A RAND NOTE

INITIATING CLINICAL TRIALS: A CASE STUDY OF EXTRACRANIAL–INTRACRANIAL ANASTOMOSIS

Geoffrey M. Anderson, James P. Kahan

September 1985

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Prepared for

The National Center for Health Services Research and Health Care Technology Assessment

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PREFACE

The randomized clinical trial is methodologically the strongest way to study the merits of medical practices. But such a trial is expensive and complicated, poses ethical issues, and is slow to reveal insights. Although its most common use is to test the efficacy and safety of innovative medical procedures, it can also test other features—such as cost-effectiveness or patient acceptability—not only of new but also of current practices. In the United States, the federal government funds most clinical trials through the National Institutes of Health.

Under contract to the National Center for Health Services Research and Health Care Technology Assessment (NCHSR), The Rand Corporation has examined clinical trials of current medical practices with the aim of obtaining a better understanding of the processes and criteria underlying NIH's decision to initiate such trials. Case studies were conducted of four potential clinical trials considered for sponsorship by different Institutes of NIH. This Note is a case study of a clinical trial of extracranial/intracranial (EC/IC) bypass for stroke prevention, sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS).

The Note should be of interest to government policymakers and to members of the research and professional health care community, particularly to those concerned with the use of clinical trials in medicine and with the question of how NIH policy directs the path of medical research in the United States.

The senior author, Geoffrey M. Anderson, M.D., is a Pew Memorial Trust Health Policy Fellow at The Rand Corporation.
The work reported here was supported by Contract 282.83.0068 with the Department of Health and Human Services, under the sponsorship of NCHSR. The main report of this investigation is:


The other case studies performed on this project are:

SUMMARY

This case study reviews the inception of a grant from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) to conduct a randomized clinical trial (RCT) of the effect of extracranial/intracranial (EC/IC) anastomosis on stroke incidence. We examine the investigators' decision to apply for the grant and the Institute's decision to fund the application.

The investigators' decision to propose the study was based on their view that an RCT of the EC/IC bypass technique was relevant to stroke prevention because stroke is a major disease, because EC/IC is of potential importance in preventing stroke, and because a trial had the potential to affect medical practice. The study was feasible because it was possible to design an appropriate study and to obtain the interdisciplinary and interinstitutional cooperation necessary to obtain the resources required for data collection and analysis, the support of multiple clinical centers for patient recruitment, and an agency willing to fund the study.

Interviews with the investigators and reviews of relevant documents permitted the following conclusions to be drawn regarding the investigators' perceptions of the relevance and feasibility of the trial:

Relevance

- Stroke has a major influence on health in terms of both its incidence and its severity.
- Stroke prevention was the most workable approach to lessening the effect of this disease, and the EC/IC procedure might benefit a considerable subset of individuals at risk for stroke.
- A trial of EC/IC anastomosis was timely; its results could affect medical practice because the technology for the procedure was stable but the benefits were not yet accepted as certain.
Feasibility

- The clinical group at the University of Western Ontario and the methodology group at McMaster University had established an ongoing relationship that made the design of complicated RCTs possible.
- The effect of the EC/IC procedure could be adequately assessed in a randomized trial of 1000 patients followed for five years.
- The investigators had high status and strong reputations and had the influence necessary to obtain the required support from other clinical centers.
- NINCDS had shown interest in funding an appropriately designed study.

The NINCDS decision to fund the EC/IC trial was made in the context of NIH grant review process. This process is divided into two major stages: (1) peer review by a Study Section, and (2) review by the Council of the relevant institute. The NIH is limited to grants of no more than five years in duration; because the EC/IC trial was planned to last eight years it was reviewed twice, once in 1977 and again in 1981/82. The 1977 Study Section review was very positive on all aspects of the scientific merit of the EC/IC grant application and specifically referred to its potential effect on the use of the procedure. The 1977 NINCDS Council meeting recommended funding the study straightforwardly. The 1981/82 review was less positive, with some discussion of potential methodological problems and disagreement on the potential effect of the results of the trial on medical practice. But NINCDS believed the renewal should be funded because the study was important and because failure to renew would mean they would receive little information for their substantial investment in the first five years of the trial.
ACKNOWLEDGMENTS

