
Organization, Review, and Administration of Cooperative Studies (Greenberg Report): A Report from the Heart Special Project Committee to the National Advisory Heart Council, May 1967

SUMMARY

Cooperative studies have been designed as a means of obtaining definite answers to significant questions not readily answerable by other means. Such studies should be initiated only if an important problem needs a rapid solution, the study is feasible and likely to answer the problem, and strong and stable leadership are assured. Protocol and operating procedures must be kept as simple as possible. Control of performance at all levels must be built into the structure.

Organizational components should include: (a) a Policy or Advisory Board, (b) an Executive or Steering Committee, (c) a Coordinating Center, and (d) data-contributing participants. All of these components must interrelate with each other and with National Heart Institute staff and, through the staff, with scientific review groups and the National Advisory Heart Council. A chart of organization is shown in Figure 1. The most important position is that of Chairman of the Steering Committee; the key component is the Coordinating Center. The performance of the Coordinating Center is continuously dependent on full-time, highly disciplined leadership that must continually maintain active lines of communication with all participants. Failure to achieve this seriously undermines the effectiveness and value of the study.

Participation in a cooperative study, with required adherence to a common protocol, can divert some scientists from original research. Conversely, others may be introduced to research methodology through participation. The benefits that can be achieved only through cooperative efforts must be carefully balanced against any adverse effects of encouraging large numbers of investigators to work in cooperative studies.

Exceedingly complex value judgments are required of reviewers, who must constantly keep in mind the need to maintain a reasonable balance within the funds appropriated for research. Their deliberations should include an

Editor's Note: The Greenberg Report, commissioned by the National Heart Institute and completed in May 1967, but never published, represents an important historical document in the evolution of procedures for the organization and operation of multicenter trials. Indeed, most of that report and the advice it provides are as timely today as it was when it was produced over 20 years ago. Publication of the report herein is done to preserve it as a citable document.

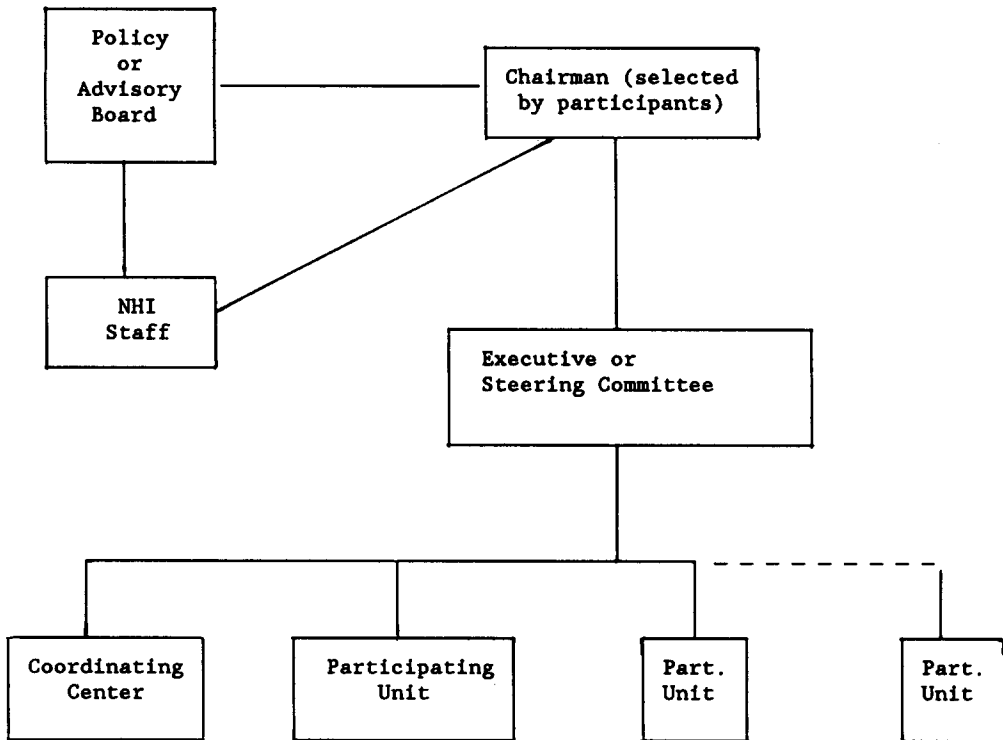


Figure 1.

evaluation of technical approaches, organization, biostatistical aspects, duration, and budget. Comprehensive annual progress reports and recall of former consultants could facilitate continuity of review. Free communication between the National Advisory Heart Council and the initial review groups is essential to enhance working relationships and understanding between these two levels of review. Approval of a preliminary study should carry with it a degree of commitment to a major study if feasibility can be demonstrated and adequate methodology developed.

