HISTORY

The Multicenter Research Group

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In recent years, the number of clinicians interested and involved in clinical research has declined.[1,2] There are many possible reasons for this development. Medical students, residents, and fellows are not closely involved in patient-based clinical investigations during training, and they are rarely exposed to the personal satisfactions associated with clinical research. At the completion of training, young clinicians interested in clinical research are faced with a variety of financial, research-support, and academic uncertainties. In response to these career uncertainties and the changing medical-economic environment, the National Institutes of Health, in collaboration with academic centers, has recently introduced new programs with funding designed to help attract young physicians into clinical research.[3] However, there are other factors that have not been previously considered that may be important in attracting and maintaining the interest of physicians in clinical research.

In this article, we examine the structure of our Multicenter Research Group (MRG) and its 25-year history of successful collaborative clinical research. The group has maintained an energetic clinical research program, published a stream of scientific articles related to clinical cardiology, and most importantly for this discussion, has retained almost the same group of core investigators since its start. Meaningful interpersonal and professional interactions are key components of our group. We describe the features of our MRG that may explain the continued motivation of the investigators and the ongoing success of the program, for these elements may be important to physicians who are considering a clinical research career, or to those wishing to establish a similar type of multicenter clinical research group in cardiology.

Our MRG was one of the first multicenter research groups established by the investigators themselves to study unresolved, open questions in clinical cardiology. There are many special features of our group, but we believe the most important is a collaborative research environment that favors investigator participation in all phases of the studies with intellectual satisfaction, scientific excitement, and professional growth that have enriched the interpersonal relationships. Little attention has been accorded in the past to such features, but they have been key elements of our MRG since its inception.

**The list of the other members of the Multicenter Research Group are listed in the Appendix.*

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BACKGROUND OF THE MULTICENTER RESEARCH GROUP

In 1976, a group of collaborating clinicians and biostatisticians from a mixture of academic and community medical centers located in different regions of the United States established the MRG in order to study the clinical course of patients who had recovered from acute myocardial infarction. The prime motivation behind this multicenter approach was the recognized need to study a large, representative postinfarction cohort so that clinical research findings would be more valid and applicable to the general population. The success with the first MRG investigation[4] led to a series of multicenter studies extending over a quarter of a century with continued involvement of nearly all the original investigators. The MRG has evolved over time with the resultant research projects reflecting a complex mixture of the open issues in clinical cardiology and the scientific and intellectual interests of the individual members of the group.

GROUP INVOLVEMENT IN ALL PHASES OF CLINICAL RESEARCH

Our MRG maintains an open, democratic participation of the investigators in all phases of the studies. All investigators are involved in each step of the research project, including selection of the project, study design, patient enrollment, planning of the statistical analysis, data analysis, and manuscript preparation. Our egalitarian structure provides a potent stimulus for extensive and diverse investigator participation.

Selection of Research Projects

The decision to undertake a particular research project follows a multistage process. Competing ideas for a particular study circulate among the group's members for many months. At planning meetings, the decision-making process is more formal. A specific area of scientific interest and a hypothesis are proposed for the group's consideration. Extensive discussions, both oral and written, are followed with a draft proposal that is subsequently circulated among the group's members. These discussions are open, serious, and detailed, and the resultant interactions help foster bonding and respect among the investigators. All investigators, regardless of academic rank, are provided adequate opportunity to offer input, to argue a point or an approach, and to add items of particular interest, and all do.

Study Design

The final stage of a study design involves group discussions by the investigative team. Here the biostatisticians play a pivotal role. We have been extremely fortunate to have had experienced biostatisticians involved in the group from the very beginning, and their active participation has been a critical factor in the creative design of various study protocols.

Completion of the Study

When the study is completed and the database opened, all investigators participate and share in the findings. The first unveiling of the data involves the entire research group with protracted discussions and interpretations of the primary findings. The initial draft of the primary manuscript is developed during this discovery meeting. Ready access to statistical expertise and to the unabridged database, plus an opportunity to be involved in data analysis and interpretation of the findings, make MRG participation a stimulating and challenging experience for all investigators.

After the primary analysis is completed, the analytic database is distributed to each interested investigator in a spreadsheet format that can be used on a personal or institutional computer for independent data analysis. The secondary analyses are frequently centered about a particular interest or a specific hypothesis held by the investigator. The staff of the MRG data center and the study biostatisticians are available to assist the investigators in these secondary analyses, and such activity is anticipated and accounted for in the initial funding proposal. The high 16:1ratio of secondary publications to each primary manuscript reflects easy access to data, an intellectual environment favoring creativity, and an authorship policy that involves the entire MRG. Open access to the data is a key element in sustaining the productivity of the investigators and in maintaining their enthusiasm.