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I. INTRODUCTION

This Note describes the major determinants of the decisions to initiate and to fund a randomized clinical trial (RCT) of extracranial/intracranial (EC/IC) bypass for stroke prevention. This section describes the sources of data. Section II briefly describes what was known about stroke prevention in 1977. In the third section, the decision to initiate the EC/IC bypass trial is described, using a model that suggests relevance and feasibility are important factors in the decision to develop a clinical trial. Section IV describes both the peer review of the scientific merit of the grant application and the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) Advisory Council's decision to recommend funding the trial. Section V draws some conclusions regarding the decisions to initiate and fund clinical trials.

The material for this Note was gathered from telephone and in-person interviews conducted in April 1985 with the following individuals:

- Dr. Michael Walker, Director of the Stroke and Trauma Program at NINCDS
- Dr. Henry J.M. Barnett, Professor and Chairman of the Department of Clinical Neurosciences, University of Western Ontario and project director of the EC/IC trial
- Dr. Sydney John Peerless, Professor and Chairman, Division of Neurosurgery, University of Western Ontario and principal neurosurgical coordinator of the EC/IC trial
- Dr. David L. Sackett, Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University, project coordinator of the EC/IC trial.

Material was also drawn from the grant applications submitted by Dr. Barnett's group to the National Institutes of Health in March 1977 and July 1981 and the summary statements prepared by the Executive Secretaries of the Study Sections that reviewed these grant applications.
II. STROKE PREVENTION AS OF 1977

In the United States in 1977, there were an estimated 180,000 deaths from stroke, making it the third leading cause of death. Stroke is not only an important determinant of mortality but also has significant effects on morbidity. The Framingham study (Gresham et al., 1975) indicates that, of the approximately two-thirds of individuals who survived an initial stroke, 31 percent needed assistance in self-care, 20 percent needed assistance in ambulation, and 71 percent had decreased vocational function at a mean of seven years of follow-up. In addition, 16 percent remained institutionalized.

The majority of strokes are caused by decreased blood flow to brain tissue. These ischemic strokes result in the death of brain tissue and a consequent loss of brain function. The loss of brain tissue is irreversible and therefore stroke therapy is not curative but preventive (i.e., therapy is directed at preventing future ischemic events).

Permanent neurological deficits due to ischemic stroke are often preceded by reversible neurological loss. If these events last less than 24 hours, they are called transient ischemic attacks (TIAs); and if they totally resolve in a period longer than 24 hours, they are called prolonged reversible neurological deficits (PRND). Individuals with TIAs or PRNDs are at high risk for subsequent stroke. Further, because ischemic strokes are associated with systemic diseases such as atherosclerosis and hypertension, individuals who have had one stroke are at high risk for subsequent ischemic events. These two groups, individuals with reversible ischemic events and those with previous strokes, are target populations for preventive therapy.

Preventive therapy is directed at reducing the risk of future ischemic events generally in three ways: (1) by modifying risk factors associated with the underlying systemic disease, (2) by modifying blood properties to reduce the risk of the formation of blood clots, and (3) by removing or bypassing areas where blood vessels are narrowed (stenosis).
The first of these falls more into the realm of health promotion and patient behavior modification than into more strictly defined clinical medicine. The modification of blood clotting properties falls into the category of medical therapy, and surgical therapy is directed at the removal or bypass of stenotic lesions.

In 1977, medical therapy meant the administration of either anti-coagulants or anti-platelet drugs. Anti-coagulants were introduced in stroke prevention in the 1950s. The studies that supported the use of these agents suffered from a myriad of methodological problems; although use of these drugs was recommended (Sandok et al., 1978), the proof of their efficacy was equivocal.