Institute staff must play an increasingly active role in cooperative studies, providing information and advice; acting as liaison between Council, review committees, and participants; and functioning in administrative and technical capacities, perhaps even as contributing members of Steering Committee or Coordinating Center staff.

INTRODUCTION

The National Heart Institute supports a number of complex cooperative studies, most of which have received initial review by the Heart Special Project Committee. The Committee believes that such studies can be an effective means, and in fact sometimes the only means, of resolving particularly pressing scientific problems. The costs in manpower and money are justified if, through a cooperative project, a definitive answer to a significant question

can be obtained more expeditiously or accurately than through the traditional means of a solo investigator.

The Heart Special Project Committee and the National Advisory Heart Council share a degree of concern regarding the impact of these long-term, usually costly projects on various segments of the scientific community. A discussion of their organization, review, and administration is all the more pertinent at the present time because of the increasing need for a sharper definition of research goals and opportunities in the cardiovascular field, and the present and possibly continuing shortage of funds coupled with a growing need to translate research progress into clinical practice. The Committee offers the comments that follow in the hope that they may be helpful in formulating guidelines for investigators, staff, and review panels, which can be used to attain maximal benefit from the coordinated utilization of talents and resources possible in a cooperative study.

DEFINITIONS

A cooperative study may be defined as an identified activity in which two or more investigators in separate institutions contribute toward a common research goal. There are basically two types. One is a multidisciplinary approach to a research problem, with representatives of the various disciplines in separate institutions. They contribute to a common goal through collaboration involving an exchange of material and findings.

The second type, of which there are more and to which this report is addressed, is the project in which investigators in a number of institutions follow a common protocol and work within a clearly defined structure for the project as a whole. Most such studies (although by no means all) are organized to pool resources in order to minimize the length of time that the numbers of subjects are needed to obtain a significant answer to a clinical or epidemiological problem. The uncontrollable variation inherent in long-term individual efforts gives way to a short-term interinstitutional variation, which is further minimized by a coordination of effort.

CRITERIA FOR GOOD STUDIES

A number of aspects of these complicated studies must be considered at the beginning, including their ability to satisfy certain criteria. A cooperative study should be initiated as a means of attaining a research goal only if:

1. The problem to be studied is an important one that must be resolved (a) from a purely scientific point of view, or (b) for the benefit of mankind through improved methods of prevention, diagnosis, and/or therapy;
2. An answer must be obtained in a relatively short time, and a multiinstitutional collaborative effort is the best way to reach a solution in the briefest period;
3. The study is feasible within the potential cooperating institutions, and likely to lead to an answer; and
4. There is assurance of adequate leadership and control of performance for the duration of the study.

The ideal cooperative study asks a clearly defined question for which a simple answer can be obtained quickly. The simpler the question, the more likely is an answer. The broader and more complex the question, the less likely is an answer to *any* question. Because of the nature of the problems they seek to solve, few cooperative studies attain the ideal of simplicity, and means must therefore be found to compensate for various degrees of complexity. Competent biometric advice, sought early for assistance in development and design of protocol, can do much to assure that, even in a complex study, analysis of the field data will lead to an answer to the original questions within a reasonable period of time. Modern techniques of management science or systems analysis might also be applied to considerable advantage.

Simplicity of protocol and operating procedures will help to maintain a high scientific level in the project. Inclusion of peripheral items that may produce data useful at some time in the future, but that are not directly related to the primary aim of the study, must be avoided in order to focus attention on answering the major question asked. Such peripheral items may, on occasion, be authorized on a sampling basis, financed preferably by a separate grant for an ancillary or collateral study.

Simplicity of protocol also makes strict adherence easier. It obviates need for major revision with attendant undue prolongation of a study because of the time required to amass new data. With careful development during a pilot phase, it should be possible to devise a protocol structured to minimize revision, yet allowing for those modifications dictated by experience and scientific advances during the course of a study.

