International co-operation in research: An opportunity to educate collaborators

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1. Introduction

Every research study requires a sound design, careful planning, good management and proper analysis. In some cases, a study is conducted in multiple sites and possibly in different countries, often in order to increase the study sample size or to compare and contrast different study populations. Multi-center studies require co-investigators and research staff not only knowledgeable about the study protocol, but that understand the reasons behind the various methodologies. Ideally, co-investigators should be involved in the development of the protocol in order to be fully vested in it, but often this may not be possible. In addition, collaborating staff at the various sites are usually not in a position to contribute to the protocol, but are the key personnel in its implementation.

Participation in collaborative research poses interesting challenges since personnel have varied professional backgrounds, strengths, interests and experiences. It is often the case that non-statistician collaborators have minimum training in research methodology and may have limited previous experience in collaborative research. Thus, questions that are of interest include: Should there be an effort to develop the statistical literacy of collaborators? Who should conduct such training, and what should be the content of such training?

If collaborators are 'statistically literate,' it is easier to build scientific accountability and responsibility (Mowery and Williams 1979). Statistical literacy is the ability to read and interpret quantitative information, to use statistics as evidence in discussions, and to think critically about statistics which are presented to us (Schield 1998). When this concept is applied to collaborators in research, it implies the understanding of the purpose behind various methodological aspects of the study protocol. Thus, statistically 'literate' collaborators understand why the sample is selected in the prescribed manner, why is randomization used in assigning interventions, why are procedures standardized across sites and personnel, and other such methodological aspects of the study. A better understanding leads to adherence with the protocol and to high quality in the implementation of the protocol.

In multi-center studies, the study coordination and the responsibility for data management and statistical analysis is typically performed centrally, by a statistical coordinating center (SCC). Typically the SCC is responsible for data entry and management procedures, data quality, and statistical analysis. An expanded role for the SCC in developing scientific responsibility and accountability of all study research collaborators is proposed. Thus, the SCC should not only be involved in training sessions on specific methods of the project, but also in conducting continuing education short courses on statistical methodology, thus essentially educating collaborators. Content possibilities abound, from the rationale for different study design decisions, to quality assurance principles, study conduct and monitoring procedures, as well as principles of statistical analyses. Implementation of such training may be a costly investment, but costs can be minimized if training is conducted alongside scheduled study team meetings. This paper presents the experience of multiple international training efforts of the International Clinical Epidemiology Network (INCLEN) and of the Department of Biostatistics of the University of North Carolina at Chapel Hill.

2. Statistical training of research collaborators

The mission of the International Clinical Epidemiology Network (INCLEN) is to promote research and training in order to improve equity, efficiency and quality in health care (www.inclentrust.org). Biostatisticians, clinical epidemiologists and other health researchers collaborate in numerous and varied research activities, often in a multi-center collaborative manner. An obvious component of the research is the provision of training in specifics of the study protocol. Less obvious is the need for understanding of research and statistical methodology on behalf of all study personnel. While the faculty and other co-investigators have received training in research methodology, local staff often have not. Also, many studies involve statistical complexities beyond those encountered during common training, such as methodology for interim analysis in clinical trials, or also the intricacies of conducting multi-center studies, such as quality assurance methods, governance among various investigators, and other practical matters.

Faculty members of the University of North Carolina at Chapel Hill, one of the original training centers for INCLEN, have participated over the years in numerous continuing education training activities for the Network, with the intent of educating statistically the research collaborators. Specific biostatistical training activities provided to research collaborators within the Network are described below.

Coordinating Multi-center Studies

A well-conducted multi-center study needs to assure standardization, uniformity of procedures, high data quality, and collaboration across sites. As INCLEN faculty began conducting multi-center studies, the need for training in such methods became more apparent. To address this need, the Department of Biostatistics at UNC, and specifically, members of its Collaborative Studies Coordinating Center (CSCC), an experienced statistical coordinating center for several large multi-center studies, conducted a training workshop for INCLEN statisticians. In addition, CSCC faculty have helped establish and train individual faculty statisticians in various countries (Chile, Thailand, India, Philippines, Colombia) in the methods of a statistical coordinating center. However successful these activities have been, the Network felt a need for non-statistician researchers to be offered such training. Co-investigators needed to be aware of the methodological reasons for the various procedures for successfully conducting multi-center studies. Thus, the coordinating center training workshop was offered to other members of the Network in one of their recent annual meetings.

Governance in collaborative efforts

In any collaborative activity and especially in multi-center studies, it is necessary that the activities be shared among the study personnel. Each must feel scientifically responsible and accountable for the integrity of the study. The organizational structure of a multi-center study should involve oversight and coordination, along with clear roles and responsibilities of all participating staff. The typical organizational structure can be explained by grouping the roles into three levels: oversight level, coordination level, and conduct level. Oversight and policy making in such studies is provided by a steering committee, composed of the principal investigators of each participating center. The coordination is usually done by a statistical coordinating center or other centralized agencies, while the conduct level is the task of the clinical sites.