The 1960s brought increasing evidence that platelet thrombi played an important role in preventing TIAs. At the same time, it was found that dipyridamole and aspirin affected platelet function and platelet aggregation (Emmons, Hardison, and Honour, 1965; Weiss and Aledort, 1967). The first clinical trial of anti-platelet agents (Acheson, Danta, and Hutchinson, 1969) did not show much benefit for anti-platelet drugs, although it suffered from a limited sample size and consequent lack of power. A later RCT (Fields et al., 1977) indicated some benefit from aspirin therapy for the combined outcomes of death, stroke, and TIA; it was not, however, statistically significant for the "hard" outcomes (death and stroke) alone. This trial also had a limited sample size and follow-up and thus was vulnerable to Type II, or false negative, error.

Surgical therapy for stroke prevention in 1977 consisted of two procedures: EC/IC, and carotid endarterectomy (CE), in which the extracranial internal carotid artery is opened, and material that has stenosed or occluded the artery is removed. According to its proponents, the potential benefits of CE are twofold: First, it increases blood flow to the brain, thereby reducing the likelihood of subsequent vascular compromise. Second, it removes atherosclerotic material that may be a source of future emboli or thrombo-emboli.

CE was first performed in 1952. It was tested in an RCT involving over 1200 patients randomly divided into surgical and non-surgical groups (Fields et al., 1970). The non-surgical group received medical
therapy that, at the time of this study, included general medical management and anti-coagulants.

Although the trial hinted at some advantages for CE for some patients, no comparison of surgical vs. non-surgical procedures showed differences that were statistically significant.¹

The results of the trial did not provide compelling evidence for the efficacy of CE, yet the procedure gained acceptance as an appropriate therapy. A recent textbook highlights this (Cutler, 1983, p. v-5):

Although the long-term outcome of endarterectomy has never been properly assessed in randomized studies, there is general agreement that patients benefit symptomatically from carotid endarterectomy if an ulcerative or occlusive lesion is found on the side appropriate to the symptoms.

In 1967, EC/IC was introduced when it was suggested that a shunt from an extracranial vessel (the superficial temporal artery) to an intracranial vessel (the middle cerebral artery) would provide a bypass for patients with occluded internal carotid or middle cerebral arteries. The artery-to-artery anastomosis procedure was first developed in Europe and later introduced to North America. By 1977, approximately 2000 EC/IC bypasses had been performed worldwide. Though there had been some anecdotal reports regarding the safety and surgical success of the procedure in terms of patency rates, there had been no controlled studies of its efficacy.

¹In addition to these equivocal findings, this study has become dated. Both surgical and medical death and stroke recurrence rates are high compared with modern standards.
III. THE DECISION TO SUBMIT THE GRANT APPLICATION

A TWO-FACTOR MODEL

We view the decision taken by investigators to initiate a study of a medical practice as a function of two general factors, relevance and feasibility (see Fig. 1). This section shows how these two factors describe the decision to submit an application for a grant to study EC/IC bypass.

Fig. 1—Determinants of the decision to submit a grant application
Relevance

Relevance has three interrelated components. The first is the importance of the disease that the medical practice purports to affect. The more people afflicted with the disease, the more dire the disease, and the greater the expense of treating the disease, the more important it is. The second component is the potential effect of the medical practice on the health burden of the disease. The more the practice might be used to treat the disease, the more relevant is an RCT of that treatment. The third component is the potential effect of an RCT on the use of the treatment—will the results of the study affect the usage pattern of the treatment? This component has two dimensions: (1) the expected strength of the evidence that will be produced and (2) the openness of the practitioner community to the results of the study. The strength of evidence produced by a study is a function of the validity of the evidence and the appropriateness of the outcome measures and is determined in large part by the design of the study. In the ideal world, the effect of a study on the practice of medicine would be directly related to the strength of evidence. However, the practice of medicine is the consequence of individual actions by many individual physicians. The effect of evidence on these individuals depends upon their interpretations of that evidence—interpretations that may be flavored by heuristics and previous practice patterns.

Feasibility

The second factor related to the initiation process is feasibility of the study, which can be divided into design and implementation components. The design issues address being able to answer the questions the study purports to ask and include such matters as specifying the protocols, deciding on the number of treatment arms, constructing the dependent measures, and determining the sample size needed to meet defined statistical criteria.