A continuing strong leadership within the framework of a well-defined administrative organization is essential for the success of any cooperative study. These complex long-term projects are often stimulated, initiated, and organized by a prominent and capable, but very busy, individual who in due course finds the demands on his or her time too great to continue in the role of driving force. He or she may delegate to others more and more of the responsibility for the study, and may even step down entirely as its guidance becomes more routine and less of a challenge with time. An individual of lesser caliber may then rise to the position of command, and if this process is repeated, the leadership gradually sinks to a lower and lower level.

One way to keep the leadership in the hands of a fully competent, inspired, and inspiring individual could be to select someone specifically for this role, either from within the study or from outside. Once located, a person who would find continuing intellectual stimulation and challenge in the study should be offered status and salary commensurate with the importance of the position. This individual could conceivably be a member of the National Heart Institute staff. Another alternative could be to rotate responsibility for leadership among two or three of the strongest and most capable participants.

Control of performance at all levels, from Coordinating Center to individual participating units, must be built into the structure. Any indication that the leadership is unable or unwilling to assume this responsibility raises the question of whether the project should be started, and initiation of any new study should perhaps be contingent on adequate evidence that discipline can and will be maintained. In an ongoing study, if performance is not satisfac-

torily monitored by the participants, then National Heart Institute staff must prod the Executive Committee to take on this responsibility.

Investigators have always recognized the need to protect the rights and welfare of patients. Policies that required a detailed and fully informed consent could lead to a situation in which double-blind randomization, so essential to many types of clinical trials, would be impossible, or possible only under circumstances that would introduce biases so great as to invalidate the results obtained. Any foreseeable problems in this regard must be openly discussed and resolved before a study is initiated.

ORGANIZATION

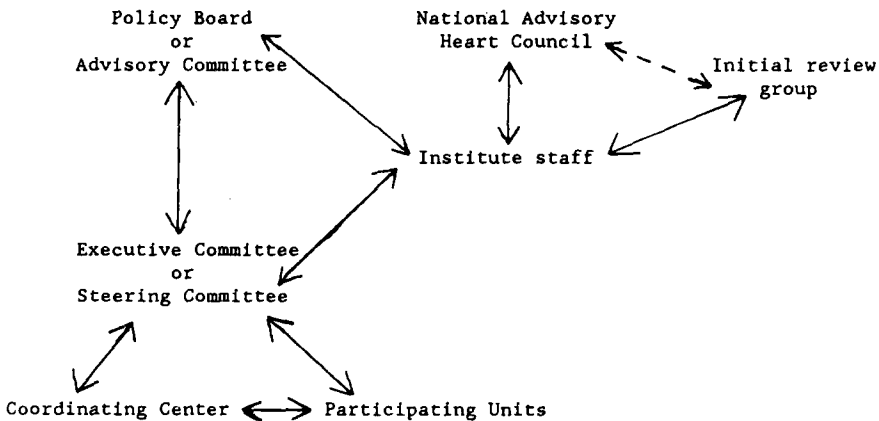
Three basic steps are essential to achieve the aims of a cooperative study:

1. Organization of local units, under good leadership, to collect data of comparable quality and in comparable amounts as the basic resource;
2. Establishment of a coordinating center to receive data from the field, collate the data, and prepare the data for use; and
3. Critical interrogation of the resource data in the Coordinating Center to answer the original questions.

These activities require a clearly defined organizational structure. On the basis of considerable past experience with cooperative studies, the Heart Special Project Committee believes that the essentials of the most effective structure follow the pattern shown in Figure 2. Some degree of flexibility must always be allowed.

The participating laboratory or clinic is the basic unit. Adequate performance at this level must be assured if meaningful data are to be obtained. One person must have overall responsibility, and this Principal Investigator, who serves as local coordinator, must be capable of establishing and maintaining a good relationship with their institution and with the heads of all of the services that may be involved in a multidisciplinary project. Stability of

Figure 2.



personnel is important. Frequent turnover, even of junior members of the team, decreases local understanding of the aims of the study, a factor which, in turn, can result in poor or haphazard data collection.