Meetings devoted to data analysis and initial manuscript preparation play a central role in developing the internal cohesiveness of the group. On many occasions the group sequesters itself in a remote locale for several days to pursue creative data analyses. With computer databases available around the clock and biostatisticians interwoven in

all the writing groups, members of the MRG fashion an initial set of manuscripts from the newly revealed database. The combination of intellectual stimulation, professional accomplishment, and camaraderie has contributed to investigator satisfaction and professional growth.

Some of the more important findings from 64 articles published by the MRG between 1983 and 2002 include: the importance of low ejection fraction as a major determinant of postinfarction mortality (1983)[4]; the relationship between left ventricular arrhythmias, left ventricular dysfunction, and postinfarction mortality (1984)[5]; the lack of association between Type A behavior and postinfarction mortality (1985)[6]; the identification of decreased heart rate variability as a risk-stratifier after myocardial infarction (1987)7; the adverse effects of diltiazem in patients with left ventricular dysfunction (1988)[8]; the independent mortality risk of living alone in the posthospital period after myocardial infarction (1992)[9]; the limited value of silent ischemia as a risk-stratifier in chronic coronary heart disease (1993)[10]; and the role of thrombogenic factors in recurrent coronary events (1999).[11]

STRUCTURE AND FUNCTION OF THE RESEARCH PROGRAM

The cohesiveness and mutual respect that are central attributes of the MRG developed early in our experience. During involvement in our first multicenter research grant, the Multicenter Postinfarction Program,[4] we realized that clinicians without a research background, experienced clinical researchers, academic investigators, and biostatisticians all learn from each other. Clinical research requires broad and varying inputs to be successful, and our mix worked well.

It is important that a research group of this nature and longevity has an involved and effective leader. The investigator who suggested the first research meeting was selected as the principal investigator in the initial NIH grant submission, and this individual continues in this role as principal investigator of the MRG with full support of the investigative team. An important feature of the MRG is the positive chemistry that has developed among the members. The vitality of the group is enhanced by frequent personal contacts and communications. The group meets at least twice a year in association with national cardiology meetings and at least every other year in a setting remote from usual responsibilities, allowing both casual and planned discussions.

The size and continuity of the group are critical factors in maintenance of easy communication and interpersonal relationships. The MRG has included 11 to 15 core investigators throughout most of its history. The typical longitudinal research study enrolls 900 to 1200 postinfarctions patients from 10 to 15 participating centers with follow-up averaging 2 years per enrolled subject. The MRG adds experienced colleagues with interest in multicenter research when there is a need for specialty knowledge and/or augmented enrollment capacity. The MRG has elected to remain of moderate size because of the scientific focus and egalitarian involvement of investigators that such size offers.

Other long-term, investigator-initiated, cardiovascular research groups that have been established during this period include Gruppo Italiano Studio Streptochinassi Infarto (GISSI)[12] and Thrombolysis in Myocardial Infarction (TIMI),[13] to name but a few. These "mega-trial" consortia are considerably larger than the MRG and have been structured in a more hierarchical fashion with less direct involvement of the enrolling center investigators in the design of the study, data management, and data analysis than the peer-to-peer equalitarian model utilized by the MRG.

The MRG has derived all of its funding from investigator-initiated research grants, mostly from the NIH, but occasionally from corporate sponsors and foundations. The MRG has obtained nearly continuous funding for 25 years with only 2 nonconsecutive years in which funding was not available. During those down periods, continuity of the group was supported in part by short-term funding from foundations and various other sources. In addition, each of the investigators of the MRG, as well as the biostatisticians, data managers, and study coordinators are also supported by grants from other on-going, unrelated research activities.

The scientific excitement generated within the MRG during the course of the research has helped maintain ongoing enthusiasm and personal involvement in the clinical investigations. Special friendships have developed among the investigators and their families, and these interactions have added an important dimension to the group. These combined professional and social relationships have enriched the experiences of the group and have contributed to the long-term success of the investigative program. Such relationships have

been particularly supportive, encouraging, and satisfying for the group's younger members.