The implementation component is the problem of actually carrying out the trial. Large clinical trials involve complex design, measurement, and analysis issues. Among the assurances necessary to obtain meaningful results from an RCT are compliance with research
protocols, patient compliance, patient follow-up, and accurate data recording. Although the clinicians who initiate the study have knowledge of the key medical issues, the successful completion of major RCTs is contingent upon access to continuing methodological expertise. Such support is often difficult to obtain and can constrain the development and completion of clinical trials.

Moreover, for many (perhaps most) major RCTs, the number of patients required for the study exceeds the population of patients that are under the direct control of the principal investigator. Therefore the investigator will have to enlist the aid of other clinicians to obtain an adequate sample. The ability to obtain such cooperation determines the feasibility of many clinical trials. Therefore, the study must appear attractive to these clinicians.

A final aspect of feasibility is funding. An RCT requires sponsorship and is feasible only to the extent that its goals and costs are congruent with the mandate and resources of a funding source. Writing a grant application is expensive and time consuming; it is likely to be undertaken only if realistic opportunities exist for funding.

AN APPLICATION OF THE MODEL

We begin our description of the decision to propose the EC/IC trial with a brief profile of the key investigators. Clinicians were at the University of Western Ontario (UWO) in London, Ontario, and methodologists were at McMaster University in Hamilton, Ontario. The UWO has a world-renowned neurosciences division with a major emphasis on neurovascular diseases. McMaster University has an equally renowned methodological center, which has historically analyzed RCTs.

The UWO staff includes representatives of the three medical specialties that were involved in the study. Dr. H. J. M. Barnett, the principal investigator for the EC/IC bypass trial, is a neurologist and Chairman of the Department of Clinical Neurological Science. Dr. S. J. Peerless, principal neurosurgical coordinator for the trial, is a neurosurgeon and Chairman of the Division of Neurosurgery. Dr. A. J. Alcock, the neuroradiological coordinator for the trial, is a neuroradiologist and Chairman of the Department of Radiology.
The McMaster methodological group was headed by Dr. D. Sackett, a clinical epidemiologist in the Department of Clinical Epidemiology and Biostatistics. Major members of his team were Dr. B. Haynes, a clinical epidemiologist, and Mr. D. W. Taylor, a biostatistician.

Relevance

Dr. H. J. M. Barnett has devoted many years to research on stroke. He has established a reputation as one of the best investigators in the field. In 1977, he was on the editorial board of several prominent journals and was the principal investigator of a major RCT of the effects of anti-platelet agents on stroke prevention.

At the time of the inception of the EC/IC trial, Dr Barnett believed that stroke was a major disease needing research, but that the research needed to be of methodologically high quality (Barnett, 1980a, p. 803):

Vascular stroke is a crushing burden for patients, families, and communities to endure. In North America it brings death to approximately one person in six. Worse still it deprives a greater number of them of mobility, sensibility, speech or intellect, or all of these. It crushes human dignity, strips its victims of independence and eliminates employability. . . . Methodologists and biostatisticians have convinced most clinical investigators, including many concerned with stroke, that a number of rigid criteria must be met before the benefits of a potential treatment can be claimed.

Thus, research on stroke meets the first criterion of relevance, because of the severity and frequency of the disease.

As we discussed earlier, stroke prevention techniques in 1977 were either medical or surgical. Medical techniques included anti-coagulation and anti-platelet therapy. Surgical techniques included CE and EC/IC bypass. Barnett believed that the efficacy of none of these techniques had been proven. On the subject of medical treatments, he wrote, "It cannot be concluded unequivocally that anti-coagulants are helpful. Similarly, it cannot be concluded that anti-coagulants have no place in TIA management" (Barnett, 1980b, p. 1218), and "By 1970, it was apparent that the prevention of stroke by anti-coagulants was less than
ideal" (Barnett et al., 1978, p. 53). For surgical treatments, he believed that "the vexed question of the overall value of [CE] is clouded by the fact it was studied in a single randomized study with insufficient number of cases" and "No convincing statement about [EC/IC's] prophylactic value will be available until the multicenter collaborative, randomized trial is completed" (Barnett, 1980a, p. 804).