The Coordinating Center is a key point in a cooperative study. Its basic functions are to (a) arrange for preparation and distribution of the protocol and data forms, (b) be responsible for or supervise distribution of drugs if required for a clinical trial, (c) transmit information and reports to participants, (d) help plan their meetings, (e) measure interinstitutional variation, (f) receive and review data from the field, and (g) perform statistical analysis of the accumulated data. Because of its important role, the Coordinating Center must be under strong and capable leadership that will remain stable for the duration of the study. In addition, the Director of the Coordinating Center must have *and use* competent statistical advice in order to meet his or her responsibilities for data analysis.

The accumulated data in the Coordinating Center are a major resource of the study. The data should be subjected to frequent analysis, including sequential analysis when possible, to assure constant awareness of current status, which is so essential for intelligent direction of the project as it progresses. The Director should be responsible for making the results of data analysis available promptly to the Chairman of the Executive or Steering Committee for use at various levels.

The Director of the Coordinating Center is in the best position to monitor performance by the participating units and he or she should be the individual with authority to carry out policing activities. However, disciplining for repeated infractions should not be the Director's responsibility, but rather should be vested in a jury of the other investigators, preferably the Executive Committee, including the Chairman.

An Executive or Steering Committee, comprised of a limited number of strong participants, should be organized to deal with operational problems, to supervise the Coordinating Center, and to make periodic performance-monitoring or problem-solving visits to participants. The position of Chairman of this Committee should be filled by the person whose role is essentially that of Director of the study and, as such, would usually be called Chairman of the study. This is the most important position in a cooperative project and the point at which the greatest strength and stability in leadership is needed. The Committee might best be separately funded, thus keeping support for its activities entirely separate from the Coordinating Center.

It should be the responsibility of the Chairman, with the help of the Executive Committee, to review the data analysis coming from the Coordinating Center and to prepare frequent reports to the participants, as well as annual reports to the National Heart Institute, the latter to be available for the information of the Heart Special Project Committee and the National Advisory Heart Council. These reports can serve to alert staff and reviewing groups to potential problem areas so that corrective steps can be taken before serious difficulties develop. The advice of the Executive Committee could and should be sought in regard to the adequacy, capability, and acceptability of potential participating units.

A Policy Board or Advisory Committee of senior scientists, experts in the field of the study but not data-contributing participants in it, is almost essential

for a large complex cooperative project. Such a group can review the overall plan, make recommendations on any possible changes (including changes in protocol and operating procedures), adjudicate controversies that may develop, and advise the National Heart Institute on such matters as the addition of new participants or the dropping of nonproductive units. Through its familiarity with all aspects of a study, its advice may on occasion be helpful to review panels as well as National Heart Institute staff. The role of the Advisory Committee should be limited, however, to offering substantive advice; it should not be involved with the funding operations or recommendations for funding if other review mechanisms are available.

The staff talents available within the National Heart Institute can be used to considerable advantage in a cooperative study, both at the Coordinating Center and in the Executive Committee. This is discussed more fully in the section on Role of the National Heart Institute.

EFFECT ON ECOLOGY OF SCIENTIFIC COMMUNITY

There are many areas in which cooperative studies, by the careful accumulation and critical analysis of factual data, may lead to more rational and effective medical practice with less reliance on simple empiricism. There are some areas in which this is the only way such results can be achieved. The balance in the scientific community as a whole can be affected, however, by diversion of sizeable numbers of investigators and the commitment of large sums of money to these studies. Regardless of the mechanism of funding (by grant or contract, through special line item or regular appropriation), an imbalance in the total research support system can conceivably develop. The present increasing emphasis on coordinated or targeted research in clinical fields makes it imperative to balance carefully any positive benefits in certain areas achievable only through well-organized cooperative efforts against any adverse effect of encouraging large numbers of investigators to work in cooperative studies.

The effects on scientific progress and individual investigators may be good or bad and depend to a large extent on the individual investigator's capabilities and interests. Participants must be fully aware of the effect on their decision-making processes of random allocation of patients, and must realize that management decisions affecting patient care may be influenced. Junior staff are frequently responsible for such decisions. It is important that they and the Principal Investigator are completely familiar with the project's protocol and its purposes, and that they are trained to reach sound and objective value judgments which, under the circumstances, are in the best interests of the patient.