One of the well-known tasks of the centralized institutions is that of assuring the collaboration of all study participating institutions in adhering to the protocol, and in enforcing standardization of procedures across sites. Another important task of the coordinating center is in managing the collaborative aggregate data and reassuring participating institutions that the use and sharing of the

data follows the desires of the project investigators. It is thus necessary that written rules and regulations be elaborated to give equal and fair access to all participating investigators.

Self-determined guidelines for data access and sharing, publication and presentation processes, and co-authorship considerations are essential. The compendium of guidelines for co-operation among the participating institutions of a multi-center study is collectively called the Governance document. This may be a simple and short document, but often it is laborious in detail and is constantly in flux. The governance document should have the approval of all sites' principal investigators. The elements of a governance document typically include sections that specify the committee structure of the study, clarify the roles and responsibilities of all involved, and a section that delineates how the institutions will interact in decision-making. Two other very important sections are usually the most controversial, since they involve sharing the data (issues of access) and sharing in the academic rewards of the research (issues of publications and co-authorship). There is no perfect model, and each study will have to struggle with setting their own guidelines.

Training research collaborators in the nuances of a governance document is a challenge internationally, as different cultures clash in their styles of group interaction. This aspect of collaborative research is not of a statistical nature, but is usually the responsibility of the statistical coordinating center. The methodology utilized for this training had been to embed it within specific research project interactions and on a 'learn-as-you-go' basis. The experience of the World Studies of Abuse in the Family Environment (WorldSAFE) in this context has been recently published (Bangdiwala et al 2003). Currently, however, specific training modules are being developed as case-studies for training research collaborators under a Leadership and Management Program (LAMP) effort.

Quality assurance

In all studies, but especially in multi-center studies when the data management activities are centralized, the statistical group 'controls' the data and hence the study; and must take steps to assure other participating investigators and institutions that it is managing it adequately. This assurance is commonly provided by developing adequate systems for staff training and quality assurance of all study aspects, especially for collecting, entering, managing and analyzing the data. These activities are done by the statistical coordinating center.

It is imperative that the need for quality be communicated and inculcated in the research staff. In one 12-center study in North America, which involved a complex, repetitive methodology for obtaining blood pressure measurements using a random-zero sphygmomanometer, one staff member took a single measurement and fabricated the remaining measurements out of laziness, thus invalidating valuable study data. In another international study, a data entry verifier confirmed all queries from the coordinating center without consulting the original paper form, and argued he was under pressure to validate the values due to the need for timely preparation of the interim monitoring external report. Such disturbing instances can easily become the norm in collaborative efforts if the staff performing such tasks do not feel that they are important or valuable tasks, and also if they feel not responsible or accountable for the scientific integrity of the study. However, if they understood the reasons behind the procedures of repeated measures to decrease the variability of the estimate, or the need for standardization of procedures, or the need for clear documentation for a potential data audit, it is possible that such misconducts would not occur. Training of all collaborators in quality assurance methods is thus essential. At the last INCLEN annual meeting, a workshop on specific methods for quality assurance was thus conducted.

Statistical interim analysis

In many studies, an independent group of advisors external to the study institutions is typically formed to provide oversight and guidance. In addition, in clinical trials where ethical considerations from conducting an experiment dictate the needs, an external data and safety monitoring board (DSMB) is often mandatory. The DSMB members include investigators, biostatisticians, and ethicists that are not from any of the study participating institutions and thus have no potential conflict of interest with study results. The DSMB is responsible for external oversight, patient safety (adverse events), monitoring study integrity and reviewing interim analyses (for the possibility of early termination).

The role of the DSMB in a clinical trial is crucial (Ellenberg et al 2002). The statistical coordinating center of a study needs to realize the importance for preparing a timely, accurate and statistically state-or-the-art report for the DSMB. Methods will of course depend on the nature of the study, but statistical methodology for interim analysis for possible early termination is usually not well-known. It is thus important to train the statisticians preparing these reports, as well as those that potentially may be invited to be members of such boards. Equally important is the need for training the non-statistician members of the DSMB, as they will need to fully understand how to interpret methods like the alpha-spending approach of Lan-DeMets if they are to function effectively in the board deliberations. Training such collaborators will aid the efficient conduct of DSMB meetings. In this context, a workshop on the composition, practicalities and statistical methods for a DSMB has been offered to non-statisticians and statisticians at an annual meeting of the Network, as well as to particular clinical research teams in China, Chile and India.

3. Discussion

The various examples presented above illustrate several key statistical concepts that required the statistical literacy training of research collaborators, members of a global network of well-trained researchers. Such additional training in statistical understanding of research methods enhanced the specific collaborative efforts. Finally, improved understanding makes the job of the statistician collaborator easier.

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RÉSUMÉ

La recherche collaboratrice implique la participation de personnel avec connaissance statistique. Donc, c'est nécessaire éduquer les collaborateurs dans la recherche en méthodologie statistique. Ce travail propose que le centre de coordination statistique conduit entraînement en méthodologie statistique pour les collaborateurs, dans le sens d´éducation continuelle. Les expériences de plusieurs entraînements réalisés par l' "International Clinical Epidemiology Network" et par le "Department of Biostatistics of the University of North Carolina at Chapel Hill" sont décrites.