Thus, Dr. Barnett believed that all of the major medical and surgical treatments for stroke met the second criterion of relevance. Any of these therapies could have important effects on the treatment of a common and devastating disease. The choice of which of these to study was based on further refinements of relevance. Dr. Barnett ruled out the medical treatments for consideration on the basis of his own ongoing research. A major RCT of anti-platelet therapy was ending in 1977 and would shortly be published, and he believed that the results of this trial would help to define the standard medical therapy for stroke prevention. This trial showed that aspirin therapy reduced the risk of death and stroke in males (Barnett et al., 1978).

Both EC/IC and CE were considered for clinical trials. Although in 1977 CE was, as now, a standard treatment for stroke prevention without any research evidence of its efficacy (Barnett, 1980b; Barnett, Plum, and Walton, 1984), Barnett did not believe that the practitioner community would accept the results of an RCT. When a practice has gained the acceptance of the medical profession, as had CE, it is difficult to obtain both funding and the cooperation of other clinicians. Even if the trial is completed, the effect of the results on medical practice may be attenuated.¹ Put another way, there was no window of opportunity in 1977 for an RCT of carotid endarterectomy.

With RCTs of anti-platelet, anti-coagulant, and CE lacking relevance for various reasons, the choice of EC/IC seemed logical by default. The technique of EC/IC was sufficiently developed to be stable and specifiable in a trial protocol, but it was not yet in widespread use.

¹Acceptance may represent a term clinicians use to deal with the uncertainties that surround medical practice. Frequently, physicians have to act with imperfect information and often develop patterned responses to specific clinical situations. The more established these patterns become, the more difficult it is to change them.
Dr. Peerless's views of the relevance of the EC/IC trial were, in large part, similar to Dr. Barnett's. As a surgeon, his interests were in the efficacy of surgical techniques; he was not directly concerned with comparisons of medical treatments. Dr. Peerless had a major interest in the EC/IC bypass technique; he had learned the technique while studying in Switzerland and was one of the first surgeons to use it in North America. Although he believed the procedure to be efficacious, he welcomed an RCT to determine its value.

Dr. Sackett had a somewhat different view of the trial's relevance. Although he shared with the other investigators the belief that the trial would shed light on how best to manage an important disease, his major personal interest was in the methodological challenge of the trial. As he saw it, that was embedded in a surgical therapy associated with perioperative mortality and morbidity but long-term benefit, compared with a medical therapy presumed to have a different pattern of benefit over time. In essence, Dr. Sackett emphasized the process of the trial rather than its content.

Feasibility

An important component of the investigators' overall perception regarding the feasibility of the proposed study was that, although they came from different disciplines, the three investigators had developed channels for communication in their previous work and were able to use these channels to develop a study that recognized the concerns of each of their disciplines. Dr. Barnett had worked with Dr. Peerless at UWO and had also worked closely with Dr. Sackett on a large multicenter clinical trial of anti-platelet drugs.

After the major outcome variables, the treatment arms, and the protocols have been defined, a major step in determining the feasibility of an RCT is the calculation of the sample size required to appropriately address the research question. It was determined that a sample of 1000 patients followed for an average of five years was required to determine the efficacy of EC/IC anastomosis in stroke prevention. The size and duration of the proposed study had important ramifications for the other components of feasibility. First, the size
of the trial indicated the need for continuing large-scale data
collection and analysis resources. Second, the trial would require the
long-term commitment of many clinical centers. Third, the trial would
be expensive and would require support from a major funding agency.

The fact that Dr. Barnett had worked with the McMaster group on a
large randomized trial of anti-platelet drugs and that members of that
group were supportive of the EC/IC trial suggested that the proposed
trial was feasible in terms of methodological support. Although the
methodologist's role was important in assuring the design feasibility of
the proposed study, the clinicians had primary responsibility for the
implementation problems of obtaining funding and cooperation of other
investigators.