Scientists who become engaged in studies that demand strict adherence to a common protocol may be diverted from other research efforts. The protocol that demands only the least common denominator acceptable to all participants may furthermore engender a low level of scientific endeavor. With little time left for original research, individual productivity may be reduced, but not necessarily completely suppressed. A person vitally interested in and capable of original research, however, will somehow find time to pursue it.

Cooperative studies must attract competent investigators as participants if they are to succeed. At the very beginning of planning, efforts must be made to prevent or at least minimize any stifling of original research. Two potential solutions appear reasonable. One is to provide adequate funds for inclusion of fully competent, conscientious subordinates on the research team who could be responsible for routine operation of the study under the guidance of the Principal Investigator, thus freeing some of the latter's time for other pursuits. An alternative and probably better approach is to encourage collateral or ancillary studies as a means not only of attracting competent investigators, but of stimulating and maintaining their interest once they become participants. Such studies must not interfere in any way with adherence to the protocol for the major study, even though they may be closely related to it, and may use the same patient material. The results obtained may be an important beneficial contribution of the cooperative study. Collateral projects, although fostered and encouraged, should be reviewed and funded separately.

The preceding two paragraphs relate to possible deleterious effects and their prevention or alleviation. On the other hand, when properly done, studies of this nature can have widespread and immensely useful effects on large groups of participants and their institutions, including accuracy in data collection; recognition of error, bias, and chance; improvement in patient care and treatment; and more widespread recognition of the condition under study. Cooperative studies may even broaden the research base in some institutions by introducing clinicians who lack investigative experience or originality to the field of research. Often these individuals are fully competent to participate in a study developed by others. Some, thus stimulated, may become interested in and capable of further investigations on their own.

REVIEW MECHANISMS

The members of review committees face serious problems when they consider fairly long-term, many-faceted cooperative studies. Complex judgments are required for evaluation of the technical approaches, as well as organization, biostatistical aspects, duration, and budget. Reviewers can hardly avoid taking into account the effects of their deliberations on the scientific community and the fact that a favorable recommendation may commit considerable sums over a period of several years. Accustomed to consideration of single projects, reviewers often find it difficult to reorient their thinking and accept the philosophy that multiinstitutional clinical trials, classified as applied research but research nonetheless, have an important place in the total support structure.

They must also constantly bear in mind that a study in the form presented to them is the end-product of a long period of development by the potential participants. It is natural that the members of the review committee, being experts in many disciplines, should call upon their own experience and think of various ways in which the study might be modified and perhaps improved. Sometimes a review committee with special interests suggests the addition of cumbersome and unworkable details to an otherwise simple and well-designed cooperative project. Reviewers must avoid the temptation to suggest

or demand major changes in study design or major modifications of protocol that will complicate the study. If major changes appear to be necessary to achieve the stated aims, a fresh start might be more appropriate.

Occasionally, an anomalous situation arises with renewal applications. A study favorably recommended at one point in time in response to a then urgent need may not require another major review for several years. In the intervening period, membership of both the initial review group and the National Heart Council changes through rotation. The study, well under way but far from completion, is thus reconsidered by essentially new groups of consultants. In their deliberations, they must carefully balance current need for the study in the light of interim scientific advance and protection of a considerable investment that might be lost if the study were not continued until sufficient data were amassed. This situation could be alleviated by having former National Heart Council or review group members present during such discussion.

Regular annual reports to both the review group and the National Heart Council would also serve to keep members up to date in regard to progress. They should be prepared by the Chairman of the study in cooperation with the Director of the Coordinating Center and the Executive Committee, and should be comprehensive delineations of the current status of the project. Such reports serve another purpose well, in that they can permit early detection of unforeseen weaknesses or problems in the study. It might then be possible to institute remedial measures before major difficulties develop.

ROLE OF THE NATIONAL HEART INSTITUTE

There is a real need for a single focal point within the National Heart Institute for coordination of cooperative studies and storage of information on all aspects of these projects. From such a point, staff can and should play an active role during the early planning phases of future projects, advising the organizers on the basis of considerable previous experience, drawing upon the stored information, and serving as liaison between review committees, the National Heart Advisory Council, and investigators. Many of the problems that have occurred in the past might be avoided if the requirements and pitfalls of cooperative studies were spelled out in advance to the applicants by experienced staff members. This type of advice is almost essential for studies organized in response to specific National Heart Advisory Council or National Heart Institute interests in selected targeted areas of research. Staff should be encouraged to use *ad hoc* consultants in this process. By the same token, review groups would profit in their later deliberations if they were apprised at the earliest possible moment and kept informed by staff of the aims, plans, and progress in the organization of any future cooperative studies. Through knowledge of the relevance of certain facets of a developing study to the programs of other institutes or bureaus, staff can also help with incorporation into the project of significant aspects that would neatly dovetail with these other program interests.