RESEARCH POLICIES

Ethics

The MRG relies on the collective judgment of the group for ethical guidance and safety, as well as on the Institutional Review Boards at each institution. For example, in one pilot pharmaceutical study, the group became uncomfortable with safety issues that surfaced in the trial, and the group decided to terminate the study despite major objections from the sponsor. A subsequent large-scale trial with the same drug was stopped prematurely because the drug was associated with increased mortality when compared with placebo. This experience during the early period of our research activity helped foster a sense of confidence in the collective judgment of the group.

Data Management

Centralized data management using state-of-the-art computerized technology is a critical component of the research activity. From its inception, the MRG established its own capacity for data management and analysis. The completed data forms obtained at each enrolling center are maintained locally with copies faxed or mailed to the studies' Coordination and Data Center for centralized data management. For clinical studies not involving a drug, the enrolling centers are periodically audited on-site by the program manager, an experienced research nurse-clinician from the Coordination and Data Center. For clinical trials involving an industry-sponsored drug, the auditing function is carried out by the sponsor, usually utilizing a paid Clinical Research Organization (CRO).

The MRG has insisted on ownership and full control of the research database throughout all its studies. This control gives the investigators full access to the data so that any and all clinically and scientifically relevant queries can be explored expeditiously and extensively without encumbrances. The MRG appreciated from the beginning that their independent assessment of the data could be lost if the scientific data were controlled by sponsors. During one study, a sponsor insisted that the MRG prematurely open the database during an ongoing trial to determine drug efficacy. The MRG controlled the data and refused this request, and the blinded study continued uninterrupted to a definitive conclusion. An inability to control the study data has been a serious problem in many clinical trials. We applaud the efforts recently initiated by the major medical journals to help investigators secure the independence that is essential for credible investigation.[14]

Core Laboratories

Involvement of the MRG investigators has been enhanced by our practice of establishing, as needed, an internal set of core laboratories and regional statistical centers distributed among members of the investigative group. Early on, an ECG core laboratory was established with the MRG investigative team at Roosevelt Hospital in New York City, and this team developed a new and more relevant ECG classification scheme for use in postinfarction clinical studies.[15] Holter ECG analysis laboratories were established at Washington University and Columbia University, and the MRG investigators were prime movers in the development and introduction of heart rate variability as a risk-stratifier in coronary heart disease.[7] We rely on the integrity of the investigator responsible for each core lab to run the lab efficiently. The core-lab directors are answerable to the MRG and to the NIH or corporation that funds the study.

Support Staff

An important ingredient in the MRG program has been a skilled support staff at the participating institutions, including data managers, study coordinators, and technical personnel. They are important partners in the research activity and have a key role in the acquisition and maintenance of quality clinical data. At many participating hospitals, this support staff has remained nearly intact through the long-term course of the research activity.

Academics and Authorship

Some of the challenges faced by our MRG have been the recognition of merit by individual investigators as reflected in authorship of manuscripts and the ascertainment of credit by young investigators. In our initial authorship policy, manuscripts were published under the group name,[4] but we soon realized that this policy compromised recognition of individual investigators. We subse-

Table 1. Collaborative Multicenter Clinical Research: Key Elements

1. Select clinical investigators and biostatisticians who can collaborate effectively;
2. Design hypothesis-based research projects that answer important unresolved clinical questions;
3. Establish a data management center and core laboratories within the investigative group, if such expertise exists;
4. Involve the entire investigative team in analysis, review, and interpretation of clinical data when each study is completed;
5. Provide the investigators with open access to the database at the conclusion of each study;
6. Derive financial support primarily from peer-reviewed research grants;
7. Maintain investigator control over all aspects of the study;
8. Engage young investigators in the research studies;
9. Predefine authorship policies;
10. Create and maintain an environment that rewards and empowers investigators; based on merit
11. Develop and maintain a strict conflict-of-interest policy;
12. Enhance group fellowship through social and cultural activities that include and involve spouses.

quently developed an authorship policy in which the sequence of the listed authors is based on the relative contributions of each investigator to the overall study including design considerations, enrollment activity, data analysis, and manuscript preparation. Furthermore, we encouraged each of the investigators to identify a specific substudy within each major study and take primary responsibility and first authorship for a derived manuscript. This approach has worked well, and virtually all the investigators within our group have been first authors on several publications. Over the years, all of the MRG investigators have advanced academically within their own institutions. It is difficult to say what role the research activity of each MRG investigator played in his or her promotions, but we believe first authorship on manuscripts was an important factor. In a similar vein, the more established investigators have encouraged younger investigators to take responsibility for hypothesis-based substudies. Inter-institutional mentor-type relationships have developed within the MRG.