Drs. Barnett and Peerless believed that their combined contacts
would permit them to recruit enough cooperating centers in the United
States and Canada to meet the sample size requirements dictated by the
study design. The ability of investigators to obtain the required
cooperation from other clinicians is based on the status of the
investigators within the profession and the benefits the cooperating
centers gain from involvement in the study. Dr. Barnett had a world
renowned reputation in the field of stroke prevention. However, Dr.
Barnett was a neurologist and the procedure to be studied was surgical.
Thus, the active participation of Dr. Peerless, a well-established
neurosurgeon, made the trial more acceptable to other centers.\(^2\)
Similarly, the inclusion of the McMaster methodological center reassured
potential cooperators of the quality of the proposed study.

The question of the value of the trial to cooperating centers goes
beyond simple scientific interest, which Drs. Barnett and Peerless
believe is ubiquitous, to other benefits. One such is payment to
clinicians who recruit and monitor patients for the trial. Another
benefit is potential academic or career development. Although

\(^2\)The importance of strong representation of all involved
specialties in the study was further highlighted by Dr. Peerless. He
suggested CE was difficult to study because the procedure is performed
by both neurosurgeons and vascular surgeons, and both of these
specialties would have to be strongly represented in any study of the
procedure. The EC/IC bypass, however, is performed almost solely by
neurosurgeons. Therefore, only one surgical specialty had to be
convinced of the relevance of the trial.
publications produced by multicenter clinical trials generally include the names of physicians in cooperating centers, almost all of the academic acclaim goes to the principal investigators. Senior investigators at cooperating centers, who head their own research programs, are therefore less likely to see benefits for themselves if they participate. Dr. Barnett obtained cooperation from other centers by recruiting junior faculty from these centers and offering them the chance to become involved in a major trial. A side benefit accompanying their involvement was the opportunity to develop contacts with senior researchers and other junior faculty through a planned series of workshops and meetings. The strong emphasis on interactions among the centers makes the proposed study more attractive initially and supplies established channels for feedback during the course of the trial.

The grant application submitted in 1977 to NINCDS by the UWO and McMaster group to study EC/IC bypass was not the first that NINCDS had received. Dr. H. Reichman in Chicago had submitted an earlier application. Dr. Reichman's original submission was turned down primarily for methodological reasons. NINCDS suggested that he re-submit, but the grant application was then turned down for methodological reasons.

Both Dr. Peerless and Dr. Barnett had been aware of the Reichman proposal; Dr. Peerless was involved in the development of that proposal, and Dr. Barnett sat on the Study Section that reviewed it. From this awareness, they learned that NINCDS was interested in funding a trial of EC/IC and that stringent methodological criteria would be necessary for any such study to be acceptable to the Institute. Dr. Barnett subsequently applied for and received a feasibility grant from NINCDS. With this support, he was able to assemble a team to design the larger study.
IV. THE DECISION TO APPROVE AND FUND THE GRANT

A grant application submitted to NIH must pass two stages of peer review. The first stage is a peer review of the scientific merit of the application and is conducted by a "Study Section," or panel of scientists selected from relevant disciplines. The second review is undertaken by an Institute-specific Advisory Council. Members of this Council are nominated by the Institute and approved by the Secretary of Health and Human Services. The Council includes both scientists and nonscientists and reviews both the scientific merit of the application and its relevance to the goals and missions of the Institute (Henley, 1977a, 1977b, 1977c).

The EC/IC trial, as originally proposed, was to last eight years. The NIH is limited to grants of five years' duration, so a renewal application was necessary. The EC/IC bypass RCT thus went through the NIH review process twice, once in 1977 and then again in 1981.

All grant applications submitted to the NIH are first processed by the Division of Research Grants (DRG), which assigns the application to a Study Section for peer review and to an Institute for potential funding. An application is usually assigned to a Study Section, which reviews similar proposals. Where no existing Study Section has the expertise required to review a major grant application, the DRG can establish a special Study Section.