Continuing communication to investigators is another important staff function. The sense of the discussions at review committee and National Heart Advisory Council levels, both favorable and critical, should be conveyed to

the participants. This is particularly important following an unfavorable recommendation or a conditional approval, or when an annual progress report indicates potential difficulty.

The hands-off philosophy, which applies to the individual research project, is not applicable to these long-term, complex, multiinstitutional projects that require commitment of large sums for their support. Staff must therefore have the authority to exert a considerable degree of control over a cooperative study. Stability of National Heart Institute personnel is important to establish the confidence essential for good rapport with the participants; division of authority or changes in personnel only create confusion and can occasionally result in dissemination of incorrect information. Each study should have assigned to it one competent staff person who would serve as Project Director or Administrator.

For some projects, particularly those initiated by National Heart Advisory Council stimulation, it may be desirable to assign a specific member of the National Heart Institute staff to an active role in the study, quite separate from the position of Project Director. Such a person could serve as a member of the Steering Committee or on the Coordinating Center staff, and might be able to assist with design of the protocol. In those studies in which the participants are unwilling or unable to exert adequate control over performance, it could become the staff member's responsibility to help police data collection and analysis.

A mechanism must be developed for early termination if unusual circumstances dictate that a cooperative study should not be continued. Such action might be contemplated if the accumulated data answer the original question sooner than anticipated, if it is apparent that the study will not or cannot achieve its stated aims, or if scientific advances since initiation render continuation superfluous. This is obviously a difficult decision that must be based on careful analysis of past progress and future expectation. If the National Heart Institute must initiate such action, it must do so only with the advice and on the recommendation of consultants.

A phased contract mechanism of support might be considered for cooperative studies. This would require comprehensive planning and review of the total project at the very beginning. Subsequent review would be necessary between phases, with continued support dependent on adequate progress during preceding phases. Under such a system, National Heart Institute staff would be even more involved than under grant support.

PRELIMINARY STUDIES

Phased progression into the major study is almost essential for a large, complex, multiinstitutional, multidisciplinary project. The first thing to be determined is whether a cooperative study can be done at all within the framework of the available manpower, material, and resources. This can be explored in carefully selected institutions working with a limited number of patients. If feasibility is established, the next logical step is a pilot project in which a few of the potential participants develop and test all aspects of the study. The need for later revision of protocol and/or operating procedures can be minimized if methodology is well worked out in a pilot study.

Preliminary studies pose serious problems, however, for both review groups and investigators. The former are disturbed by the implication of a moral commitment to a larger study. The latter find it difficult to believe that proof of feasibility and a successful pilot operation do not automatically assure support for a larger study. They are faced with waning enthusiasm and possible loss of trained, interested personnel if there is an interval between the phases.

Initial plans would define the points at which feasibility and adequacy of methodology will be determined. If both are satisfactorily demonstrated, then the major study should logically proceed. Thus, an application for a preliminary study should include tentative plans for the major effort, with suggested means for its implementation and estimates of duration and cost. Obviously, only an approximation can be offered far in advance and a considerable degree of flexibility must be understood, but the applicants should be able to provide general information.

Cooperative studies are characterized by large expenditures of effort and money, complex and rigid structure and protocol, and unusual requirements in continuity of support. For these reasons, approval of support for a feasibility study imparts momentum that can be arrested only with difficulty and potential hardship on the investigators. Support of a feasibility study should therefore be recommended only after a thorough and critical evaluation of the potential contribution of the major study in relation to overall National Heart Institute programs. Both feasibility and pilot studies are designed to provide direct knowledge and experience regarding cost, methodology, and requirements of the proposed major study so that both the investigators and reviewing bodies can better judge the prospects and nature of expected rewards. Since neither feasibility studies nor pilot studies should be construed as any form of commitment of support for the major study, they should be planned as separate steps, which could be terminated with minimal dislocation if support of the major study is not approved.

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