Operational Considerations

Early on, the MRG decided that major financial support should be derived primarily from peer-reviewed, NIH-funded, research grants. Budgets for each component of the proposed research activity including patient enrollment, core labs, data management, and primary as well as secondary statistical analyses are developed at the time of grant application. We follow the funding arrangement established by the NIH. The overall research grant funds are deposited in the institution of the principal investigator, and funds are distributed to each participating center or core lab in accordance with the approved budget. We follow the same arrangement when funded by a corporate sponsor. Since corporate studies do not go through an independent, external peer-review process, the MRG maintains a policy of developing the initial draft protocol and reviewing the final version for potential biases stemming from conflicts of interest between scientific principles and commercial orientation of the sponsor.

When contracting with a corporate sponsor, we follow NIH guidelines and require that each site has access to its own data. The MRG permits publishing data from a single center within the multicenter study, but only after the primary multicenter manuscript has been published.

Conflicts of interest can compromise many decisions in the planning, conduct, and interpretation of observational studies or clinical trials. To avoid this type of influence the MRG adopted the Relman conflict of interest policy in 1984[16] and the Healey guidelines[17] in 1991. The MRG continues a strict conflict-of-interest policy for all investigators and their immediate family members.

A summary of the key elements involved in the longevity and the success of the group are highlighted in Table 1.

SUCCESSION

The transition of leadership to the next generation of clinical investigators is a challenge. We have approached this transition by asking each of the MRG senior investigators to identify one or two younger investigators from their institution and actively involve them in the research activities of

the group. Presently, we have five committed younger investigators participating in the MRG program. Their activity within the group has resulted in a bi-directional learning experience between the younger and older investigators. The involvement of younger investigators in the MRG has expanded their research knowledge and experience and enhanced their ability to become principal investigators on their own NIH-R01 grants unrelated to the MRG. These younger investigators are providing new direction for planned studies by the MRG, especially regarding molecular genetic investigations. The senior investigators believe that the MRG should allow this transition to evolve on its own, thus encouraging the younger investigators to work out their own solutions to organization and directional challenges as they develop. We anticipate that a similar bonding experience will take place among the younger members of the group as the succeeding generation of investigators selects their principal investigator during the next grant submission by the MRG.

At this time, we cannot be certain that the MRG will successfully pass to a new generation of investigators. There is no mandate that it must. The MRG has been and continues to be a vibrant endeavor valued by all. Its future depends on the interplay of personality, changing medical landscape, and fiscal realities, none of which is entirely predictable.

COMPARISON OF THE MRG WITH THE NIH NETWORK APPROACH

Our MRG was established without any external stimulus. We determine the research agenda and apply to the NIH or corporations for support of investigator-initiated research proposals. In contrast, the NIH-NHLBI network approach provides a stimulus and a framework for investigative groups to work together utilizing a cooperative agreement with substantive involvement and oversight by the NIH staff. The network approach permits new protocols to be plugged in as the research program develops. The MRG works on one specific, investigator-initiated, R01-funded research grant at a time, with each study lasting for 4 to 5 years in duration. Subsequent research grants are usually based on hypotheses related to findings from the prior grant. Our MRG program was established 25 years ago, whereas the NIH network mechanism was introduced within the past 5 years.

CONCLUSION

The MRG provides a generally applicable model for organizing clinical investigators into a moderate-sized, collaborating multicenter research group with an equalitarian structure that contributes to collegial productivity. The personal satisfactions and professional growth that developed within the MRG are emphasized for they are important, under-appreciated ingredients for attracting, developing, and retaining clinical investigators in today's challenging medical environment.

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APPENDIX

Other members of the Multicenter Research Group include: David Oakes, Ph.D., Mary W. Brown, M.S., Wojciech Zareba, M.D., Ph.D., Charles L. Odoroff, Ph.D. (deceased), University of Rochester Medical Center, Rochester, NY; Monty Bodenheimer, M.D., Long Island Jewish-Hillside Medical Center, New Hyde Park, NY; Joseph L. Fleiss, Ph.D., Columbia University, New York, NY; John A. Gillespie, M.D., Buffalo, NY; Ronald J. Krone, M.D., Washington University School of Medicine, St. Louis, MO; Edgar Lichstein, M.D., Maimonides Hospital, New York, NY; and Frank I. Marcus, University of Arizona Health Science Center, Tucson, AZ.

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