A special Study Section was established under the auspices of the DRG with the assistance of the NINCDS to review the EC/IC bypass proposal because the grant application had a large budget ($4.3 million over 5 years), and it was an application to conduct a large trial of a clinical practice involving the cooperation of neurologists, neurosurgeons, and neuroradiologists.

The special Study Section had nine members: three neurosurgeons, three neurologists, a neuroradiologist, a methodologist, and a financial consultant. The executive secretary was Dr. F. N. McFarland from DRG, and the liaison representative from NINCDS was Ms. J. Benedict. The Study Section reviewed the grant application as part of a site visit held May 3-4, 1977.
The review process is based on group discussion by the Study Section. The process itself is divided into two stages: (1) a vote on whether to approve the grant application, and (2) if the application is approved, an assignment of a priority score. The executive secretary of the Study Section produces a succinct summary of the group's discussion and recommendations in a Summary Statement or "pink sheet." The Study Section "enthusiastically recommended" the application for funding. Its overall view is expressed in this quotation from the pink sheet.

The proposed evaluation of an anastomosis to prevent or treat stroke addresses an extremely important problem. The applicant and his collaborators at the University of Western Ontario and at McMaster University constitute a highly competent and experienced leadership group to conduct this clinical trial. The statistical and epidemiological planning has been thorough and the various program co-ordinators are fully capable of evaluating and interpreting the large amount of data to be accumulated. The Study Section feels strongly that a clinical trial such as this is necessary to establish the validity of this anastomotic procedure so that in future this operation will either be done less frequently if it turns out to have a low utility in treating stroke or it will be done more frequently and with confidence if it turns out to be genuinely useful in treating stroke.

The support of the Study Section for the trial was shown not only in the written statement but also in the priority score assigned to the application. Once a trial has been approved, each member of the Study Section is asked to assign a priority score to the grant application, with a score of 1.0 representing a most meritorious and 5.0 representing a least meritorious application. The scores of the Study Section members are averaged and then multiplied by 100 to give a three-digit priority score. The EC/IC bypass trial received a rating of 111, indicating that most of the Study Section members gave it the best possible priority score.

Once the grant application has been reviewed by the Study Section, it is then sent to an Institute Advisory Council for further review. The Council's duty is to assure that the proposed study meets the missions of both the NIH in general and the particular Institute. This process involves establishing a priority list. The position of an
application in this hierarchy is closely related to the priority score determined by the Study Section, but in certain cases the Council may shift the position of an application in the hierarchy to reflect the Institute's objectives. Once the priority list has been set, grants are awarded in turn to each grant on the list until the money available to the Institute is exhausted.

It is NINCDS policy to award most funds through grants rather than contracts. Grant applications have to meet very strict methodological criteria and exhibit the ability to maintain strong support from methodologists in order to be funded. Trials of stroke prevention therapies were clearly within the mandate of NINCDS, so this grant application met the criterion of relevance to its mission. Further, as indicated earlier, NINCDS had supported the grant application. The extremely good priority score from the Study Section and the congruence of the study goals with the NINCDS mandate resulted in its approval for funding in late May 1977.

The grant began on July 1, 1977. As is common in the case of multicenter trials, patient recruitment was not as high as predicted. Also, the trial was recruiting more patients with mild disease than expected. Both of these factors resulted in the need to increase the length of the original study from eight to ten years. The study also had to expand its list of participating centers from solely North American centers to include European and eventually Japanese centers.

The renewal application was received on July 1, 1981, and a special Study Section established by NINCDS undertook a site visit in November 1981. The Study Section had seven members: three neurosurgeons (two of whom, including the chairman, were from the 1977 Study Section), two neurologists (including one from the 1977 Study Section), a methodologist, and a financial consultant. The executive secretary was Dr. H. Weinstein of NINCDS.

