co-applicant or main collaborat or status. This letter should be accompanied by the protocol that has usually taken shape at this stage. On the other hand, statisticians should be discouraged from wanting to see their names as co -authors of papers when they have not been formally involve d. If a statistician appears as a co -author he/she must have been allowed to be in control of the overall analysis and the writing and interpretation of the results. This practice will force the statistician to estimate the amount of his or her time involved in the various stages of the project: conception of the design of the study, selection of the statistical methods, performing the actual analysis and writing the results and their (mathematical) interpretation. Even if no payment is involved, as in mos t cases, a cost should be attached if only to help the costing of research. In failing to do this, statisticians themselves have a share in the current trivialization of their contribution by many in the medical profession. Almost every statistician has en countered a case where the main analysis has been done by them, but where their name is only written in the acknowledgement, and not as a co -author, on the grounds that their analysis took only 1% of the space occupied by the publication. (This of course raises legal and ethical issues of intellectual ownership which are outside of the scope of this paper.)

Membership of a professionally qualified statistician in the research team, with collaborator status, should be mandatory. And, by signing the letter of consent of publication with the other co -authors and

co-applicants, the statistician will certify and take responsibility for the quality of the methods used and will be able and prepared to defend it. And the statistician's affiliation and contact deta ils will be on file as in the case of the other collaborators. We are not proposing anything new here. This is very much the standard practice of the MRC, the NCI and the NIH, among other institutions that have been promoting by example the conduct of responsible research.

We have brought up only a few examples to illustrate some of the innumerable problems statisticians encounter while discharging their duty of enhancing the quality of the methods used in medical research. An actual problem is that there are very few statisticians at all. Young statisticians (and mathematicians in general) are easily lured into pharmaceutical companies or city corporations which offer them stability and remuneration, while most of the statistical jobs in medical research a re three-year contracts. These fixed-term contracts come as a result of the grants that are allocated for fixed periods of the research projects that are undertaken, and are generally acquired in the form of PhD studentships. And the issue is further confu sed by the fact that the number of completed PhD studentships is a very important factor in the career progression of the principal investigator, leaving no motivation for the continuity to maturity of a research team.

Of course it is perhaps impossible to change the nature of research funding, but perhaps it is possible to make the effort to preserve the position of statistics in medical research by encouraging every research or academic institution to feature an independent statistics unit that provides the statistical expertise. Statistics is unique in that. in a typical university, there is, on the one hand, a department of statistics in which the work is often somewhat theoretical and, on the other hand, there are many statisticians working in diverse applied areas, in particular of course medical research. The most effective way of organizing things is often not clear, but our own preference is for the different research teams in the university and university hospitals to be allocated a statistician, and for that statistician to be formally part of the research team.

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