Although the investigators recalled the 1977 site visit as pleasant and ultimately rewarding, the 1981 visit was remembered as much more adversarial— to the point they believed that the grant would not be renewed. The investigators perceived the review as "amateurish," and the Institute perceived that the investigators regarded the renewal more as a progress report than a full application for funding.
The conclusion taken from the pink sheet of the 1981 review was:

This is a significant study being carried out in an impressive fashion. Its overall importance, in terms of its potential impact on patient treatment, was discussed and there was some difference of opinion. The committee discussed the question of the advisability of having a monitoring committee have access in some way to the data. No consensus could be reached. The special review committee believed that the highest priority should be given to data collection and that expenditures on travel and workshops could be substantially reduced without jeopardizing the study.

This is much less glowing than the 1977 review. There was apparent agreement that the study was well run and, in spite of the earlier recruitment problems, had an excellent chance of recruiting and following the required number of patients. There was some discussion of methodological problems in the 1981 review that were not noted in 1977, but the most striking difference was the change in the perception of the reviewers regarding the relevance of the trial. The 1977 review suggested the trial dealt with an important problem and would do much to determine the appropriate use of EC/IC anastomosis. The 1981 review indicated that there was disagreement regarding the effect of the trial on patient treatment. The criticism of expenditures on travel and workshops reflects a disagreement with Barnett's view that these benefits greatly aided the recruitment of cooperating clinical centers.

The decrease in enthusiasm was reflected in the priority scores assigned by the section members. The 1977 grant application had a priority score of 111, the 1981 renewal application received a score of 177. If Study Section priority scores were the sole determinant of application funding, the renewal would have fallen below the "pay line," or lowest rated funded application, and it would not have received funds.

The grant application and the review were sent to the Advisory Council of NINCDS in January of 1982. The Council took into consideration not only the scientific merit of the application as reflected in the priority score but also the relationship of the proposed study to the goals and missions of NINCDS. The EC/IC trial was
the largest clinical trial under NINCDS sponsorship, and the Institute had invested over $4 million in the first five years of the study. Cessation of the study before its completion would leave the question of EC/IC anastomosis unanswered and would provide very little useful information on the natural history of stroke. The Council apparently believed that the trial was relevant to NINCDS goals and that the substantial investment in the trial would be wasted were the grant not renewed. It therefore recommended funding the renewal application. The Institute refunded the EC/IC trial for four additional years.
V. CONCLUSION

The initiation and funding of a grant application to conduct an RCT of EC/IC bypass can be understood in the framework of a model consisting of two factors: relevance and feasibility. Some general conclusions regarding the determinants of relevance and feasibility can be drawn from our case study of this process.

Relevance is based on the perceived effect of the disease, on the appropriateness of the treatment at test for the disease, and on the perceived effect of the proposed research on the use of that treatment. The investigators believed that stroke was a major cause of death and disability and that EC/IC anastomosis was one of several potentially major techniques available to help prevent stroke. The decision to study EC/IC anastomosis rather than CE or a medical intervention was based to a large extent on the perception that a window of opportunity was open to test EC/IC, but that CE was already too well entrenched in medical practice to conduct an RCT on it. The most promising medical therapy, anti-platelet drugs, had been recently tested in an RCT.

Feasibility is based on the ability to design an adequate study and to overcome the logistical hurdles in carrying it out. The principal investigators believed they had designed a methodologically sound study and could marshal the resources required to complete the large multicenter clinical trial dictated by the sample size calculations. This perception was based on the well-developed relationship between the clinical group at the University of Western Ontario and the methodological group at McMaster, on their ability to elicit cooperation from other clinical centers, and on positive signals from NINCDS that a methodologically sound proposal to conduct an RCT on EC/IC would be funded. It seems apparent from this RCT that feasibility is at least in part a function of the stature of the investigators. Investigators with high stature are perceived as having the experience necessary to run studies and hence are better able to elicit cooperation from other clinicians, methodologists, and sponsoring agencies.
The EC/IC trial twice successfully completed the NIH grant application review process. Although the Advisory Council of NINCDS believed the trial was relevant and feasible in both of its reviews, the Study Section judged it to be less relevant in 1981 than it had been in 1977. The Advisory Council's decision to recommend funding the renewal application in spite of the Study Section's reservations (which placed the renewal below the pay line) was based on the perceived interest of NINCDS in completing this large clinical trial.
BIBLIOGRAPHY


